SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Thiol-ene addition reactions on unsaturated carbohydrates

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List of abbreviations

Ac = acetyl group

AIBN = azo-bis-isobutyronitrile

Bn = benzyl group

Bz = benzoyl group

DCM = dichloromethane

DMF = dimethyl-formamide

DPAP = 2,2-dimethoxy-2-phenyl-acetophenone

eq = equivalent

HFIP = hexafluoro-isopropanol

MALDI-ToF MS = Matrix Assisted Laser Desorption and Ionization - Time of Flight Mass Spectrometry

MAP = 4-methoxy-acetophenone

NMR = Nuclear Magnetic Resonance spectroscopy

rt = room temperature

TLC = thin layer chromatography

1. Introduction

Carbohydrates are essential building blocks of living organisms, their biological roles are extremely varied. They are important carriers of biological information, and in order to gain deeper understanding of them, their synthesis is paramount. Derivatives bearing *O*-glycosidic bonds are generally too unstable in biological environments to allow thorough studies, therefore we find it important to synthesize more stable derivatives, bearing sulfur in the place of the glycosidic oxygen. These compounds can shed light on the yet unknown characteristics of carbohydrates playing complex roles. Amongst the glycosidic bonds the formation of the 1,2-*cis*-α-thioglycosidic bond is notoriously difficult, there is no general method described so far. In my PhD work our main goal was developing and studying a method with which this problem could be solved.

2. Literature overview

Instead of the glycosidic oxygen if the electron structurally very similar sulfur is chosen as heteroatom, derivatives more resistant to enzymatic and acidic hydrolysis can be synthesized. These characteristics allow broader applications of carbohydrate derivatives in molecular recognition and pharmaceutical studies as well. Formation of thioglycosides was extensively researched in the past decades, and numerous synthetic methods have been developed.

2.1 Synthesis of 1,2-*trans*- and 1,2-*cis*-1-thiosugars

The relative conformation of the anomeric group and the substituent at position 2 can be either 1,2-*cis*-, or 1,2-*trans.* The difficulties in the synthesis of these glycosides are extremely different. Formation of the 1,2-*trans*-*O*- and *S*-glycosidic bonds is usually easy because participating groups can be used at position 2, leading to high or complete stereoselectivity. Synthesis of 1,2-*cis*-*α*-configured derivatives is, however, a notoriously challenging task. There is no method describing selective *cis* control *via* neighbouring group participation, and in aqueous media the mutarotation of thiols is minimal, so interconversion between α and β derivatives is difficult as well. Because of their high biological importance there is great interest towards 1,2-*cis*-α-1-thiosugars, however, few methods have been published in this topic.

1,2-*trans*-1-thiosugars can be epimerised into 1,2-*cis* configuration *via* acid mediated reaction. Different, benzoyl protected 1-thiopentoses and -hexoses were treated with the Lewis acid $TiCl_4$ in pyridine, obtaining the desired 1,2-*cis* derivatives. Protected, *gluco* and *galacto* configured 1,6-anhydrosugars can be converted into α-1-thiosugars with high yield and complete stereoselectivity. Opening of 1,3-dioxolane ring of carbohydrates with bis-(trimethylsilyl)-sulfide is possible in the presence of trifluoromethane sulfonate. Using cumene hydroperoxide as radical initiator, thioacetic acid can be added to protected 2-acetoxy-D-glucal, thus obtaining the 1,2-*cis*-α-1-thiosugar after selective deprotection. However, these methods cannot be used on all kinds of substrates, only with specific carbohydrate configurations or requiring specific protecting groups.

2.2. Radical mediated thiol-ene addition reaction

The radical mediated thiol-ene addition reaction is an excellent method for the synthesis of thio-connected glycoconjugates. The reaction can be considered a click reaction, therefore it is fast, provides high yields, using a small amount of initiator or catalyst is enough to start the reaction, the workup procedure is simple, the reaction is not sensitive to the presence of oxygen or water, and can be used with a broad range of substrates. It can be initiated by oxygen, and also sonically, thermally and *via* light irradiation, although there are thiols which can be added without using catalyst or initiator. During my work I used a cleavable photoinitiator, 2,2-dimethoxy-2-phenylacetophenone (DPAP).

