Contents

1 Neighbouring Group Participation in O-Glycosilation

> Stereoselective Glycosilation reactions are one of the most challenging tasks for synthetic glycochemists. Protective Building Blocks on the glycosides contribute significantly in attaining the required stereochemistry of the resulting glycoside.

→ Strategic Installation of Protective Groups in C-2 position vincinal to anomeric carbon, renders neighbouring group participation

1.1 Some Biological Aspects

Introduction Slide:

- Lactose: Build up from Glucose and Galactose (Epimers)
- ATP used for energy in cell
- Cellulose is complex carbohdrate, that forms main structural component of plant cell walls, making up to 33% of all vegetable matter
- Daunomycin: used for acute myeloid leukemia, administered via injection to a vine. Interacts with the DNA via intercalation and inhibits macromolecular biosynthesis
- Erythromycin: Used in treatment of various bacterial infections. It is the 271st most commonly prescribed medication in the US, has bacteriostatic activity
- Heparin: blood antivogualant, increases the activity of antithrombin. Used in treatment of heart attacks and unstable angina. Isolated from Dog Liver hepar is the greek word for liver

Cell Surface Glycans

Diverse Class of macromolecules that participate in many key biological processes including cell-cell comunication. The glycan covering that surrounds the cell surface termed glycocylyx can both promote and hinder binding of canonical protein ligandds to cell surface receptors

1.2 Overview Carbohydrates

> Biomolecule composed of carbon (C), hydrogen and oxygen

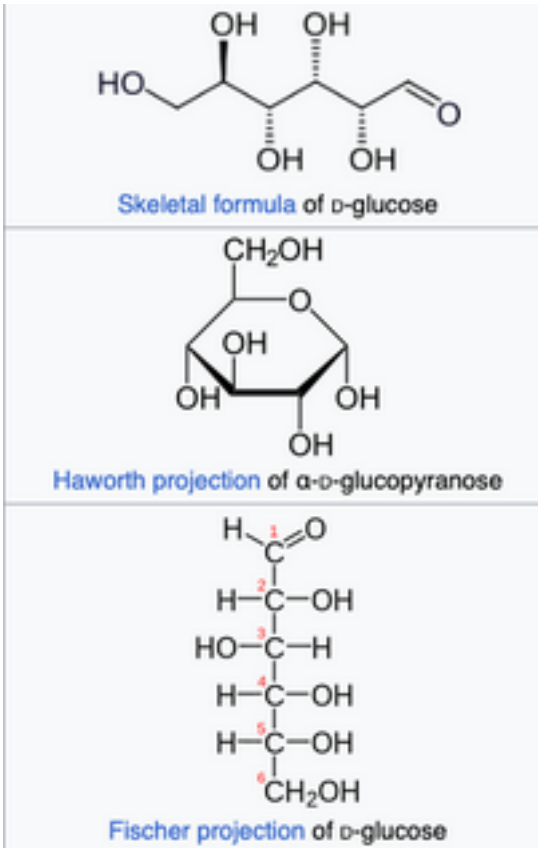

Figure 1: 91be7f7c151416f3d3064bd96a076a1c.png

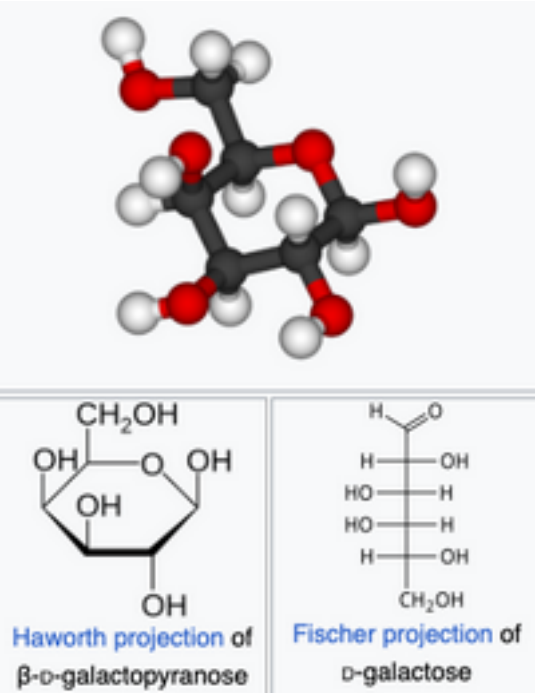

Figure 2: 994bad737fd30dbdf9deb56318769c4a.png

Division:

- Monosaccharides: Glucose, Galactose, Fructose Xylose
- Disacharrides: Sucrose, Lactose, Maltose
- Oligosaccharides 3-9; Maltodextrines, Raffinose
- Polysaccharides >9: Starch, Amylose, Glycogen, Cellulsoe

1.3 Some facts about glycosidation

Glycosidation is the most crucial step in the oligosaccharide synthesis. Main problen in the glycosilation is the structural complexity of the carbohydrate.

