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MOLECULAR-MECHANICS CALCULATIONS FOR CYCLIC ACETALS OF PENTOFURANOSES, RELATED PENTITOLS, AND *C*-GLYCOSIDES*

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ABSTRACT

Molecular-mechanics calculations are reported for the geometries and energies of 2,3- and 3,5-*O*-isopropylidene-α- and -β-D-ribo- and -L-lyxo-furanoses, and for the 2,3- and 3,5-*O*-methylene derivatives of 1,4-anhydro-D-ribitol and -L-lyxitol and the related *O*-isopropylidene derivatives. Calculations were also performed for model compounds of *C*-glycosides, where the hydroxyl group of the ribo- and lyxo-furanose derivatives was replaced by a methyl group. The results are discussed in terms of conformational equilibria, constitutional equilibria of 2,3- and 3,5-*O*-alkylidene derivatives, and configurational equilibria (anomeric and C-4-epimeric). The predictions are generally in good agreement with the available experimental data.

INTRODUCTION

Molecular mechanics (empirical force-field calculations) are an established method for the calculation of the geometries and energies of hydrocarbons and of molecules containing a variety of heteroatoms[1]. The precision and reliability of this type of calculation is encouraging their application to stereochemical problems of carbohydrates, and a number of calculations on pyranoses with force fields at various levels illustrate this development[2–7]. An improved force field for ethers and alcohols has been developed recently in our laboratories[8–10] and we now report the first applications of force-field calculations (employing this force field) to conformational, configurational, and constitutional equilibria of furanoses.

The acid-catalysed reaction of aldehydes and ketones with polyhydric alcohols often yields mixtures of cyclic acetals[11–13]. Pyranoses form cyclic acetals between *cis*- and *trans*-1,2-diols, yielding 1,3-dioxolane rings, or between 1,3-diols, yielding 1,3-dioxane rings; aldehydes usually react in the latter fashion, whereas ketones prefer to form 1,3-dioxolane rings. For furanoses, 1,3-dioxolane ring formation is the usual reaction, provided that a *cis*-1,2-diol group is available. The formation of measurable

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amounts of 1,3-dioxane derivatives of such furanoses (*e.g.*, 3,5-*O*-alkylidene derivatives) has not been reported. However, xylose, where HO-2 and HO-3 are *trans*-disposed, affords such derivatives[14-16].

Our interest in the ease of formation of 3,5-*O*-alkylidene derivatives from several furanoses[17] prompted a calculation of the geometries and energies of the 2,3- and 3,5-*O*-alkylidene derivatives of furanoses and similar compounds having *cis*-hydroxyl groups on C-2 and C-3. These compounds include both anomers of D-ribo- and L-lyxo-furanose, 1,4-anhydro-D-ribitol and -L-lyxitol, and their α and β 1-*C*-methyl derivatives, which may be considered as *C*-glycosides of ribofuranose and lyxofuranose*. Such computations require that the energies of *all* conformations be evaluated. From the present study, the conformational equilibria of the reaction products are therefore also available. Furthermore, from the energies of the C-1- and C-4-epimeric 2,3-*O*-alkylidene derivatives (the anomers, and compounds having *ribo* and *lyxo* configurations, respectively), configurational equilibria at C-1 and C-4 can be assessed.

METHOD

The energy of a molecule is determined in molecular mechanics by the sum of bond-stretching and angle-bending energies, non-bonded (van der Waals and electrostatic) interactions, and torsional energy. Electrostatic interactions are treated as point-charge interactions in our force field, with charges derived from CNDO/2 calculations on every conformation. An effective dielectric constant of 1.0 is used[8-10]. Torsional energy is usually employed in molecular mechanics to cover repulsions between vicinal bonds and has energy minima[1] at torsion angles of $\pm 60°$ and 180°. The anomeric effect, which originates[18-20] from electrostatic interactions *and* electron back-donation stabilising a COCO torsion angle of 90°, is covered in our force field by an additional torsional-energy term for COCO torsion angles with energy minima[10] at $\pm 90°$. The torsional potential of the OCOH torsion angle will also finally require such a term, but no related experimental data are available for the parameterisation. Fortunately, this term would be important only if different rotamers about the C–O bond of the anomeric hydroxyl group were to be compared. In all of the calculations reported here, only the rotamer usually found in the crystals of carbohydrates and stabilised by the *exo*-anomeric effect[12] was considered. This rotamer has the OCOH torsion-angle gauche and the CCOH angle anti. Such a torsional-energy term for OCOH therefore has no effect on the present calculations.

All of the molecules studied here also have a hydroxyl group at either C-2 or C-5; for each compound, two of the three C–O rotamers form an intramolecular hydrogen-bond, with the exception of **3** and **9** where all three rotamers are intra-

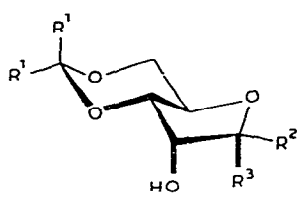
*Absolute configurations have been denoted in the discussion because the conformational nomenclature of ref. 21 depends on absolute configuration. The calculated numbers are valid for both enantiomers.

