Anomeric Bond-Character in the Pyranose Sugars

Abstract. *Evidence from determinations of crystal structure relating to the shortening of carbon-oxygen bonds in the anomeric position in pyranose sugars is presented. There is a high degree of probability that the C(1)-O(1) bond is shortened by about 0.04 Å relative to the other C-O single-bond lengths, except in the case of an axially oriented glycosidic group where there is evidence of a distinction between the two ring C-O bonds.*

Information concerning the electronic structure of the cyclic monosaccharides in the vicinity of the ring oxygen and the anomeric carbon atom is of central importance to understanding the conformation and configurational changes that take place when the molecules pass from the solid crystalline state to that of aqueous solution. On dissolution from a relatively static environment in which the molecule is hydrogen-bonded to like neighbors (and in some cases one or two water molecules) to a dynamic situation in which it is surrounded by water molecules in equilibrium with their ions, a variety of different hydrolysis reactions may take place. These give rise to the phenomenon of mutarotation. Mutarotation data are interpreted in terms of equilibria involving α- and β-pyranoses, α- and β-furanoses and acylic molecules, and each cyclic sugar behaves differently (*1*).

It is not surprising that reactions of this type are extremely sensitive to the electronic structure of the region of the molecule involved. What is surprising is that these electronic differences are large enough in saturated molecules to result in differences in interatomic distances of the magnitude that can be observed in the crystalline state by the method of crystal structure determination.

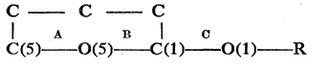
The observation that the anomeric C(1)-O(1) bond is shorter than other C-O bonds in a pyranose sugar has persisted throughout the results of crystal structure determinations, since the study of α-glucose by McDonald and Beevers in 1952 (*2*). The early work on β-arabinose (*3*), rhamnose monohydrate (*4*), cellobiose (*5*), α-glucose monohydrate (*6*), and β-glucose (*7*), all reported relatively short C(1)-O(1) bonds, with reservations concerning the significance of this observation. Since Robertson and Sheldrick (*8*) observed no bond shortening in α-methyl-D-galactoside-6-bromohydrin, they suggested that it was a property of the free sugars only.

From our experience, the advent of the automatic single-crystal diffractometer has shortened the most probable time for a crystal-structure determination by a factor of about seven and increased its accuracy by a factor of about three. As a result, more precise data relating to this observation are now available and are presented in Table 1. In the equatorial C(1)-O(1) bonds, shortening is consistently observed at a very high probability (*9*), with $\Delta l/\sigma$ between 5 and 10; Δl is the difference between bond lengths, and σ is the estimated standard

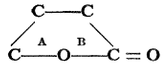
Table 1. Variations of bond length in carbohydrates. The numerical data are as follows. The first two columns give mean bond distances in angstroms, with the spread of the observed designated distances in the molecule in parentheses; the bonds involving the glycosidic and ring oxygens, **O(1) and O(5)**, are excluded. The third column gives the mean value of 3σ, as estimated by the authors of the papers describing the structure determinations. The other three columns give the observed differences, ΔC-O, between the C-O bond lengths designated and the mean in column 2, in the case of the pyranose for **C(5)-O(5)** designated **A**; **O(5)-C(1)** designated **B**, and C(1)-O(1) designated **C**; **R** indicates the end group. In the case of the γ-lactone A is the Δ(C-O) and B is the Δ(O-C=).*

Compound	Mean bond lengths†			Δ_{C-O} (10^{-3} Å)				Ref.
	C-C (Å)	C-O (Å)	3σ (10^{-3}Å)	A	B	C	R	
			C(1)-O(1) equatorial					
β-D-Glucose	1.519(18)	1.424(13)	12	+13	+09	−41	(H)	*13*
β-L-Lyxose	1.525(29)	1.411(31)	18	+11	+24	−47	(H)	*14*
Cellobiose	1.518(29)	1.418(13)	12	+19	+17	−37	(H)	
	1.526(15)	1.420(09)		+16	+05	−23	(Glucose)	*13*
Methyl β-maltoside	1.517(25)	1.428(18)	22	+02	−01	−53	(CH_3)	*15*
Methyl β-D-xyloside	1.515(19)	1.417(11)	12	+08	+05	−27	(CH_3)	*16*
Mean values	1.520	1.421						
σ	.0009	.0009						
			C(1)-O(1) axial					
α-D-Glucose	1.523(24)	1.417(12)	9	+10	+09	−28	(H)	*17*
β-D, L-Arabinose	1.527(18)	1.425(15)	12	+22	+09	−29	(H)	*18*
β-D-Arabinose	1.534(31)	1.437(23)	30	+03	−16	−55	(H)	*19*
α-D-Xylose	1.517(18)	1.425(06)	15	+20	+04	−26	(H)	*20*
α-D, L-Mannose	1.522(18)	1.422(33)	9	+21	+23	−28	(H)	*21*
Methyl α-D-glucoside	1.519(25)	1.424(13)	12	+10	−10	−13	(CH_3)	*22*
Methyl β-maltoside	1.524(19)	1.428(12)	22	+12	−20	−12	(Glucose)	*15*
Sucrose	1.525(14)	1.418(10)	9	+18	−10	+02	(Fructose)	*23*
Mean values	1.523	1.421						
σ	.0006	.0007						
			γ-Lactones					
Galactono-γ-lactone	1.525(44)	1.420(42)	15	+44	−62			*24*
Glucurono-γ-lactone	1.522(22)	1.421(37)	15	+54	−81			*25*
Mean values	1.524	1.420						
σ	.0019	.0017						

