Ab Initio LCAO-MO Calculations on α-D-Glucopyranose, β-D-Fructopyranose, and their Thiopyranoid-ring Analogues. Application to a Theory of Sweetness

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Ab initio SCF LCAO-MO calculations at the STO-3G level have been performed on the title compounds and the results are discussed in terms of net atomic charges and Mulliken population analysis, with a view to providing an explanation for the greater sweetness observed in the case of the thio analogues.

There is considerable interest at present in the design of synthetic sweeteners.[1] Concomitantly, there has been intense investigation of the structural and mechanistic aspects associated wth sweetness; however, it is still not possible to predict *a priori* whether a novel structure will be sweet. A particularly interesting observation is that the thiopyranoid-ring analogues of α-D-glycopyranose (**1**) and β-D-fructopyranose (**2**), namely 5-thio-α-D-glucopyranose (**3**) and 6-thio-β-D-fructopyranose (**4**), have been found to be significantly sweeter than (**1**) and (**2**), respectively, when tasted in crystalline form.[2] Conjectural explanations have been offered to account for the greater sweetness of the two thio sugars.[2] In an effort to determine the effects responsible for the observed differences, we have performed *ab initio* quantum mechanical calculations on (**1**)—(**4**), and the results are discussed in terms of net atomic charges and Mulliken population analysis.

A calculation on β-D-fructopyranose (**2**) has been reported previously from this laboratory;[3] however, no *ab initio* studies on the thio sugars (**3**) and (**4**) have been published, possibly because of the lack of crystallographic data for geometrical input. In the present study the input geometries for (**1**) and (**2**) were their neutron diffraction crystal structures;[4,5] in the case of (**4**), data from a recently-determined *X*-ray crystal structure[6] were employed, and, in the case of (**3**), the geometry was based on data obtained from an *X*-ray structural determination of its penta-acetate (**5**),†[7] the hydroxy groups being oriented as in α-D-glucopyranose. The approach takes into account the greater ring puckering in thiopyranoid sugars than in the oxygen analogues,[8] and allows an estimate of the degree

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of intramolecular hydrogen bonding (excluding solvent effects) in addition to an indication of the acidities and basicities of the hydroxy groups.

The net atomic charges (Q) derived by Mulliken population analysis for (**1**)—(**4**) are listed in Table 1. It is seen that the sulphur atoms in (**3**) and (**4**) appear to carry partial positive charges, whereas C-5 and C-6, the carbon atoms attached to sulphur in (**3**) and (**4**), respectively, carry partial negative charges. This apparent accumulation of charge on these carbon atoms may have a profound effect on the sweetness of (**3**) and (**4**), since these centres are believed to be either the hydrophobic component of the saporous unit [as in (**4**)] or adjacent to it [as in (**3**)].[9] It is also seen that the anomeric carbon atoms in the thio sugars (**3**) and (**4**) appear to carry charges that are significantly less positive than those on the corresponding atoms in (**1**) and (**2**). Thus, there is an essentially complete reversal of charge distribution over the sulphur and the neighbouring carbon atoms in (**3**) and (**4**) relative to that over the corresponding atoms in (**1**) and (**2**).

Table 1. Net atomic charges for pyranoids (**1**)—(**4**) in units of elementary charge.

