Carbohydrate Research, 206 (1990) 21–39
Elsevier Science Publishers B.V., Amsterdam

Diagnostic structural criteria for the anomeric effect in carbohydrates and inferences of general significance on their scope and limitations*†

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(Received February 13th, 1989; accepted for publication, January 26th, 1990)

ABSTRACT

A systematic analysis of 529 carbohydrate structures that contain O–C–O units, retrieved from the Cambridge Structural Database, was performed with regard to the bond lengths (C–O) and bond (C–O–C and O–C–O) angles as they depend on the dihedral angles in the sequence C–O–C–O–C. This dependence was then interpreted in terms of the anomeric effect. Known and new concepts that concern the manifestations of the anomeric and *exo*-anomeric effects were thus reassessed. A set of structural criteria of diagnostic value was defined which, together with qualifying arguments, allow evaluation of the scope and limitations of these stereoelectronic effects in carbohydrate systems.

INTRODUCTION

The anomeric effect[2–6], first observed in carbohydrate derivatives[5,6] and named by Lemieux[6b], has been studied widely both experimentally and theoretically[7–11].

The original observations[5,6] dealt with the tendency of Y (= OR or Hal) in a pyranose system (Fig. 1A) to assume an axial conformation, contrary to what is expected from steric arguments in conformational analysis. However, it soon became clear that, in addition to this criterion, *i.e.*, relative stability or *energy*, the anomeric effect in a system is also manifest in its *structure*[4c,8c,d,15–19], *e.g.*, variable bond lengths and bond angles within the anomeric moiety, and *reactivity*[2c,3], *i.e.*, variation of rates of attack at or around the anomeric center. Also, it is clear that the anomeric effect operates in both of the heteroatom-containing parts of an anomeric moiety, as has been well exemplified for the pyranose system, in which the glycoside was said to exhibit an "*exo*-anomeric effect"[21] of enhanced magnitude (ref. 21a contains also a set of structural data in dealing with *a pair* of anomers).

Rationalization was first provided in terms of electrostatic interactions[5] (Fig. 1A), *i.e.*, destabilization of the equatorial form by repulsive, parallel dipoles, and, later, in

* Structure and Conformation of Heterocycles, Part 16. For Part 15, see ref. 1.
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** Part of the Raymond and Beverly Sackler Faculty of Exact Sciences.

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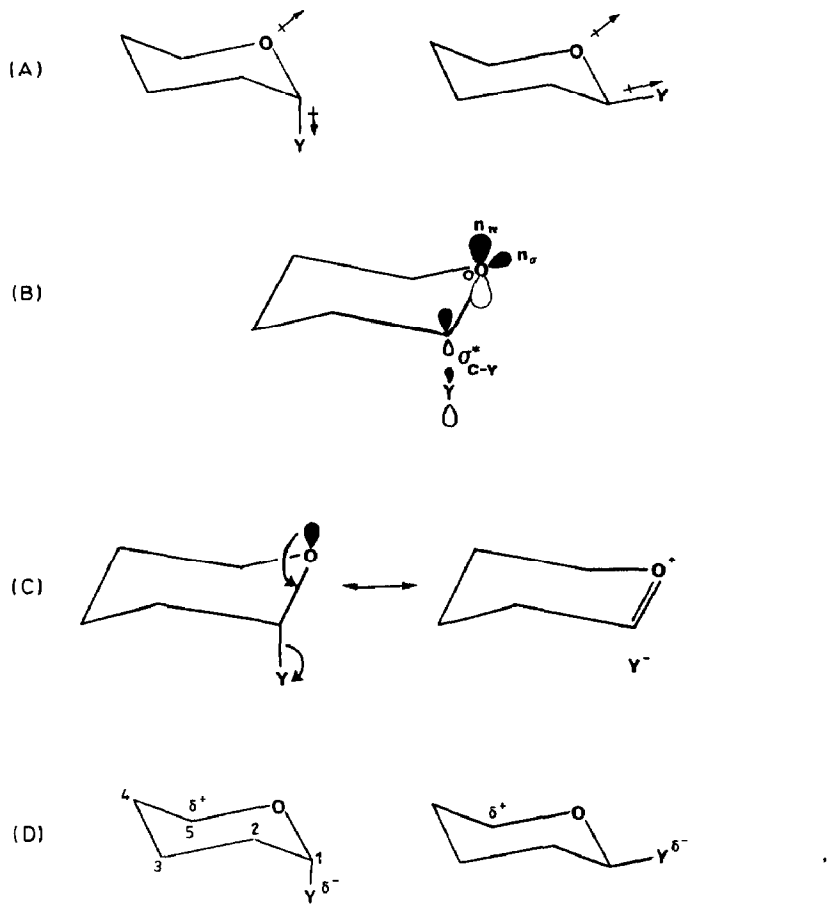


Fig. 1. Proposed models for the rationalization of the anomeric effect: (A) dipole–dipole interactions; (B) n_p-σ^* molecular orbital mixing; (C) double bond–no bond resonance (hyperconjugation); (D) polar bond–polar bond interaction.

molecular orbital terms by delocalisation of an n_p lone pair of electrons on O into the σ^* orbital of the adjacent C–Y bond (Fig. 1B) and hence its stabilization[4c,7]. The latter interpretation has gained ground recently[12] along with its (conceptually similar) valence-bond counterpart (Fig. 1C), *i.e.*, double bond–no bond resonance[4c,h,13] or hyperconjugation[8k,9]. Additional suggestions have also been made[4i,13] in terms of interactions of bonded electron pairs of the C–O and C–Y bonds (Fig. 1D).

It has recently become apparent that pitfalls may be encountered when using the criteria of relative stability or reactivity in interpretative theories without careful qualification (see below). However, structural parameters, if critically evaluated, appear to be more reliable probes for both understanding the anomeric effect and using it as a diagnostic tool.

To examine the structural criterion in carbohydrates[2,4a,b,f,h,j,6] and related compounds, we have retrieved 428 citations of carbohydrate structures from the Cambridge

Structural Database[24] (September 1987 version) and analysed the data according to established procedures[24–27] (*cf.* ref. 20 for an earlier, preliminary study of 111 entries in the CSD file, where less stringent qualifying arguments were applied and, hence, similar but not as convincing conclusions were arrived at). The bond lengths and bond angles within the anomeric moiety C–O–C–O–C were scrutinized. The variation of these parameters as a function of conformation had been discussed often in the context of the occurrence of the anomeric effect[4c,7a,8c,d,15–21,23]. The reassessment reported below was undertaken in order to prevent misuse or misunderstanding (as frequently encountered), by defining the scope and limitations of the correlation between structural paramaters and conformation and electronic *vs.* steric interactions[20]. This reassessment was carried out by statistical analysis of the large body of data retrieved[20,23,24]. The Cambridge Structural Database is now recognized to be an invaluable source of information for probing chemical properties[27] or inferring on reactivity[28].

Methodology. — In developing our approach, we sought to (*a*) extend and generalize the notion of an intimate relationship between the conformation of the anomeric moiety and its covalent parameters, (*b*) establish whether there is any statistically valid evidence for this correlation, and (*c*) use a large data set of crystal structures from various laboratories, thus allowing the assumption that errors due to variations in precision are not systematic and they, along with random interference of crystal forces with molecular parameters, may cancel out in the background noise. Consequently and importantly, no qualification should be necessary concerning the juxtaposition of crystallographic data to those in other phases. It is the *correlation* between conformation and geometrical parameters[28] that is of interest and not the conformations as such (*cf.* ref. 28, p. 154).

All structures containing a C–O–C–O–C fragment were retrieved using CONNECTIVITY criteria and the *CONNSER* program. The FAMILY was then defined using the *BIBSER* program and all carbohydrate structures were assembled. The bond parameters were secured using *RETRIEVE*, and the *GEOM* program enabled isolation and systematization of all the geometrical data in the anomeric moiety. Finally, *BIBSER* was used to retrieve the literature references.

In a series of small data-management programs, the above retrieved data were classified and purged. The entries were checked individually and recorded on specially designed cards (Fig. 2). Thus, a "crude" data set of 884 anomeric units was obtained. "Spurious" elements were then eliminated in order to maximize accuracy and consistency. This trimming process involved discarding structures having R factors of >0.1 or appreciable disorder within or near the anomeric moiety as well as eliminating "perturbed" structures (Fig. 2). The perturbations consisted of double bonds, triple bonds, or carbonyl groups attached to the C–O–C–O–C moiety and overlapping C–O–C–O–C groupings. This, qualifying procedure left 529 carbohydrate anomeric units for analysis, of which 191 units occurred in cyclodextrins (cyclomalto-oligosaccharides) which were treated separately for reasons elaborated below.