* For example, for pyranose



and for γ-lactones



† The mean values are calculated from

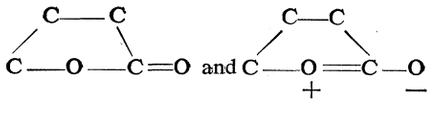
$$l = \sum_i \left(\frac{1}{\sigma_i^2}\bar{l}_i\right) \Big/ \sum_i \left(\frac{1}{\sigma_i^2}\right)$$

deviation. The values for Δ C-O (Table 1) in the ring oxygen bonds show a positive trend; this is a marginal observation, but it appears to be more definite for the free sugar than the pyranoside.

In the axial series, there is a distinction between the C(1)-O(1) bonds for the free sugars and the pyranosides. In the former, the shortening is in agreement with the results for the equatorial series, but in the glycosides it is much smaller or not observed. Rather it is the disproportionation of the two ring oxygen bond lengths that is more striking, with the C(1)-O(5) shorter and the C(5)-O(5) longer than average. This observation requires more confirmation with greater experimental precision, since a shift in the ring oxygen position will simultaneously lengthen one bond and shorten the other. However, it appears from these results, that there is a correlation between the C(1)-O(1) bond shortening and the lengths of the adjacent ring oxygen bonds that merits serious consideration. When the C(1)-O(1) bond is short, both the ring oxygen bonds are long; whereas a "normal" C(1)-O(1) bond is accompanied by differences between the two ring oxygen bonds.

The spread in the C-C and C-O bond lengths, given in parentheses in columns 1 and 2 of Table 1, generally exceeds 3σ. While this might be ascribed to a consistent underestimate of the standard deviations obtained from least-squares refinement procedures, it is important to realize that the steric environment formed by the adjacent bonds is different, to a more or less degree, for every C-C or C-O link in these molecules. By excluding the possibility of variations in single-bond length of the order of 0.005 Å, we might be missing a clue to further research.

The feature that does emerge quite definitely from this survey is the shortening of the anomeric C(1)-O(1) bonds. Comparable bond shortenings are also shown in Table 1 for two accurate determinations on γ-lactones, which are interpretable in terms of the valence-bond resonance between



This anomeric effect appears therefore to be an electronic perturbation of about half of the magnitude of the γ-lactone resonance. The term "anomeric effect" is familiar in carbohydrate chemistry (*10*). It has been used to describe the phenomenon that the axially substituted α-glycosides are more stable than the equatorially oriented β-isomers; even when the latter corresponds to the smaller conformational instability factors. The effect has been interpreted in terms of dipole-dipole interaction between the electrons in the anomeric bonds and the lone-pair electrons on the ring oxygens (*11*). The bond-shortening anomeric effect may well involve an enhancement of electron density in the anomeric bond (hence a shorter and stronger bond) at the expense of the ring oxygen electron density, but we do not yet have a theoretical model which permits us to calculate quantities, such as bond orders, that can be directly related to the interatomic distances.

Sundaralingam (*12*) has discussed the evidence for C-O bond-shortening in the furanose moiety of nucleotides and obtains a striking relationship between C-O bond length and C-C-O bond angles, which suggests that changes in valence angles and bond distances can be correlated through hybridization theory. No simple furanose molecules have been studied, and the precision of the observations which Sundaralingam seeks to correlate is less than in this study, by reason of the added complexity of the molecules. In general, however, a similar pattern of bond-shortening in the formally saturated glycosidic part of the molecules is observed.

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Erythrocyte Abnormality in Human Myopathy

Abstract. *Erythrocyte ghosts isolated from myopathic patients responded to 10^{-4} molar ouabain with a dramatic increase in adenosine triphosphatase activity, while identical preparations from normal donors were inhibited by the same drug. These results have been interpreted in terms of a disease-related change in membrane integrity bearing upon function of the transport enzyme.*

Myopathies have been attributed to a deficiency in ion transport, and this in turn has been associated with the cellular membranes. It has also been suggested (*1*) that the defect may be generalized to the extent that membranes of the erythrocytes share the fault. In the white Pekin duck (*2*) there occurs, as a function of myopathy, reversal of the characteristic inhibitory response of membrane adenosine triphosphatase to the cardiac glycoside, ouabain. The transport enzyme ($Na^+ + K^+$ adenosine triphosphatase) from normal muscle sarcoplasmic reticulum and from hemolyzed erythrocytes was inhibited by $10^{-4}M$ ouabain; identical preparations from myopathic animals were stimulated by the glycoside. We related this to changes in membrane integrity—changes correlated with demonstrable myopathy.