

Anomeric effect in carbohydrates—an *ab initio* study on extended model systems

P KALIANNAN†, S VISHVESHWARA and V S R RAO*

Molecular Biophysics Unit, Indian Institute of Science, Bangalore 560 012, India

† Present address: Department of Physics, Government Arts College, Krishnagiri 635 001, India

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Abstract. The anomeric effect is studied at the *ab initio* Hartree-Fock level using extended model systems. This has enabled us to study the effect of substitution on the anomeric effect and the Δ^2 -effect in greater detail. An attempt is made to compare the results with available experimental data.

Keywords. Anomeric effect; carbohydrates; model systems.

1. Introduction

The anomeric effect discovered by Edwards (1955) and Lemieux (1958) and Chu (1958) has gained theoretical support by several *ab initio* studies in the past decade (Wolfe *et al* 1969; Jeffrey *et al* 1972, 1974, 1978; Jeffrey and Yates 1979, 1980, 1981; Schaefer 1981; Vishweshwara and Rao 1982; Allinger 1984). Although there is a general agreement between theory and experiment, certain aspects, like the correlation between the substituent on oxygen at C1 and the anomeric energy (Stoddart 1981), the Δ^2 effect (Reeves 1949; Durette and Harton 1971) which arises due to the axial orientation of the OH group on C2 of a pyranose, are not clear. The anomeric effect is generally recognised as the property of the O5–C1–O1 fragment. However, the experimental results (Reeves 1950; Stoddart 1981) include to some extent, factors like the other intra and intermolecular interactions including the effect of solvents. On the other hand, theoretically, the anomeric effect can be studied as a phenomenon associated only with the (O–C–O) fragment. Hence, related properties, like the *exo*-anomeric effect, the Δ^2 effect and the effect of substitution, can be studied as a perturbation on the (O–C–O) fragment. One can consider a number of model systems with appropriate substituents on the various atoms of methane-diol molecule. In view of this, the systems 1,1-dihydroxyethane, 1,1-dimethoxyethane, 1,1,2-trihydroxyethane and 2,2-dimethoxyethanol are studied at the *ab initio* level. The results obtained, along with those of other previous theoretical studies have been used to analyse the trends in properties associated with the anomeric effect. Also, the results are compared with experimental values whenever possible.

* To whom all correspondence should be addressed.

2.

2.1 Method

The calculations were carried out mainly at the RHF/STO-3G level (Hehre *et al* 1969) using a DEC-10 version of GAUSSIAN 74 (Hehre *et al* 1975). Although, it is desirable that all calculation be carried out at a higher level basis set and with complete geometry optimization, it was not possible to achieve that level of sophistication because of the size of the systems and computer time. However, the conclusions drawn from these studies are valid since on detailed comparison, the present results are in general agreement with the earlier more sophisticated calculations carried out on smaller systems.

2.2 Model systems and geometry

Relevant portions of the carbohydrate moieties have been modelled with smaller molecules. To investigate the anomeric effect in 2-deoxy pyranoses and 2-deoxy pyranosides, 1,1-dihydroxyethane and 1,1-dimethoxyethane have been taken as model systems respectively (figure 1). To investigate the Δ^2 effect in simple and 1-O-methylpyranosides, 1,1,2-trihydroxyethane and 2,2-dimethoxyethanol (figure 2) have been considered as model systems respectively.

