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SEMIEMPIRICAL STUDY ON THE  
SUBSTITUTION MECHANISM OF CARBOHYDRATES<sup>1</sup>

C. H. Hamann, S. Pleus, R. Koch, and K. Barghorn

Carl von Ossietzky-Universität, Fachbereich Chemie, Postfach 25 03, 26111 Oldenburg,  
Germany; e-mail: hamann@chemie.uni-oldenburg.de

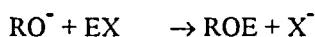
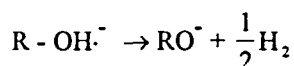
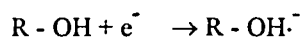
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ABSTRACT

The electroreductive conversion of carbohydrates in aprotic media leads to radical anions which stabilize to anions. Subsequent ex-situ reaction with alkylating or acylating reagents results in the formation of ether or ester derivatives at different C-positions. For instance, the reaction of D-glucal anions with benzyl bromide gives a clear preference of the substitution at OH-4 over OH-3 and OH-6. This is explained with the help of the semiempirical methods MNDO, AM1 and PM3. It turned out that the electrochemically initiated substitution pattern corresponds to the order of stability of the intermediates (different D-glucal anions) as given by the Gibbs free energies. The calculations were extended to other carbohydrates, e.g., D-galactal, D-xylal and D-arabinal. The discussion of the performance of the three methods leads to the result that AM1 is suited best for use with carbohydrates.

## INTRODUCTION

The electroreductive conversion of carbohydrates (ROH) in DMF/LiBr as supporting electrolyte leads to radical anions which stabilize to anions by abstraction of a hydrogen atom from one of the hydroxyl groups. The following ex-situ reaction with alkylating or acylating reagents (EX) results in the formation of ether or ester derivatives at different C-positions.<sup>2</sup>



The variation of electrochemical parameters such as electrode material, supporting electrolyte, solvent and reduction potential did not show significant influence on the substitution patterns.<sup>3,4</sup>

Quantum chemical calculations were employed to gain insight into the mechanistic aspects of the substitution reaction, in particular to determine factors which govern the experimentally observed substitution pattern. The semiempirical molecular orbital program MOPAC<sup>5</sup> was used to perform calculations with the three most popular methods MNDO,<sup>6</sup> AM1<sup>7</sup> and PM3.<sup>8,9</sup> These methods differ among other things in the description of hydrogen bonding which is essential for the calculation of carbohydrates. The quasi non-existent treatment of hydrogen bonding in MNDO was one of the main reasons for the development of the next method, AM1. Here, the energies of hydrogen bonds are reproduced reasonably well with geometries which are still slightly faulty. Although PM3 is an improvement in this context, there are several deficiencies within this parametrisation and hence, PM3 is not regarded as superior over AM1. The latter two methods, however, should be significantly better suited for the calculation of carbohydrates than MNDO. All three methods are used in this study in order to assess their performance and to propose a general approach for the calculation of related systems.

The first system of interest for us is the unsaturated monosaccharide D-glucal (see Fig. 1).

