Conformational equilibria of methyl α-L-arabinopyranosides in solution

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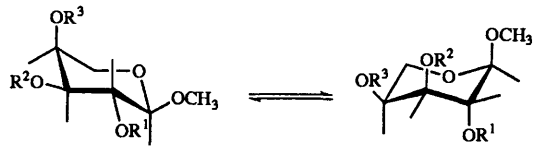
Experimental NMR studies on methyl α-L-arabinopyranosides in $CDCl_3$, pyridine and dioxane have shown that the equilibria between conformers are displaced in favour of the $^4C_1$ conformer, except in the case of 2-substituted derivatives in $CDCl_3$. The experimental data and a theoretical analysis aimed at explaining them in terms of intramolecular and stereoelectronic solvent effects are presented. It appears that certain electrostatic interactions and the anomeric effect, which favour $^1C_4$ in conformational equilibria are particularly important in 2-substituted derivatives provided no disruption of intramolecular H-bridges takes place. This explains the experimental findings and throws further light on the interplay of effects which determine conformational equilibria in solution.

Introduction and statement of the problem

Despite considerable progress in experimental and computational methods, the nature of the factors determining the preferred conformations of oligosaccharides in different solvents is still far from clear and the heights of the energy barriers separating the various conformations of these molecules is still a largely open question.[1-6] The available experimental evidence is not sufficient to discriminate between different assumptions about the nature and interplay of these factors. Therefore, it is necessary to introduce appropriate theoretical treatments, such as can be obtained by molecular mechanics (MM) and/or quantum schemes, extended to take solvent effects into account.[7,8] This consideration has inspired the combined experimental and theoretical work on the conformational equilibria of substituted methyl α-L-arabinopyranosides reported in this paper.

Interest in these equilibria was aroused by ^{13}C NMR studies of muscaroside A.[9] The latter is a triterpenoid glycoside with a glycone moiety built up of α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranosyl chain. The ^{13}C NMR chemical shifts of the 4 and 5 carbon atoms of the arabinopyranosyl residue were shifted upfield with respect to those of the methyl α-L-arabinopyranoside, used in the literature as a standard for interpreting glycosylation shifts. In addition, a change in the $^3J_{H,H}$ coupling constant of the anomeric proton (4 Hz, to be compared with 7–8 Hz, the values for the expected conformation for methyl α-L-arabinopyranoside) was also observed. These experimental results suggested a change in the conformational population $^4C_1 \rightleftharpoons {}^1C_4$ for the arabinopyranosyl unit of the muscaroside A, possibly related to the substitution at position 2. To confirm this suggestion 2-acetyl (2Ac), 2-benzoyl (2Bz), 3-benzoyl (3Bz) and 4-benzoyl (4Bz) substituted methyl α-L-arabinopyranosides were prepared and their conformational equilibria analysed by ^1H NMR in different solvents.

All equilibria between the $^1C_4$ and $^4C_1$ conformers are found to be close to 50% for each, but they are slightly shifted in favour of the latter conformer in all cases except the 2-substituted molecules in $CDCl_3$. The free energy differences are very small (*cf.* Table 1); nevertheless, the anomaly is extremely unlikely to be due to experimental errors. Therefore the nature of the effects which determine it is worth investigating, and a theoretical analysis is in order, if only to provide guidelines for further experimental work. The very small energy differences involved and the need to discriminate between different effects are no doubt a serious obstacle in this direction; however, as the work reported here has demonstrated, it is possible to overcome it, at least to the extent required for interpretational purposes, by adopting computational methods based on chemical concepts, such as force-fields (molecular mechanics) and hybridization. These methods have made it possible to find a highly plausible explanation for the anomaly at hand. The effect analysis that has been necessary to find that explanation may be interesting also for other applications. Indeed, it is to a large extent a continuation of work by Lemieux,[10-12] Tvaroska,[4,7,13] and Hoffman[14] and their co-workers.



