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NEW RESULTS ON THE BENZYLATION OF SATURATED MONO- AND DISACCHARIDES— A SEMIEMPIRICAL STUDY

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ABSTRACT

The electroreductive conversion of saturated carbohydrates in aprotic media and the subsequent quenching with benzyl bromide results in the formation of benzyl ethers at different C-positions. The application of the semiempirical method AM1 for the calculation of the thermodynamic stability of the intermediate anions formed allows a correct prediction of the observed substitution pattern for the saturated monosaccharides methyl α -D-glucoside, methyl α -D-mannoside, methyl α -D-galactoside, and the unsaturated monosaccharide D-glucal. It is shown that the inclusion of solvent effects via the COSMO continuum model is essential, as it reduces the effect of intramolecular hydrogen bonding as the sole stabilization mode in the gas phase. The results for the disaccharide sucrose are somewhat ambiguous, the three observed substitution positions are among the four most stable calculated anions. This particular system appears to be too complex to be represented by a single conformation.

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INTRODUCTION

Previously, we reported a semiempirical study on the substitution mechanism of 1,2-unsaturated monosaccharides (D-glycals) in order to determine factors which govern the experimentally observed substitution pattern.^[1] This pattern was obtained by an electroreductive conversion of D-glycals into radical anions which stabilize to anions by abstraction of a hydrogen atom from one of the hydroxyl groups and subsequent capturing in an ex-situ reaction by usual electrophiles such as alkyl or acyl halides.^[2]

The variation of electrochemical parameters such as electrode material, supporting electrolyte, solvent and reduction potential does not show significant influence on the substitution patterns. On condition that the electrophile is sterically undemanding, the substitution patterns observed may be chiefly governed by the same parameters as found with chemically induced reactions, i.e., acidity and spatial orientation of different hydroxyl groups. Otherwise, if sterically shielded electrophiles (trityl chloride) are used, the reaction occurs completely under steric control, i.e., the hydroxyl group at C-6 which is the most accessible one, is transformed into an ether.

The order of reactivity of D-glycals is primary (OH-6) > allylic (OH-3) ≥ secondary (OH-4).^[3] The electrochemically initiated benzylation and methylation of D-glucal and D-galactal give a clear preference of the substitution at OH-4 over OH-3 and OH-6. Whilst not consistent with the above order of reactivity, these results do agree with those obtained by chemically induced benzylation of D-glucal.^[3] We assume^[2] that due to inter- and intramolecular proton migration, the sugar anions generated in the initial step undergo rearrangements that lead to the establishment of an equilibrium distribution. Parameters that direct the adjustment of this equilibrium are the acidity of different OH-groups and the possible formation of hydrogen bonds. According to Guthrie et al.^[3] the produced alcoholate species exhibits greater thermodynamic stability when the anionic group is located at C-4. Consequently, substitution will occur mainly at this position.

To clarify the situation, quantum chemical calculation have been employed.^[1] In this case the semiempirical molecular orbital program MOPAC^[4] was used to perform calculations with the three most popular methods MNDO^[5], AM1^[6], and PM3^[7,8] in order to assess their performance and to propose a general approach for the calculation of related systems.

We have investigated the stabilities of the neutral glycal molecule as well as its radical anions and the subsequent anions in several conformations. Furthermore, the partial charges of the neutral and radical anion species have been calculated.

It has turned out that the electrochemically initiated substitution pattern corresponds to the order of stability of the intermediates (different D-glycal anions) as given by their free Gibbs energies. In other words, the thermodynamical stabilities of the anions is the selectivity determining factor. The calculations have then been extended to other similar systems, i.e., D-arabinal and D-xylal. Here again, the experimental results are in agreement with the calculated order of stability of the anions. The discussion of the performance of the three methods has led to the result that AM1 is the method of choice for subsequent studies on carbohydrates.