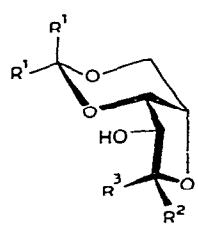
molecularly hydrogen-bonded. Preliminary calculations showed that, within a series of molecules where all of the C–O rotamers are hydrogen-bonded, the relative energies are within 1 kcal.mol^{-1}, the same as within the series lacking hydrogen bonds. Therefore, not all of the rotamers of the hydroxyl group were calculated in the full study, but only those without a hydrogen bond, *i.e.*, for 2,3-*O*-alkylidene derivatives, the C-4–C-5–O-5–H anti form, and for 3,5-*O*-alkylidene derivatives, the C-3–C-2–O-2–H anti form. A potential-function for hydrogen bonding included in the force field was found to have (with the exception of **3** and **9**) only a small effect on the relative energies.

At present, the major limitation to the quantitative agreement of calculated and experimental energies is the treatment of solvation. The calculations refer to the molecule in the gas phase or in non-polar solvents. However, carbohydrates are usually studied in relatively polar solutions; even when non-polar solvents are used, *e.g.*, in n.m.r. experiments, the polarity of the solution may be high because of the high concentration of the carbohydrate solute. Solvation by good hydrogen-bond acceptors decreases the importance of intramolecular hydrogen-bonding, and, for such solvents, the relative energies of conformations that lack intramolecular hydrogen-bonds, as described here, are more meaningful than those with full inclusion of hydrogen bonding. At present, it is not known what level of numerical agreement between calculated and experimental energies can be achieved, or, in other words, which portion of the experimental energy-values is due to solvent effects, and which to the intramolecular potential, respectively.

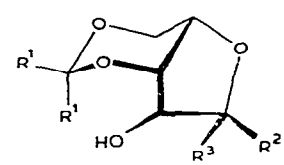
CONFORMATIONAL EQUILIBRIA AND MOLECULAR GEOMETRIES

3,5-O-Alkylidene derivatives. — The pseudorotational flexibility of the tetrahydrofuran (THF) ring in furanoses is restricted nearly completely by annelation with a cyclic acetal ring, especially in 3,5-*O*-alkylidene derivatives. The *trans*-fused 3,5-*O*-alkylidene-D-ribofuranoses (**1**–**6**) possess only one rigid conformation, with





$^4T_3$



$^3T_4$

1 $R^1 = R^2 = R^3 = H$
2 $R^1 = Me, R^2 = R^3 = H$
3 $R^1 = Me, R^2 = H\ R^3 = OH\ (\alpha)$
4 $R^1 = Me, R^2 = OH, R^3 = H\ (\beta)$
5 $R^1 = R^3 = Me, R^2 = H\ (\alpha)$
6 $R^1 = R^2 = Me, R^3 = H\ (\beta)$

7 $R^1 = R^2 = R^3 = H$
8 $R^1 = Me, R^2 = R^3 = H$
9 $R^1 = Me, R^3 = OH, R^2 = H\ (\beta)$
10 $R^1 = Me, R^3 = H, R^2 = OH\ (\alpha)$
11 $R^1 = R^3 = Me, R^2 = H\ (\beta)$
12 $R^1 = R^2 = Me, R^3 = H\ (\alpha)$

TABLE I

STERIC ENERGIES (KCAL.MOL^{-1}) CALCULATED FOR 3,5-*O*-ALKYLIDENE DERIVATIVES

1	30.24	**7a**	26.43	**4**	28.64	**10a**	25.20
		7b	31.47			**10b**	33.53
2	34.40	**8a**	29.58	**5**	34.40	**11a**	31.40
		8b	37.96			**11b**	38.32
3	24.23	**9a**	21.63	**6**	34.85	**12a**	30.94
		9b	29.52			**12b**	38.43

the THF ring in the $^3T_4$ conformation[21], whereas two conformations are possible for the *cis*-fused 3,5-*O*-alkylidene-L-lyxofuranoses (**7–12**). Only the hydroxyl group on C-2 is free to rotate in these molecules.

The calculated geometry of 1,4-anhydro-3,5-*O*-methylene-D-ribitol (**1**) contains several highly strained bond-angles, especially at C-2 and C-3 of the THF ring, of only 99 and 99.5°, respectively. The THF ring is in a nearly ideal $^3T_4$ conformation, and torsion angles of 60 $\pm$3° are found in the 1,3-dioxane ring, which is unusual because the C–C–C part of the ring is usually flattened[10] as a consequence of the trans fusion and the accompanying bond-angle deformations. The *O*-isopropylidene analogue **2** having an axial methyl group at C-2 of the 1,3-dioxane ring has the OCO part of this ring flattened, due to transannular repulsions associated with the isopropylidene group, but the THF ring is unaffected. Similar results are found for compounds **3–6**.