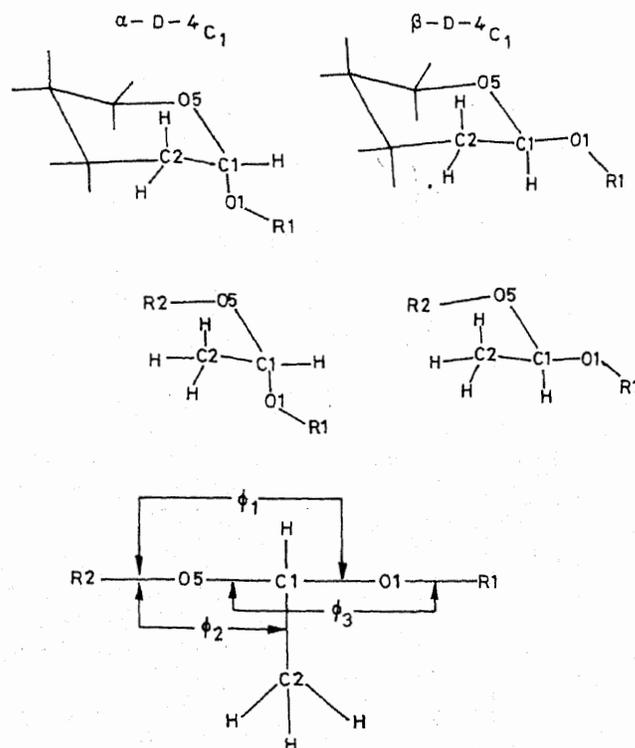


Figure 1. Relation between conformations of 2-deoxy pyranoses and 1,1-dihydroxyethane ($R_1 = R_2 = H$); and 2-deoxy pyranosides and 1,1-dimethoxyethane ($R_1 = R_2 = CH_3$).

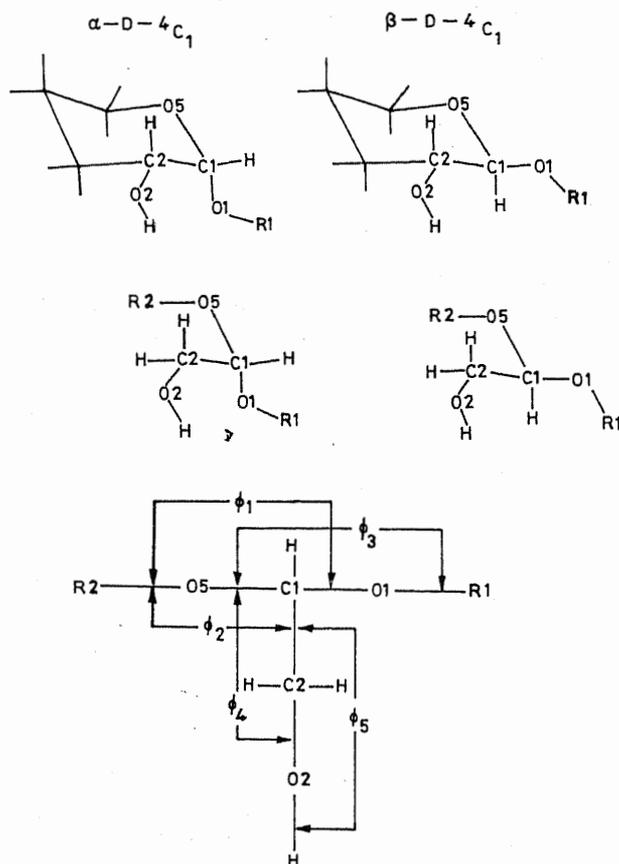


Figure 2. Relation between conformations of pyranoses and 1,1,2-trihydroxyethane ($R_1 = R_2 = \text{H}$); and pyranosides and 2,2-dimethoxyethanol ($R_1 = R_2 = \text{CH}_3$) (OH at C2 is axial for mannose-like pyranoses and pyranosides).

Standard values of bond lengths (Pople and Gordon 1967) ($\text{C-C} = 1.54 \text{ \AA}$, $\text{C-O} = 1.43 \text{ \AA}$, $\text{C-H} = 1.09 \text{ \AA}$, $\text{O-H} = 0.96 \text{ \AA}$) and tetrahedral valence angles were used to fix the various atoms in these molecules. Corresponding to a model for $\alpha\text{-D-}^4\text{C}_1$ configuration of a pyranose or a pyranoside the dihedral angles ϕ_1 and ϕ_2 were fixed at 60° and -60° respectively. For $\beta\text{-D-}^4\text{C}_1$ configuration the dihedral angles were fixed as $\phi_1 = 180^\circ$ and $\phi_2 = -60^\circ$. For 1,1,2-trihydroxyethane and 2,2-dimethoxyethanol values of ϕ_4 of 180° and -60° describe the equatorial and axial disposition of C2 hydroxyls respectively.

By varying the dihedral angle ϕ_3 in steps of 60° energies were computed in each case for 1,1-dihydroxyethane and 1,1-dimethoxyethane. Calculations were repeated for 1,1-dimethoxyethane using the available optimized angles for dimethoxymethane (Gorenstein *et al* 1977). In the case of 1,1,2-trihydroxyethane and 2,2-dimethoxyethanol energies were computed by varying the dihedral angles ϕ_3 and ϕ_5 after fixing ϕ_1 , ϕ_2 and ϕ_4 at respective values corresponding to the model

for α -D- 4 C $_1$ or β -D- 4 C $_1$ configuration for both axial and equatorial orientations of C2-OH bond.