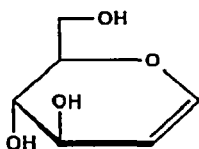


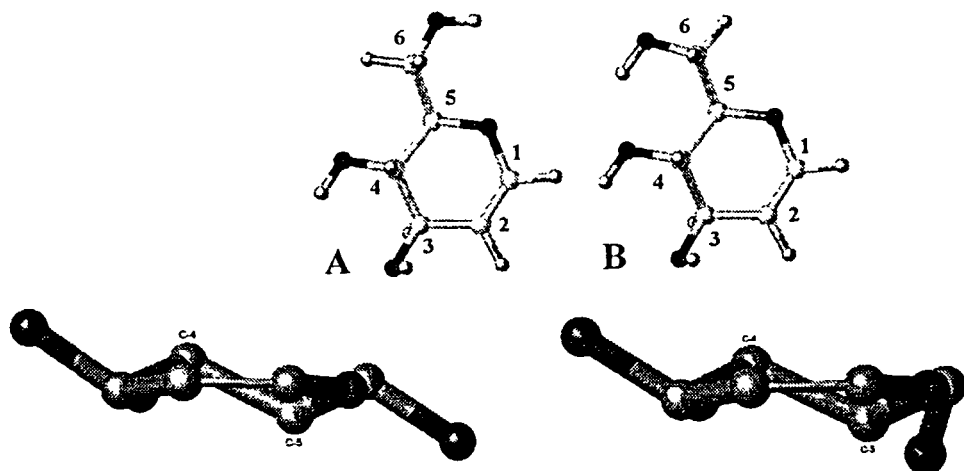
Figure 1. Structure of D-glucal

In a first step, the potential energy surfaces of the neutral molecule, its radical anion and the anion are searched for local minimum structures. The two most stable conformations which have very similar heats of formation are then discussed in the subsequent RESULTS AND DISCUSSION section. Optimization of the radical anions were performed within the Unrestricted Hartree-Fock framework. Furthermore, we investigated the influence of entropic effects and included the calculation of thermochemical properties so that we can give a Gibbs free energy for each structure. Both heats of formation and Gibbs free energies refer to a temperature of 298 K.

The next step is the examination of the electrostatic potential surfaces for the conformations of the neutral molecule.<sup>10</sup> The area of the lowest electron density should be oriented towards the negative electrode surface during adsorption due to the strong electric field in front of the electrode. Therefore, it can be assumed that the area with the lowest electron density is the probable place of the electron transfer from the electrode to the molecule.

The partial charges of the hydrogen ( $q_H$ ) and the oxygen ( $q_O$ ) atoms in the molecule (index M) and the radical anion (index RA) are also calculated. The difference in the partial charges ( $q_H - q_O$ ) in the hydroxyl group indicates the strength of the O-H bond. The smaller the difference, the weaker is the bonding in the group. Of all hydroxyl groups, the one with the weakest O-H bond is the position where the highest probability of the hydrogen detachment is given (acidity).

Comparison of the experimentally observed selectivity of the substitution with the calculated relative energetic ordering of the anions provides further insight into the mechanism of the reaction.



**Figure 2.** Geometries of the most stable conformations of neutral D-glucal

After the investigation of D-glucal it is straightforward to study its C-4-epimer D-galactal to test the procedure described above. Additional calculations are performed for the 1,2-unsaturated pyranoidic pentoses D-xylal and D-arabinal.

## RESULTS AND DISCUSSION

### D-glucal

For D-glucal we attained two conformations (Fig. 2) with nearly identical heats of formation (Table 1).

The geometries of conformers **A** and **B** differ in the orientation of the freely rotatable CH<sub>2</sub>OH-group. In conformer **A**, it forms a hydrogen bond between the hydrogen atom of OH-6 and the ring oxygen atom, whereas **B** possesses a hydrogen bond between the hydrogen atom at OH-6 and the oxygen atom at OH-4. Both conformations belong to a <sup>4</sup>H<sub>3</sub> conformation. Corresponding <sup>5</sup>H<sub>4</sub> conformations are found to be clearly less stable.

As shown in Table 1, the difference in the heats of formation for both conformers is only a few tenths of a kcal/mol, and - not surprisingly - the three methods also predict different conformations as the most stable one. Taking into account entropic effects, only

**Table 1.** D-glucal: Heats of formation  $\Delta H_f^M$  and Gibbs free energies  $\Delta G^M$  of the neutral molecule (in kcal/mol)

Method	Conformation A	Conformation B	Difference A-B
$\Delta H_f^M$			
AM1	-177.40	-177.45	0.05
PM3	-159.13	-158.99	-0.14
MNDO	-166.87	-165.45	-1.42
$\Delta G^M$			
AM1	-202.83	-203.63	0.80
PM3	-184.81	-185.59	0.77
MNDO	-193.36	-191.83	-1.53

**Table 2.** D-glucal: Heats of formation  $\Delta H_f^{RA}$  and Gibbs free energies  $\Delta G^{RA}$  of the radical anion (in kcal/mol)