The conformational equilibria of the 3,5-*O*-alkylidene-1,4-anhydro-L-*lyxo* derivatives **7–12** are determined by the strong repulsion experienced by an axial alkyl group at C-4 of a 1,3-dioxane ring. This interaction destabilises the $^3T_4$ conformations by 6–8 kcal.mol^{-1} (Table I), and *lyxo* derivatives exist in the $^4T_3$ conformation exclusively. The calculations reveal heavy torsion-angle deformations in the 1,3-dioxane ring, caused by the relaxation of bond angles. In fact, no markedly bent bond-angles are found in these structures. The higher stability of the *cis*-fused *lyxo* over the *trans*-fused *ribo* derivatives must be caused by the higher flexibility of the *cis*-fused bicyclic system.

The lyxose structures can be compared with the X-ray structure of a 3,5-*O*-isopropylidene-D-xylofuranosyl-β-nucleoside[22], which exhibits the same 1,3-dioxane ring-conformation (equatorial C-4 alkyl substituent) as predicted in our calculations for the *lyxo* derivatives, and with torsion angles in close agreement (found[22] for O-4–C-4–C-5–O-7, 73°; calc. for **8**, 71°; for **10**, 74°).

2,3-O-Alkylidene derivatives. — Wire models of the 2,3-*O*-alkylidenefuranose backbone can adopt four double-envelope conformations of minimum bond-angle strain. Although non-bonded and torsional interactions may cause twisting of the geometry, only four major energy-minima are to be expected for the backbone, in close relation to these conformations. Except for a few molecules (**21** and **22**), the geometry obtained after energy minimisation is best described as an envelope conformation. For **21** and **22**, the $^oT_4$ conformation was deduced. In the discussion and in Table II, the energy minima are denoted by the symbols for the ideal envelope forms[21]

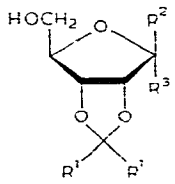
TABLE II

STERIC ENERGIES (KCAL.MOL^{-1}) CALCULATED FOR 2,3-*O*-ALKYLIDENE DERIVATIVES (AN ASTERISK INDICATES A CONFORMATION WHICH IS NOT AN ENERGY MINIMUM)

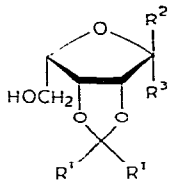
Compound and C-4–C-5 conformation		$^{o}E/^{a3}E$	$E_o/^{a3}E$	$^{o}E/E_{a3}$	E_o/E_{a3}
13	gg	29.30	28.94	30.34	32.02
	ga	29.44	29.32	30.42	32.23
	ag	29.38	29.76	29.81	31.63
14	gg	29.58	30.20	33.15	33.52
	ga	29.38	30.81	33.24	33.48
	ag	28.95	30.04	32.73	33.31
15	gg	22.21	23.39	*	26.61
	ga	21.96	23.10	*	26.53
	ag	21.71	22.70	*	26.21
16	gg	22.14	*	25.71	25.26
	ga	22.05	21.29	25.60	25.06
	ag	21.84	21.95	25.30	25.22
17	gg	32.07	31.62	*	34.54
	ga	31.79	31.08	*	34.39
	ag	31.67	30.81	*	34.21
18	gg	30.60	*	34.19	36.28
	ga	30.40	33.56	33.94	36.13
	ag	30.26	33.34	33.79	36.00
19	gg	31.77	30.59	32.49	32.32
	ga	31.26	29.04	32.20	31.52
	ag	31.22	28.45	32.56	31.04
20	gg	31.78	29.88	*	33.18
	ga	31.50	29.32	*	32.47
	ag	31.09	28.72	*	*
21	gg	23.19	22.81	*	26.09
	ga	23.06	21.67	*	25.53
	ag	23.34	21.95	*	
22	gg	21.29	21.71	*	24.90
	ga	23.53	20.39	*	24.13
	ag	23.72	20.60	*	24.60
23	gg	*	30.92	*	
	ga	34.01	29.77	*	33.67
	ag	33.56	29.92	*	
24	gg	33.15	32.72	*	35.66
	ga	32.07	31.50	*	34.93
	ag	32.09	31.62	*	

even when they are twisted. Each one of the four backbone conformations has three rotamers about the C-4–C-5 bond, and therefore twelve conformations had to be compared in the calculations for 2,3-*O*-alkylidene derivatives.

For 1,4-anhydro-2,3-*O*-methylene-D-ribitol (**13**), seven conformations were calculated to have similar energies, and in six of these, the 1,3-dioxolane ring is in the ^{a3}E conformation (Table II, Fig. 1). The general instability of E_{a3} conformations, also observed in all other 2,3-*O*-alkylidene derivatives, is caused by transannular repulsions, and is therefore more pronounced in such *O*-isopropylidene derivatives



13 $R^1 = R^2 = R^3 = H$
14 $R^1 = Me, R^2 = R^3 = H$
15 $R^1 = Me, R^2 = H, R^3 = OH$
16 $R^1 = Me, R^2 = O-, R^3 = H$
17 $R^1 = R^3 = Me, R^2 = H$
18 $R^1 = R^2 = Me, R^3 = H$



