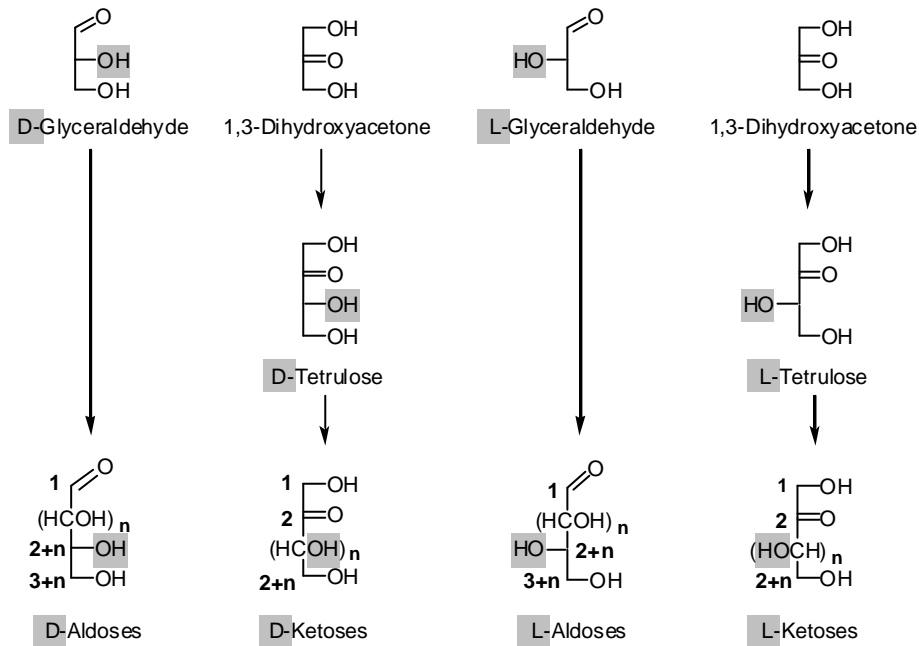


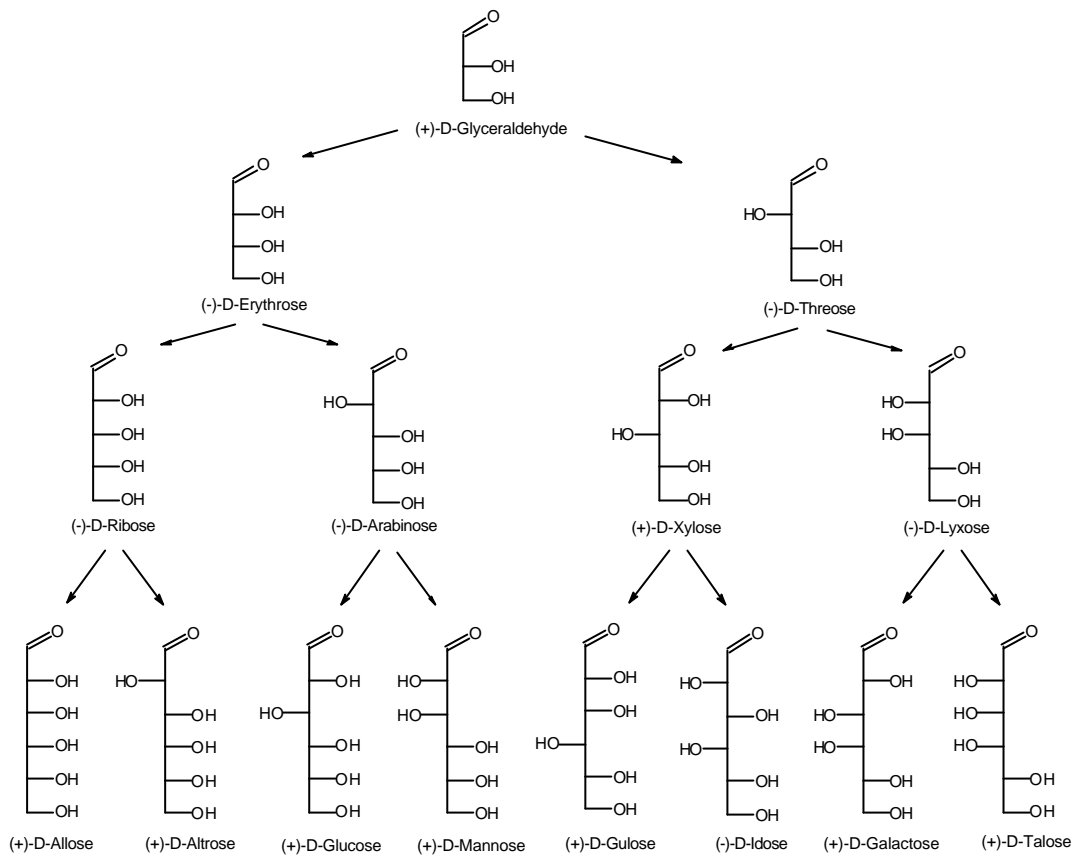
# Structure of saccharides

## Monosaccharides

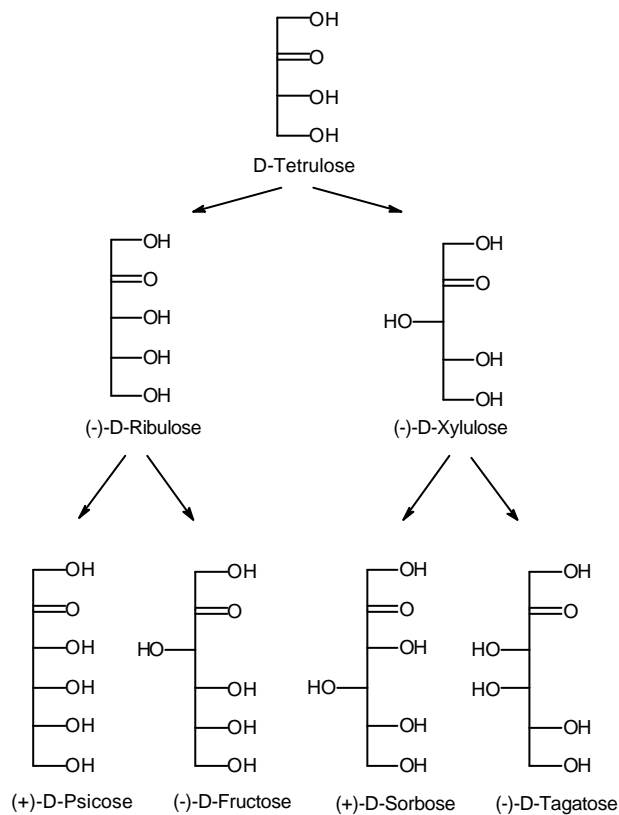
Carbohydrates exist as aldoses, which are polyhydroxyaldehydes, and ketoses, being polyhydroxyketones. Their open-chain forms can be suitably represented by Fischer projections. Aldoses and ketoses can be of different chain length and are all derived from glyceraldehyde. A formal insertion of a stereogenic (HCOH)-group between the carbonyl carbon atom and the  $\alpha$ -C-atom of glyceraldehyde leads to aldotetroses and further successive (HCOH)-group insertions between the carbonyl carbon atom and the adjacent stereogenic center to aldopentoses and aldohexoses. By an analogous sequence the group of ketoses branches out from 1,3-dihydroxyacetone, leading to tetuloses, pentuloses, and hexuloses.



The group of aldoses is derived from glyceraldehyde, ketoses can be built up from 1,3-dihydroxyacetone.