Statistical analysis was performed on this data set using the SPSS-X package[29] operated by a small house program, in order to calculate mean values and standard

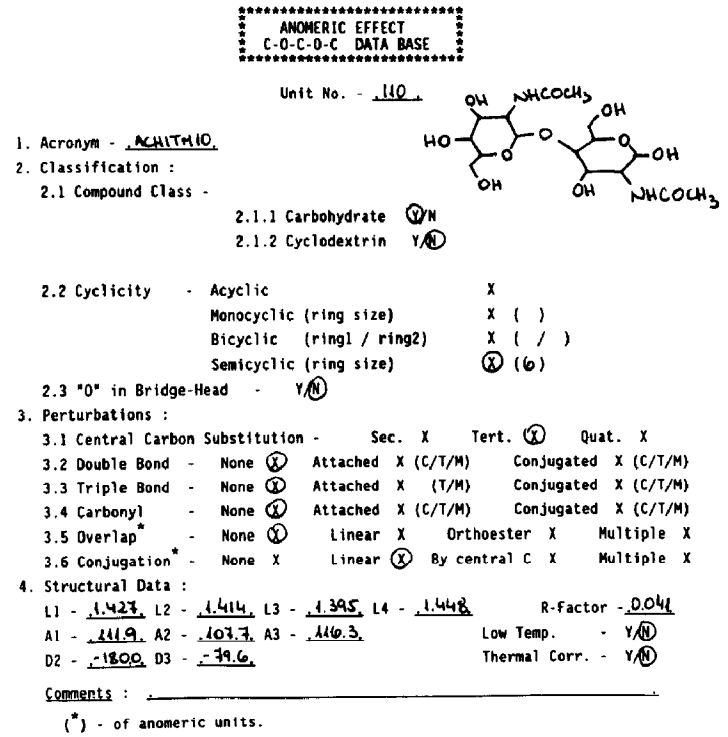


Fig. 2. Sample card for entries in the local C–O–C–O–C database after retrieval from the Cambridge Structural Database.

deviations, sign tests, and *t* distributions, and to draw X/Y graphs and histograms. Since there were many instances of confusion with regard to configuration and conformation, the definitions stated below and depicted in Figs. 3 and 4 were used: (*a*) The aa, $ag^{\pm}$, $g^{\pm}g^{\pm}$, and $g^{\pm}g^{\mp}$ conformations of the C–O–C–O–C moiety were considered, where a = anti (antiperiplanar) and g = gauche (synclinal); hence, ag and aa refer to equatorial glycosides and gg to axial glycosides (*cf.* Fig. 3); (*b*) a was defined as the range ± 160–$180°$ and g as the range ± 30–$90°$; (*c*) the bond lengths (L) and bond angles (A) in the anomeric pyranoses are defined as $C\text{-}5\overset{L1}{-}O\text{-}5\overset{L2}{-}C\text{-}1\overset{L3}{-}O\text{-}1\overset{L4}{-}R$, and the dihedral

A1 A2 A3

angles (D) correspondingly, *i.e.*, D2 = C-5O-5–C-1O-1 and D3 = O-5C-1–O-1R (*cf.* Fig. 3); (*d*) within these definitions, the pyranose glycosides were considered in two pairs (Fig. 4): axial α-D-$^4C_1$ (g^+g^+) and β-D-$^1C_4$ (g^-g^-); equatorial α-D-$^1C_4$ (ag^+) and β-D-$^4C_1$ (ag^-) as well as the corresponding α-L and β-L enantiomers.

The results are displayed in list and histogram form for maximum clarity.

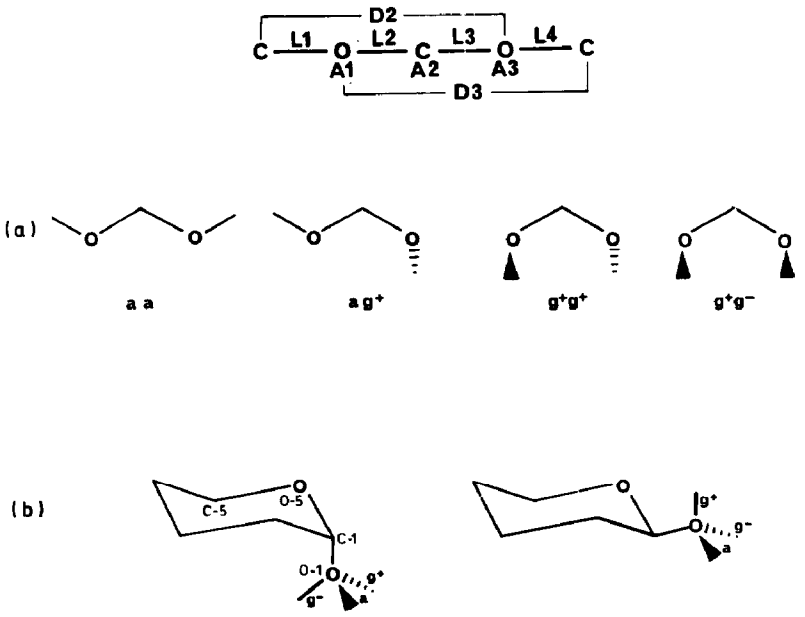


Fig. 3. Definitions and numbering of the C–O–C–O–C grouping in the basic molecule: (a) dimethoxymethane, (b) $^4C_1$ pyranose model; L, bond length; A, bond angle; D, dihedral angle.

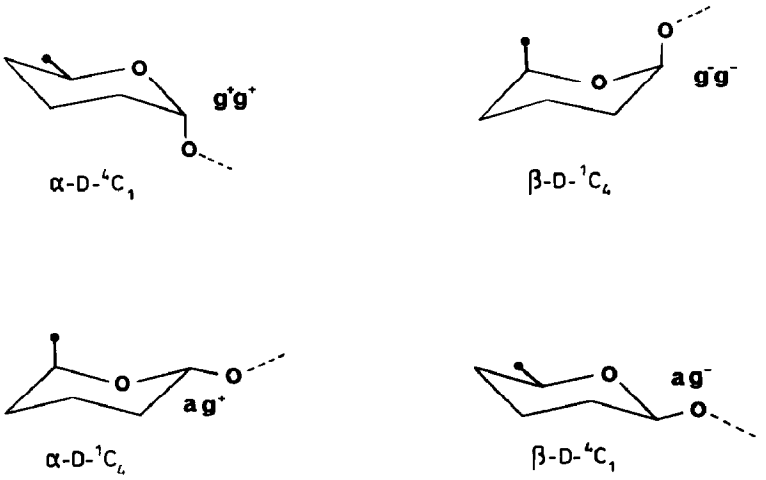


Fig. 4. α-D and β-D conformations: $^4C_1$ and $^1C_4$.

RESULTS AND DISCUSSION

The three-dimensional histogram in Fig. 5 depicts the initial "crude" data set of 884 units, and that in Fig. 6, which is accompanied by a list of data (Table I), provide an overall picture of the trimmed data set, amounting to 529 anomeric units.

The most striking feature is the relatively large ratio of $g^{\pm}g^{\pm}$ (*i.e.*, axial) (119) to ag (equatorial) (90) glycosidic units. By extending the structure-correlation method[28], namely that "a distribution of sample points corresponding to observed structures will tend to be concentrated in low-lying regions of the potential energy surface" (*cf.* ref. 28, p. 154), it may be assumed that the greater occurrence of the $g^{\pm}g^{\pm}$ glycosidic structures reflects their general higher stability than the ag isomers, both being favoured markedly over the aa forms. The virtual absence of aa and ga structures in the purged data base reflects the low relative stability of any form with D3 = a and is corroborated by theoretical probes (see below). However, this effect should not be attributed solely to the anomeric effect (*i.e.*, to the lack of antiperiplanar lone pairs), since steric effects work in the same direction[23].

The $g^{+}g^{-}$ units consist of the 1,3-dioxane or 1,3-dioxolane moieties and they were included in the histogram only since they occur in certain carbohydrate derivatives, but they are not involved in the structure-correlation rationale.