19 $R^1 = R^2 = R^3 = H$
20 $R^1 = Me, R^2 = R^3 = H$
21 $R^1 = Me, R^2 = H, R^3 = OH$
22 $R^1 = Me, R^2 = OH, R^3 = H$
23 $R^1 = R^3 = Me, R^2 = H$
24 $R^1 = R^2 = Me, R^3 = H$

as **14** than in methylene derivatives. An important factor for the conformational equilibrium of the THF ring appears to be the preference of the hydroxymethyl group for a pseudo-equatorial position, as can be seen in the equilibrium of the E_0/E_{a3} and $^0E/E_{a3}$ conformations of **13**, and the energies calculated for **14**. The $E_0/^{a3}E$ and $^0E/^{a3}E$ conformations were calculated to be in a roughly balanced equilibrium in **13**, which is shifted towards the $^0E/^{a3}E$ form in the isopropylidene derivative **14**. This situation is explained by buttressing of the isopropylidene group on the pseudo-axial H-2 and H-3, which are pushed toward the hydroxymethyl group in the $E_0/^{a3}E$ conformation.

For 2,3-*O*-isopropylidene-α-D-ribofuranose (**15**), a conformational equilibrium was obtained which closely resembles that calculated for ribitol **14**. The van der Waals repulsion experienced by the pseudo-axial hydroxyl group in the $^0E/^{a3}E$ conformation, and the energy gained through the anomeric effect, which stabilises conformations having a C–O–C–O torsion angle close to 90°, balance out. An effect also observed in the calculations of other derivatives having a pseudo-axial substituent at C-1 or C-4 in the $^0E/E_{a3}$ conformation was first found in **15**; the strong repulsion between the isopropylidene group and the pseudo-axial substituent is sufficient to invert the 1,3-dioxolane ring (on a pseudorotation-like pathway involving twisting of the backbone) into the $^0E/^{a3}E$ conformation.

For the β anomer **16**, it might be expected that, because of the van der Waals interactions, more $^0E/^{a3}E$ conformer would exist than in the case of **15**. Yet, the electrostatic attraction of the hydroxyl and the hydroxymethyl groups at C-1 and C-4, as well as the anomeric effect, produce more of the $E_0/^{a3}E$ conformer (Fig. 1).

Experimental data on related molecules indicate a higher stability of the $E_0/^{a3}E$ conformation than the calculations indicate for 2,3-*O*-isopropylidene-D-ribofuranose. X-Ray structures of 2,3-*O*-isopropylidene-α- and -β-D-ribofuranosyl nucleosides show the $E_0/^{a3}E$ conformation[23,24], but the n.m.r. coupling constants observed for such molecules indicate that not only this form is present in solution. In models for the $E_0/^{a3}E$ conformation of the β anomer (1,5-anhydro-2,3-*O*-benzylidene-β-D-ribofuranose[25], 2,3-di-*O*-acetyl-1,5-anhydro-β-D-ribofuranose[26], and 1,5-