	Charge Q			
Atom	(**1**)	(**2**)[a]	(**3**)	(**4**)[a]
C-1	0.184	−0.005	−0.011	−0.021
C-2	0.066	0.239	0.075	0.044
C-3	0.066	0.060	0.065	0.053
C-4	0.055	0.066	0.064	0.053
C-5	0.065	0.066	−0.127	0.068
C-6	0.008	0.003	0.009	−0.212
H(C-1)	0.065	0.070	0.059	0.059
H′(C-1)	—	0.055	—	0.077
H(C-2)	0.072	—	0.069	—
H(C-3)	0.055	0.073	0.054	0.049
H(C-4)	0.053	0.064	0.051	0.070
H(C-5)	0.070	0.052	0.075	0.079
H(C-6)	0.055	0.064	0.051	0.075
H′(C-6)	0.063	0.080	0.046	0.076
O-1	−0.322	−0.317	−0.312	−0.306
O-2	−0.310	−0.331	−0.311	−0.317
O-3	−0.317	−0.313	−0.317	−0.315
O-4	−0.312	−0.322	−0.314	−0.309
O-5[S]	−0.280	−0.318	0.117	−0.308
O-6[S]	−0.305	−0.285	−0.308	0.098
H(O-1)	0.200	0.209	0.195	0.200
H(O-2)	0.197	0.196	0.194	0.212
H(O-3)	0.193	0.195	0.191	0.195
H(O-4)	0.188	0.200	0.187	0.191
H(O-5)	—	0.201	—	0.177
H(O-6)	0.194	—	0.190	—

[a] A value of 0.96 Å was used for all O–H bond lengths.

The charge distributions referred to above are presumably manifestations of the anomeric effect,[10] and are considered to arise from stabilizing orbital interactions between a nonbonded occupied orbital on the heteroatom in the ring and the antibonding orbitals [σ^*(C–O), π^*(C–O)] of the exocyclic C–O bond at the anomeric centre. In the case of (**3**) and (**4**) these interactions may result in a partial positive charge on the sulphur atom, and in a corresponding lengthening of the sulphur–anomeric carbon bond owing to coulombic effects (see ref. 11). In contrast, the negative charges on C-5 and C-6, in (**3**) and (**4**), respectively, and the positive charges on the sulphur atoms should lead to coulombic attraction between these centres and hence to a shortening of the C-5–S and C-6–S bonds. The bond lengths obtained from the X-ray crystallographic structural determinations of (**4**)[6] and (**5**)[7] are as follows: C-2–S in (**4**), 1.828 Å; C-1–S in (**5**), 1.814 Å; C-6–S in (**4**), 1.807 Å; C-5–S in (**5**), 1.823 Å. Using data from the literature[12] an average value of 1.811 Å has been obtained for the C–S bond length in sulphides. The discrepancy in the expected trend in the case of the C-5–S bond may simply be reflective of the use of data from the penta-acetate (**5**).

Using the net atomic charges at the oxygen atoms as a measure of their basicity, the following decreasing sequence of basicities can be derived from the data in Table 1. (**1**): O-1 > O-3 > O-4 > O-2 > O-6; (**2**): O-2 > O-4 > O-5 ≃ O-1 > O-3; (**3**): O-3 > O-4 > O-1 ≃ O-2 > O-6; (**4**): O-2 > O-3 > O-4 ≃ O-5 > O-1. The net negative charge on O-3 is greater than that on O-4 in both (**1**) and (**3**), suggesting that the assignment[13] of HO-4 and O-3 to the AH and B groups, respectively, in the

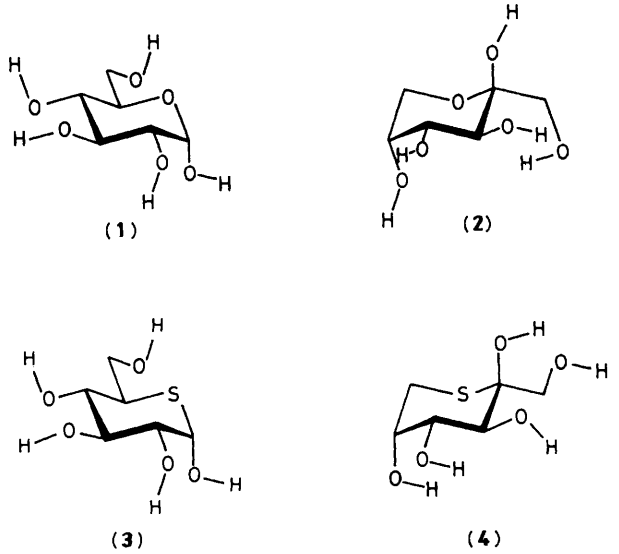

Table 2. Some non-bonded overlap populations $\zeta_{O,H}$ (× 10^4) and distances $r_{O\cdots H}$ between oxygens and hydroxy hydrogens in (**1**), (**2**), (**3**), and (**4**).