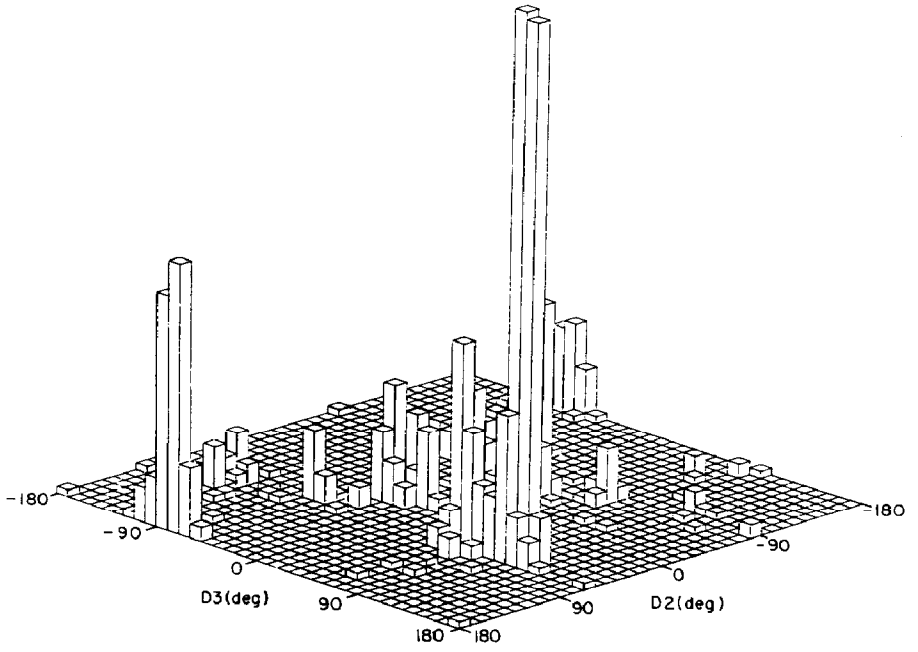


Fig. 5. 3D-Histogram of a "crude" data set of carbohydrate structures using C–O–C–O–C connectivity (see text and Fig. 3). Occurrence is shown as function of the two dihedral angles in the anomeric moiety, D2 (C-5O-5–C-1O-1) and D3 (O-5C-1–O-1C-7). For further details, see Fig. 6.

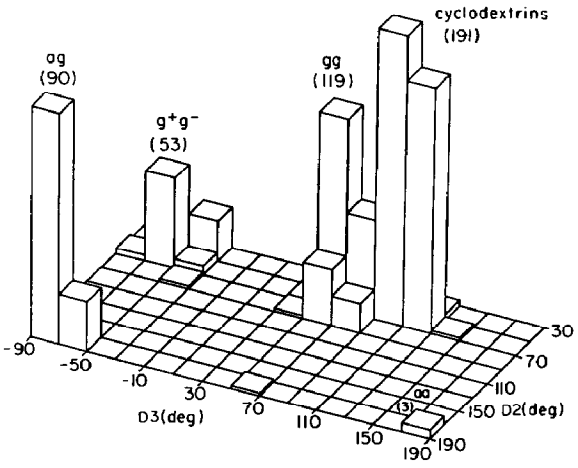


Fig. 6. 3D-Histogram of 529 carbohydrate structures using C–O–C–O–C connectivity and after suitable purging (see text and Fig. 2). Occurrence is shown as function of the two dihedral angles in the anomeric moiety, D2 (C-5O-5–C-1O-1) and D3 (O-5C-1–O-1C-7), within the generalized range shown on the axes (g^+g^- refers to 1,3-dioxanes and 1,3-dioxolanes which occur in some of the structures).

TABLE I

Mean bond lengths (L,Å), bond angles (A,°), and standard deviations (σ) for the C–O–C–O–C moiety ($3 \times \sigma$ deviating values were excluded from the data base)

Conformation	*Population*	*L1*	*L2*	*L3*	*L4*	*A1*	*A2*	*A3*
aa	(3)	1.438	1.404	1.409	1.440	111.1	105.2	109.5
σ		0.004	0.008	0.004	0.010	0.7	0.6	0.6
$3 \times \sigma$		0	0	0	0	0	0	0
ag^-	(90)	1.436	1.425	1.389	1.439	111.9	107.6	114.7
σ		0.010	0.013	0.013	0.014	1.3	0.8	1.5
$3 \times \sigma$		0	2	1	0	0	2	0
g^+g^+	(119)	1.437	1.416	1.405	1.430	113.5	112.0	113.8
σ		0.014	0.014	0.016	0.017	2.1	1.0	2.0
$3 \times \sigma$		2	2	1	1	1	1	3
g^+g^-	(53)	1.434	1.421	1.416	1.431	108.1	108.5	109.8
σ		0.017	0.015	0.012	0.013	5.0	3.4	3.2
$3 \times \sigma$		0	0	0	1	0	0	0

The subsequent 2D histograms have D3 as the abscissae, *i.e.*, the geometrical parameters of the anomeric moiety are analysed in each class as a function of the *exo* (O-5C1—O-5–R = D3) dihedral angle, whereas the *endo* dihedral angle C-5O-5–C-1O-1 = D2 is a or g by virtue of the initial choice of the six-membered ring. The histograms in Figs. 7 and 8 depict the dependence of the O–C-1–O bond lengths and C–O–C bond angles in the equatorial and axial pyranosides, respectively, and are

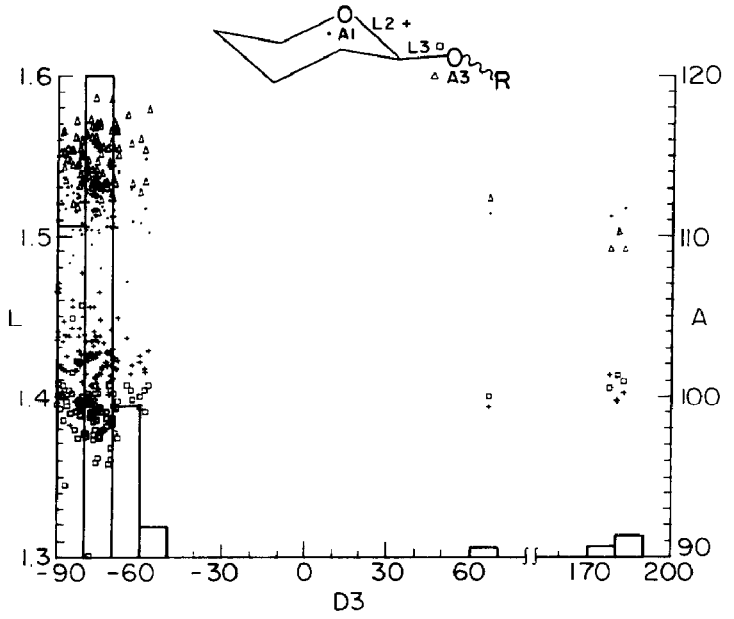


Fig. 7. Histogram of equatorial glycosides, showing the dependence of the O-5–C-1–O-1 bond lengths (L2+, L3□) and of C–O–C bond angles (A1●, A3△) in the C-5–O-5–C-1–O-1–C-7 anomeric moiety on the O-5C-1–O-1C-7 (*exo*)-dihedral angle, D3. The entire class includes $^1C_4$-ag$^+$ (mainly α-D) and $^4C_1$-ag$^-$ (mainly β-D) forms ("normalised" to appear under ag$^-$), only one example of $^4C_1$-ag$^-$, and three aa forms.

supplemented by the data in Table II. In order to perceive better the real interrelation of structural parameters in these systems, the data set was purged of another constraining factor of steric nature, namely, polycyclicity. This was done by considering only "semi-cyclic" (Figs. 3 and 4) pyranosides.

In order to carry out a detailed and reliable analysis, these data were resolved first into the pyranosidic subclasses (Fig. 4), then into methyl and R glycosides. This approach had been used by Tvaroska and Kozar[19] but only on a hand-picked data set. The histograms are recorded in Figs. 9–12 and the statistical details in Tables III and IV.

The data in Tables I and II and the histogram in Fig. 7 indicate several basic features for *equatorial* glycosides.

(*a*) Practically all of the ag species are concentrated in the D3 range of ±50–90° and mainly in the ±70–90° region. Contrary to a previous hypothesis[20], no correlation was found between bond lengths and bond angles with the magnitude of the D3 dihedral angles. Hence, dependence of the strength of the *exo*-anomeric effect on the orientation of the n_p lone pair cannot be inferred.