3. Results

3.1 1,1-dihydroxyethane

The energies for 1,1-dihydroxyethane computed as a function of ϕ_3 after fixing the other dihedral angles at values mentioned in §2.2 are given in table 1. The table shows that the minimum occurs at $\phi_3 = 60^\circ$ and -60° corresponding to the α -D- 4 C $_1$ and β -D- 4 C $_1$ configurations respectively. However, the minimum for the β -D- 4 C $_1$ configuration is about 2.5 kcal mol $^{-1}$ higher in energy than that for the α -D- 4 C $_1$ configuration. This difference represents the anomeric energy and is slightly higher than the value (2.24 kcal mol $^{-1}$) obtained using methanediol (Vishveshwara and Rao 1982) as a model system. However, the 4-31G value is 4.7 kcal mol $^{-1}$ (Jeffrey *et al* 1972). It is interesting to note from the table and figure 3 that for β -D- 4 C $_1$ configuration ϕ_3 favours -60° over 60° by about 0.6 kcal mol $^{-1}$ and the conformation with $\phi_3 = 0^\circ$ is almost of equal energy as the one with $\phi_3 = 60^\circ$. Such a preferred eclipsed conformation was also found in methanediol (Jeffrey *et al* 1972) and this is due to favourable dipolar interaction in the conformation with $\phi_3 = 0^\circ$.

In the β -D- 4 C $_1$ configuration, the distinction between $\phi_3 = -60^\circ$ and $+60^\circ$ was not possible using methanediol as a model system. However, the difference in the energy between these two conformations cannot be considered as *exo*-anomeric energy (as defined by Jeffrey and Yates 1981) since in this case it arises purely due to steric reasons and the interaction of bond dipoles and lone pairs on oxygen of the -O-C-O- fragment is identical in both $\phi_3 = -60^\circ$ and $+60^\circ$ conformations. The calculated *exo*-anomeric energies (the energy difference between $(\phi_1, \phi_3) = (60^\circ, 180^\circ)$ and $(60^\circ, 60^\circ)$ conform-

Table 1. STO-3G conformational energies of 1,1-dihydroxyethane.

Configuration ^a	ϕ_3 (degree)	Relative energy (kcal mol $^{-1}$)
α -D- 4 C $_1$	0	3.69
	60	0.00 ^b
	120	2.46
	180	3.08
	-120	3.96
	-60	3.15
β -D- 4 C $_1$	0	3.05
	60	3.08
	120	6.93
	180	7.50
	-120	6.26
	-60	2.49

^a For α -D- 4 C $_1$ configuration, $(\phi_1, \phi_2) = (60^\circ, -60^\circ)$; for β -D- 4 C $_1$ configuration, $(\phi_1, \phi_2) = (180^\circ, -60^\circ)$.

^b Total energy = -225.9693089 hartrees.

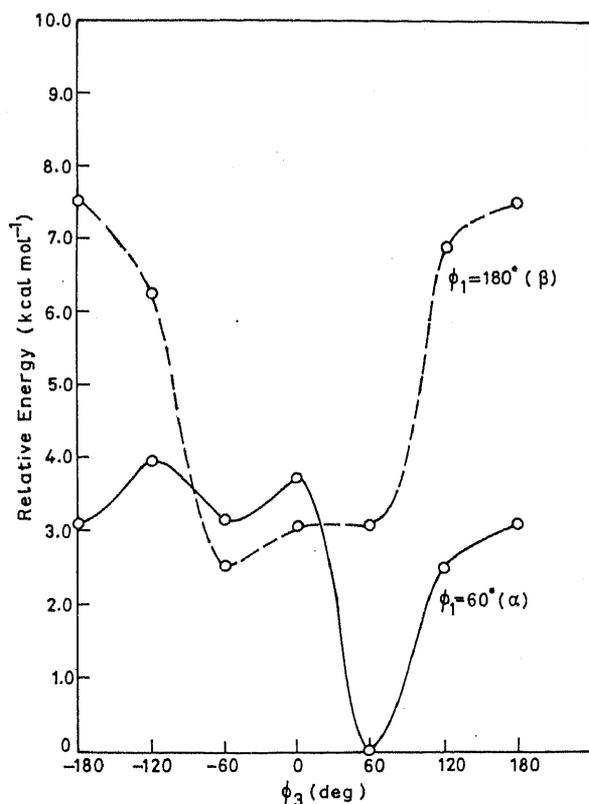


Figure 3. Relative energies drawn as a function of ϕ_3 for internal rotation in 1,1-dihydroxyethane, for fixed values of ϕ_1 .