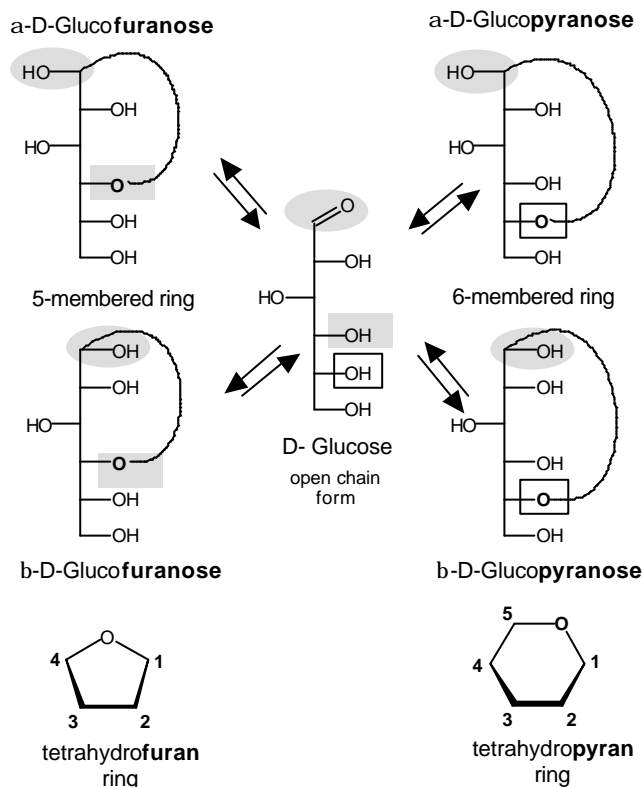
The acyclic forms of D-aldoses drawn as their Fischer projections.



The acyclic forms of D-ketoses drawn as their Fischer projections.

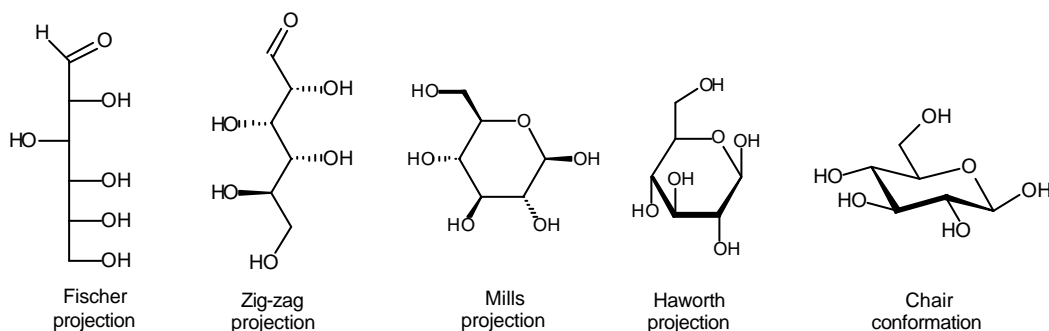
## Monosaccharides form cyclic hemiacetals

Monosaccharides exist preferably as cyclic hemiacetals and hemiketals. These arise from the intramolecular nucleophilic attack of a hydroxyl–oxygen atom at the carbonyl carbon atom of the acyclic species. Depending on which hydroxyl group of the monosaccharide chain reacts with the carbonyl group, 5- or 6-membered rings are formed which are called furanoses and pyranoses, respectively, in analogy to their unfunctionalized heterocycle analogs, tetrahydrofuran and tetrahydropyran.



The formation of 5- and 6-membered monosaccharide rings is exemplified by the aldose D-glucose.

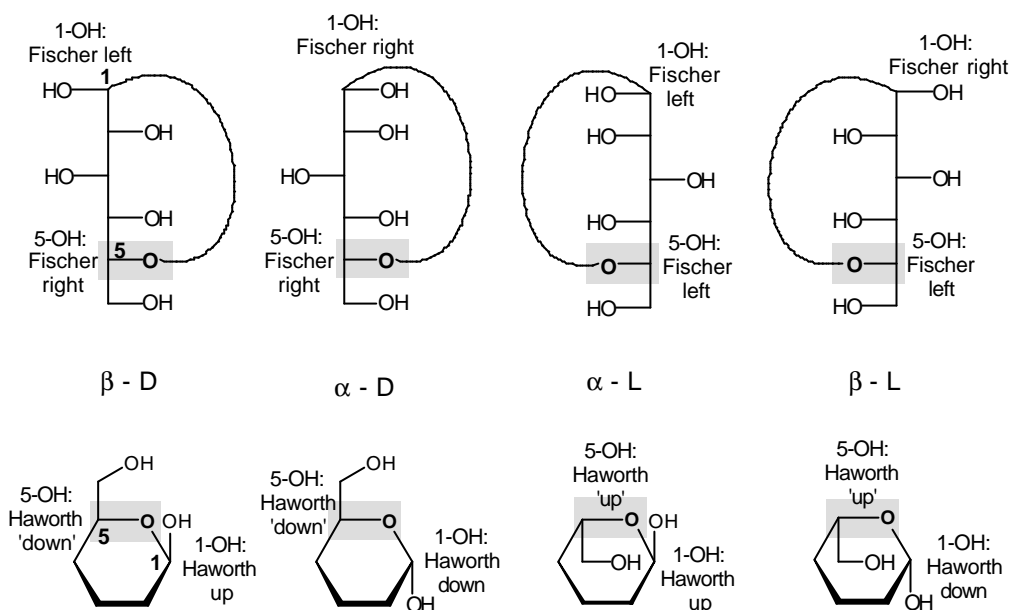
## Representation of monosaccharide structures