This success prompted us to investigate the possibility of extending the AM1 method to more complicated systems, i.e., saturated carbohydrate systems. The method of the electrochemically initiated introduction of protecting groups was recently applied to several non-reducing saturated mono- and disaccharides.^[9-11] From that list we

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Table 1. Substitution Patterns of Benzyl Ethers of α -D-protected Mono- and Disaccharides Obtained via Initialising Electrochemical Step

Reactant	Experimental substitution pattern at C-positions in %						di- and tri-substituted products
	2-	3-	4-	6-	1'-	3'-	
 methyl α-D-glucoside	43	3	8	13			33
 methyl α-D-mannoside	76	13		3			8
 methyl α-D-galactoside	28	32		25			15
 sucrose	48				39	13	
 D-glucal		27	47				26

chose the benzylation of the monosaccharides methyl α -D-glucoside, methyl α -D-mannoside, methyl α -D-galactoside, and the disaccharide sucrose for the current study. The experimental results are summarized in Table 1. For a comparison the experimental data for D-glucal are also included in this table. Data for chemically initiated benzylations are available,^[2,3,12-23] however, the outcome strongly depends on the method employed in the reactions.^[2,24-26]

As shown in the preceding paper,^[1] the AM1-calculated Gibbs free energies of the intermediate anions serve as the substitution-controlling measurement for the unsaturated carbohydrates used therein.

In accordance with this procedure, optimization of the neutral molecules was started from known x-ray structures of the carbohydrates, followed by a thorough manual search for the most stable conformation (shown in Figure 1) that included consideration of the rotational conformations of all OH- and the flexible hydroxymethylene groups. Typically, the three most stable conformations of each molecule were chosen as starting geometries for the optimization of the possible anions (in 2-, 3-, 4- and 6-position for the monosaccharides and additionally in 1', 3', 4' and 6'-position for sucrose). Here again, additional directed searches were carried out in order to find other stable conformations of the anions. In the following discussion however, we concentrate on the most stable conformer of each anion. The calculations were performed within the Restricted Hartree-Fock framework and the influence of entropic effects was included so that a Gibbs free energy at 298 K for each structure is reported.

Another attempt to model these systems more realistic is the inclusion of solvent effects. Here, intramolecular hydrogen bonding becomes less important as a stabilization mode. When placing a molecule in a polarizable continuum, it has the possibility to gain a stabilizing energy contribution from the interaction with the "dielectric solvent", an implicit intermolecular hydrogen bonding. The corresponding experiments have been undertaken in DMF at ambient temperature, with its dielectric constant of 37 used for the calculations. The calculations were performed with the COSMO module^[27] within MOPAC 2000,^[28] which has slight improvements over the one in MOPAC 93.

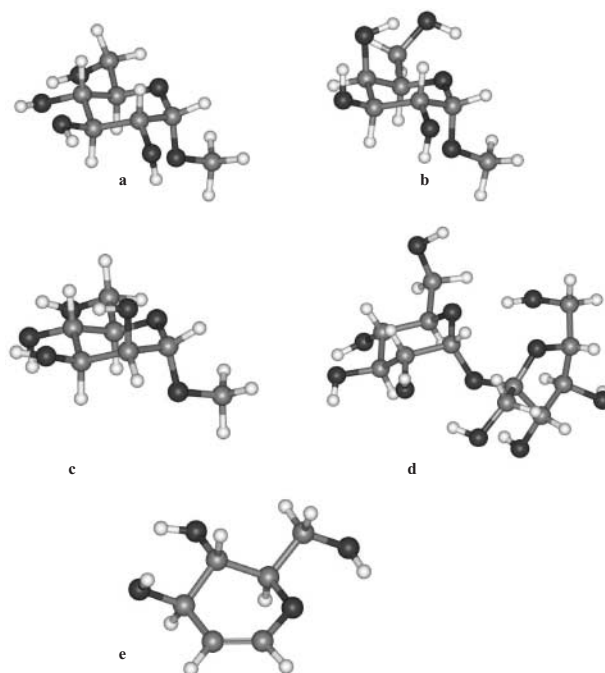


Figure 1. Most stable calculated conformations of a) methyl α -D-glucoside b) methyl α -D-galactoside c) methyl α -D-mannoside d) sucrose e) D-glucal.