$^4C_1$ $^1C_4$

2 Ac: $R^1 = Ac, R^2 = R^3 = H$
3 Ac: $R^1 = R^3 = H, R^2 = Ac$
4 Ac: $R^1 = R^2 = H, R^3 = Ac$

Experimental and computational procedures

Preparation of the arabinose derivatives

The compounds 3Bz and 4Bz were prepared by treatment of methyl α-L-arabinopyranoside (1 g) with benzoyl chloride (1.3 cm^3) in dry pyridine (40 cm^3) for 30 min at 70 °C. The reaction mixture was treated with ice and extracted with $CHCl_3$. The organic layer was evaporated and the solid (2.3 g) chromatographed on a SiO_2 column with benzene containing increasing amounts of diethyl ether as eluent. The fraction containing the monobenzoates mixture was further purified by TLC ($CHCl_3$:acetone = 7:3, two runs) to give 3Bz (108 mg) and 4Bz (93 mg). The compounds 2Bz and 2Ac were prepared from the 3,4-(prop-2-ylidene) derivative of the methyl α-L-

Table 1 Energy differences between $^4C_1$ and $^1C_4$ conformers in different solvents

Molecule	$CDCl_3$		Dioxane		Pyridine	
	ΔG_{tot}/kcal mol^{-1} [a]	ΔG_{exp}/kcal mol^{-1} [b]	ΔG_{tot}/kcal mol^{-1} [a]	ΔG_{exp}/kcal mol^{-1} [b]	ΔG_{tot}/kcal mol^{-1} [a]	ΔG_{exp}/kcal mol^{-1} [b]
2Ac	0.686	0.480	−1.210	−0.480	−4.484	−1.000
3Ac	−1.081	−1.040	−1.091	−0.800	−1.922	−0.520
4Ac	−2.423	−0.800	−1.408	−1.000	−5.660	−1.040

[a] Values for the super-molecule MM computation + anomeric effect + solvent contribution. [b] ΔG_{exp} is the experimental free energy value obtained from the conformer concentration values observed by NMR techniques: $\Delta G_{exp} = -RT \ln ({}^4C_1/{}^1C_4)$.

Table 2 ^{1}H NMR chemical shifts (δ), coupling constants[a] (Hz) and conformational population of 2Bz, 3Bz, 4Bz and 2Ac in $CDCl_3$, [$^2H_5$]pyridine and [$^2H_8$]dioxane

	1-H	2-H	3-H	4-H	5-H	5′-H[b]	$^4C_1$	$^1C_4$
2Bz	4.69 d	5.23 dd	4.02[c]	4.02[c]	3.81 dd	3.71 dd	31	69
$CDCl_3$	(3.17)	(4.88; 3.17)			(11.72; 8.06)	(11.72; 4.88)		
[$^2H_5$]Pyridine	4.74 d	6.09 dd	4.34[c]	4.34[c]	4.34[c]	3.82 dd	82	18
	(6.84)	(7.57; 6.84)				(12.70; 2.20)		
[$^2H_8$]Dioxane	4.22 d	5.16 dd	3.75[d]	3.81 m	3.88 dd	3.53 dd	68	32
	(5.86)	(7.81; 5.86)			(11.96; 4.39)	(11.96; 2.20)		
3Bz	4.26 d	3.99 dd	5.11 dd	4.17 m	4.06 dd	3.67 dd	85	15
$CDCl_3$	(7.32)	(9.77; 7.32)	(9.77; 2.93)		(12.70; 2.93)	(12.70; 0.98)		
[$^2H_5$]Pyridine	4.73[c]	4.73[c]	5.74 dd	4.69 m	4.34 dd	3.87 dd	75	25
			(8.54; 3.66)		(12.21; 3.91)	(12.21; 2.20)		
[$^2H_8$]Dioxane	4.21 d	3.81 dd	4.98 dd	4.04 m	3.89 dd	3.60 dd	79	21
	(6.59)	(9.03; 6.59)	(9.03; 3.42)		(12.21; 3.66)	(12.21; 1.71)		
4Bz	4.16 d	3.79 dd	3.86 dd	5.33 m	4.11 dd	3.61 dd	79	21
$CDCl_3$	(6.59)	(9.28; 6.59)	(9.28; 3.17)		(13.18; 2.93)	(13.18; 1.22)		
[$^2H_5$]Pyridine	4.59 d	4.56 dd	4.36 dd	5.83 m	4.33 dd	3.86 dd	86	14
	(7.08)	(7.08; 9.28)	(9.28; 3.66)		(12.94; 2.44)	(12.94; 1.22)		
[$^2H_8$]Dioxane	4.11 d	3.58[c]	3.7 dd	5.30 m	4.04 dd	3.60[c]	82	18
	(6.84)		(9.28; 3.42)		(12.34; 2.69)			
2Ac	4.52 d	4.97 dd	3.83[e] m	3.91[f] m	3.75 dd	3.64 dd	34	66
$CDCl_3$	(3.42)	(5.37; 3.42)			(11.96; 8.06)	(11.96; 4.39)		
[$^2H_5$]Pyridine	4.57 d	5.83 dd	4.17 dd	4.26 m	4.28 dd	3.72 dd	82	18
	(6.84)	(8.79; 6.84)	(8.79; 3.42)		(13.43; 3.66)	(13.43; 3.17)		