Different projections for the structure of the open chain and the cyclic form of  $\beta$ -D-glucose. They are all identical in terms of their absolute configurations, as can easily be shown for each stereogenic center applying the CIP convention.

## The anomeric configuration

The new stereogenic center generated by hemiacetal ring closure is called the anomeric center. The two possible stereoisomers are referred to as anomers, designated as  $\alpha$  or  $\beta$  according to the stereochemical relationship between the anomeric center and the configuration of the most distant stereogenic center. If the hydroxyl groups bound to this center point in the same direction (*cis*), this anomer is called the  $\alpha$ -anomer, when they are pointing in opposite directions (*trans*), it is named  $\beta$ . Anomers are diastereomers.

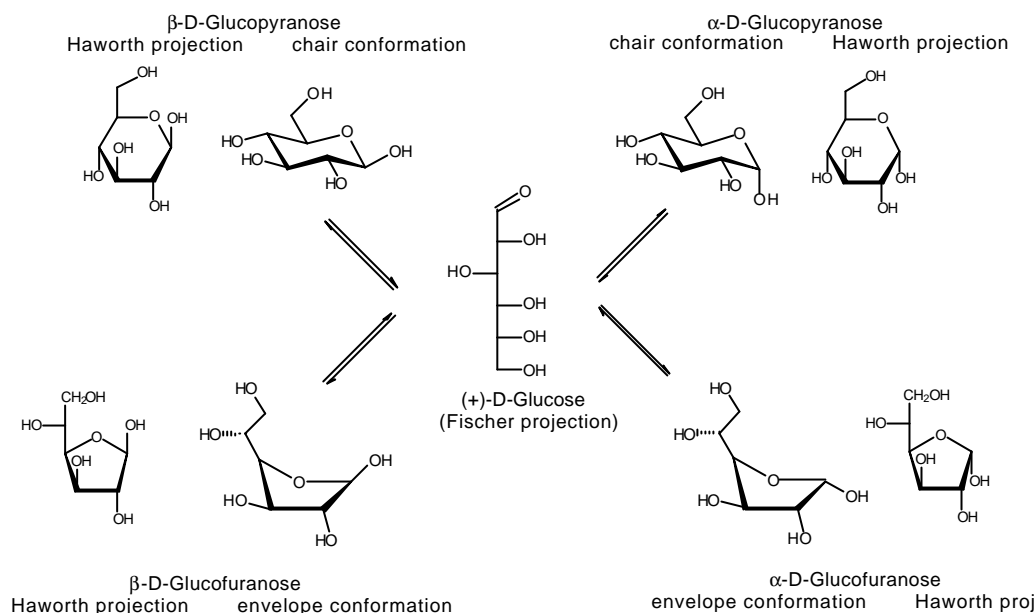


Corresponding structures of  $\alpha$ - and  $\beta$ -anomers of monosaccharide hemiacetals of the D- and L-series, represented as Fischer and Haworth projections; the correct numbering of the carbohydrate ring is indicated.

Thus, for D-glucose and all compounds of the D-series,  $\alpha$ -anomers have the hydroxyl group at the anomeric center projecting downwards in Haworth formulae;  $\alpha$ -L-compounds have this group projecting upwards. The  $\beta$ -anomers have the opposite configurations at the anomeric centers, i.e. the hydroxyl group projects upwards and downwards for  $\beta$ -D- and  $\beta$ -L-compounds, respectively. A wavy line is used for the anomeric bond when the anomeric configuration is not specified.