ations for α -D-⁴C₁ and that between (180°, 180°) and (180°, -60°) conformations for β -D-⁴C₁ configurations) are 3.08 and 5.01 kcal mol⁻¹ for the α -D-⁴C₁ and β -D-⁴C₁ configurations respectively. The increased *exo*-anomeric energy as compared to that in methanediol is due to the added steric interaction between the -CH₃ group on C1 and the proton on O1 in (60°, 180°) and (180°, 180°) conformations respectively in α -D-⁴C₁ and β -D-⁴C₁ models.

3.2 1,1-dimethoxyethane

The computed energies of 1,1-dimethoxyethane are given in table 2. The variation of energy with ϕ_3 is shown in figure 4. The lowest energy configuration is again equivalent to the α -D-⁴C₁ and is favoured by about 0.6 kcal mol⁻¹ over the β -D-⁴C₁. The energy difference between α and β configurations is small (0.6 kcal mol⁻¹) when compared to that (2.5 kcal mol⁻¹) in 1,1-dihydroxyethane, suggesting that a methoxyl substituent at C1 carbon reduces the anomeric energy significantly. The *exo*-anomeric energies are 7.24 and 9.20 kcal mol⁻¹ respectively for the α -D-⁴C₁ and β -D-⁴C₁ configurations, and the increase in *exo*-anomeric energy is due to increased steric effects between the -CH₃ groups on O1 and C1 in (ϕ_1, ϕ_3) = (60°, 180°) and (180°, 180°) conformations. It thus

Table 2. STO-3G conformational energies of 1,1-dimethoxyethane.

Configuration ^a	ϕ_3 (deg.)	Relative energy (kcal mol ⁻¹)	
		Standard geometry	Optimized geometry
α -D- ⁴ C ₁	0	217.70	
	60	0.00 ^b	-1.02
	120	2.60	
	180	7.24	
	-120	22.95	
	-60	224.20	
β -D- ⁴ C ₁	0	6.29	
	60	7.24	
	120	23.72	
	180	9.81	
	-120	4.79	
	-60	0.61	-0.44

^a as in table 1; ^b total energy = -303.1273774 hartrees.

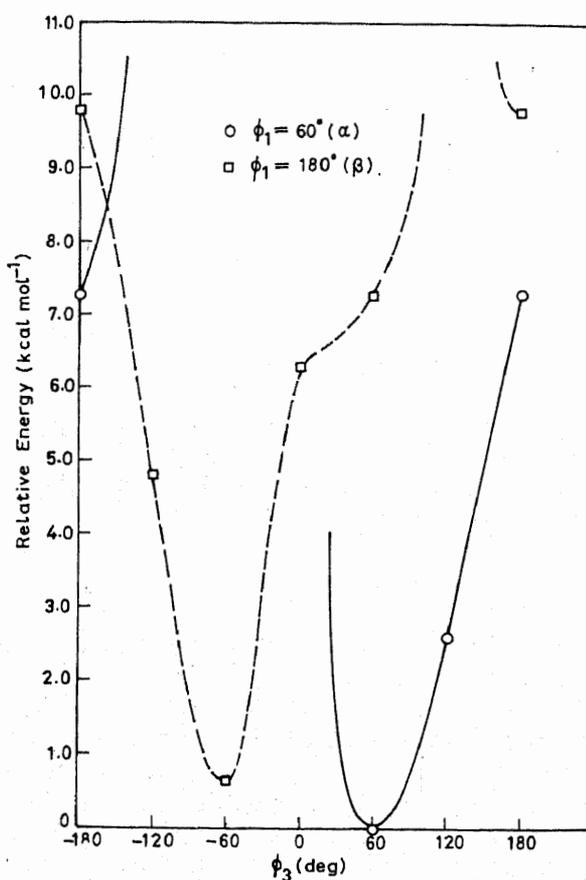


Figure 4. Relative energies drawn as a function of ϕ_3 for internal rotation in 1,1-dimethoxyethane for fixed values of ϕ_1 .

seems that a methoxyl substituent at the C1 carbon reduces the anomeric energy and increases the *exo*-anomeric energy. The energies obtained using the STO-3G optimized bond angles of dimethoxymethane (Gorenstein *et al* 1977) also lead to the same value for the anomeric energy (table 2).