(*b*) The equatorial species consist of $^4C_1$ ag$^-$ and, after the careful trimming process, there were only few $^1C_4$ ag$^+$ and no $^4C_1$ ag$^+$ forms left (the only example of $^4C_1$ ag$^+$ which is imposed by steric constraints was eliminated in the last purge). The prevalence of ag$^-$ forms had been noted[21a] and has been invoked by Booth *et al.*[30]. Our assertion[20] that this is not so was erroneous, due to the fact that we analysed a smaller

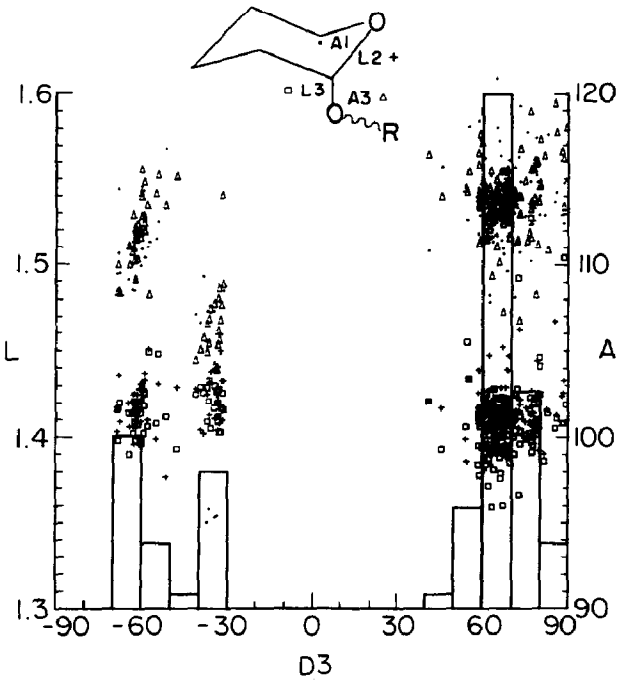


Fig. 8. Histogram of axial glycosides (on the right), showing the dependence of the O-5–C-1–O-1 bond lengths (L2+, L3 □) and of C–O–C bond angles (A1 •, A3 △) in the C-5–O-5–C-1–O-1–C-7 anomeric moiety on the O-5C-1–O-1C-7 (*exo*)-dihedral angle, D3. This class includes both *α*-D-$^4C_1$ (g^+g^+) and *β*-D-$^1C_4$ (g^-g^-) forms, "normalised" to appear under g^+g^+. For the sake of comparison, the g^+g^- species (*i.e.*, 1,3-dioxanes and 1,3-dioxolanes) have been included in this framework (on the left).

database with insufficient discrimination and without applying the $^1C_4/^4C_1$ differentiation (this point is discussed below).

(*c*) As expected[4c,7a,8c,d,15–21,23], the C-1–O-1 bonds (L3, 1.389 Å) are considerably shorter than their O-5–C-1 counterparts (L2, 1.425 Å). Similarly, the C-1–O-1–R bond angles (A3, 114.7°) are larger than the C-5–O-5–C-1 angles (A1, 111.9°). This difference is probably the most significant feature of the equatorial glycosides and is a clear manifestation of the *exo*-anomeric effect in terms of n-σ^* mixing or hyperconjugation (*cf.* Fig. 1B and 1C, respectively).

These observations are strengthened and qantified in the more detailed analysis of the data in Table III, and depicted in Fig. 9 (for bulky R glycosides) and in Fig. 10 (for methyl glycosides), and allow the following additional observations.

(*d*) Whereas the geometrical parameters (L2 and A1) in the "endo" part of the anomeric moiety are practically the same in equatorial R glycosides and methyl glycosides, they differ appreciably for the "exo" part: both L3 and A3 (especially the former) are notably larger in the R glycosides than in the methyl derivatives. We feel compelled to attribute this to a steric effect, brought about by the more bulky R groups.

(*e*) No difference could be discerned between the $^1C_4$ and $^4C_1$ conformations and,

TABLE II

Dihedral angle dependence of structural parameters (with their s.d.'s) of the C–O–C–O–C groupings in axial and equatorial glycosides

		L				*A*		
		ring		*exo*		*ring*		*exo*
D3	*Frequency*	*L1*	*L2*	*L3*	*L4*	*A1*	*A2*	*A3*
Equatorial glycosides (D2 = anti)								
−50 to −60	3	1.439 (0.016)	1.420 (0.007)	1.400 (0.009)	1.422 (0.009)	112.2 (2.3)	107.8 (1.0)	115.5 (2.3)
−60 to −70	14	1.434 (0.009)	1.422 (0.009)	1.391 (0.009)	1.437 (0.011)	111.9 (1.3)	107.6 (0.6)	114.8 (1.6)
−70 to −80	44	1.435 (0.011)	1.426 (0.013)	1.385 (0.012)	1.439 (0.015)	111.8 (1.2)	107.7 (0.9)	114.5 (1.6)
−80 to −90	27	1.438 (0.010)	1.424 (0.016)	1.392 (0.014)	1.443 (0.013)	111.9 (1.5)	107.5 (0.9)	114.8 (1.2)
Axial glycosides (D2 = gauche)								
50–60	5	1.434 (0.017)	1.411 (0.004)	1.409 (0.009)	1.425 (0.007)	114.1 (2.1)	111.5 (0.3)	112.8 (1.4)
60–70	51	1.435 (0.014)	1.416 (0.014)	1.401 (0.016)	1.430 (0.017)	113.2 (1.3)	112.4 (1.1)	113.4 (1.4)
70–80	19	1.436 (0.013)	1.416 (0.011)	1.412 (0.015)	1.433 (0.015)	113.7 (1.0)	111.9 (0.9)	114.3 (1.8)
80–90	5	1.440 (0.011)	1.408 (0.017)	1.409 (0.015)	1.434 (0.009)	113.6 (1.2)	111.9 (0.5)	116.3 (1.2)

in fact, the former is so sparsely populated in the equatorial data set (1 and 3 in the R and methyl glycoside groups, respectively) that statistical analysis is not meaningful and, hence, unwarranted.

The *axial* glycosides are the main feature of the general histogram in Fig. 8 and the data in Table II.

(*a*) The conformations are normalised to g^+g^+ although they consist of the two possible $^4C_1$ g^+g^+ and $^1C_4$ g^-g^- forms.

(*b*) The bulk of the population is concentrated in the range 60°–80° and there is no correlation of the bond lengths and bond angles with the magnitude of the *exo* dihedral angle (D3).

(*c*) The O-5–C-1–O-1 bonds do not differ much in magnitude, with the C-1–O-1 (L3) bond being usually somewhat shorter than the O-5–C-1 bond (L2). The same is true

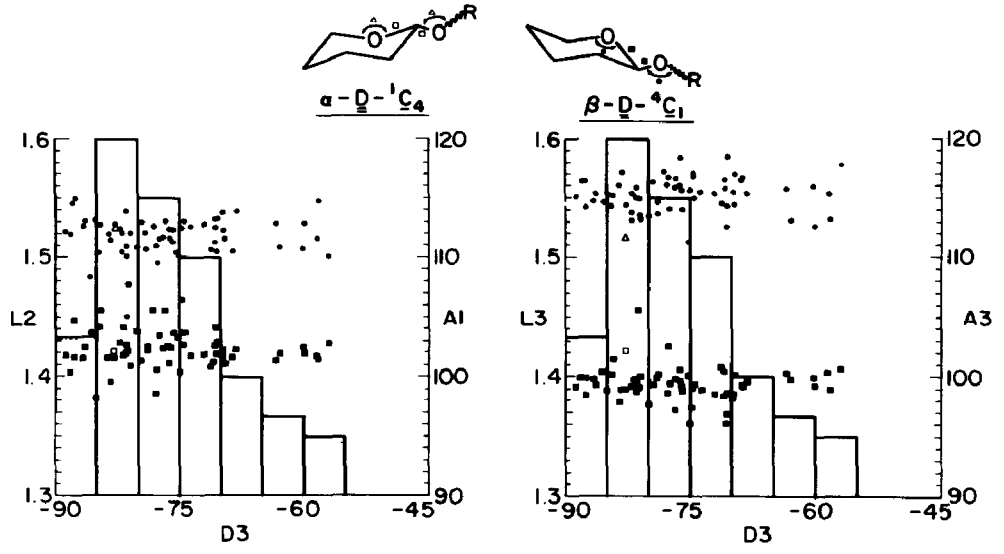


Fig. 9. Histograms of equatorial R glycosides (R ≠ Me), that detail the dependence of the O-5–C-1 bond lengths (L2 □) and C-5–O-5–C-1 bond angles (A1 △) in α-D-$^1C_4$ and β-D-$^4C_1$ forms (L2 ■ and A1 ●) and of the C-1–O-1 bond lengths (L3 □) and C-1–O-1–C-7 bond angles (A3 △) in α-D-$^1C_4$ and β-D-$^4C_1$ forms (L3 ■ and A3 ●), on the O-5C-1–O-1C-7 (*exo*)-dihedral angle, D3.