Method	Conformation A	Conformation B	Difference A-B
$\Delta H_f^{RA}$			
AM1	-180.75	-180.37	-0.37
PM3	-161.11	-160.38	-0.73
MNDO	-171.79	-170.00	-1.79
$\Delta G^{RA}$			
AM1	-207.76	-207.15	-0.62
PM3	-188.59	-187.84	-0.75
MNDO	-198.90	-197.06	-1.85

the AM1- and PM3-calculated Gibbs free energies favour structure **B** over **A** by almost 1 kcal/mol. Usually, the inclusion of entropies into the calculation of energies is not necessary. On rare occasions however, if the difference between structures is very small, the entropy can influence the relative ordering (see Table 1).

For the radical anion, a similar behaviour was found. Here again, the differences between the two conformations are enhanced when  $\Delta G$  is calculated (Table 2).

The electrostatic potential surface calculation for the neutral molecule reveals that the most positive area is located around C-1 (we abstain from a graphic illustration of the potential surfaces, because it is only meaningful as a coloured one). This implies that the electron transfer from the electrode to the molecule will probably take place at this electron-deficient region. After the transfer the most positive area has switched to the

**Table 3.** D-glucal: Partial charges  $q$  and their differences of the neutral molecule (M: molecule, H: hydrogen, O: oxygen). Minimal values are printed boldface.

Method	Position	Conformation A			Conformation B		
		$q_H^M$	$q_O^M$	$q_H^M - q_O^M$	$q_H^M$	$q_O^M$	$q_H^M - q_O^M$
AM1	OH-3	0.205	-0.322	<b>0.527</b>	0.205	-0.322	<b>0.527</b>
	OH-4	0.222	-0.321	0.543	0.227	-0.335	0.562
	OH-6	0.208	-0.320	<b>0.528</b>	0.219	-0.323	0.542
PM3	OH-3	0.190	-0.307	0.497	0.191	-0.308	<b>0.499</b>
	OH-4	0.205	-0.304	0.509	0.210	-0.317	0.527
	OH-6	0.189	-0.303	<b>0.492</b>	0.197	-0.307	0.504
MNDO	OH-3	0.183	-0.321	<b>0.504</b>	0.184	-0.322	<b>0.506</b>
	OH-4	0.195	-0.316	0.511	0.198	-0.324	0.522
	OH-6	0.190	-0.320	0.510	0.191	-0.322	0.513

**Table 4.** D-glucal: Partial charges  $q$  and their differences of the radical anion (RA: radical anion, H: hydrogen, O: oxygen). Minimal values are printed boldface.

Method	Position	Conformation A			Conformation B		
		$q_H^{RA}$	$q_O^{RA}$	$q_H^{RA} - q_O^{RA}$	$q_H^{RA}$	$q_O^{RA}$	$q_H^{RA} - q_O^{RA}$
AM1	OH-3	0.197	-0.406	0.607	0.197	-0.408	0.605
	OH-4	0.197	-0.364	<b>0.561</b>	0.204	-0.378	<b>0.582</b>
	OH-6	0.216	-0.364	0.580	0.216	-0.364	<b>0.580</b>
PM3	OH-3	0.190	-0.400	0.590	0.191	-0.401	0.592
	OH-4	0.189	-0.350	<b>0.539</b>	0.195	-0.364	0.559
	OH-6	0.200	-0.350	0.550	0.198	-0.349	<b>0.547</b>
MNDO	OH-3	0.172	-0.383	0.555	0.172	-0.384	0.556
	OH-4	0.171	-0.349	<b>0.518</b>	0.175	-0.360	<b>0.535</b>
	OH-6	0.187	-0.351	0.538	0.183	-0.353	<b>0.536</b>

CH<sub>2</sub>OH group (C-6) and the highest electron density can be found at the position of the transfer (C-1).

Concerning the acidity of a hydroxyl function, we have to consider the differences in partial charges of the hydrogen ( $q_H$ ) and oxygen ( $q_O$ ) atoms in the respective bonds. The smallest difference in partial charges ( $q_H - q_O$ ) correlates with the weakest bond and thus bearing the hydrogen atom with the highest acidity. The hydrogen and oxygen partial charges of the O-H groups and their differences are summarized in Table 3 for the neutral molecule and in Table 4 for the radical anion.