[a] Accurate to within ±0.25 Hz. [b] The proton on C-5 giving the higher field signal is designated 5′-H. [c] Overlapped signals in each row. [d] Further coupled to the hydroxy proton at C-3 occurring under the 5-H signal at δ 3.88. [e] Further coupled to the hydroxy proton at C-3, δ 3.25 (d, 8.8 Hz). [f] Further coupled to the hydroxy proton at C-4 δ 2.50 (d, 8.0 Hz).

arabinopyranoside obtained by treatment of methyl α-L-arabinopyranoside (600 mg) with dry acetone (5 cm^3) and $CuSO_4$ (2 g) for two days at room temperature. The prop-2-ylidene derivative was in part benzoylated by the above procedure and in part acetylated with Ac_2O and AcONa to give, after acid opening of the prop-2-ylidene ring with oxalic acid, 2Bz (42 mg) and 2Ac (50 mg), respectively. The characterization of all compounds was based on the ^{1}H NMR data reported in Table 2.

Determination of equilibria

The conformational equilibria in $CDCl_3$, [$^2H_8$]dioxane and [$^2H_5$]pyridine of substituted methyl α-L-arabinopyranosides were determined by ^{1}H NMR spectra at 400 MHz measured with a Bruker AM 400 instrument, equipped with a dual probe at 30 °C. The coupling constants were obtained on a first-order basis as direct peak spacing from spectra measured using a spectral width of 4000 Hz and a 32K datablock. Eqn. (1) was used

$$^3J_{H_1,H_2} = 8.1P + 1.0(1 - P) \qquad (1)$$

to estimate the conformer population[15] where subscripts 1 and 2 specify the protons linked to C-1 and C-2 (standard numbering).

Determination of geometries and energies of the isolated molecules

For the reasons mentioned in the introduction, this part of our work was carried out using AMBER molecular mechanics (MM) computations.[16,17] The option for the relative permittivity proportional to interatomic distances was chosen, so as to take the shielding between neighbouring atoms and polarization into account. For the sake of simplicity, the benzoyl group was replaced by the acetyl group; doubts as to the legitimacy of this simplification were dispelled by *ad hoc* measurements on the 2Ac derivative in $CDCl_3$ and pyridine (Table 2). The geometries were obtained according to Weiner and co-workers[18,19] with initial coordinates from experimental X-ray measurements of methyl α-L-arabinopyranoside crystals.[20] The required net atomic charges were obtained from *ab initio* STO-3G computations and rescaled to ensure consistency with the charges used by Ha *et al.*[21] for monosaccharides.

Construction of MOs over hybrid AOs

The hybrid atomic orbitals were determined by our maximum localization (ML) criterion[22,23] with the geometries of the two chair forms obtained for each molecule from AMBER computations. The MOs (here consisting of bond orbitals and of lone pair hybrids) were then determined by the IML-EHT method,[24] a version of EHT using ML hybrids as a basis and Streitwieser's ω-technique[25] for iterations. The electron distribution was described by assigning the Mulliken populations of the hybrid orbitals to their centroids and leaving the positive holes centred at the nuclei.