	(**1**)		(**2**)[a]		(**3**)		(**4**)[a]	
Groups	$r_{O\cdots H}$	$\zeta_{O,H}$	$r_{O\cdots H}$	$\zeta_{O,H}$	$r_{O\cdots H}$	$\zeta_{O,H}$	$r_{O\cdots H}$	$\zeta_{O,H}$
O-1 · · · H(O-2)	2.93	1.01	3.90	0.03	2.89	0.84	2.05	61.86
O-3 · · · H(O-2)	2.80	3.40	3.61	−0.21	2.73	4.17	3.55	−0.36
O-3 · · · H(O-4)	3.33	−0.09	3.03	0.33	3.28	−0.01	2.19	38.95
O-4 · · · H(O-3)	2.67	7.09	3.60	−0.32	2.63	8.03	3.14	−0.16
O-4 · · · H(O-5)	—	—	2.55	8.52	—	—	3.10	0.90
O-5[S] · · · H(O-1)	2.62	3.98	3.60	0.07	2.93	2.93	6.16	0.00
O-6[S] · · · H(O-1)	4.36	0.00	2.35	21.94	4.89	0.00	3.17	2.63
O-6[S] · · · H(O-2)	6.67	0.00	2.59	2.76	6.81	0.00	2.93	4.67

[a] A value of 0.96 Å was used for all O–H bond lengths.

principal saporous unit of (**1**) is correct and that the same assignment may be extended to the thio sugar (**3**). For β-D-fructopyranose (**2**), the anomeric hydroxy group (HO-2) and O-1 have been identified[14] as possible AH and B groups, respectively; the corresponding atoms in (**4**) have also been assigned[2] to an AH,B system. However, in both (**2**) and (**4**), it appears that O-2 is more basic than O-1, implying that the assignment of groups to the AH,B system in these compounds should be reversed.

The presence of intramolecular hydrogen bonding, as indicated by positive non-bonded overlap populations[3] (see Table 2), between O-4 and the HO-3 proton in (**1**) and (**3**), fortifies the AH and B characters of HO-4 and O-3, respectively. Moreover, the increased overlap in (**3**) relative to that in (**1**) indicates the presence of a stronger intramolecular hydrogen bond in the thio sugar (**3**); this feature would be expected to enhance the binding of (**3**) with the receptor and might be one of the reasons why (**3**) is sweeter than (**1**). However, this suggestion may have to be tempered as a result of the particular geometrical model used for (**3**). In (**4**) there is no indication of intramolecular hydrogen bonding between the ring heteroatom and the HO-1 proton, whereas there is in (**2**) (see also ref. 3). However, there appears to be a strong hydrogen bond between O-1 and the HO-2 proton in (**4**), which is not present in (**2**); such a bond would fortify the AH and B characters of HO-1 and O-2, respectively, a feature which might be partially responsible for the greater sweetness of (**4**). This proposition is predicated upon the new assignment of groups to the AH,B system in (**2**) and (**4**) (see above).§ It is noteworthy that in (**4**) there is a second strong hydrogen bond between O-3 and the HO-4 proton, which is also not present in (**2**).

§ In the earlier theoretical study,[3] a hydrogen bond between O-1 and the HO-2 proton was indicated to be the main intramolecular interaction in α-L-sorbopyranose, and its presence was invoked as a possible contributing factor to the observed lower sweetness of L-sorbose relative to that of D-fructose. However, in contrast to (**4**), the AH and B groups in α-L-sorbopyranose have been assigned to HO-2 and O-1, respectively; consequently, the intramolecular hydrogen bond between these groups attenuates their binding to the receptor.

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