**Table 5.** D-glucal: Heats of formation  $\Delta H_f^A$  and Gibbs free energies  $\Delta G^A$  of the anions (kcal/mol)

Method	Anion 3			Anion 4			Anion 6		
	Conf. A	Conf. B	Diff. A-B	Conf. A	Conf. B	Diff. A-B	Conf. A	Conf. B	Diff. A-B
$\Delta H_f^A$									
AM1	-177.84	-178.37	0.53	-180.70	-184.46	3.75	-	-178.07	-
PM3	-162.84	-163.29	0.44	-165.60	-174.43	8.83	-159.52	-169.45	9.93
MNDO	-163.84	-162.91	-0.93	-167.56	-168.38	0.82	-160.06	-162.81	2.75
$\Delta G^A$									
AM1	-203.84	-204.00	0.16	-206.74	-209.84	3.10	-	-203.73	-
PM3	-188.15	-189.47	1.33	-191.98	-200.76	8.78	-184.55	-195.04	10.50
MNDO	-188.94	-188.91	-0.03	-192.68	-194.25	1.57	-185.16	-188.73	3.57

In general, the calculated differences in partial charges in the neutral molecule are relatively small. The calculations predict the hydrogen atom in the OH-3 group to have the highest acidity, closely followed by the OH-6 hydrogen atom and the hydroxyl group at position 4 as the one with the lowest acidity.

More important is the order of the calculated acidity in the radical anion because the detachment of the hydrogen atom takes place in this species. Naturally, the calculated order of acidity changes after the electron transfer from the electrode to the molecule. In the radical anion the acidity is the highest at the OH-4 group, followed by the OH-6 and OH-3 functions. This is true for all methods, except for PM3 which predicts conformer B to have the lowest partial charge difference at the OH-6 group (see Table 4).

The hydrogen separation produces three possible anions, named after the C-positions, again in several conformations. Optimization of these structures with all three methods predict unanimously conformer B as the most stable one (Table 5). AM1 does not even find a minimum structure for anion 6 corresponding to conformer A. There is also agreement between MNDO, AM1 and PM3 that anion 4 is thermodynamically favoured over the other anions (which are of comparable stability, Table 6). Only PM3 finds anion 3 to be several kcal/mol less favourable than anion 6.

These computationally derived data are now compared to experimental data of substitution patterns (EX: BnBr) obtained in our group.<sup>11</sup>

In the case of the electrochemically initiated benzylation of D-glucal, a clear preference for substitution at OH-4 is observed, i.e., 3- vs. 4-OH = 27 : 47. The remaining



**Table 6.** D-glucal: Gibbs free energies  $\Delta\Delta G^A$  of the anions (kcal/mol) relative to anion 4

Method	Anion 3	Anion 4	Anion 6
$\Delta\Delta G^A$			
AM1	5.84	0.0	6.11
PM3	11.29	0.0	5.72
MNDO	5.31	0.0	5.52

**Table 7.** Synoptical table of the results of D-glucal

	Acidity of the radical anion	Stability of the anions	Experimental substitution pattern <sup>11</sup>
Ordering of positions	4 > 6 > 3	4 > 3 ≥ 6	4 > 3 > 3,4 > 3,6 > 4,6

26% are distributed to different di-*O*-substituted products, i.e., 15% of the 3,4-di-*O*-substituted-, 6% of the 3,6-di-*O*-substituted- and 5% of the 4,6-di-*O*-substituted benzyl ether is formed. Altogether, these results lead to the following order of substitution of the hydroxyl groups 4 > 3 > 3,4 > 3,6 > 4,6. These findings are summarized in Table 7, together with the calculated radical anion acidity and the thermodynamical stability of the anions.

The experimental results are in agreement with the calculated order of stability of the anions, i.e., the thermodynamical stability determines the substitution position.