## Mutarotation

Each crystalline free sugar is a discrete stereoisomer. On dissolution in water however, the hemiacetal ring opens and reforms to give products with different ring sizes and configurations at the anomeric center. This equilibration occurs with all reducing saccharides and is accompanied by a change in optical rotation known as mutarotation. It can be acid- and base-catalyzed.

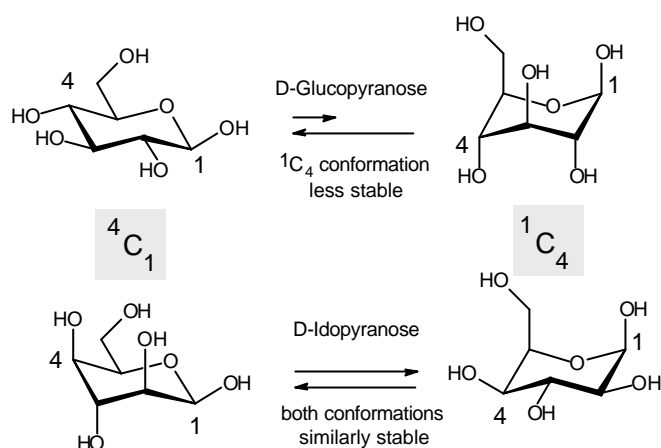


Mutarotation of D-glucose in solution leads to a mixture of  $\alpha$ - and  $\beta$ -pyranoses as well as  $\alpha$ - and  $\beta$ -furanoses. In addition to the structures shown, several other species can be involved in mutarotation including the acyclic hydrate and even septanoses and oxetanoses.

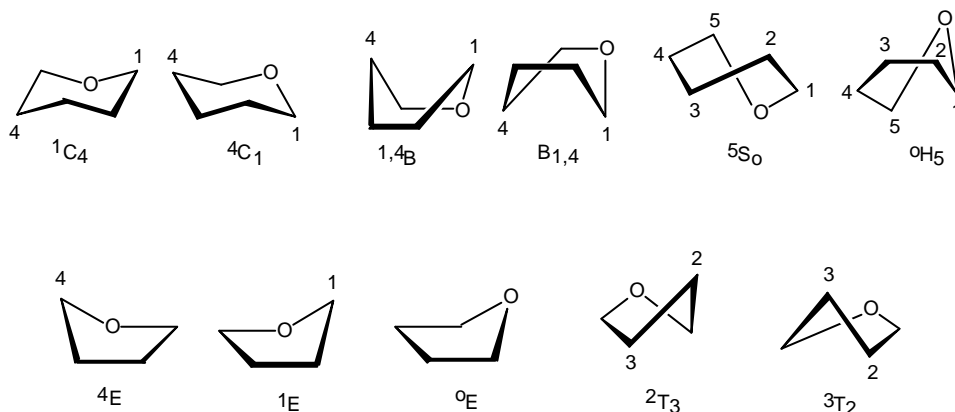
### Conformations of monosaccharides

Like cyclohexane, the 6-membered ring of monosaccharides also exists in two isomeric chair conformations, which are specified as  ${}^1C_4$  and  ${}^4C_1$ , respectively, where the letter C stands for 'chair' and the numbers indicate the carbon atoms located above or below the reference plane of the chair, made up by C-2, C-3, C-5 and the ring oxygen.

The conformational shape of a pyranose is mainly governed by the relative stability of the two possible chair conformations which are both free of torsional strain, but one of which, in most cases, is clearly energetically unfavored because of van der Waals interactions of the ring substituents. Thus, the  ${}^1C_4$  conformation of  $\beta$ -D-glucopyranose is clearly unfavored compared to its  ${}^4C_1$  conformation because the van der Waals repulsion of the 1,3-diaxially positioned ring substituents result in a free energy difference between the two chairs of approximately 25 kJ/mol. Consequently only one, the  ${}^4C_1$  conformation of  $\beta$ -D-glucose is observed by NMR spectroscopy. On the other hand, as expected from their configurations, the energy difference between both chair conformations of  $\alpha$ -idose and  $\alpha$ -altrose is so small, that consequently both forms can be observed in the NMR spectrum.