Computations of solvation complex energies

The structure and energies of the solvation complexes were estimated by AMBER computations on the supermolecules formed by the given molecules with pyridine or dioxane molecules. In these supermolecules each OH group of the arabinoside was initially assumed to form an H-bond with a solvent molecule, and then the geometry was optimized by MM

Table 3 Electric dipole moments μ, molecular radii a and MM energies of the free molecule E

Molecule	Conformer	μ/D	a/Å			E/kcal mol^{-1}
			is. mol.[a]	pyr. s.c.[a]	diox. s.c.[a]	
2Ac	$^4C_1$	2.37	3.82	6.86	6.89	−15.09
2Ac	$^1C_4$	5.35	3.81	6.87	6.78	−11.80
3Ac	$^4C_1$	1.79	3.83	6.78	6.71	−12.10
3Ac	$^1C_4$	4.62	3.85	6.85	6.77	−7.34
4Ac	$^4C_1$	2.92	3.81	6.85	6.78	−9.50
4Ac	$^1C_4$	3.47	3.78	6.84	6.79	−5.03

[a] 'is. mol.', 'pyr. s.c', and 'diox. s.c.' stand for the isolated molecule and the solvation complexes in pyridine and dioxane, respectively.

energy minimization. The assumed solute–solvent H-bonds were confirmed by this procedure.

Inclusion of bulk solvent effects

The bulk solvent effects were estimated according to the continuous model.[26-28] The solute was represented as a set of discrete electric charges q_i immersed in a cavity formed by a continuous polarizable dielectric, and the total conformational free energy in solution, G_{tot},[7,28] was treated as the sum of the free energies, G_u, of the solute molecules (in the case of $CDCl_3$ solutions) or of the solvation complexes (in the other cases) plus a free energy term, G_{sol}, representing the solute–solvent interaction. The G_u values were replaced by the computed energies on the grounds that the rotational entropy contributions should be negligible and the vibrational ones should be sensibly the same for both conformers (and hence would not affect differences between conformers). Following from this,[7] the term G_{sol} was then written as the sum of three contributions [eqn. (2)] where G_{el}, G_{disp} denote the electrostatic,

$$G_{sol} = G_{el} + G_{cav} + G_{disp} \quad (2)$$

dispersion and specific solute–solvent interaction free energy contributions, respectively; G_{cav} denotes the 'cavitation' energy, *i.e.* the energy required for the given solvent to form cavities sufficiently large to accommodate the solute molecules. A fourth term G_{spec} associated with specific solute–solvent interactions appears in the original formulation of eqn. (2); in our procedure it was included in G_u because eqn. (2) was applied directly to solvation complexes when the latter were expected to be formed.

The term G_{el} was computed according to the continuous reaction-field model,[7,28] by the expression given in eqn. (3)

$$G_{el} = -14.39 \times \frac{\mu^2}{a^3} \times \frac{\varepsilon - 1}{2\varepsilon + 1} \quad (3)$$

where ε is the relative permittivity of the solvent, a is the cavity radius $a_u + a_v$, with a_u the molecular radius, a_v the thickness of the first solvation sphere and μ is the electric dipole moment of the solute.

The radii were determined, under the assumption of a roughly spherical shape, from the molecular volumes of the isolated molecules or the solvation complexes. These volumes were obtained by the algorithm given in ref. 29 from the areas accessible to the solvent, defined as the convolution surface of the van der Waals spheres of each atom of the molecule plus the radius of the solvent molecule.[30] The radii thus obtained for the free conformers (Table 3) were very close to one another.

The electric dipole moments were determined using AMBER geometries and AM1 charges, the latter being chosen because they appear to provide a point-charge description of sugar molecules (*e.g.* glucose) yielding electric dipole moments more realistic than scaled STO-3G point charges. The μ values of the various arabinosides were found to be markedly different, in agreement with chemical intuition (Table 3).

