Theoretical Study on Alkylation and Esterification of Methyl 3,6-Anhydro-α-D-galactopyranoside

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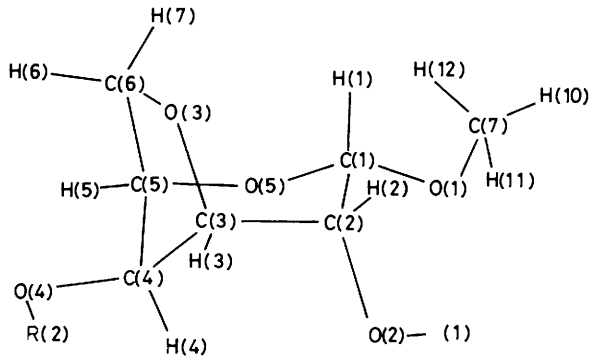
Molecular mechanics and *ab initio* molecular orbital calculations were performed on the neutral and anionic forms of methyl 3,6-anhydro-α-D-galactopyranoside. Results from these calculations suggest that in alkylation and esterification the higher reactivity at O(4) than at O(2) is due to the stabilization of the corresponding anion rather than to steric hindrance. This conclusion is also supported by results from the comparison of the calculated molecular surfaces exposed to nucleophilic attack at these particular positions.

Recently it has been shown that the phase-transfer technique is well suited for regioselective monobenzylation[1,2] and monotosylation[3,4] of glycopyranosides with unsubstituted hydroxys at C(2) and C(3). The experimental results indicate a higher reactivity at position 2 than at 3, due probably to higher acidity of HO(2).[1,4] It was also reported that steric hindrance seems to be relatively unimportant.[5] That an inductive effect cannot account for the reactivity of the hydroxy group was indicated by unimolecular esterification of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside.[6] This compound is esterified selectively at HO(3) rather than at HO(2).

In order to probe in more detail the reactivity of carbohydrates in reactions of nucleophilic substitution we studied methyl 3,6-anhydro-α-D-galactopyranoside (MGALP). This is an especially well suited system for the investigation of nucleophilic substitution because the molecule is rigid enough to prevent major structural changes after ionization in alkaline medium, and it also contains an axially orientated HO(2) group which is expected to be very reactive due to the inductive effect of the adjacent oxygen atoms. Data collected from our experiments show that alkylation and esterification occur predominantly at the O(4) position of MGALP.[7] This result may be due to electronic or stereoselective effects, especially in systems with steric hindrance. To investigate these possibilities we carry out quantum-chemical calculations on the stability of the neutral and anionic forms of MGALP analogues.



(1)

a; R(1) = R(2) = H
b; R(1) = C(8)H_3, R(2) = H
c; R(1) = H, R(2) = C(8)H_3
d; R(1) = C(8)H$(CH_3)_2$, R(2) = H
e; R(1) = H, R(2) = C(8)H$(CH_3)_2$

Methods

Ab initio molecular orbital calculations were done at the Hartree–Fock level with the STO-3G basis set, using a version of the GAUSSIAN80 systems of programs.[8] The equilibrium structures for *ab initio* single point calculations were first determined with the molecular mechanics method elaborated by Allinger and his co-workers[9] and incorporated in the MM2 programs.[10] The starting point geometry was taken from ref. 11.

To compare steric accessibility we applied a method developed recently by Liebman *et al.*[13] This method (the SURVOL procedure) utilizes the evaluation of the exposed surface to probe the ability of an individual atom, or groups of atoms within a molecule, to interact with another reactant. The van der Waals surface of each atom is simulated by a set of points randomly generated at uniform density at the fixed van der Waals radius. These points are then compared with the atom list to determine if they occur within the van der Waals radius of any other atom (*i.e.*, are buried in an atom–atom interface) or are exposed. The ratio of points exposed to the total number of points (the third entry in Table 3) yields a ratio of the exposed to theoretically available surface areas for each atom.