3.3 1,1,2-Trihydroxyethane

In this system corresponding to a model for α -D- 4 C₁ and β -D- 4 C₁ configurations $\phi_4 = 180^\circ$ and -60° represent the equatorial and axial orientations of C2-OH group respectively as mentioned in § 2. Energies were calculated as a function of ϕ_3 by fixing ϕ_5 (figure 2) in all the three staggered orientations and the values are given in table 3. The minimum energy conformation ($\phi_3, \phi_5 = 60^\circ, -60^\circ$) for α -D- 4 C₁ configuration when C2-OH is equatorially oriented, has about 2.2 kcal mol⁻¹ lower energy than the β -D- 4 C₁ configuration ($\phi_3, \phi_5 = -60^\circ, 60^\circ$) and this is the anomeric energy. On the other hand, when the hydroxyl group at C2 is axially oriented the anomeric energy is 2.4 kcal mol⁻¹. The calculated *exo*-anomeric energies (the energy difference between (ϕ_1, ϕ_3) = (60°, 180°) and (60°, 60°) conformations for α -D- 4 C₁ and that between (180°, 180°) and (180°, -60°) conformations) for β -D- 4 C₁ configurations, with the lowest

Table 3. STO-3G conformational energies of 1,1,2-trihydroxyethane.

Configuration ^a	ϕ_4	ϕ_3	ϕ_5		
			60	180	-60
α -D- 4 C ₁	180 (C2-OH equatorial)	0	6.14	5.85	3.70
		60	2.60	2.00	0.00 ^b
		120	4.67	3.27	2.34
		180	3.58	2.12	6.09
		-120	4.08	4.06	7.70
		-60	5.07	5.00	3.81
β -D- 4 C ₁		0	2.70	5.12	5.49
		60	3.44	4.85	5.00
		120	10.41	6.91	7.04
		180	10.21	6.41	8.00
		-120	5.85	7.01	8.54
		-60	2.17	4.41	5.12
α -D- 4 C ₁	-60 (C2-OH axial)	0	4.11	5.29	5.15
		60	0.21	1.85	1.61
		120	2.50	4.02	4.20
		180	3.44	4.85	5.00
		-120	4.58	6.11	6.03
		-60	3.81	5.00	5.07
β -D- 4 C ₁		0	4.31	5.05	3.10
		60	2.59	3.37	6.40
		120	5.89	8.25	10.88
		180	8.28	10.48	8.28
		-120	7.64	9.57	6.45
		-60	4.01	5.66	2.63

Angles in degrees and energies in kcal mol⁻¹).

^a as in table 1; ^b total energy = -299.7922451 hartrees.

Table 4. The calculated anomeric energies in R1-O5-C1H(R3)-O1-R2 systems.

R1	R2	R3	Anomeric energy (kcal mol ⁻¹)	Exo-anomeric energy (kcal mol ⁻¹)		Reference
				α -D- ⁴ C ₁	β -D- ⁴ C ₁	
H	H	H	2.2 ^a (4.7) ^b [3.75] ^c	2.2 (4.7) [3.75]	4.4 (6.5) [5.09]	Vishveshwara and Rao (1982) Jeffrey <i>et al</i> (1972) Jeffrey <i>et al</i> (1978)
CH ₃	H	H	(3.0)	(4.3)	(6.4)	Jeffrey <i>et al</i> (1974)
CH ₃	CH ₃	H	(2.57)	(2.57)	(5.09)	Jeffrey <i>et al</i> (1978)
			1.57	1.57	1.76	Vishveshwara and Rao (1982)
H	H	CH ₃	2.49	3.08	5.01	Present work
CH ₃	H	CH ₃	(2.44)			Jeffrey and Yates (1981)
CH ₃	CH ₃	CH ₃	0.61	7.24	9.2	Present work
H	H	CH ₂ -OH axial	2.4 (4.49)	3.23	5.7	Present work Present work
CH ₃	H	CH ₂ -OH axial	(2.89)			Jeffrey and Yates (1981)
CH ₃	CH ₃	CH ₂ -OH axial	0.18	7.25	10.1	Present work
H	H	CH ₂ -OH equatorial	2.17 (3.89)	2.12	4.24	Present work Present work
CH ₃	H	CH ₂ -OH equatorial	(1.74)			Jeffrey and Yates (1981)
CH ₃	CH ₃	CH ₂ -OH equatorial	0.12	15.70	18.0	Present work