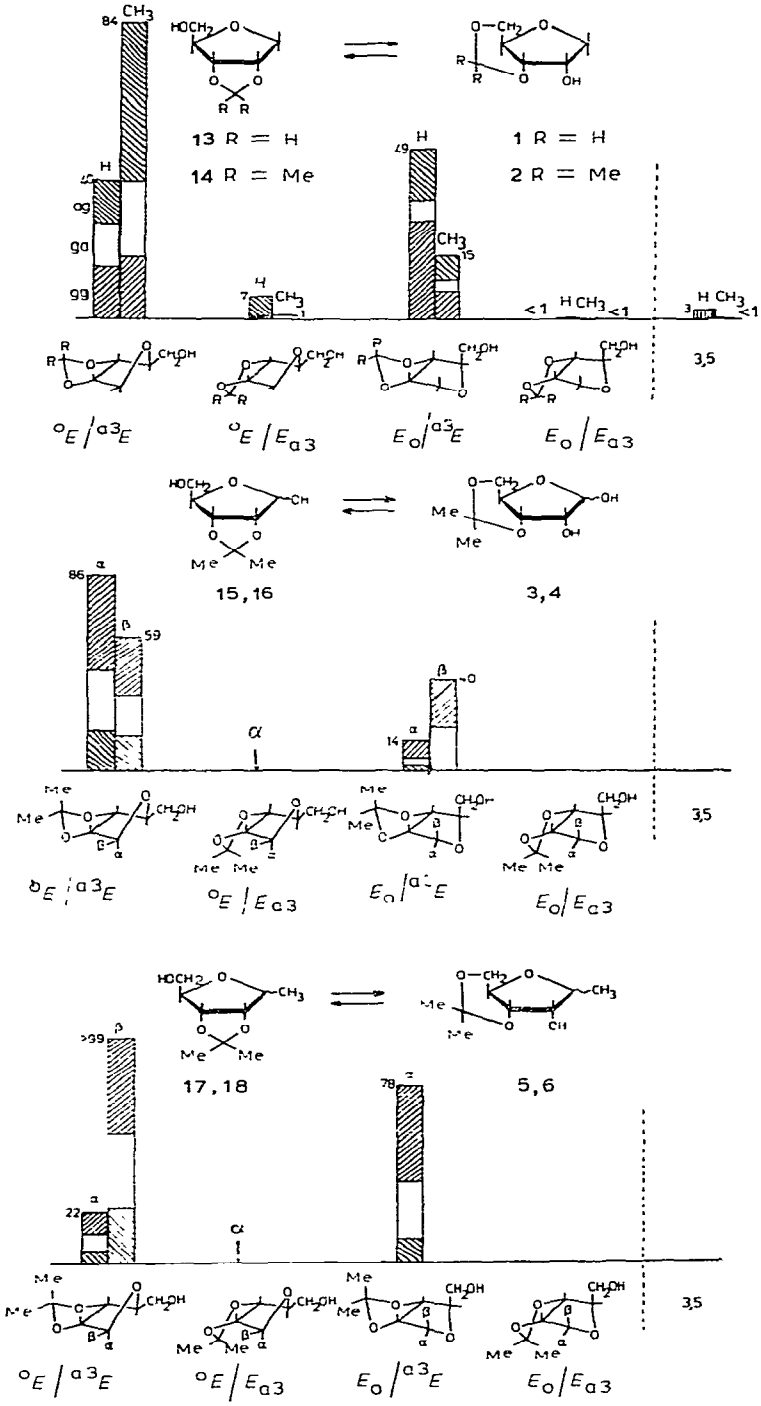


Fig. 1. Composition (%) of equilibrium mixtures of *ribo* derivatives, calculated from steric energies (Tables I and II) with Boltzmann's law at 25°. Rotamers about the C-4–C-5 bond are distinguished by the lining within the bars. An exclamation mark (!) indicates that the conformation is not an energy minimum (see text).

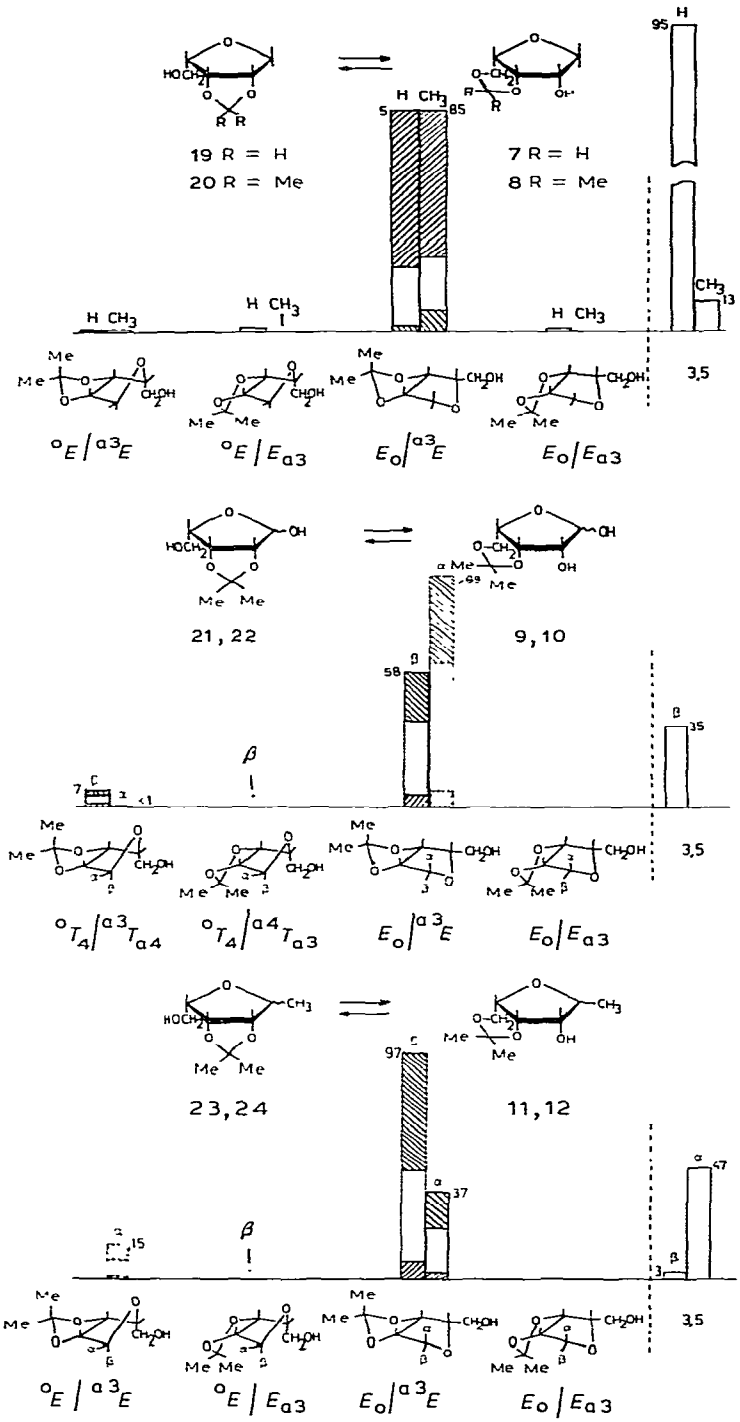


Fig. 2. Composition (°o) of equilibrium mixtures of *lyxo* derivatives at 25° (for full explanation, see Fig. 1).