Results

Results in Table 1 show that quantum-mechanical calculation yields a lower energy for the geometry optimized with the molecular mechanics method than for the crystal structure. The difference in energy between crystal structure and the geometry optimized with molecular mechanics (by 16.35 kcal mol^{-1}) is significant. From the inspection of the geometries it appears that this is partially due to underestimation of the O(1)–C(7) bond length from a crystal structure determination. This value changes during optimization by 0.06 Å, whereas other parameters are only slightly modified. The total molecular energies of the anionic $O(2)^-$ and $O(4)^-$ forms were also calculated both in the crystal structure and the equilibrium geometry of the neutral species, calculated with molecular mechanics. Geometry optimization affects the results only quantitatively, for the $O(4)^-$ anionic form remains preferred over $O(2)^-$.

In order to probe for a possible steric effect, we also calculated total energies of MGALP substituted with bulky

Table 1. Total molecular energies (in hartrees) calculated with the STO-3G basis set for neutral and anionic species of MGALP

Species[a]	Standard geometries[a]	Optimized geometries[b]
(**1a**)	−638.023 643	−638.049 698
Anionic O(2)$^-$ form	−637.215 514	−637.226 230
Anionic O(4)$^-$ form	−637.216 124	−637.232 055
(**1b**)		−676.629 644
(**1c**)		−676.635 628
(**1d**)		−753.789 319
(**1e**)		−753.796 192

[a] From ref. 11. [b] Obtained from optimization with the molecular-mechanics method[9] using the MM2 program.[10]

methyl or isopropyl groups at O(2) and O(4). Equilibrium geometries for these compounds were also determined using the MM2 procedure[10] with the option that allows rotation over a particular bond, followed by full optimization of bond distances and angles. An increment of 5° was applied for dihedral angles C(8)-O(2)-C(2)-C(1) and C(8)-O(4)-C(4)-C(3). *Ab initio* single point calculations for the resulting geometries indicate that the difference in total energies of two isomers is nearly 4 kcal mol^{-1}.

Discussion

It would have been preferable to compare the energies of all species after full optimization with quantum-mechanical methods. However, the size of the molecules restricted us to the use of the molecular mechanics method for the energy-minimization problem, followed by single point *ab initio* molecular-orbital calculations. Although calculations with the STO-3G basis set reproduce with good agreement properties of neutral species, the results for anionic forms are less certain. Nevertheless, all the results point to the conclusion that the anionic form with the ionized O(4)H group is more stable than one with O(2)H ionized. This relation also holds for neutral compounds with bulky methyl and isopropyl substituents at these positions. It therefore seems that in this particular case steric effects are of only secondary importance.

Results of molecular-mechanics calculations (Table 2) also support this conclusion for the difference in steric energy between the analogues of MGALP with bulky substituents at O(2) and O(4) is within 1 kcal mol^{-1}.

Results presented in Table 3 show that difference in accessibility of O(2) and O(4) calculated for the molecules in their anionic and un-ionized forms is only by *ca.* 3% [O(4) over O(2)] and therefore it is very unlikely that this factor considerably affects substitution at O(2). Preferential formation of O(4)R derivatives is due rather to electronic stabilization than to steric hindrance around O(2).

Based on the results from the experimental and the theoretical investigations we can conclude that the higher reactivity for nucleophilic substitution at O(4) of methyl 3,6-anhydro-α-D-galactopyranoside is probably a result of the stabilization of the corresponding form, and also of the resulting derivative. Data from *ab initio* molecular-orbital calculations do not indicate that the presence of bulky substituents should favour the formation of O(4)R derivatives. Rather, the difference in total energies between the O(2)R and O(4)R isomers suggests that the equilibrium is shifted towards the O(4)R form, in good agreement with experimental results.

Table 2. Steric energies (in kcal mol^{-1}) for methyl and isopropyl derivatives of MGALP calculated by molecular mechanics

Derivative	Steric energy
(**1b**)	43.65
(**1c**)	43.07
(**1d**)	46.39
(**1e**)	45.78

Table 3. Reactive surface area as determined by SURVOL Monte Carlo simulation for the anionic species at O(2) and O(4)

	Reactive surface area		Accessibility ratio
Atom	O(2)	O(4)	
O(2)	16.74*	12.22	0.59
O(4)	11.38	17.55*	0.62

* Ionized.

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