Owing to the closeness of the a values, the G_{cav} differences between conformers were treated as second-order corrections and neglected. The dispersion terms G_{disp} include attractive and repulsive interactions between non-bonded nearest neighbour solute and solvent molecules. The dispersion terms G_{disp} of eqn. (2) were assumed to be negligible for the conformers of the same molecule, in accordance with considerations and computations by Tvaroska and Kozar.[7]

Results and discussion

As mentioned, Table 2 shows that 2Bz and 2Ac are present in $CDCl_3$ mainly in their $^1C_4$ form, at variance with 3Bz and 4Bz. However, in pyridine and in dioxane the $^4C_1$ conformers always predominate. This suggests that in the latter case the solvation effects prevail over intrinsic effects (including anomeric effects); in the former the converse is true. Conformational equilibria in solution are known to be sensitive to the nature of the solvent, especially to its polarity. Such is the case of 2-methoxytetrahydropyran (2-MeO–THP, MTHP), which can be considered as a simplified model of a monosaccharide and whose conformational equilibria were studied particularly by Lemieux[10-12] and Tvaroska[4,7,13] and their co-workers. Lemieux has stressed the importance of hydrogen bonds both intramolecular and with the solvent; Tvaroska has attributed greater importance to the influence of water seen as a bulk effect. Experimental studies[31-34] of both the permittivity and the nuclear relaxation of disaccharides dissolved in water have shown that there are water molecules bound to sugar molecules which have relatively long residence times, and therefore move with the monosaccharide and not with bulk water. NMR and IR spectra[35] have shown that all the hydroxy groups of α- and β-glucose in DMSO (dimethyl sulfoxide) are strongly H-bonded to the solvent, which breaks intramolecular H-bonds. Since the DMSO molecule has a greater radius (2.46 Å) than the pyridine and the dioxane molecule (2.14 and 2.015 Å, respectively) it is plausible that two pyridine or dioxane molecules associate with a sugar molecule without steric hindrance. Thus it seems that although bulk solvent effects are certainly important the formation of solvation complexes should not be ignored.

Relevant effects according to MM and IML-EHT computations

The MM results for the isolated arabinoside molecules (Table 4) predict that the $^4C_1$ conformations are always the more stable ones; therefore, these results are in qualitative agreement with the experimental results in the low relative permittivity solvent, $CDCl_3$, except for 2Ac. As to the latter, indications concerning the origin of the 2Ac anomaly are found by analysing the electrostatic attraction and repulsion contributions to the total energy of the various atom pairs.

(*i*) In the case of 2Ac, significant differences are found

Table 4 Partial and total energies[a] (kcal mol^{-1}) from MM computations

	2Ac	3Ac	4Ac
Stretching	−0.035	−0.055	−0.041
Bending	0.286	0.704	0.751
Torsional	2.977	2.297	2.916
van der Waals	−0.332	−0.265	−1.390
E_{el}[b]	−13.387	−20.459	−18.779
H-bond[c]	0.057	−0.598	−0.427
$E_{1\text{-}4}$nb[d]	0.257	0.836	0.658
$E_{1\text{-}4}$el[e]	6.883	12.779	11.842
Total	−3.294	−4.760	−4.470

[a] The energy differences shown are those between the indicated contributions to the total energy for the $^4C_1$ conformer and the $^1C_4$ conformer as given by the AMBER program. [b] E_{el} refers to the electrostatic interactions. [c] H-bond stands for hydrogen bond energies computed with 10–12 potentials. [d] $E_{1\text{-}4}$nb refers to 1–4 non-bonded interactions. [e] $E_{1\text{-}4}$el refers to 1–4 electrostatic interactions.

between the attractive terms associated with the atom pairs O11–H21 (−11.72 kcal mol^{-1} †) in the $^4C_1$ conformer and O4–H21 (−17.19 kcal mol^{-1}) in the $^1C_4$ conformer. According to MM, both atom pairs are involved in H-bonds. The presence and strength of the latter is experimentally confirmed by the fact that the exchange of the hydroxy protons expected to be engaged in the H-bonds is slower than for the other protons; the ^{1}H NMR spectra of 2Ac in $CDCl_3$ show scalar couplings between the hydroxy and the carbinol protons at C-3 and C-4 (standard numbering) up to 65 °C (see Table 2). The structural origin of the energy differences in question can be found by examining the MM geometries. The first H-bond in the sequence O4–H21–O20–H25–O24 of 2Ac $^1C_4$ has a geometry close to linear (141° at H21), while the other is bent (*ca.* 90°). In 2Ac $^4C_1$ the two bridges (O24–H25–O20–H21–O11) are both bent (90–100°). The difference in the corresponding energy contributions must therefore be attributed to the directional properties of the electrostatic interactions associated with lone pair hybrids. Also the lone pairs of other oxygen atoms give large contributions to the differences in stability of the conformers.