In the first step of the reaction, the thiyl radical is formed. This will add reversibly onto the double bond during the propagation step, forming a carbon centered radical intermediate. It is important to note that because this is an electrophilic reaction, the double bond has to be electron rich. Electron withdrawing groups can worsen the conversion or even inhibit the reaction. This newly formed carbon radical will, in the chain transfer step, abstract a hydrogen radical from a thiol, forming a new thiyl radical while it itself is stabilised, and the thiyl radical continues the chain reaction. During the fragmentation or reverse propagation step, the carbon radical degrades into a thiyl radical and the double bond bearing starting compound. If the intermediate carbon radical has too low stability, its lifetime will not be long enough to let the chain transfer step happen.

Dondoni and co-workers used the photoinitiated thiol-ene addition for the formation of thiodisaccharides for the first time. They coupled 1-thioaldoses to the exocyclic double bond of pyranoside 5- and furanoside 4-exomethylenes. The reactions completed with excellent yields and full regioselectivity, along with full or good stereoselectivity, forming (1→5) and (1→6) linked thiodisaccharides. This research group also synthesized (1→2)-*S*-linked pseudodisaccharides *via* addition of thiosugars to glycals. The thiol always connected to position 2, however, the reactions require high thiol excess and the stereoselectivity was strongly dependent on the configuration of the glycal.

At the University of Debrecen, Department of Pharmaceutical Chemistry and Organic Chemistry, radical mediated hydrothiolation reactions of 2-substituted glycals and 2,3-unsaturated glycals were examined. Click conditions were achieved, the reactions completed with minimal thiol excess and high yields, therefore the method can be used to synthesize thiodisaccharides and *S*-connected glycoconjugates. During hydrothiolations of 2-acetoxy-glycals the sulfur radical connects to the anomeric center, affording the 1,2-*cis*-α-1-thioglycosidic bond with complete stereoselectivity.

It has been observed that the efficiency of the addition is strongly dependent on the temperature and the configuration of the glycals. While the reaction of 2-acetoxy-D-glucal with 1-thioglucose-peracetate completed with excellent conversion at room temperature, the other 2-substituted carbohydrates reacted with the thiols with a significantly lower conversion. At lower temperatures a significant increase was observed in the conversion, and further cooling gave the same conversions as

the ones observed in the *gluco* cases. Also, increasing the temperature was proven to be detrimental for the conversion.

3. Goals

1,2-*cis*-α-thioglycosides are important carbohydrate mimetics, however, their extensive use is limited because of their difficult synthesis. The results at our Department showed that the otherwise very tedious-to-form 1,2-*cis*-α-thioglycosidic bond can be synthesized with complete stereoselectivity by photoinitiated thiol-ene addition reaction if 2-substituted glycals are used as the alkene partner. Our goal was to continue the studies regarding the effects of the temperature and the conformation of the carbohydrate reactants, and also to expand the range of unsaturated carbohydrates and thiols, optimise the reaction conditions and get a better view on the scope and limitations of the reaction.

Our goal was to study the effects of the different conditions on reactions of variously configured unsaturated carbohydrates (peracetylated, 2-substituted D- and L-glycals, various 2,3-unsaturated derivatives with different aglycones) and various thiols (aliphatic and bifunctionalised aliphatic thiols, amino acids, 1-thiosubstituted carbohydrates). We also aimed to develop an efficient reaction route to form 1,2-*cis*-α-1-thiosugars and from them a broad spectrum of α-α-adducts. On the 2,3-unsaturated glycosides (*O*-, *C*-, *N*- glycosides) we investigated the effects of the aglycone and enoside configuration upon the reaction.

3. Methods

The reactions were monitored by TLC chromatography. The products were purified using flash column chromatography. The structures of the compounds were determined by one- and two-dimensional ^{1}H, ^{13}C, COSY and HSQC NMR measurements, as well as MALDI-ToF and ESI MS measurements. Optical rotations were measured at room temperature with an automatic polarimeter.