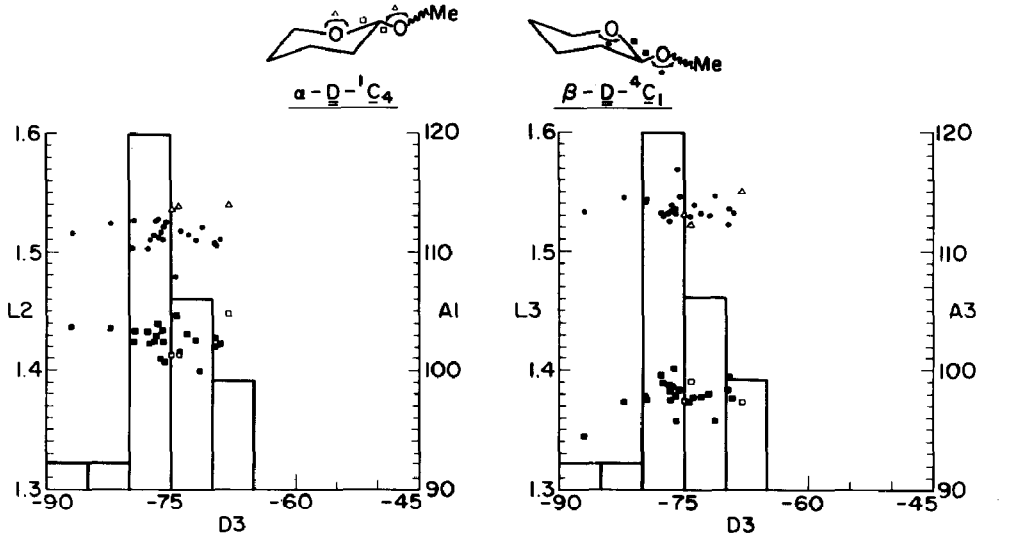


Fig. 10. Histograms of equatorial methyl glycosides, that detail the dependence of the O-5–C-1 bond lengths (L2 □) and C-5–O-5–C-1 bond angles (A1 △) in the α-D-$^1C_4$ and β-D-$^4C_1$ forms (L2 ■ and A1 ●) and the C-1–O-1 bond lengths (L3 □) and C-1–O-1–C-7 bond angles (A3 △) in the α-D-$^1C_4$ and β-D-$^4C_1$ forms (L3 ■ and A3 ●) on the O-5C-1–O-1C-7 (*exo*)-dihedral angle (D3).

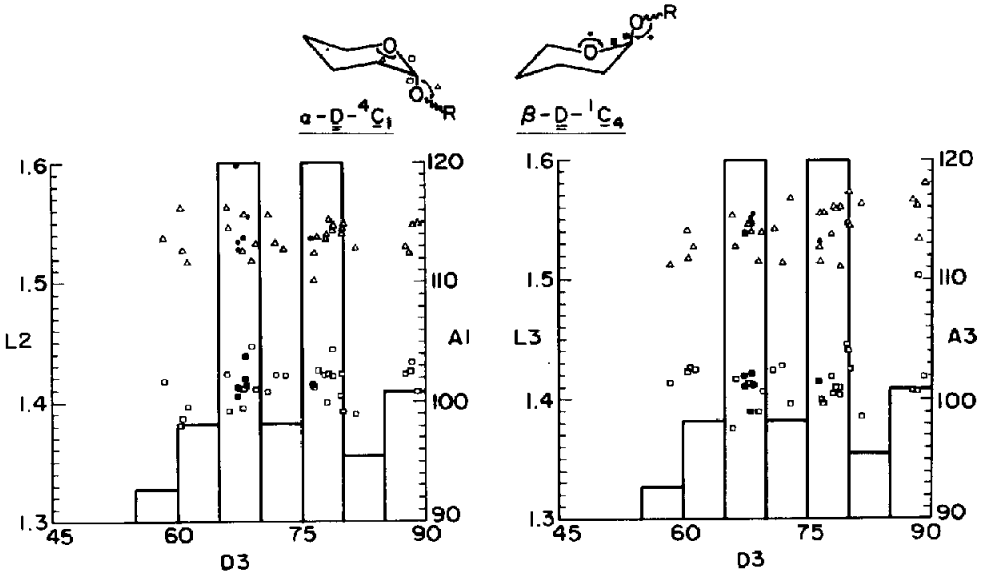


Fig. 11. Histograms of axial R glycosides (R ≠ Me) that detail the dependence of the O-5–C-1 bond lengths (L2 □) and C-5–O-5–C-1 bond angles (A1 △) in α-D-$^1C_4$ and β-D-$^4C_1$ forms (L2 ■ and A1 ●) and the C-1–O-1 bond lengths (L3 □) and C-1–O-1–C-7 bond angles (A3 △) in α-D-$^1C_4$ and β-D-$^4C_1$ forms (L3 ■ and A3 ●) on the O-5C-1–O-1C-7 (*exo*)-dihedral angle (D3).

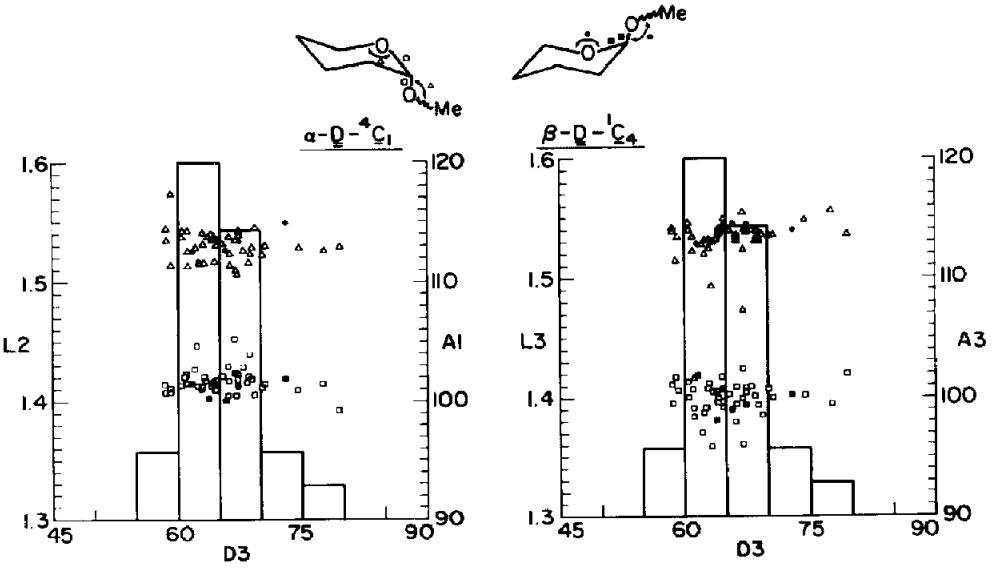


Fig. 12. Histograms of axial methyl glycosides that detail the dependence of the O-5–C-1 bond lengths (L2 □) and C-5–O-5–C-1 bond angles (A1 △) in the α-D-$^1C_4$ and β-D-$^4C_1$ forms (L2 ■ and A1 ●) and of the C-1–O-1 bond lengths (L3 □) and C-1–O-1–C-7 bond angles (A3 △) in the α-D-$^1C_4$ and β-D-$^4C_1$ forms (L3 ■ and A3 ●) on the O-5C-1–O-1C-7 (*exo*)-dihedral angle (D3).

TABLE III

Mean bond lengths (L,Å), bond angles (A,°), dihedral angles (D,°), and standard deviations (σ) in axial and equatorial pyranosides (*cf.* Fig. 4)

Equatorial R glycosides ($ag^{\pm}$)

	α-D-$^1C_4$ (ag^+)				β-D-$^4C_1$ (ag^-)			
	R = Me		*R ≠ Me*		*R = Me*		*R ≠ Me*	
	Frequency							
	3		*1*		*22*		*62*	
L1	1.438	(0.012)			1.434	(0.009)	1.436	(0.010)
L2	1.426	(0.020)			1.428	(0.011)	1.424	(0.014)
L3	1.380	(0.010)			1.379	(0.013)	1.392	(0.010)
L4	1.443	(0.009)			1.431	(0.011)	1.442	(0.014)
A1	113.8	(0.2)			111.5	(1.1)	111.9	(1.3)
A2	107.2	(0.6)			107.6	(0.7)	107.6	(0.9)
A3	113.4	(1.4)			113.7	(1.0)	115.1	(1.4)
D2	183.3	(9.5)			177.0	(3.1)	177.1	(3.3)
D3	72.4	(3.8)			−75.8	(4.2)	−76.0	(8.1)

Axial R glycosides ($g^{\pm}g^{\pm}$)

	α-D-$^4C_1$ (g^+g^+)				β-D-$^1C_4$ (g^-g^-)			
	R = Me		*R ≠ Me*		*R = Me*		*R ≠ Me*	
	Frequency							
	41		*27*		*6*		*6*	
L1	1.433	(0.013)	1.440	(0.012)	1.435	(0.009)	1.434	(0.023)
L2	1.417	(0.011)	1.413	(0.017)	1.412	(0.008)	1.417	(0.012)
L3	1.399	(0.014)	1.412	(0.016)	1.399	(0.013)	1.412	(0.011)
L4	1.429	(0.016)	1.435	(0.015)	1.421	(0.016)	1.428	(0.017)
A1	112.9	(1.3)	113.9	(1.3)	113.4	(0.8)	114.2	(1.1)
A2	112.2	(1.1)	112.0	(0.9)	112.9	(1.1)	111.6	(0.6)
A3	113.3	(1.4)	114.4	(2.0)	113.9	(0.6)	114.1	(0.9)
D2	62.3	(4.6)	62.9	(7.5)	−63.0	(2.8)	−69.4	(6.7)
D3	65.5	(4.7)	74.9	(8.6)	−66.0	(3.9)	−69.3	(3.5)

for the C–O–C bond-angles, the *exo* C-1–O-1–R (A3) angle being slightly larger than C-5–O-5–C-1 angle (A1). This similarity was attributed[20] to partial cancellation of the *endo* and *exo* effects in the anomeric moiety, *i.e.*, a cross-hyperconjugation (*cf.* Fig. 1-iii) and discussed in similar terms independently by Praly and Lemieux[21c].