anhydro-D-riburonic esters[27]), the $J_{1,2}$ and $J_{3,4}$ values are less than 0.5 Hz. For 2,3-*O*-benzylidene-β-D-ribofuranose, these couplings are reported to be $J_{1,2}$ <0.5 Hz, and $J_{3,4}$ 0.8 and 1.3 Hz for the *exo*- and *endo*-phenyl isomers, respectively[25]. For 2,3-*O*-isopropylidene-D-riburonic acid β-nucleosides, $J_{1,2}$ values of 0.58 and 0.89 Hz, and $J_{3,4}$ values of 1.82 and 1.77 Hz were found[23,28]. The $J_{3,4}$ values especially are larger than would be expected for the $E_o/^{a3}E$ conformation found in the crystal. For α anomers, only $J_{3,4}$ is useful for the determination of the conformation. In 2,3-*O*-isopropylidene-D-riburonic acid α-nucleosides, $J_{3,4}$ 0.5–0.9 Hz was found[23,27]. In view of the many factors influencing the value of the coupling constant, the precise position of the conformational equilibria cannot be assigned from these data.

Replacement of the anomeric hydroxyl group of **15** and **16** by a methyl group gives compounds **17** and **18**, which serve as model compounds for the conformational and configurational behavior of *C*-glycosides. Electrostatic interactions and the anomeric effect do not play an important part in these compounds, and van der Waals effects determine the conformational energies. The situation for the β anomer **18** is unambiguous; the conformation having pseudo-equatorial alkyl groups at both C-1 and C-4 ($^{o}E/^{a3}E$) is adopted. The α anomer **17** can have either the *endo* (C-1) or *exo* (C-4) substituent in the pseudo-equatorial position, and the former is preferred. This situation is in agreement with the X-ray structure of an α-*C*-glycoside of D-ribofuranose[29], and with available n.m.r. coupling constants of α- and β-*C*-glycosides[29–31]. The X-ray crystal structure of the α-C-glycoside also shows a nearly unperturbed $E_o/^{a3}E$ conformation, further supporting our observation that the 2,3-*O*-alkylideneribofuranose ring-system is not easily distorted.

Calculations in the *lyxo* series confirm the rule that a pseudo-equatorial hydroxymethyl group strongly stabilises a conformation. For the 2,3-*O*-alkylidene-1,4-anhydro-L-lyxitols **19** and **20**, the $E_o/^{a3}E$ conformation of the THF ring is very preponderant (Fig. 2).

All of the isopropylidene derivatives having the *lyxo* configuration show the inversion of the 1,3-dioxolane ring mentioned in the case of **15**, thereby avoiding the $^{o}E/E_{a3}$ conformation. This preference is retained in the lyxofuranose derivatives **21** and **22**; the α form adopts the $E_o/^{a3}E$ conformation exclusively, having a pseudo-equatorial hydroxymethyl group and a favorable geometry for the anomeric effect, and this conformation is also strongly preponderant for the β form (Fig. 2). This finding is supported by the coupling constants observed for 2,3-*O*-isopropylidene-L-lyxuronic acids (α, $J_{1,2}$ <0.5 Hz[32]; β, $J_{1,2}$ ~4 Hz[33]; $J_{3,4}$ for both anomers, 4–4.5 Hz[32,33]).

The *lyxo* *C*-glycosides **23** and **24** fit the pattern shown by the *ribo* derivatives **17** and **18**. The β anomer again favours the di-pseudo-equatorial conformation, which now is $E_o/^{a3}E$, whereas the α anomer is in an equilibrium in which the conformation having the *endo* substituent pseudo-equatorial is preponderant (Fig. 2).

EQUILIBRIA OF 2,3- AND 3,5-*O*-ALKYLIDENE DERIVATIVES

Angle-bending strain favours 2,3- over 3,5-derivatives, whereas the latter are more favoured in terms of bond eclipsing (torsional energy). As mentioned before, the *cis*-fused *lyxo*-3,5-derivatives are more able to relax angle-bending strain by adjusting torsion angles than the *trans*-fused *ribo*-3,5-derivatives. The equilibria of 1,4-anhydro-2,3- and -3,5-*O*-methylene-D-ribitols (**13** and **1**) and -L-lyxitols (**19** and **7**) are therefore quite different; in the ribitol derivatives, the 2,3-form is preferred, with a Gibbs energy difference of 2.09 kcal.mol^{-1} (Tables II and III), whereas the lyxitol system prefers the 3,5-form, with a Gibbs energy of 1.62 kcal.mol^{-1}. In these energies, the entropy effect favouring the 2,3-form is included because of the conformational diversity of this constitutional isomer, and this effect is probably underestimated because of the flexibility of the 2,3-form as compared with the rigid 3,5-form, at least in the case of ribose.