The photoinitiated reactions were carried out in a borosilicate flask by irradiation with a mercury lamp giving maximum emission at 365 nm. The lamp was covered with a water cooling immersion coating. The samples were placed up to 2 cm from the lamp. The samples were not bubbled through with inert gas and were not stirred during the irradiation steps. Low temperatures were achieved by immersing the samples into liquid nitrogen-acetone cooling bath.

4. New scientific results

4.1. Reactions with 2-substituted hexoglycals

The previous examinations with 2-substituted hexoglycals were continued on a broad spectrum of glycals and thiols. As unsaturated compounds we used 2-acetoxy-D-glucal, 2-acetoxy-D-galactal, 2-acetamido-D-glucal, 2-acetoxy-L-fucal and 2-acetoxy-D-maltal, as thiol *n*-propyl- and isopropyl-mercaptan, thioacetic acid, ethane dithiol monoacetate, thioglycolic acid, 2-mercaptoethanol, *N*-acetyl-L-cysteine, β-1-thioglucose-, β-1-thiogalactose-, β-1-thiomaltose-, α- and β-1-thiomannose peracetate.

First, 2-acetoxy-D-glucal was coupled to short chained aliphatic and functionalised aliphatic thiols, examining the effects of temperature upon the reaction. First, 5 eq of *n*-propylmercaptan and isopropyl mercaptan were used as thiols, and at room temperature the yields were low, less than 35%. In order to shift the equilibrium towards product formation we used 3x5 eq thiol excess, and found that the conversion and the isolated yield increased significantly, to over 50%. Cooling the reaction mixture to 0°C was beneficial as well, using 1x5 eq of the thiol was enough to achieve twice the conversion observed at rt. Reactions with ethane dithiol monoacetate, 2-mercaptoethanol and thioglycolic acid showed higher conversions than the previously discussed aliphatic thiols, and a lesser thiol excess was enough for the high conversions. Cooling was beneficial in all cases. The addition of 2-mercaptoethanol to 2-acetoxy-D-galactal shows the effects of temperature well: at rt the product was isolated with 58% yield whereas at -80 °C the yield was 86%, and a smaller excess was enough to reach the high conversion.

The reaction was investigated on a disaccharide thiol and a disaccharide glycal as well. First we examined the additions of 1-thiomaltose-peracetate to unsaturated monosaccharides, starting with adding 1-thiomaltose-peracetate to 2-acetoxy-D-glucal. At rt the conversion was minimal, however, lowering the temperature resulted in a gradual, significant increase. At -80 °C the yield was the highest, 58%. The same was observed with additions to 2-acetoxy-D-galactal, at -40 °C the isolated yield was 35%, and cooling the reaction mixture to -80 °C the yield was 75%. In the case of 2-acetamido-D-glucal, however, the optimal temperature was -40 °C where the yield was 65%, and lowering the temperature to 80 °C decreased the yield to 33%. Following the additions of the disaccharide thiol we investigated reactions of a disaccharide glycal, the 2-acetoxy-D-malto glycal. Additions of *N*-acetyl-L-cysteine completed with similar, 75-80% conversions at -20 and -40 °C, however, at -80 °C the yield was as low as 56%. The same was observed with the addition of 1-thioglucose-peracetate, where the optimal temperature was between -20 and -40 °C, and with the addition of the disaccharide thiol, where the yield was highest at -40 °C (35%).

As observed in the previous studies, the thiols were added to position 1 with complete regio- and complete 1,2-*cis*-α-stereoselectivity. The efficiency of the reactions depended mostly on the stability of the carbon centered radical intermediates. The stability of that intermediate mostly depends on the difference between the activation energy barriers of the propagation and reverse propagation steps, which is determined by the relative energy levels of the intermediate carbon centered radical and the ones of the starting materials (the unsaturated carbohydrate and the thiyl radical). Only in a few cases studied was the intermediate stable enough at rt to allow the reaction to complete with good conversions, however, cooling led to significant improvement. Although cooling was beneficial in all cases, the optimal temperature was dependent on the substituents and configurations of the glycals, and also on the characteristics of the thiols. We presume that if the temperature is too low it will over-stabilise the

alkyl-thiyl radicals, shifting the equilibrium towards the reverse propagation step, however, it can also be possible that the too low temperature inhibits the hydrogen abstraction step.