These observations are also supported by the analysis of the resolved set of axial structures listed in Table III and depicted in Fig. 11 (R glycosides) and Fig. 12 (methyl glycosides). Thus, comparing the *axial* methyl and R glycosides, it can be seen that, due to steric effects, the latter have larger *exo*-anomeric parameters (in particular dihedral angles, D3). However, for the methyl glycosides, the C-1–O-1 bonds are *appreciably* shorter than the O-5–C-1 bonds. This behaviour has been attributed by Kirby and co-workers[2c,19] to a higher electronegativity of the ring oxygen (O-5) of glycopyrano-

TABLE IV

Mean bond lengths (L,Å), bond angles (A,°), dihedral angles (D,°), and standard deviations (σ) in geometrically biased g^+g^+ systems: cyclodextrins (6-membered axial anomers) and furanosides (5-membered quasi-axial anomers) as well as g^+g^- *endocyclic* systems: 1,3-dioxanes and 1,3-dioxolanes

	Cyclodextrins (*181*)[a]	*Furanosides* (*15*)[b]	*1,3-Dioxanes* (*31*)[b]	*1,3-Dioxolanes* (*13*)[b,c]
L1	1.447(0.017)	1.439(0.015)	1.434(0.017)	1.427(0.015)
L2	1.416(0.019)	1.423(0.014)	1.418(0.015)	1.431(0.016)
L3	1.416(0.018)	1.405(0.014)	1.414(0.013)	1.420(0.010)
L4	1.435(0.015)	1.431(0.009)	1.429(0.014)	1.430(0.007)
A1	114.0(1.2)	110.0(2.2)	111.3(2.0)	106.2(3.6)
A2	110.7(1.2)	111.5(1.0)	111.0(1.1)	103.9(0.4)
A3	118.4(1.3)	113.8(2.7)	111.6(2.0)	106.8(1.4)
D2	56.5(2.6)	88.9(12.9)	61.8(3.2)	36.3(5.7)
D3	108.4(6.8)	73.4(13.3)	−61.4(3.9)	−36.0(3.0)

[a] After purging the 191 strong data base for deviations larger than 3σ. [b] After purging data base for attached double bonds, triple bonds, or carbonyl groups, or of those with overlapping anomeric groupings. [c] After excluding also bicyclic derivatives having an O atom in the bridge.

sides, as compared to simple alkoxy or acetal oxygens, due to inductive electron withdrawal by the oxy substituents on the ring.

All of the modifications of bond length in the O–C–O grouping discussed above, due to the anomeric effect, are superimposed on a basic bond-shortening of C–X in any CX_n, where X is any electronegative heteroatom. This type of bond shortening[31] has been taken into account[20] and discussed within the context of molecular mechanics[32].

A hitherto neglected set of parameters involves the unusually long C-5–O-5 (L1) and O-1–R (L4) bonds (Tables III and IV). The enhanced bond-lengths L1 and L4 are not correlated with L2 and L3, respectively. Hence, they seem not to be due to a hybridization effect related to the anomeric effect, but are probably related to the basic shortening of the O–C–O bonds as discussed above.

An important facet of carbohydrate crystal structure concerns hydrogen bonds to the anomeric oxygens and, in particular, their dependence on the positions of the oxygens and the surrounding conformation. The data base (Table II) contains 42 hydrogen bonds with 25 in the equatorial (ag^-) group and 17 in the axial (g^+g^+) group. In the former group, 21 occur on O-5 and 4 on O-1. These numbers indicate a higher electron density on O-5 in the equatorial glycosides due to hyperconjugation (*exo*-anomeric effect) *vs.* cross-hyperconjugation, respectively. The scatter of the data (bond lengths and bond angles) is not affected by the hydrogen bonds and there is no clear evidence for a preferred orientation around the oxygens that would indicate lone-pair directionality[38].

Certain C–O–C–O–C systems with biased structures due to geometrical constraints were excluded from the statistics by the purging procedure. They exist in unusual conformations and their geometrical parameters (all or some) are not characteristic of the anomeric effect (*cf.* Table IV).

The cyclodextrins (cyclomalto-oligosaccharides) are basically g^+g^+ structures but with much larger *exo*-dihedral angles (D3 = 108°) and relatively longer C-1–O-1 bonds, as imposed by the macrocyclic structure. The O–C–O bond lengths are similar and close to those observed in the g^+g^+ class. Of the bond angles, only A3 is abnormally large.

Furanosides are also g^+g^+ structures, but D2 is distorted (90°) and the glycosidic moiety is in a quasi-axial position on the five-membered ring. The smaller A1 bond angle and the longer L2 bond reflect the constraints imposed by the five-membered ring[34]. Thus, the anomeric effect is perturbed but the *exo*-anomeric effect is normal.

The g^+g^- structures occur mostly as cyclic acetals. Only monocyclic structures were considered, among which the 1,3-dioxanes exhibit almost normal anomeric behavior. The 1,3-dioxolanes, however, are in between *envelope* and *half-chair* forms[34a] with intermediate D2 and D3 dihedral angles of similar magnitude, necessarily long O–C–O bonds[34b] and small bond angles, and practically no anomeric effect. Thus, the geometrically constrained five-membered ring is over-ruling the relatively small stereoelectronic effects. It may be unsafe to take relative stabilities alone, in terms of D2 and D3 as generally valid criteria for the anomeric effect, and confirmation is required by structural parameters.

In terms of reactivity, Perrin *et al.*[35] have presented results which question the demand for antiperiplanar lone pairs in the postulated[3] stereoelectronic control of amidine hydrolysis. This issue is now under debate.

We have reported results[12] which substantiate the contention that the anomeric effect is not due to dipole–dipole interaction but to n_p-σ^* mixing or hyperconjugation (see above). The evidence now presented provides additional support, at least for the latter theory.

Finally, the seemingly straightforward diagnostic parameter, namely, the central bond angle O-5–C-1–O-1 (A2) was not included in our preliminary report[20] because of its sensitivity to *non-anomeric*, largely steric factors, such as a quaternary C-1 and the fact that the initial, small data set[20] was not purged thoroughly. It is now included and the result (Tables III and IV) is a clear dependence of A2 on the conformation of the C–O–C–O–C moiety: 105° in aa, 108° in ag, and 112° in g^+g^+. Strangely, A2 is slightly larger (112.5°) in axial methyl glycosides as compared to bulkier R groups, contrary to expectations on steric grounds. Again, no correlation was found between A2 and the magnitude of D3 in each set. This dependence of A2 on conformation of the anomeric moiety had been pointed out[11,16–19,21] as behaviour related to the anomeric effect, and has been discussed[33] and rationalized in PMO terms. However, some doubts were expressed[23] and Allinger, in his parameterization of MM2 for the anomeric effect[36], attributed this dependence of A2 largely to VdW repulsions.