The ML hybrid orbitals have allowed us to estimate the electrostatic interactions between O4 and O20, which are in *syn*-diaxial positions in the $^1C_4$ conformers. Owing to the strong localization assumption on which it is based, the IML-EHT yields degenerate hybrids determined up to a unitary transformation when there are two lone pairs. Therefore, the lone pair hybrids obtained for O4, which is hydrogen bonded to O20, may be replaced by new hybrids *via* a unitary transformation such that one of the two lone pair orbitals should point to the O4–H21 direction. In the case of 2Ac this reorientation brings about an energy decrease of *ca.* 30 kcal mol^{-1} due essentially to the stronger attractive interaction between the lone pair 4(2) and the nucleus O20.

(*ii*) The electrostatic repulsion differences show that the corresponding destabilization of the $^1C_4$ conformer with respect to the $^4C_1$ one is progressively greater along the series 2Ac, 3Ac and 4Ac, since they amount to −3.68, 9.67 and 22.45 kcal mol^{-1}, respectively. The origin of this trend is probably to be found in the repulsive interactions associated with O11, which is bound to C2 (Fig. 1), for in the $^1C_4$ conformation these repulsions are smaller than in 3Ac and 4Ac (12.16, 13.00 and 13.45 kcal mol^{-1}). This result is in agreement with Lemieux' considerations about the role of the oxygen linked to C-2 in the stability of monosaccharides similar to those studied here.[11,12]

(*iii*) Lone pairs may give rise to the anomeric effect. The IML-EHT method has allowed us to extend Hoffman's analysis of this effect[14] to include hybridization. According to computations on the model compound 2-methoxytetrahydropyran, the axial anomer is stabilized by 1.96 kcal mol^{-1} with respect to the equatorial one. Since the energy differences we are interested in are of the same order of magnitude and the anomeric effect is solvent sensitive, it has been included in the evaluation of the total energy differences. Estimates of orbital interactions on the MTHP model compound clearly show that the gain in stabilization of the anomer with the methyl group in the axial position is due to a combination of the O_{ring} lone-pair p orbital with the σ*(CO) orbital, whereas the other lone-pair orbital does not mix with that bond orbital and is practically an atomic sp hybrid resulting from the combination of two sp^3 hybrids.

(*iv*) As follows from the above remarks, the solvation and solvent effects play a decisive role in stabilizing or destabilizing the various conformers. This holds in particular for the H-bonded solvation complexes, which are expected to be important in pyridine and dioxane solutions and not in $CDCl_3$. For one thing, as a result of H-binding to the solvent, the O11–O4 electrostatic interaction energies appear to favour the $^1C_4$ conformers; this means that the discriminating role of these energies is reduced in pyridine and dioxane solution. On the other hand, the free energies of interaction with the bulk solvent, which depend on the electric dipole moments, enhance