We presume that in the case of 2-substituted hexoglycals the fast, reversible thiyladdition step and the exceptional stability of the $^4C_1$ chair conformer assure the 1,2-*cis*-α-stereoselectivity of the reaction. The starting hexoglycals are in an interconversion equilibrium between $^4H_5$ and $^5H_4$ half chair conformers. Although the thiyl radical can attack both conformers from both sides, the only productive attack is the one where it occurs from bottom face onto the $^4H_5$ conformer, resulting in the stable, C-2 centered radical intermediate, which has extraordinary stability owing to the bulky C-6 substituent. Attacks from other faces would flip the pyranose ring into high-energy skewed boat conformations that would quickly decompose. According to our findings, additions to 2-substituted D-hexoglycals occur exclusively through the aforementioned route. Analoguously, the $^1C_4$ conformer is exceptionally stable in the case of L-hexoses (like L-fucal), so reactions occur through the respective $^5H_4$ half chair and $^1C_4$ chair conformers.

4.2. α-1-thiosugars and trehalose type α-α-thiodisaccharides

Although there are numerous methods for the synthesis of trehalose and its analogue thiotrehalose, there are no generally applicable methods for the synthesis of other α-α-thiodisaccharides known in the literature. The main obstacle in these cases is the formation of α-carbohydrate thiols, however we have developed a method with which these thiols can be synthesized from the respective 2-substituted glycals in two steps. Using photoinitiated thioladdition the thioacetic acid can be coupled to the glycal, forming 1,2-*cis*-α-*S*-acetyl adducts, which in turn can be selectively *S*-deacetylated, giving the α-glycosyl thiols. This thiol can be coupled to 2-substituted glycals, giving thiodi- tri- and tetrasaccharide derivatives. The key step in this reaction route is the formation of α-*S*-acetyl derivatives, from which the 1,2-*cis*-α-1-thiosugars can be synthesized.

During the optimisation studies we observed that although DPAP was enough in all cases for the initiation of the reaction, in many cases the conversion could have been improved by adding a co-initiator. In those cases, a photosensitiser compound, MAP (4-methoxy-acetophenone) was added to the reaction mixture, which improved the conversion in all cases. In other cases, acridine orange was used as co-initiator. We have also observed that increasing the length of an irradiation cycle from 15 min to 60 min led to significant improvement in the conversion, also giving extra thiol excess before each cycle was beneficial. In some cases hexafluoro-isopropanol (HFIP) was added in order to prevent the thioacetic acid from deprotonation.

This newly developed method gave way to the efficient synthesis of a multitude of 1-*S*-acetyl derivatives. The reaction with 2-acetoxy-D-glucal completed with 60% yield, the one with perbenzoylated 2-benzoyloxy-D-glucal with 44%, the one with 2-acetoxy-D-galactal with 77%, the one

with 2-acetoxy-L-fucal with 96%, the one with 2-acetamido-D-glucal with 80%, the one with 2-acetoxy-D-allal with 56%, and the one with a 2-acetoxy-D-maltal with 58% isolated yield, respectively.

These 1-*S*-acetyl derivates were selectively S-deacetylated to give the corresponding thiols. Each reaction completed with high yield. The thiols were then used to form trehalose type α-α-thiodisaccharides. Using photoinitiated thiol-ene addition we successfully synthesized 24 α-α-thio-linked oligosaccharides. As starting unsaturated glycal we used 2-benzoyloxy-D-glucal, 2-acetoxy- and 2-acetamido-D-glucal, -galactal, -allal, -maltal and -L-fucal, and we have obtained all possible combinations of the di-, tri- and tetrasaccharide mimetics. All reactions completed with good to excellent yields at -40 or -80°C.