^a The values represented without any bracket are obtained at the STO-3G level; ^b Numbers in parentheses are the 4-31G values; ^c Numbers in square brackets are the 6-31G* values.

energy value of ϕ_5 are given in table 4. As in the model systems for 2-deoxy sugars, the *exo*-anomeric energy is higher for β -D-⁴C₁ than for α -D-⁴C₁ configurations.

3.4 2,2-dimethoxyethanol

The computed energies as functions of ϕ_3 and ϕ_5 corresponding to the α -D-⁴C₁ and β -D-⁴C₁ configurations with the C2-OH equatorial and C2-OH axial orientations are given in table 5. The *exo*-anomeric energies were calculated in the same way as for 1,1,2-trihydroxyethane and are given in table 4. In some conformations ($\phi_3 = 0^\circ$ and -60° for α -D-⁴C₁) due to the closeness of the bulky methyl groups the energies are very high (table 5). The energy difference between that for β -D-⁴C₁ and α -D-⁴C₁ configurations with C2-OH equatorial is only 0.12 kcal mol⁻¹ (considering the lowest energy conformation with respect to ϕ_5), indicating that the anomeric energy is very small in systems with methoxyl substituent. Similarly the energy difference between that for β -D-⁴C₁ and α -D-⁴C₁ configurations with C2-OH axial is (0.56-0.38) = 0.18 kcal mol⁻¹.

Using the optimized bond angles the energies for a few conformations have been computed and these values are shown in table 6. It is interesting to note that the anomeric energy is increased slightly in each case though the absolute energies are

Table 5. STO-3G conformational energies of 2,2-dimethoxyethanol.

Configuration ^a	ϕ_4	ϕ_3	ϕ_5		
			60	180	-60
α -D- ⁴ C ₁ (C2-OH equatorial)	180	0	219.80	219.70	217.80
		60	2.23	1.84	0.00 ^b
		120	4.68	3.38	2.75
		180	18.04	15.71	99.16
		-120	30.18	29.71	120.20
		-60	225.90	—	—
β -D- ⁴ C ₁		0	5.78	8.24	8.61
		60	7.63	8.91	9.01
		120	120.34	30.51	31.25
		180	101.13	18.16	20.78
		-120	4.48	5.54	7.14
		-60	0.12	2.40	3.06
α -D- ⁴ C ₁ (C2-OH axial)	-60	0	218.15	219.13	219.04
		60	0.38	1.64	1.38
		120	2.80	4.00	4.11
		180	7.63	8.91	9.00
		-120	22.90	24.30	23.95
		-60	224.98	225.90	225.80
β -D- ⁴ C ₁		0	7.87	8.06	6.36
		60	17.63	16.86	98.85
		120	30.02	31.31	120.59
		180	10.69	12.53	10.68
		-120	6.28	7.75	4.82
		-60	2.22	3.43	0.56

(Angles in degrees and energies in kcal mol⁻¹)^a as in table 1; ^b total energy = -376.9500425 hartrees.

lowered from those obtained using standard bond angles. The anomeric energy with C2-OH equatorial is equal to 0.37 kcal mol⁻¹ and with C2-OH axial it is (0.88 - 0.43) = 0.45 kcal mol⁻¹.

4. Discussion

From the simplest model of methanediol a closer model of pyranosides is approached by substituting the hydrogens on O5, and O1 by methyl groups and the hydrogen on C1 by methyl and hydroxymethyl groups as the case may be. Since the theoretical studies carried out here do not take into account the solvent effect or the intermolecular interactions, the results presented refer to isolated molecules in vacuum. The results presented above and those of previous theoretical studies summarised in table 4 bring out the following points.

(1) As the model system is closer to pyranosides, the theoretically computed anomeric energy decreases and the *exo*-anomeric energy of the α and β forms increases. It can be seen from table 4 that the anomeric energy decreases as the atoms O5, O1 and

Table 6. STO-3G conformational energies of 2,2-dimethoxyethanol using optimized angles given in Gorenstein *et al* (1977).