However, this explanation does not hold if sterically demanding electrophiles are used. Then the reaction occurs completely under steric control. In case of trityl chloride as the electrophile only the hydroxyl group at C-6, which is the most accessible one, was tritylated in case of D-glucal.<sup>11</sup> This trend, a preferred substitution of the primary OH group at C-6 is also found in case of the acylation (EX: Ac<sub>2</sub>O, AcCl). Here, the high degree of 6-substitution - the amount of the 6-*O*-acyl ester was up to 78% - is caused by the tendency of ester derivatives to undergo migration of the acyl groups to more accessible positions.

All of the three semiempirical methods employed in this study have predicted the correct outcome and could confirm the experimental findings. However, in the calculation

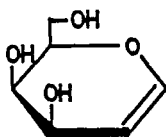


Figure 3. Structure of D-galactal

Table 8. D-galactal: Heats of formation  $\Delta H_f^M$  and Gibbs free energies  $\Delta G^M$  of the neutral molecule (in kcal/mol)

Method	Conformation A	Conformation B	Difference A-B
$\Delta H_f^M$			
AM1	-178.07	-177.15	-0.92
PM3	-160.17	-158.76	-1.41
MNDO	-165.70	-165.54	-0.16
$\Delta G^M$			
AM1	-205.38	-203.08	-2.30
PM3	-186.76	-186.15	-0.61
MNDO	-193.06	-191.93	-1.13

of the heats of formation and Gibbs free energies of the neutral molecule, MNDO contradicts the other two methods. Due to the improved description of hydrogen bonding (among others) in AM1 and PM3, they appear more trustworthy than MNDO for comparable studies. Some minor inconsistencies in the PM3 calculations of the anions and radical anions lead to the conclusion that AM1 is the most reliable semiempirical method for these systems. We can therefore recommend AM1 as the method of choice for subsequent studies on carbohydrates.<sup>12</sup>

#### D-galactal, D-xylal, D-arabinal

As mentioned in the introduction, the above-described procedure was extended and tested on other similar systems. In the following we will discuss the performance of the employed semiempirical methods. In case of D-galactal (Fig. 3), again two conformations with similar energies are found and again, both structures are  $^4H_3$  conformers. All three methods predict conformation A to be more stable (Table 8).

**Table 9.** D-galactal: Heats of formation  $\Delta H_f^{RA}$  and Gibbs free energies  $\Delta G^{RA}$  of the radical anion (in kcal/mol)

Method	Conformation A	Conformation B	Difference A-B
$\Delta H_f^{RA}$			
AM1	-182.43	-181.42	-1.01
PM3	-164.52	-164.77	0.25
MNDO	-172.81	-171.92	-0.89
$\Delta G^{RA}$			
AM1	-209.71	-209.13	-0.03
PM3	-191.25	-191.88	0.63
MNDO	-199.79	-198.96	-0.83

**Table 10.** D-galactal: Partial charges  $q$  and their differences of the radical anion (RA: radical anion, H: hydrogen, O: oxygen). Minimal values are printed boldface.

Method	Position	Conformation A			Conformation B		
		$q_H^{RA}$	$q_O^{RA}$	$q_H^{RA} - q_O^{RA}$	$q_H^{RA}$	$q_O^{RA}$	$q_H^{RA} - q_O^{RA}$
AM1	OH-3	0.192	-0.376	<b>0.568</b>	0.191	-0.376	<b>0.567</b>
	OH-4	0.228	-0.358	0.586	0.229	-0.361	0.590
	OH-6	0.219	-0.364	0.583	0.232	-0.359	0.591
PM3	OH-3	0.184	-0.37	0.554	0.184	-0.371	<b>0.555</b>
	OH-4	0.229	-0.361	0.590	0.240	-0.363	0.603
	OH-6	0.196	-0.349	<b>0.545</b>	0.235	-0.380	0.615
MNDO	OH-3	0.166	-0.362	0.528	0.166	-0.361	0.527
	OH-4	0.183	-0.339	<b>0.522</b>	0.180	-0.332	<b>0.512</b>
	OH-6	0.186	-0.352	0.538	0.191	-0.340	0.531

The differences between the two radical anion structures (Table 9) are for all methods less than a kcal/mol, consistent with the previous findings.