Other principal conformations of pyranoses are half-chair (H), boat (B), and skew (S) conformation, which are named as indicated. The chair is by far the most stable and only the skew conformation has an energy minimum in a similar range, but this is still some 20 kJ higher than the chair. Principal conformations of the furanose ring are the envelope forms ( ${}^1E$ ,  $E_1$ ,  ${}^2E$ ,  $E_2$ ,  ${}^3E$ ,  $E_3$ ,  ${}^4E$ ,  $E_4$ ,  ${}^0E$ ,  $E_0$ ) and the twist forms ( ${}^0T_1$ ,  ${}^1T_0$ ,  ${}^1T_2$ ,  ${}^2T_1$ ,  ${}^2T_3$ ,  ${}^3T_2$ ,  ${}^3T_4$ ,  ${}^4T_3$ ,  ${}^4T_0$ ,  ${}^0T_4$ ).



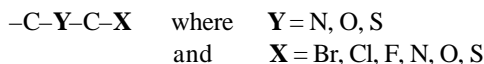
In addition to intramolecular van der Waals interactions, carbohydrate conformations are determined by some other factors, such as electrostatic interactions as well as intramolecular hydrogen bond formation and especially the anomeric effect.

### The anomeric effect

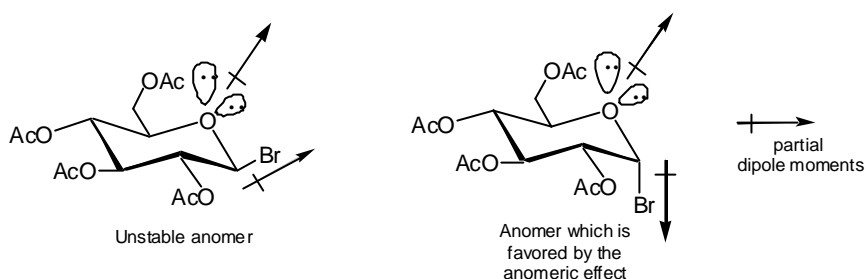
The equatorially positioned substituents of a carbohydrate ring are, for steric reasons, the most energetically favored, compared to their axial counterparts, as is the case in every molecule with a chair conformation. However, the anomerically bound groups in carbohydrates do not follow this rule completely: For D-pyranoses, D-pyranosides and especially carbohydrate derivatives with electronegative groups at the anomeric center the anomeric  $\alpha$ -configured derivatives with the anomeric group located in an axial position are often more stable than would be predicted from the steric interactions they have with adjacent substituents. An aqueous solution of D-glucose, for example, contains the  $\alpha$ - and the  $\beta$ -form in a ratio of 36:64, and the effect is even pronounced for D-mannose, where the  $\alpha$ : $\beta$ -ratio is 69:31. The unusual preference of the sterically unfavored axial position over the

equatorial position at the anomeric center has been termed the 'anomeric effect' by R. Lemieux.

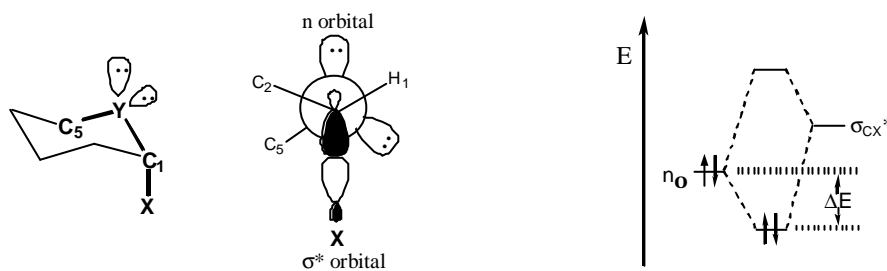
The anomeric effect was discovered in the case of carbohydrates but has been found to be of general importance for molecules, where two heteroatoms are bound to a tetrahedral center. Thus, the essential group for the appearance of an anomeric effect is



The anomeric effect can be explained in several ways. It partly involves a dipole-dipole effect based on intramolecular electrostatic interactions of two dipoles next to the anomeric center. One of the two dipoles arises from the two lone electron pairs of the endocyclic carbohydrate ring oxygen. The other dipole points along the polarized bond between the anomeric carbon atom and its bound atom X. Anomeric configurations, where the two dipoles partially neutralize each other are favored over the diastereomers where the anomeric configuration leads to partial intramolecular addition of the two dipoles. The anomeric effect virtually ensures the axial configuration of an electronegative substituent at the anomeric center such as in the case of acetobromoglucose, where the  $\beta$ -anomer is unknown.