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RESULTS AND DISCUSSION

Methyl α -D-Glucoside

According to the above described procedure, the most stable conformation of each possible anion of methyl α -D-glucoside was located. Their energies are summarized in Table 2 as well as the energies of the COSMO-optimized "solvated" anions (anion 2 stands for a deprotonated hydroxyl group in 2-position).

Using the AM1 Hamiltonian, the order of anion stability is calculated as $4 > 2 > 3 \gg 6$. The experimental results of the benzylation of methyl α -D-glucoside show quite a different substitution pattern: here, position 2 is most favored, followed by positions $6 \geq 4 \geq 3$. The situation is drastically altered when performing the calculations with the continuum approach. Now the anion at the 2-position becomes thermodynamically the most stable conformation with a percentage of 80% (according to Boltzmann), in agreement with the experimental data (43%). The 3-, 4- and 6-positions play a somewhat less important role, both in experiment (3:8:13%) and calculation (17:0:3%). Our approach can identify the main product, however, it has difficulties in getting the correct ordering of the byproducts. Consequently the necessity to include solvation effects into the calculations is clearly seen. The pure gas phase results give a wrong energetic ordering, mainly due to strong intramolecular stabilization of the anion at the 4-position.

Methyl α -D-Mannoside and Methyl α -D-Galactoside

The next molecules investigated were methyl α -D-mannoside and methyl α -D-galactoside. Here again, the gas phase calculation predicts the same energetic ranking of the four anionic positions for both systems as in the foregoing case, in clear contrast to the experimental pattern which almost excludes the occurrence of 4-substituted products. The COSMO study of methyl α -D-mannoside correctly yields the 2-position as the most favorable (89%), followed by the 3-position (11%), and the least stable 6- and 4-positions (both 0%) (Table 3).

Table 2. Calculated Anions of Methyl α -D-glucoside: Heats of Formation ΔH_f^{298} , Gibbs Free Energies ΔG^{298} and $\Delta\Delta G^{298}$ Relative to Anion 2 (kcal/mol)

AM1	Anion 2	Anion 3	Anion 4	Anion 6
ΔH_f^{298} (kcal/mol)	-304.49	-303.92	-307.09	-299.88
ΔS^{298} (cal/K mol)	101.30	100.72	99.73	96.53
ΔG^{298} (kcal/mol)	-334.68	-333.93	-336.81	-328.65
$\Delta\Delta G^{298}$	0.00	0.75	-2.13	6.03
AM1-COSMO	Anion 2	Anion 3	Anion 4	Anion 6
ΔH_f^{298} (kcal/mol)	-404.84	-404.03	-401.57	-402.67
ΔS^{298} (cal/K mol)	111.38	111.02	110.55	112.16
ΔG^{298} (kcal/mol)	-438.03	-437.11	-434.51	-436.09
$\Delta\Delta G^{298}$	0.00	0.92	3.52	1.94

**Table 3.** Calculated Anions of Methyl α -D-mannoside: Heats of Formation ΔH_f^{298} , Gibbs Free Energies ΔG^{298} and $\Delta\Delta G^{298}$ Relative to Anion 2 (kcal/mol)

AM1	Anion 2	Anion 3	Anion 4	Anion 6
ΔH_f^{298} (kcal/mol)	-307.11	-306.26	-307.26	-300.93
ΔS^{298} (cal/K mol)	97.59	96.54	100.07	95.06
ΔG_f^{298} (kcal/mol)	-336.19	-335.03	-337.08	-329.26
$\Delta\Delta G^{298}$	0.00	1.16	-0.89	6.93
AM1-COSMO	Anion 2	Anion 3	Anion 4	Anion 6
ΔH_f^{298} (kcal/mol)	-403.94	-403.15	-399.85	-400.65
ΔS^{298} (cal/K mol)	112.5	111.02	110.35	111.05
ΔG_f^{298} (kcal/mol)	-437.47	-436.23	-432.73	-433.74
$\Delta\Delta G^{298}$	0.00	1.23	4.73	3.72