On the other hand, the isopropylidene derivatives prefer the 2,3-form in every case studied. This is clearly due to the fact that the 3,5-*O*-isopropylidene derivatives contain an axial methyl group at C-2 in a 1,3-dioxane ring. It is known that an axial methyl group at this position is 4.0 kcal less stable than an equatorial group[34], and a similar energy value is expected to destabilise the 3,5-*O*-isopropylidene derivatives. For the ribitol derivatives **2** and **14**, the 3,5-derivative is 6.8 kcal.mol^{-1} less stable than the 2,3-derivative. For the α-D-riboses **3** and **15**, the energy difference is calculated to be only 3.5 kcal.mol^{-1}, but this is mainly an effect of intramolecular hydrogen-bonding, because there is no conformation for the free hydroxyl group of **15** without an intramolecular hydrogen-bond. For the β derivatives **4** and **16**, the energy difference is larger (6.8 kcal.mol^{-1}), supporting this conclusion. In the *C*-glycosides, the equilibria are equally favourable for the 2,3-derivatives. We conclude

TABLE III

AVERAGE ENERGIES AND GIBBS ENERGIES OF 2,3-*O*-ALKYLIDENE DERIVATIVES

Compound	*Average energy (kcal.mol^{-1})*	*Gibbs energy (kcal.mol^{-1})*
13	29.33	28.15
14	29.27	28.44
15	22.03	21.18
16	21.87	20.93
17	31.18	30.29
18	30.38	29.75
19	28.54	28.05
20	29.02	28.46
21	21.88	21.13
22	20.32	19.54
23	29.91	29.38
24	31.78	30.91

that *ribo*-3,5-derivatives cannot be found in equilibria involving ketones. However, it may be expected that aldehydes, which yield 1,3-dioxane derivatives lacking the axial methyl group, can form 3,5-derivatives under suitable conditions of kinetic control.

The 3,5-forms of the *lyxo* derivatives are also less stable when *O*-isopropylidene derivatives are considered. However, the equilibria shown in Fig. 2 exhibit considerable proportions of 3,5-derivatives in some cases. A high stability is predicted for the β anomer of lyxose, but of most interest is the preference of methylene derivatives for the 3,5-*O*-alkylidene form. As before, this can be generalised for all cyclic acetals (*e.g.*, benzylidene derivatives), because the reason for the different results for methylene and isopropylidene derivatives involves the axial methyl group in the 1,3-dioxane ring of *O*-isopropylidene derivatives. Therefore, the favoured benzylidene derivatives of lyxofuranose should have the 3,5-structure.

ANOMERIC AND C-4-EPIMERIC EQUILIBRIA OF 2,3-*O*-ISOPROPYLIDENEPENTOFURANOSES AND OF *C*-GLYCOSIDES

The most frequent epimerisation-reaction in carbohydrate chemistry, anomerisation, is easily studied under true equilibrium conditions. Epimerisation at C-4, necessary for the interconversion of *ribo* and *lyxo* derivatives, is not possible directly, but the uronic acid esters can be equilibrated by base and this also allows the relative energies of the parent *ribo* and *lyxo* derivatives to be estimated[35]. Another method of equilibration of *C*-epimeric compounds has been developed by Ohrui and Emoto, who employed the *retro*-Michael reaction of cyanomethyl and related compounds, mainly in studies of the relative energies of *C*-glycoside anomers[29]. These are the three groups of equilibration data to which our calculated energies are compared.

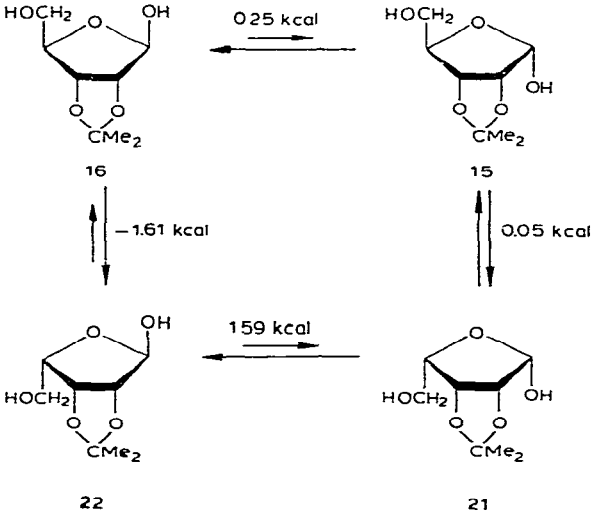


Fig. 3. Anomeric and C-4-epimeric equilibrium of D-ribofuranoses and L-lyxofuranoses at 25°.

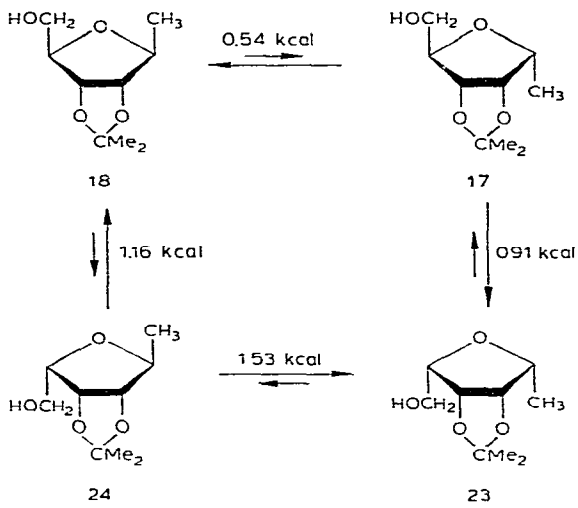


Fig. 4. Epimeric equilibria (C-1 and C-4) of D-ribofuranosyl and L-lyxofuranosyl *C*-methyl glycosides.