Also unfavorable lone pair-lone pair interactions have been used to explain the anomeric effect. Most importantly however, the anomeric effect is a stereoelectronic effect, in which a lone pair of electrons located in a  $n$ -molecular orbital of the atom Y overlaps with the antibonding  $\sigma^*$ -orbital of the C-X bond. This favorable  $n_{\text{Y}} \rightarrow \sigma_{\text{CX}}^*$  delocalization of nonbonding electrons ('negative hyperconjugation') is only possible with an anti-periplanar arrangement of the involved orbitals as found in the axial anomer. This interaction is also reflected by bond length changes, slightly shortening the Y-C1 bond while lengthening the C1-X bond.

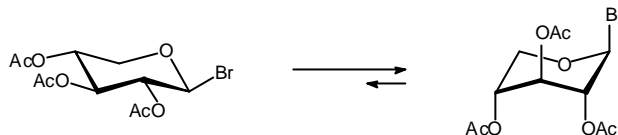


Favored anomer due to  $n_{\text{Y}} \rightarrow \sigma_{\text{CX}}^*$  delocalization of nonbonding electrons which is possible with an anti-periplanar arrangement of the involved orbitals. A significant effect is obtained when the  $\sigma_{\text{CX}}^*$  orbital is of low energy.

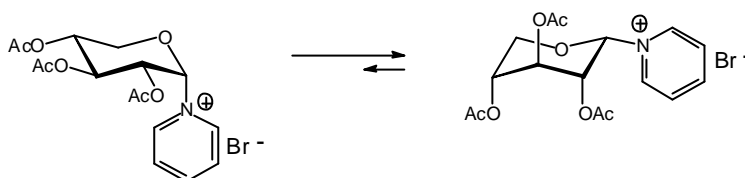
The anomeric effect is of a different size for every specific case. It is strongly influenced by the substituent at C-2. When this is equatorial, as in glucose and galactose, the anomeric effect is weakened, and is enhanced in the case of an axial C-2-substituent as in mannose. Moreover, the nature of the anomeric group is of crucial influence for the anomeric effect, as it is proportional to the electronegativity of the anomericly bound atom. Solvents also influence the anomeric effect, such that increased polarity of the solvent used

decreases the influence of the anomeric effect on the equilibration of the two alternative conformers in solution.

The anomeric effect may even lead to conformational changes as for  $\beta$ -xylopyranosyl bromide which prefers the sterically unfavored  ${}^1C_4$  conformation due to the strong anomeric effect of the bromo atom.



If the substituent at the anomeric center is clearly electropositive compared to the anomeric carbon, such as a positively charged nitrogen atom, the same electrostatic considerations as stated for the anomeric effect lead to the stabilization of the anomer with the equatorially positioned anomeric group. This effect, which is causally no different from the anomeric effect, has been termed the 'reverse anomeric effect'. It is assisted by the fact that an equatorial ring position is energetically favored due to steric reasons, especially in the case of a large substituent like a pyridinium group.



An anomeric pyridinium group, for example, leads to a reverse dipole at the anomeric carbon and consequently a 'reverse anomeric effect' is observed.

In alkyl glycopyranosides the anomeric effect operates not only along the endocyclic C-1 oxygen bond but also along the exocyclic C-1 oxygen bond. The anomeric effect leading to preferred conformations of the exocyclic alkoxy group is called 'exo-anomeric effect'. Again it is an anti-periplanar arrangement of a lone pair on the aglycon oxygen and the C1-O5 bond which determines the favored conformation. In axially configured acetals the exo-anomeric effect is less important because it operates in the opposite direction than the 'endo-anomeric effect'. However, in an equatorial acetal the exo-anomeric effect is dominant and dictates the preferred conformation of the aglycon alkoxy group.