Table 10 gives the partial charges for the two radical anion conformations. The results are irregular. Depending on the method used, one can favour either position 3, 4 or 6. As seen before, the analysis of partial charges in the radical anion is not very meaningful.

The relative energies of the three possible anions again become the decisive factor for the position where the dehydrogenation takes place. Table 11 summarizes the results of these calculations. Conformation B is found to be almost exclusively the more stable

**Table 11.** D-galactal: Heats of formation  $\Delta H_f^A$  and Gibbs free energies  $\Delta G^A$  of the anions (kcal/mol)

Method	Anion 3			Anion 4			Anion 6		
	Conf. A	Conf. B	Diff. A-B	Conf. A	Conf. B	Diff. A-B	Conf. A	Conf. B	Diff. A-B
$\Delta H_f^A$									
AM1	-177.79	-177.50	-0.29	-180.32	-182.82	2.50	-173.95	-177.05	3.10
PM3	-166.64	-169.17	2.53	-168.29	-176.57	8.28	-159.31	-168.75	9.44
MNDO	-164.80	-164.63	-0.17	-168.22	-169.67	1.45	-161.77	-163.80	2.03
$\Delta G^A$									
AM1	-202.62	203.07	0.45	-205.10	-208.10	3.00	-200.08	-203.48	3.41
PM3	-191.45	-195.32	3.87	-193.11	-201.41	8.30	-186.30	-195.14	8.84
MNDO	-191.90	-190.63	-1.26	-194.25	-195.45	1.20	-188.71	-190.55	1.84

**Table 12.** D-galactal: Gibbs free energies  $\Delta\Delta G^A$  of the anions (kcal/mol) relative to anion 4

Method	Anion 3	Anion 4	Anion 6
$\Delta\Delta G^A$			
AM1	5.03	0.0	4.62
PM3	6.09	0.0	6.27
MNDO	3.55	0.0	4.90

one and again, there is agreement between MNDO, AM1 and PM3 that anion 4 is thermodynamically favoured over the other anions (Table 12).

The electrochemically initiated benzylation of D-galactal takes place selectively at the 4-OH group (64%) followed by the 3-OH group (13%). The amount of the 6-O-benzyl ether was only 3%, the amount of the disubstituted products 18% (i.e., 3,4-di-O-benzyl ether 6%, 3,6-di-O-benzyl ether 5%, 4,6-di-O-benzyl ether 7%) and 1% of the tri-O-benzyl ether. The clear preference for the hydroxyl group in position 4 is also given in case of the methylation, e.g., 3- vs. 4-OH: 26:46%.<sup>11</sup> Again, the experimental data are in agreement with the calculations.

The next two molecules of interest are the simpler carbohydrates D-xylal and D-arabinal (Fig. 4). In both cases only one conformation is found to be relevant because the freely rotatable CH<sub>2</sub>OH-group in the previously examined systems is now missing. A discussion of the energies of both the neutral molecule and the radical anion can therefore be omitted.

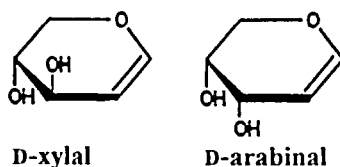


Figure 4. Structures of D-xylal and D-arabinal

**Table 13.** D-xylal: Partial charges  $q$  and their differences of the radical anion (RA: radical anion, H: hydrogen, O: oxygen). Minimal values are printed boldface.

Method	Position	$q_{\text{H}}^{\text{RA}}$	$q_{\text{O}}^{\text{RA}}$	$q_{\text{H}}^{\text{RA}} - q_{\text{O}}^{\text{RA}}$
AM1	OH-3	0.195	-0.41	<b>0.605</b>
	OH-4	0.195	<b>-0.366</b>	<b>0.561</b>
PM3	OH-3	0.189	-0.402	0.591
	OH-4	0.186	<b>-0.402</b>	<b>0.588</b>
MNDO	OH-3	0.170	-0.384	0.554
	OH-4	0.167	<b>-0.348</b>	<b>0.515</b>

**Table 14.** D-arabinal: Partial charges  $q$  and their differences of the radical anion (RA: radical anion, H: hydrogen, O: oxygen). Minimal values are printed boldface.