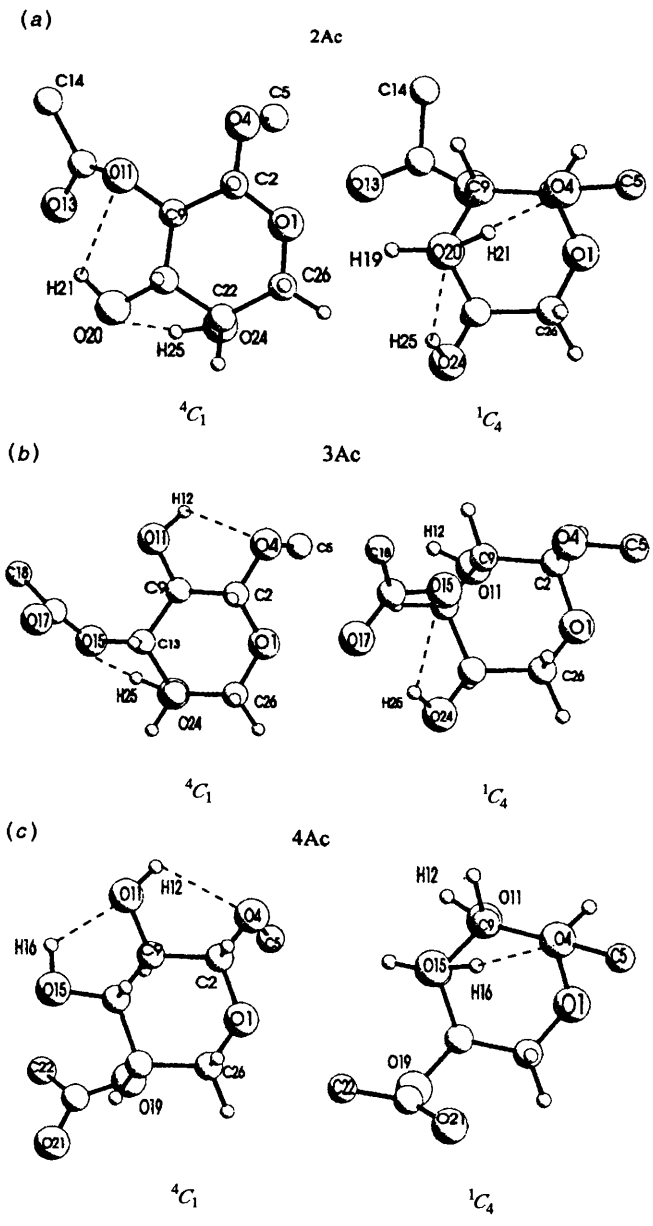


Fig. 1 Computed AMBER structures of the three methyl α-L-arabinopyranosides

† 1 cal = 4.184 J.

the total free energy differences between the conformers of the same molecule (*cf.* Table 1).

Quantitative estimates

From what has been said, it appears that the greater stability of the $^1C_4$ 2Ac conformer in $CDCl_3$ is probably brought about by quantitative changes in the balance of the interactions discussed above, due to solvation and/or to solvent-dependent intramolecular effects. Quantitative estimates were therefore indispensable and were obtained by the methods mentioned above. They are reported in Table 5.

The computational procedures have been summarized above. The computed free energy differences between the two conformers in $CDCl_3$, computed according to eqn. (2), are shown in Table 1. When added to the anomeric effect contribution they are in satisfactory agreement with the experimental results, except for 4Ac. The less satisfactory results for the latter may be due to the choice of a spherical geometry, which in this case is a particularly rough approximation. The IML-EHT scheme also shows that, when the $^1C_4$ 2Ac conformer is perturbed by the two H-bonded pyridines, the O4–H21 electrostatic energy decrease after reorientation of the lone pair hybrids (*vide supra*) becomes *ca.* 50 kcal mol^{-1}.

If the solvation and bulk effects are taken into account as described above, the computed and experimental trends are in reasonable agreement for both pyridine and dioxane solutions. The largest deviation is found for 2Ac in dioxane; it may be attributed to the persistence of intramolecular H-bonds with strengths comparable to that of the solvation H-bonds, in agreement with the low mobility of H21 inferred from its scalar coupling with H19 (see Fig. 1, conformation $^1C_4$).

Table 5 Electrostatic energy (kcal mol^{-1}) differences[a] associated to the oxygen atoms 11 and 4

O4[b]	O11[b]	2Ac	3Ac	4Ac
[Isolated molecules][c]				
(1)	(1)	10.49	75.20	56.58
(1)	(2)	125.40	22.37	8.04
(2)	(1)	101.79	168.14	137.17
(2)	(2)	267.57	150.26	116.49
(1)	nu	−129.23	−318.75	−254.65
(2)	nu	−524.31	−208.04	−148.20
nu	(1)	−162.48	−231.46	−168.95
nu	(2)	−523.72	−650.21	−528.03
cc		505.24	416.92	318.23
cc		−1339.79	−1425.11	−1099.73
nn		917.10	1174.21	936.70
Total		82.55	181.71	155.19
[Pyridine solutions][c]				
cc		607.40	569.58	590.80
nc		−1529.80	−1411.27	−1460.16
nn		950.53	852.07	879.97
Total		28.13	10.15	10.84

[a] The energy differences shown are those between the contributions of oxygens 4 and 11 to the energy of the $^4C_1$ and $^1C_4$ conformer. [b] The symbols (1), (2) and 'nu' denote the two lone pairs and the nucleus of the oxygen atom heading the column. The abbreviations 'cc', 'nc', 'nn' denote the three contributions to the electrostatic energy differences associated to the orbital charges centred in the hybrid centroids (letter c) and to the nuclei (letter n). [c] The two sections of the Table refer to the molecules isolated and perturbed by pyridines, respectively; 'Total' refers to the difference between the total electrostatic energies estimated for the $^4C_1$ and the $^1C_4$ conformer.