- Mechanistic pathway depends on many factors: Concentration of particiPatinc moieties, reaction temperature, hydrogen bonding, solvent, nature of the leaving group and promoter
- Mechanism of glycosilation lies at the interface of $S_N1 - S_N2$ reaction, the continioum expands in both direction
- **Destabilization and greater reactivity of the oxocarbenium, causes the nucleophilic part to attack in a concerted process S_N2**
- **Stability of the Carbocation contributes the dissociative two step S_N1 reaction. (Studied by Codee et al by mapping a ensemble of conformations in a conformational energy landscape study)
- Protective Groups enable to shift this $SN1/SN2$ spectrum to attain desired stereochemical outputs

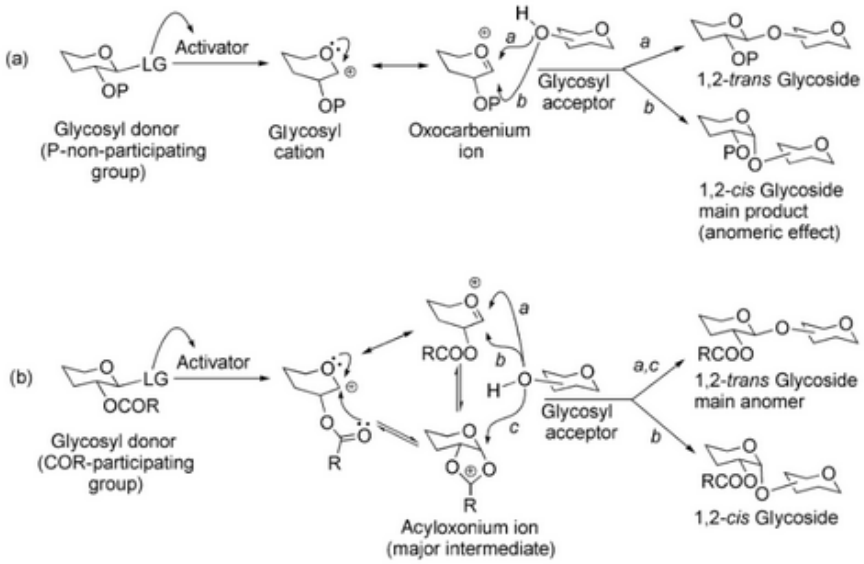

Figure 3: 662f172aedef74c3f5dc21fafedebf72.png

1.4 Formation fo 1,2 Trans glycosides

An acyl protecting group in the vincinal C-2 position is widely accepted as the participating group facilitating the formation of the 1,2-trans glycoside.

- Electron Deficient Acyloxonium ion forms, this blocks of the alpha face, inducing the attack of the nucleophile from the opposite side leading to the trans glycoside
- Cis and Trans → Cis Hydroxyl group of anomerica carbon and the substittuent of the carbon its bondet are on the same side, Trans opposite

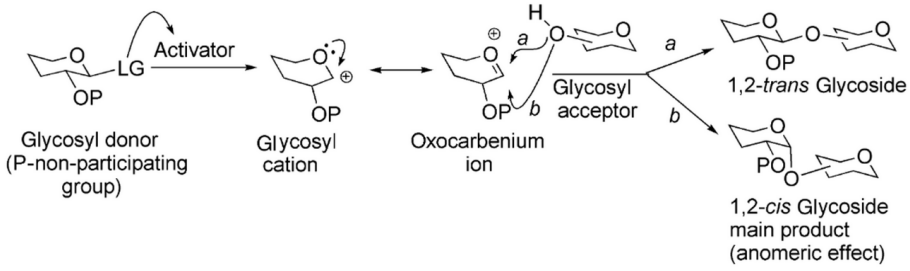

Figure 4: 9f54d602cb6d0c26a4a737de411646ab.png

1.5 Acetyl and Benzoyl Protecting Grou

In the scheme on **Slide 15** both were activated under air with catalytic amounts of methanesulphonic acid.

→ Significant 1,2-trans selectivity means neigbhouring group parcitpitation

1.6 Leuvinioyl protective groups

can be cleaved by using AcOH again yielding selective 1,2 trans glycosides and is a substitute to acetyl or benzoyl protection. Often one can also use this masked protecting group, Thioacetal!

1.7 Pivalate Protecting groups

Another participating ester group, the neopentyl group introduced here reduces probability of for a nucleophilic attack at the oxocarbenium centre instead of the anomeric carbon.

- Removal often requires harsher condition, the one with the tert-dimethylsilyl in the scheme can be cleaved of with the help ov fluoride anions.
- The one with the olefinic bond needed hydroboration oxidation
- Cyanopivaloyl ester protection group showed high versatility, → reduces formation of the orthoester intemidiate. Can be cleaved of by hydrogenation in the precense of Pd-C this allows for orthogonal deprotection

On slide 20 this is a orghogonal deprotaction where all the protectibe groups can be deprototected in onestep to yield the desired product

1.8 Notes to the non-ester participating groups

Problem is that the ester groups are electron withdrawing and reduce the reactivity of the glycosyl doners. But this C-2 protection help the formation of the desired stereochemical output.

- **Slide 23** Typcial MOM methoxymethyl or also BOM benzyloxymethyl protective groups.
- Activation of the glycoside donor, happens through a combination of NIS and IN(OTF) the nthe nucleophilic attack of the acceptor follows

Again Mechanism on Slide 24:

- Formation goes through a oxocarbenium intermediate. This was shown by Kulkarni and Co-workeds which made an efficient neighbouring group participation and enabiling the $\pi - \pi$ interaction between the p orbitals of the oxonium ion intermediate and the aromatic ring