In the case of the methyl α -D-galactoside, the continuum calculations find that positions 2, 3, and 6 are equally favorable (31:43:26%), i.e., the anions have the same thermodynamic stability (Table 4). This is in excellent agreement with the experiment, where the product distribution for quenching with benzyl bromide is 32% 3-, 28% 2-, and 25% 6-substitution, together with some disubstituted products.

Sucrose

A more complicated example is the disaccharide sucrose. In contrast to the above discussed monosaccharides, this system possesses eight centers for deprotonation and hence eight possible anions have to be taken into account. The experiment shows substitution in 2-, 1'-, and 3'-position, while the gas phase calculations without solvation find positions 4' and 2 to be the most stable ones (Table 5). When including the COSMO continuum model all anions are predicted to lie within a range of 3.5 kcal/mol, with anion 4' having the lowest energy. The stabilities of the experimentally

Table 4. Calculated Anions of Methyl α -D-galactoside: Heats of Formation ΔH_f^{298} , Gibbs Free Energies ΔG^{298} and $\Delta\Delta G^{298}$ Relative to Anion 2 (kcal/mol)

AM1	Anion 2	Anion 3	Anion 4	Anion 6
ΔH_f^{298} (kcal/mol)	-302.28	-302.60	-305.70	-298.73
ΔS^{298} (cal/K mol)	102.35	98.12	96.65	99.89
ΔG_f^{298} (kcal/mol)	-332.78	-331.84	-334.50	-328.50
$\Delta\Delta G^{298}$	0.00	0.94	-1.72	4.28
AM1-COSMO	Anion 2	Anion 3	Anion 4	Anion 6
ΔH_f^{298} (kcal/mol)	-403.83	-403.84	-399.77	-403.39
ΔS^{298} (cal/K mol)	110.81	111.42	110.56	111.87
ΔG_f^{298} (kcal/mol)	-436.85	-437.04	-432.72	-436.73
$\Delta\Delta G^{298}$	0.00	-0.19	4.13	0.12



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Table 5. Calculated Anions of Sucrose: Heats of Formation ΔH_f^{298} , Gibbs Free Energies ΔG^{298} and $\Delta\Delta G^{298}$ Relative to Anion 2 (kcal/mol)

AMI	Anion 2	Anion 3	Anion 4	Anion 6	Anion 1'	Anion 3'	Anion 4'	Anion 6'
ΔH_f^{298} (kcal/mol)	-551.15	-548.40	-541.39	-543.24	-550.01	-548.65	-553.34	-548.81
ΔS^{298} (cal/K mol)	129.93	129.54	121.56	128.07	126.25	129.23	123.74	123.64
ΔG_f^{298} (kcal/mol)	-589.87	-587.00	-577.61	-581.40	-587.63	-587.16	-590.21	-585.65
$\Delta\Delta G^{298}$	0.00	2.87	12.25	8.46	2.24	2.71	-0.35	4.21
AMI-COSMO	Anion 2	Anion 3	Anion 4	Anion 6	Anion 1'	Anion 3'	Anion 4'	Anion 6'
ΔH_f^{298} (kcal/mol)	-661.30	-660.46	-658.85	-658.96	-662.42	-661.90	-661.83	-661.02
ΔS^{298} (cal/K mol)	156.67	157.52	157.94	155.68	153.99	154.75	157.48	156.97
ΔG_f^{298} (kcal/mol)	-707.99	-707.40	-705.92	-705.35	-708.31	-708.02	-708.76	-707.80
$\Delta\Delta G^{298}$	0.00	0.59	2.07	2.64	-0.32	-0.03	-0.77	0.19