Conclusions

The above analysis allows the explanation of the peculiarities in the conformational equilibria reported in the experimental section in terms of structural characteristics of the free molecules under study and of environmental effects.

The fact that in the case of 2Ac, the $^1C_4$ conformation predominates in $CDCl_3$, whereas in all other cases the equilibrium is shifted towards the $^4C_1$ conformer, appears to be due to the fact that the contributions liable to favour the $^1C_4$ conformers are the anomeric effect and the polarization effect of the solvent.

The study of the isolated molecules has shown that there is a smaller difference in stability between the two conformers of 2Ac than between those of 3Ac and 4Ac; the effects responsible for that are the formation of hydrogen bridges and electrostatic repulsions. However, the MM computations do not go so far as to predict for 2Ac the observed inversion of the conformer stability ratio, nor are there grounds to believe that account of the entropic factor or more sophisticated computational techniques would change the situation. This confirms the intuitive expectation that, in the last analysis, the solute–solvent interactions must be the factors which modify the effects mentioned so as to further favour the $^1C_4$ conformer of 2Ac in the $CDCl_3$ solutions. Apart from minor perturbations, those interactions come into play indirectly by affecting the anomeric effect and directly through the electrostatic solute–solvent interactions G_{el}. The latter is the most important factor in favour of $^1C_4$ 2Ac in as much as the electric dipole moment of that conformer is particularly high (Table 3).

This conclusion is supported by the computational results showing that in the case of free solute molecules the conformational energy difference in favour of the $^4C_1$ conformer of 2Ac is lower than the same difference in 3Ac and 4Ac by 1.5 and 1.2 kcal mol^{-1}, respectively, owing to a lower repulsive electrostatic contribution. This difference, though small, turns out to be decisive in $CDCl_3$, a solvent which leaves intramolecular H-bridges practically unchanged; in fact 3Ac does not adopt preferentially the $^1C_4$ conformation, at variance with 2Ac, because the differences in the polarization effect of the solvent and the anomeric effect are not large enough to make the $^1C_4$ conformer more stable. In the case of 4Ac the dipole moments of the two conformers are not much different and therefore the polarization effect of $CDCl_3$ is predicted to be nearly the same for the two conformers.

In pyridine and dioxane the stabilization of the $^4C_1$ conformer appears to result mainly from specific solute–solvent interactions, which break some of the intramolecular H-bonds and thus suppress at least in part those interactions which favour the stability of $^1C_4$ 2Ac in $CDCl_3$. Further support in this direction is provided by the fact that the formation energies of the adducts 4-HO–MTHP + pyridine and 4-HO–MTHP + dioxane are predicted by MMX[36] and AM1 computations[37] to be significantly smaller when the hydroxy group is H-bonded to pyridine and dioxane than when it forms an intramolecular H-bond. *Ad hoc* computations have shown that this result is a consequence of H-bond formation and of the arrangement of the solvent molecules.

The computational results on which this conclusion is based could perhaps be improved from the quantitative point of view, despite the technical and conceptual difficulties encountered in attempts to extract from these highly sophisticated methods a clear-cut separation of effects and to handle very small conformational energy differences in comparatively large molecules. However, it is legitimate to believe that, since the methods used here rest on the fundamental chemical theory of valence and on chemical intuition, they are sufficiently reliable to make the above analysis significant. Of course, the best use (and further assessment) of that analysis will be to design further experimental work with suitable model molecules.

Acknowledgements

The authors thank the Italian National Council of Research (CNR) and the Ministry of Research of Italy for support.

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Paper 5/06517H
Received 3*rd October* 1995
Accepted 1*st November* 1995