Method	Position	$q_{\text{H}}^{\text{RA}}$	$q_{\text{O}}^{\text{RA}}$	$q_{\text{H}}^{\text{RA}} - q_{\text{O}}^{\text{RA}}$
AM1	OH-3	0.193	-0.419	0.612
	OH-4	0.203	<b>-0.367</b>	<b>0.570</b>
PM3	OH-3	0.189	-0.416	0.605
	OH-4	0.200	<b>-0.350</b>	<b>0.550</b>
MNDO	OH-3	0.172	-0.389	0.561
	OH-4	0.173	<b>-0.349</b>	<b>0.522</b>

For D-xylal and D-arabinal, all methods consistently calculate the highest acidity in the radical anion at the OH group in position 4 (Table 13 and 14). They also predict unanimously the anion with the hydrogen atom detached in position 4 to be more stable than its position 3 counterpart (Table 15-18) although the difference is much smaller here (about 1 kcal/mol, compared to 4-6 kcal/mol in glucal and galactal).

Although the calculated stability differences between the two formed anions are relatively small, the experimental substitution pattern is reproduced correctly. In case of

**Table 15.** D-xylal: Heats of formation  $\Delta H_f^A$  and Gibbs free energies  $\Delta G^A$  of the anions (kcal/mol)

Method	Anion 3	Anion 4
$\Delta H_f^A$		
AM1	-123.63	-125.36
PM3	-115.54	-117.15
MNDO	-116.19	-118.23
$\Delta G^A$		
AM1	-148.11	-149.90
PM3	-140.28	-140.91
MNDO	-139.80	-141.87

**Table 16.** D-arabinal: Heats of formation  $\Delta H_f^A$  and Gibbs free energies  $\Delta G^A$  of the anions (kcal/mol)

Method	Anion 3	Anion 4
$\Delta H_f^A$		
AM1	-125.82	-126.41
PM3	-121.24	-121.74
MNDO	-117.18	-119.00
$\Delta G^A$		
AM1	-148.99	-149.65
PM3	-144.37	-144.88
MNDO	-140.66	-142.56

**Table 17.** D-xylal: Gibbs free energies  $\Delta\Delta G^A$  of the anions (kcal/mol) relative to anion 4

Method	Anion 3	Anion 4
$\Delta\Delta G^A$		
AM1	1.79	0.0
PM3	0.63	0.0
MNDO	2.07	0.0

**Table 18.** D-arabinal: Gibbs free energies  $\Delta\Delta G^A$  of the anions (kcal/mol) relative to anion 4

Method	Anion 3	Anion 4
$\Delta\Delta G^A$		
AM1	0.66	0.0
PM3	0.51	0.0
MNDO	1.90	0.0

the benzylation of D-xylal a marked preference for the substitution of the OH-group at C-4 is found – the amount of the 4-*O*-benzyl ether was up to 70%, corresponding to the larger difference determined with the more reliable method AM1. The substitution pattern obtained in case of D-arabinal reflects the calculated very small differences between position 3 and 4 as mentioned above. Here, 35% of the 4-*O*-benzyl ether and 25% of the 3-*O*- as well as 35% of the disubstituted products were isolated.<sup>11</sup>

## CONCLUSIONS

We now have tested our computational approach on four systems. In agreement with the first finding, the study of the additional test sets support that AM1 appears to be the most reliable method of the three semiempirical Hamiltonians employed herein. It could be also confirmed that the thermodynamic stabilities of the formed anions are responsible for the observed reactivity, not the partial charges in the radical anions.

It has been demonstrated that computational methods, in particular the semiempirical AM1, are useful additions to the list of methods for the explanation of substitution patterns on carbohydrates. During the analysis of different molecular properties of the species involved in the substitution mechanism, the stabilities of the anions turn out to be the selectivity-determining factor with one restriction: The steric demand of the electrophile can take over the control over the substitution position, and the whole mechanism is no longer thermodynamically controlled.

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