Configuration ^a	ϕ_4	ϕ_3 (degrees)	ϕ_5	Total energy (hartrees)	Relative energy (kcal mol ⁻¹)
α -D- ⁴ C ₁	180	60	-60	-376.9521362	0.00
β -D- ⁴ C ₁	180	-60	60	-376.9515434	0.37
α -D- ⁴ C ₁	-60	60	60	-376.9514508	0.43
β -D- ⁴ C ₁	-60	-60	-60	-376.9507408	0.88

^a as in table 1.

C1 get methylated. Thus, as the model system becomes closer to the pyranoside, the theoretically computed anomeric energy decreases. Similar trends are predicted both by the STO-3G and the 4-31G basis sets, although the STO-3G anomeric energies are smaller compared to the 4-31G values. The experimentally reported anomeric energies range from 0.55 to 2.2 kcal mol⁻¹ (Durette and Harton 1971; Stoddard 1971). The various entries in the table lead us to conclude that the anomeric energy of 4.7 kcal mol⁻¹ obtained for methanediol by the *ab initio* method for the first time (Jeffrey *et al* 1972) at the 4-31G level can in fact approach the experimental value with the improved model and the increased level of sophistication in the basis set. The theoretical estimates of the *exo*-anomeric energies increase on methylation of C1 and oxygens (which can be clearly attributed to steric effect), for which although experimentally computed values are not available all the observed crystal structures of α and β methyl pyranosides (Jeffrey *et al* 1978; Jeffrey and Taylor 1980) correspond to (*g, g*) and (*t, g*) conformations respectively.

One point that emerges out of the results tabulated in table 4 is that the order of anomeric energy as a function of substituent on C1 as given by Allinger (1984) i.e., methoxy > hydroxy does not correspond to the theoretical estimate. Perhaps in this case as mentioned in §1, the experimental estimate of anomeric energy includes the interaction of the aglycone with other atoms of the pyranosides and the interaction with the solvent molecules.

(2) The results of the model compounds containing the C2-OH group show that the anomeric energy is greater when the group is axially oriented than when it is in the equatorial position. This has been recognised as the Δ^2 -effect (Reeves 1949; Durette and Harton 1971) which can be understood in terms of the dipolar interactions. The C-O bonds on adjacent carbon atoms ($\text{O}-\text{C}-\text{C}-\text{O}$) interact more favourably in the *trans* orientation than in the *gauche* orientation. This phenomenon is different from the *gauche* effect (Wolfe 1972), in which the preference for the *trans* and the *gauche* orientations of the polar bonds is reversed. This happens because the bonds interacting in the systems exhibiting the *gauche* effect have opposite polarity. The difference between the two types of interactions are depicted in figure 5, where 5a, 5b and 5c correspond to the models of β -⁴C₁ pyranose, α -⁴C₁ pyranose and a model for the *gauche* effect respectively. The arrows in the figure indicate the direction of the dipoles and it can be seen that the *gauche* interactions in figure 5a are unfavourable and that in 5c are favourable when the C2-OH is axially oriented as in the β -⁴C₁ pyranose and that

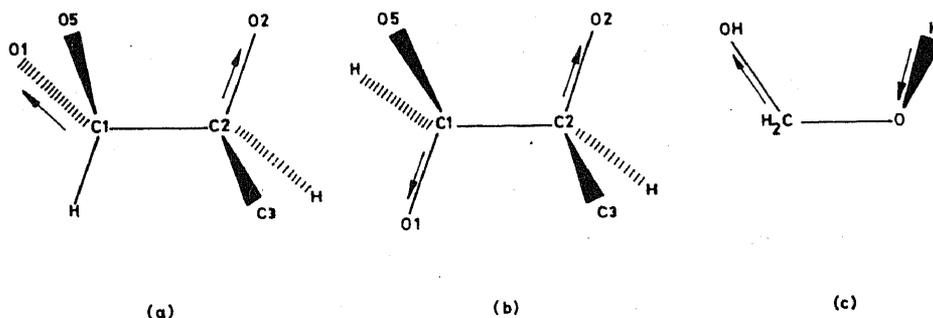


Figure 5. The dipolar interactions in models representing (a) β -C2-OH axial, (b) α -C2-OH axial and (c) *gauche* effect.