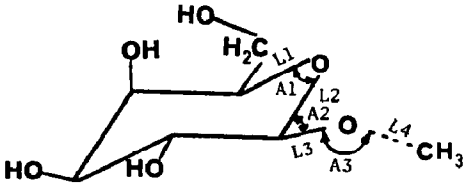
The values of A2 calculated for a variety of basic systems in a related study[22d], where a similar, albeit weaker trend was seen in C–O–C–C–C moieties, are presented in Tabel V. The anomeric effect appears to be at most a minor cause in this strong conformational dependence of A2. Supporting evidence has been provided by Jaroszewski *et al.*[37], who showed that any C–O bond exhibits a bond bending (or tilting)

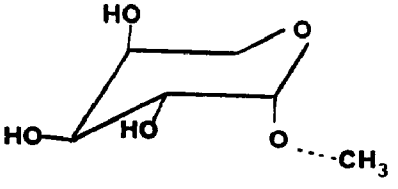
TABLE V

Calculated values of the central X–C–Y angle (A2, °) of the anomeric moiety (C–X–C–Y–C) in: aa, ag^+, and g^+g^+ conformations (*cf.* Fig. 3) for dimethoxymethane (DMM), 2-methoxytetrahydropyran (MOTHP), 2-ethyltetrahydropyran (ETHP), methyl propyl ether (MPE), pentane (PENT), and ethylcyclohexane (ECH) *vs.* the statistical (STAT) carbohydrate (CARB) values (cf. Table I)

		Conformation		
System	*Method*	g^+g^+	ag^-	*aa*
CARB	STAT	112.0	107.6	105.2
DMM	*ab initio*[a]	112.8	109.6	106.4
	MM2-AE	111.3	109.0	106.3
MOTHP	MM2-AE	108.7	105.5	[c]
ETHP	MM2-AE	112.7	108.8;111.5[b]	107.6
MPE	MM2-AE	113.2	109.4;112.5[b]	108.8
PENT	MM2-AE	115.5	113.6	112.0
ECH	MM2-AE	115.1	112.5	110.1

[a] Calculated using GAUSSIAN 80 at the 4-31G//4-31G level. [b] Two values, for ag^- and g^-a, respectively. [c] The aa form of 2-methoxytetrahydropyran did not converge to a minimum but "slipped" over to the ag^- form[22d]





	MBDGAL 01	MBLARA 10
L1	1.437 (1.439)	1.440 (1.434)
L2	1.429 (1.424)	1.419 (1.418)
L3	1.402 (1.390)	1.414 (1.393)
L4	1.443 (1.423)	1.438 (1.423)
A1	112.3 (111.1)	114.1 (112.8)
A2	105.3 (107.4)	108.5 (112.9)
A3	113.1 (113.0)	113.2 (113.1)
D2	-179.3 (176.9)	64.1 (62.1)
D3	-77.2 (-77.6)	73.5 (68.9)

Fig. 13. The $^4C_1$ carbohydrates: methyl β-D-galactopyranoside (MBDGAL 01), methyl β-L-arabinopyranoside (MBLARA 10), and the list of their geometrical parameters in the C–O–C–O–C fragment, as calculated by MM2-AE and observed[39,40] (X-ray crystallography, in parenthesis).

TABLE VI

Diagnostics for the anomeric effect (AE) in carbohydrate systems[a]

Systems and population analysis	*Examples*
Pyranosides: axial glycosides (g^+g^+)	119
equatorial glycosides (ag^- and aa)	93
Biased systems: cyclodextrins (g^+ 108)	181
furanosides (89 g^+)	15
1,3-dioxanes (g^+g^-)	31
1,3-dioxolanes (g^+g^- and ss)	13

Structural criteria
Conformational dependence of bond lengths and bond angles:

	C-5		O-5		C-1		O-1		C-7
	D2	*D3*	*L1*	*A1*	*L2*	*A2*	*L3*	*A3*	*L4*
Equatorial glycosides[b]	177	−76	1.436	111.9	1.425	107.6	1.389	114.7	1.439
Equatorial glycosides (aa)[c]	180	180	1.438	111.1	1.404	105.2	1.409	109.5	1.440
Axial glycosides[d]	63	66	1.437	113.5	1.416	112.0	1.405	113.8	1.430
Cyclodextrins[e]	57	108	1.447	114.0	1.416	110.7	1.416	118.4	1.435
Furanosides[f]	89	73	1.439	110.0	1.423	111.5	1.405	113.8	1.431
1,3-Dioxanes[g]	62	−61	1.434	111.3	1.418	111.0	1.414	111.6	1.429
1,3-Dioxolanes[h]	36	−36	1.427	106.2	1.431	103.9	1.420	106.8	1.430

[a] Anomeric amoiety C-5–O-5–C-1–O-1–C-7; L, bond length; A, bond angle; D, dihedral angles: D2 C-5O-5–C-1O-1 and D3 O-5C-1–O-1C-7; a = antiperiplanar, g = gauche (synclinal), s = synperiplanar. [b] *exo*-Anomeric effect only, hence: L2 > L3, A1 < A3, small A2[j]. [c] 3 Examples; only steric effects and basic O–C–O bond shortening observed. [d] Anomeric effect + *exo*-anomeric effect, hence: L2 ≥ L3, A1 ~ A3, large A2[j]. [e] Anomeric effect + *exo*-anomeric effect, as in (*d*) with special constraints. [f] Anomeric effect with special constraints + *exo*-anomeric effect. [g] Anomeric effect + anomeric effect but strict ring constraints prevail. [h] Severe ring constraints determine structural parameters of anomeric moiety. [j] Characteristic behavior of A2, may not be due to the anomeric effect.

phenomenon. In a O–CH_2–O fragment, this phenomenon becomes more acute, the O–C–O and H–C–H planes are then not orthogonal, and the dihedral angle (and with it the O–C–O bond angle, A2) is dependent on the conformation. The MM2-AE results (Table V) were obtained without any special parameterization for C–O tilting and account, therefore, only for VdW repulsion, which strengthens our argument.

Fig. 13 contains a basic set for the $^4C_1$ structures, methyl β-D-galactopyranoside[39] and methyl β-L-arabinopyranoside[40], together with the calculated (MM2-AE) *vs.* observed geometrical parameters of the C–O–C–O–C moiety. The calculation was performed using a recent modification[1] of the parameterization[36] of MM2(82) for the anomeric effect. The agreement with the statistical values is satisfactory (*cf.* Table VI), bearing in mind that the variation in substitution is bound to influence the anomeric parameters to some extent.

We sought to clarify how and to what extent the anomeric effect affects the structural parameters in C–O–C–O–R moieties in carbohydrates. The diagnostic scheme in Tabel VI aims to delineate the scope and limitations of the existing criteria. It is concluded that the structural parameters are the most characteristic manifestation of

the anomeric effect rather than the energy (relative stability) factors. The small magnitude[3,4] of the latter and the sensitivity to other (*e.g.*, steric) effects make it vulnerable to misinterpretation[22,23].

ACKNOWLEDGMENTS

The calculations were performed on a CYBER 170/990 computer at the Computational Center of Tel-Aviv University. We thank Professor Zipora Shakked for help in the early stages of data retrieval, Mrs. Sarah Weinman and Mrs Michaela Vardi for technical assistance, Professors Uri Shmueli and Israel Goldberg for advice, and Professor J. D. Dunitz for comments on the manuscript.