Average steric energies of the epimers were obtained from the steric energies of the single conformations, employing Boltzmann's law. The mole fractions thus available were also used to calculate the entropies of mixing, and in this manner the Gibbs energies of the epimers were calculated for the 2,3-*O*-isopropylidene derivatives, neglecting effects of solvation, vibration, and rotation (Table III).

As Fig. 3 shows, the compounds having the anomeric hydroxyl group in the *exo* configuration are favoured for the 2,3-*O*-isopropylidene-D-ribo- and -L-lyxofuranoses (**15**⇄**16** and **21**⇄**22**), in agreement with experience[29]. The equilibrium of the C-4 epimers for the O-*exo* anomers (**16**⇄**22**) favours the C-*endo* form (Fig. 3); in agreement with these results, Kotick and Leland found the same preference in the equilibrium of β-D-riburonic and α-L-lyxuronic esters. The practically identical energies of the C-4-epimeric, O-*endo* anomers **15** and **21** indicate a balanced equilibrium.

The "*C*-glycosides" **17**/**18** and **23**/**24**, besides showing different conformational equilibria than those of the hydroxyl analogues, also exhibit a different configurational stability (Fig. 4). The most stable of the four epimeric compounds is the *endo-lyxo* form **23**, which is calculated to be more stable than the *endo-ribo* form **17** and the *exo-lyxo* form **24**. The same position of anomeric equilibrium was found[29] for a mannofuranosyl-*C*-glycoside having the same configurational situation at the THF ring. The calculations further indicate that the *exo-ribo* epimer **18** is the second most-stable form, which is not in agreement with the results of Ohrui and Emoto[29], who found a preference for the C-*endo* anomer for several *C*-glycosides having the *ribo* configuration. This disagreement may have several reasons. First, the calculation might underestimate the stability of the C-1/C-4-*trans* isomers, either for entropy reasons (these forms are more flexible than the *exo-ribo* form with its envelope conformation having two pseudo-equatorial alkyl groups), or because of an over-

estimation of the van der Waals repulsions experienced by the axial groups, which we have noted before in the conformational equilibrium of the 2,3-*O*-isopropylidene-D-ribofuranoses. A second reason might be solvent effects neglected in the calculation. However, a more important reason seems to be that the experimental data refer to compounds having not a methyl group, but a (mono- or di-)cyano- or alkoxycarbonyl-methyl group. According to CNDO/2 calculations, which we performed to determine charge densities on all atoms, the methyl group carries a negative charge. This probably originates from an electron donation similar to the anomeric effect from the oxygen lone-pairs of the THF ring. The cyanomethyl and alkoxycarbonylmethyl groups, however, have a partially positive carbon. The system calculated therefore has electrostatic interactions different from those studied experimentally[29]. On the other hand, the equilibrium studied by Kotick and Leland[35] (see above) is more comparable with our calculated system. Here the experiment was done on COOR derivatives, and the calculations on CH_2OH derivatives, both having a positively charged carbon. We conclude that the calculations indicate that C-4-epimeric equilibria are different in *ribo* and *lyxo* derivatives.

CONCLUSIONS

It has been shown that molecular-mechanics calculations can be applied with reasonable success to the evaluation of conformational, configurational, and constitutional energies of carbohydrates, not only for pyranoses, but also for such less-regular frameworks as the trioxabicyclo[3.3.0]octanes and trioxabicyclo[4.3.0]nonanes discussed above. In the conformational equilibria, good agreement was found with available experimental data in most cases, with the exception of the 2,3-*O*-isopropylidene-D-ribofuranoses for which the destabilisation of the conformation having a pseudo-axial substituent is probably overestimated. The results obtained for *C*-glycosides can be summarised in the conformational rule that the *endo*-alkyl group prefers the pseudo-equatorial position on the THF ring. The calculations give a correct presentation of the configurational equilibria of 2,3-*O*-isopropylidene-D-ribo- and -L-lyxo-furanoses. In the configurational equilibria of the *C*-glycosides, a disagreement with some of the available experimental data was found, but we believe that this is mainly due to an unsuitable choice of models.

The energies of 3,5-*O*-alkylidene-D-ribo- and -L-lyxo-furanoses, which were the original aim of this study, encourage the attempted synthesis of these isomers. In the *ribo* series studied, the energies were mostly too high for measurable amounts of 3,5-isomers to be found at equilibrium; on the other hand, their energies are not so high as to preclude completely their formation under suitable conditions. The formation of 3,5-*O*-alkylidene derivatives is most probable when cyclic acetals are produced, rather than cyclic ketals. The situation in the *lyxo* series is more in favour of the 3,5-*O*-alkylidene derivatives; 3,5-*O*-isopropylidene derivatives are calculated to be only slightly less stable than the 2,3-analogues, while the 3,5-form is preferred for methylene derivatives. In the lyxose series, under equilibrating conditions, cyclic

ketals should therefore contain only small proportions of the 3,5-isomers, whereas cyclic acetals should preferentially comprise 3,5-derivatives.

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