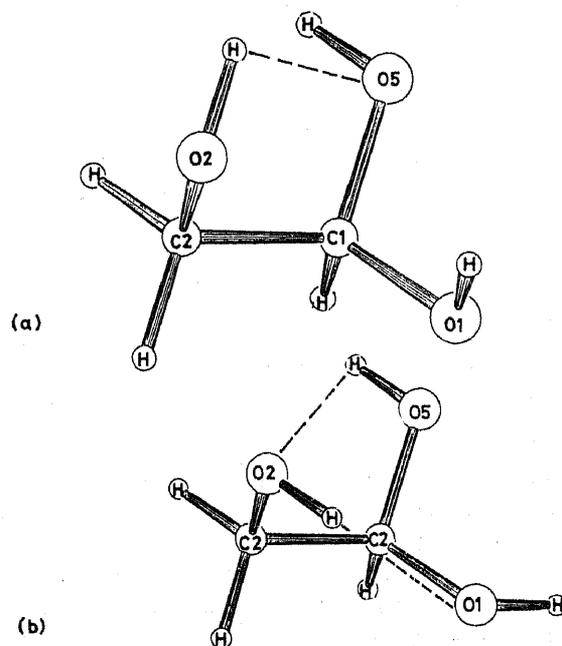


Figure 6. Ortep projections of 1,1,2-trihydroxyethane (a) $(\phi_4, \phi_5) = (60^\circ, 60^\circ)$ and (b) $(\phi_4, \phi_5) = (-60^\circ, -60^\circ)$.

the C2-O2 bond dipole has *gauche* interaction with both the C-O bonds of the O-C-O fragment (figure 5a). The C2-O2 bond makes a *gauche* and a *trans* interaction with the two dipoles of the O-C-O fragment in the axially oriented α - 4 C₁ (figure 5b), equatorially oriented β - 4 C₁ and α - 4 C₁ pyranoses. Thus, the β -form of the axially oriented C2-OH is more destabilized than the equatorial orientation, leading to the Δ^2 -effect.

The magnitude of this dipolar interaction leading to the Δ^2 effect however depends on factors like the substituents on other atoms of the ring, the solvent and so on. For

instance, the above studies on the isolated model systems show that the tendency to form a good hydrogen bond is favoured as far as possible. In all the models with a C2-OH group, when one considers the conformations with the O2 being approximately equidistant from O1 and O5, the O2-H bond prefers to orient towards O1 and O5. This is perhaps due to the fact that the lone pairs of O1 are oriented towards O2, whereas the lone pairs of O5 point away from O2, thus resulting in a better hydrogen bond in the cases where O2-H is oriented towards O1. Thus the destabilization due to the axial disposition of C2-OH is further modified by interactions of the hydrogen bond type. In the model 1,1,2-trihydroxyethane with C2-OH axial, the β - 4C_1 form is stabilized by two H-bond-like interactions as shown in figure 6. Since O5 has a CH₃ group in 1-methoxyethanediol, the O5-H...O2 interaction is absent resulting in the reduced stability of the β - 4C_1 form in this model compound. This is in agreement with the 4-31G estimated values for the Δ^2 effect (including H-bond type of interactions) in 1,1,2-trihydroxyethane (0.6 kcal mol⁻¹, table 4) and 1-methoxyethanediol (1.2 kcal mol⁻¹, Jeffrey and Yates 1981). The STO-3G evaluated Δ^2 effects are generally very low (table 4) probably because it underestimates the dipolar interactions.

Thus, the above detailed analysis confirms the qualitative description of the Δ^2 -effect given by Reeves (1950) which states that the destabilization of the β -form arises due to the unfavourable dipolar interaction when the C2-OH is axially oriented. The magnitude of this effect is however dependent to a considerable extent on other intra and intermolecular interactions.

5. Conclusions

When the anomeric effect is defined as the property directly associated with the -O5-C1-O1- fragment of carbohydrates, the study of a series of model compounds have led to the following conclusions:

- (1) In all the model compounds studied, the anomeric effect decreases when O1 has a -CH₃ substituent in place of hydrogen. Hence, the experimentally observed reverse trend must be due to interactions not directly connected with the O-C-O fragment.
- (2) The Δ^2 effect, as suggested by Reeves is due to dipolar interactions and it is different from the *gauche* effect. The actual magnitude of this effect depends on other types of interactions which occur in a given system.

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