REFERENCES

1 P. Aped, Y. Apeloig, A. Ellencweig, B. Fuchs, I. Goldberg, M. Karni, and E. Tartakovsky *J. Am. Chem. Soc.*, 109 (1987) 1486–1495.
2 (*a*) W. A. Szarek and D. Horton, (Eds.), *Anomeric Effect. Origins and Consequences*, ACS Monograph, Vol. 87, Washington, D.C., 1979; (*b*) A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, Berlin, 1983; (*c*) *idem. ibid.*, pp. 57–61 and 78–135.
3 P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Wiley, New York, 1983.
4 (*a*) R. U. Lemieux, in P. de Mayo (Ed.), *Molecular Rearrangements*, Vol. III, pp. 709–769, Interscience, New York, 1964; (*b*) S. J. Angyal, *Angew. Chem. Int. Ed. Engl.*, 8 (1969) 157–166; (*c*) C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.*, 4 (1969) 39–97; (*d*) E. L. Eliel, *Acc. Chem. Res.*, 3 (1970) 1–8; *Angew. Chem. Int. Ed. Engl.* 11 (1972) 739–750; *Kem. Tidskr.*, 81 (1969) 22–27; (*e*) J. C. Martin, *Ann. Chim. Res.*, 6 (1971) 205–218; (*f*) R. U. Lemieux, *Pure Appl. Chem.*, 25 (1971) 527–548; (*g*) N. S. Zefirov and N. M. Schechtman, *Usp. Khim.*, 40 (1971) 593–624; (*h*) J. F. Stoddart, *Stereochemistry of Carbohydrates*, Wiley, New York, 1971; (*i*) S. Wolfe, *Acc. Chem. Res.*, 5 (1972) 102–111, and references therein; (*j*) H. Paulsen, *Staerke*, 27 (1975) 397–405; (*k*) I. Tvaroska and T. Bleha, *Chem. Pap.*, 39 (1985) 805–847.
5 J. T. Edward, *Chem. Ind. (London)*, (1955) 1102–1104.
6 (*a*) R. U. Lemieux and N. J. Chu, *Abstr. Pap. Am. Chem. Soc. Meeting*, 133 (1958) 31N; (*b*) R. U. Lemieux, *ibid.*, 135 (1959) 5E.
7 (*a*) C. Altona, Ph.D. Thesis, University of Leiden, 1964; (*b*) E. A. C. Lucken, *J. Chem. Soc.*, (1959) 2954–2960.
8 (*a*) S. David, O. Eisenstein, W. J. Hehre, L. Salem, and R. Hoffmann, *J. Am. Chem. Soc.*, 95 (1973) 3806–3807; (*b*) O. Eisenstein, Nguyen T. Anh, Y. Jean, A. Devaquet, J. Catacuzene, and L. Salem, *Tetrahedron*, 30 (1974) 1717–1723; (*c*) G. A. Jeffrey, J. A. Pople, and L. Radom, *Carbohydr. Res.*, 38 (1974) 81–95; (*d*) G. A. Jeffrey, J. A. Pople, S. Binkley, and S. Vishveshwara, *J. Am. Chem. Soc.*, 100 (1978) 373–379; (*e*) D. G. Gorenstein, J. B. Findlay, B. A. Luxon, and D. Kar, *J. Am. Chem. Soc.*, 99 (1977) 3473–3479; D. G. Gorenstein and D. Kar, *ibid.*, 99 (1977) 672–677. (*f*) S. Wolfe, M. -H. Whangbo, and D. J. Mitchell, *Carbohydr. Res.*, 69 (1979) 1–26; (*g*) A. Pross, L. Radom, and N. V. Riggs, *J. Am. Chem. Soc.*, 102 (1980) 2253–2259; (*h*) C. Van Alsenoy, L. Schafer, J. N. Scarsdale, J. O. Williams, and H. J. Geise, *J. Mol. Struct. (Theochem)*, 86 (1981) 111–117; (*i*) L. Schafer, C. Van Alsenoy, J. O. Williams, J. N. Scarsdale, and H. J. Geise, *ibid.*, 76 (1981) 349–361; (*j*) P. v. R. Schleyer and A. J. Kos. *Tetrahedron*, 39 (1983) 1141-1150; (*k*) P. v. R. Schleyer, E. D. Jemmis, and G. W. Spitznagel, *J. Am. Chem. Soc.*, 107 (1985) 6393–6394; (*l*) H. B. Bürgi, J.-M. Lehn, and G. Wipff, *ibid.*, 96 (1974) 1956–1957; (*m*) J. -M. Lehn and G. Wipff, *ibid.*, 96 (1974) 4048–4050.
9 (*a*) L. Radom, in I. D. Csizmadia (Ed.), *Molecular Structure and Conformation*, Elsevier, Amsterdam, 1982; (*b*) R. Hoffman, L. Radom, J. A. Pople, P. v. R. Schleyer, W. J. Hehre, and L. Salem, *J. Am. Chem. Soc.*, 94 (1972) 6221–6223.
10 N. D. Epiotis, W. R. Cherry, S. Shaik, R. L. Yates, and F. Bernardi, *Top. Curr. Chem.*, 70 (1977) 1–242.
11 I. Tvaroska and T. Kozar, (*a*) *Carbohydr. Res.*, 90 (1981) 173–185; (*b*) *J. Am. Chem. Soc.*, 102 (1980) 6929–6936; (*c*) *Theor. Chim. Acta*, 53 (1979) 9–19.

12 B. Fuchs, A. Ellencweig, E. Tartakovsky, and P. Aped, *Angew. Chem. Int. Ed. Engl.*, 25 (1986) 287–289.
13 E. L. Eliel and C. A. Giza, *J. Org. Chem.*, 33 (1968) 3754–3758.
14 (*a*) S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc., B*, (1971) 136–145; (*b*) S. Wolfe, L. M. Tel, W. J. Haines, M. A. Robb, and I. G. Csizmadia, *J. Am. Chem. Soc.*, 95 (1973) 4863–4870.
15 (*a*) H. M. Berman, S. C. Chu, and G. A. Jeffrey, *Science*, 157 (1967) 1576–1577; (*b*) G. A. Jeffrey, J. A. Pople, and L. Radom, *Carbohydr. Res.*, 25 (1972) 117–131; (*c*) G. A. Jeffrey, ref. 3a, Ch. 4 and references therein.
16 S. Arnott and W. E. Scott *J. Chem. Soc., Perkin Trans. 2*, (1972) 324–335.
17 S. Perez and R. H. Marchessault, *Carbohydr. Res.*, 65 (1978) 114–120.
18 J. Tvaroska and T. Kozar, *Chem. Zvesti*, 35 (1981) 425–440.
19 A. J. Briggs, R. Glenn, P. G. Jones, A. J. Kirby, and P. Ramaswamy, *J. Am. Chem. Soc.*, 106 (1984) 6200-6206, and references therein.
20 B. Fuchs, L. Schleifer, and E. Tartakovsky, *Nouv. J. Chim.*, 8 (1984) 275–278.
21 (*a*) R. U. Lemieux, S. Koto, and D. Voisin, ref. 2a, Ch. 2; (*b*) R. U. Lemieux and S. Koto, *Tetrahedron*, 30 (1974) 1933–1944; (*c*) J.-P. Praly and R. U. Lemieux, *Can. J. Chem.*, 65 (1987) 213–223.
22 (*a*) T.-C. Wu, P. G. Goekjan, and Y. Kishi *J. Org. Chem.*, 52 (1987) 4821–4823; (*b*) P. G. Goekjan, T.-C. Wu, H.-Y. Kang, and Y. Kishi, *ibid.*, 52 (1987) 4823–4825; (*c*) S. A. Babirad, Y. Wang, P. G. Goekjan, and Y. Kishi *ibid.*, 52 (1987) 4825–4827; (*d*) H. Senderowitz, L. Schleifer, P. Aped, and B. Fuchs, *Tetrahedron Lett.*, in press.
23 A. Cossé-Barbi and J.-E. Dubois, *J. Am. Chem. Soc.*, 109 (1987) 1503–1511.
24 F. H. Allen, S. Bellard, M. D. Brice, B. A. Cartwright, A. Doubleday, H. Higgs, T. Hummelink, B. G. Hummelink-Peters, O. Kennard, W. D. S. Motherwell, J. R. Rodgers, and D. G. Watson, *Acta Crystallogr., Sect. B*, 35 (1979) 2331–2339.
25 F. H. Allen, O. Kennard, and R. Taylor, *Acc. Chem. Res.*, 16 (1983) 146–153.
26 R. Taylor and O. Kennard, *Acta Crystallogr., Sect B*, 39 (1983) 517–525.
27 F. H. Allen, O. Kennard, D. Watson, L. Brammer, A. G. Orpen, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, (1987) s1–s19.
28 H. B. Bürgi and J. D. Dunitz, *Acc. Chem. Res.*, 16 (1983) 153–161.
29 Statistical Program SPSS-X. Release 2.0, Northwestern University, 1987.
30 H. Booth. T. B. Grindley, and K. A. Khedhair *J. Chem. Soc., Chem. Commun.*, (1982) 1047–1048.
31 (*a*) H. A. Bent, *Chem. Rev.*, 61 (1961) 275–311, and references therein; (*b*) J. Hine, *J. Am. Chem. Soc.*, 85 (1963) 3239–3244.
32 N. L. Allinger, M. R. Imam, M. R. Frierson, Y. Young, and L. Schäfer, in N. Trinajstic (Ed.), *Mathematics and Computational Concepts in Chemistry*, Horwood, London, 1986, pp. 8–17.
33 B. M. Pinto, H. B. Schlegel, and S. Wolfe, *Can. J. Chem.*, 65 (1987) 1658–1662.
34 B. Fuchs, *Top. Stereochem.*, 10 (1978) 1–94; (*a*) p. 63; (*b*) p. 30, and *cf.* W. J. Adams, H. J. Geise, and L. S. Bartell, *J. Am. Chem. Soc.*, 92 (1970) 5013–5019.
35 C. L. Perrin and O. Nuñez, *J. Am. Chem. Soc.*, 108 (1968) 5997–6003.
36 L. Nørskov-Lauritsen and N. L. Allinger, *J. Comput. Chem.*, 5 (1984) 326–335.
37 J. W. Jaroszewski, B. Jensen, L. Nørskov-Lauritsen, and M. G. Ettlinger, unpublished results.
38 A. Vedani and J. D. Dunitz, *J. Am. Chem. Soc.*, 107 (1985) 7653–7658.
39 S. Takagi and G. A. Jeffrey, *Acta Crystallogr., Sect. B*, 34 (1978) 2006–2010.
40 S. Takagi and G. A. Jeffrey, *Acta Crystallogr., Sect. B*, 34 (1978) 1591–1596.