Table 6. Calculated Anions of D-glucal: Heats of Formation ΔH_f^{298} , Gibbs Free Energies ΔG^{298} and $\Delta\Delta G^{298}$ Relative to Anion 3 (kcal/mol)

AM1	Anion 3	Anion 4	Anion 6
ΔH_f^{298} (kcal/mol)	-178.37	-184.46	-178.07
ΔS^{298} (cal/K mol)	85.99	85.17	86.08
ΔG_f^{298} (kcal/mol)	-204.00	-209.84	-203.73
$\Delta\Delta G^{298}$	0.00	-5.84	0.27
AM1-COSMO	Anion 2	Anion 3	Anion 4
ΔH_f^{298} (kcal/mol)	-274.46	-274.99	-272.45
ΔS^{298} (cal/K mol)	93.89	94.36	92.85
ΔG_f^{298} (kcal/mol)	-302.44	-303.11	-300.12
$\Delta\Delta G^{298}$	0.00	-0.67	2.32

observed positions 2, 1' and 3' lie within the same range as the one at position 6' which is not detected.

In this specific example the theoretical model can calculate the tendency of ease of substitution correctly, however, it does not allow a correct prediction of the observed substitution pattern. Therefore, other factors have to be held responsible for the observed experimental results. It is, for example, known that sucrose exists in at least two conformers in solution.^[29] This is given by SIMPLE ¹H NMR isotope-shift measurements, which show two intramolecular hydrogen-bonded conformations even in polar aprotic solvents, in which the 2-oxygen of the glucose portion acts as the acceptor for either the 1'-OH or 3'-OH of the fructose moiety.^[29-31] The switch from one form to the other requires a minor rotation within the intersaccharide linkage only, thus largely retaining the overall molecular geometry. A molecular dynamics simulation in vacuum^[32] finds five local minimum energy conformations where the intramolecular hydrogen bond is retained in all but one. Therefore, it seems likely that such a complex system is not treated adequately by the approach used in the present study.

D-Glucal

The procedure in this paper differs from its predecessor publication^[1] in the inclusion of solvent effects by means of the COSMO model. In order to validate the results from the previous study, we have included calculations for D-glucal in a simulated DMF continuum. The results from Table 6 show that the energy difference between the three positions diminishes, but in an even better agreement with the observed data, correctly yield the energetic ranking $4 \geq 3 > 6$ (75:24:1%). Thus, the application of the COSMO approach to unsaturated carbohydrates is also valid.

CONCLUSIONS

We have extended our previous semiempirical study on unsaturated carbohydrates to their saturated counterparts. In accordance with our procedure described, the stability



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of the anions formed was investigated with AM1. However, in clear contrast to the earlier results on unsaturated carbohydrates, the calculated gas phase stabilities are not sufficient to reproduce the experimentally observed substitution pattern for the benzylation of the herein examined saturated carbohydrates. In every saturated and unsaturated system in the current and the previous publication, the anion in position 4 is clearly favored. This appears to be a systematic weakness of the semiempirical method which could be attributed to intramolecular hydrogen bonding in the gas phase, the only stabilization mode available to the anions formed, leading to different energetic ordering of the anion stabilities.

Inclusion of simulated solvent effects gave a much more realistic description of the studied system. It has been demonstrated that the COSMO approach in conjunction with AM1 is very reliable in predicting the correct thermodynamic stabilities and hence the substitution pattern for both saturated and unsaturated monosaccharides. For the even more complex oligosaccharides, the results are somewhat less selective. It is no longer possible to model the system with only one most stable conformation. Other methods for obtaining information about populated anion conformations (for instance molecular dynamics) will be more useful. With this information our procedure can then be applied to the generated conformers and should also yield reliable results.

In the previous publication, it was shown that on rare occasions entropic effects might be necessary to obtain reliable energies. Herein, the calculated entropy does not improve the overall outcome, the relative anion stabilities derived from heats of formations and Gibbs free energies are almost identical.

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