4.3. Additions to 2,3-unsaturated glycosides

Following the reactions of 1,2-unsaturated carbohydrates we focused our attention to reactions with 2,3-unsaturated derivatives. We examined the effects of the atom forming the glycosidic bond on the addition. We also examined the roles of the temperature and the configuration of the unsaturated glycoside and their effects on the stereoselectivity and conversion.

First we compared different types of initiation on the 2,3-unsaturated 2,3-dideoxy-D-*erythro*-hexopyranosyl *O*-ethyl glycoside. Adding β-1-thioglucose-peracetate to this compound gave the C-2 axially coupled product in all cases. In Scheme 7 the differences between the photoinitiated method, thermic activation and triethlyborane-catechol mediated method are shown.

The previously examined *O*-ethyl glycoside was then reacted with functionalised alkyl thiols. Addition of ethane dithiol monoacetate at 0 °C completed with good conversion and yield (69%), however at -80°C the yield was only a third of the previous one. The same was observed with this thiol and 2-substituted glycals as well, where the optimal temperature was 0° C too. In the case of thioglycolic acid, the optimal temperature was -80 °C, which again correlates with our previous findings. Here, at 0 °C the yield was 46% while at -80 °C the yield was 68%. These compounds, owing to their functions at position 2, can be building blocks for branched oligosaccharides in the future.

Afterwards the reaction was extended to 2,3-unsaturated D-*erythro*-hexopyranosides with further aglycones (2-bromoethyl, phenyl, allyl), and found that the reactions completed with excellent yields at low temperature. The effects of the C-4 substituent was examined on a 2,3-unsaturated ethyl-D-*threo*-hexopyranoside, where, surprisingly, regioisomeric mixtures were obtained, containing 2-deoxy-3-thio and 3-deoxy-2-thio derivatives.

Additions to 2-substituted 2,3-unsaturated *O*-glycosides were also examined, with focus on the effects of the substituents at C-2 position on the regio- and stereoselectivity of the addition reactions. The starting unsaturated compounds were inseparable mixtures of α-β anomers. We have observed that the regioselectivity of the reaction can be effectively controlled through substitution at position 2, the

additions completed with full regio- and stereoselectivity. The stereochemical outcome of the reactions were mostly dependent on the configuration of the thiol. The higher reactivity of the α unsaturated anomer was also noteworthy. Although there was a significant amount of β anomer in the starting unsaturated compounds, no β ethyl glycosides could have been isolated as product.

Following the successful additions to *O*-glycosides, we focused our attention to *C*-glycosides, where we examined the differences in the reactivity of terminal and internal double bonds. We added 1-thioglucose-peracetate to the unsaturated C-allyl glycoside, and found that using 1.0 eq of thiol resulted in the addition occurring only on the terminal double bond, giving the product with 40% yield. Increasing the ratio of the thiol to 2,5 eq only this product was isolated as well, albeit with higher yield. The internal double bond was intact in both cases.

Finally, we examined the additions to *N*-glycosides. The starting 2,3-unsaturated *N*-glycoside was an inseparable α-β mixturee in this case too. The reaction with 1-thioglucose- and thioxylose-peracetate was unsuccessful at rt and 0°C, however, lowering the temperature allowed the reaction to complete with moderate yield. We found that the addition products were all β glycosides. Since the radical mediated thiol-ene addition reaction requires electron rich double bonds to complete, we assume that the electron density of the unsaturated bonds are very different in the α and β anomers. Similarly to the reactions with the 2-acetoxy-2,3-unsaturated derivatives, the stereochemical outcome was determined by the configuration of the thiols.

5. Summary

During my course of work I have examined the photoinitiated thiol-ene addition reactions of 2-substituted hexoglycals, and 2,3-unsaturated glycosides. We have studied the effects of the applied temperature, as well as the effects of the unsaturated carbohydrates' and thiols' structure and configuration on the conversion and stereochemical outcome of the reactions. In the case of 2-substituted glycals we observed complete 1,2-cis-α-stereoselectivity, however the conversion was significantly dependent on the the applied temperature and the structure and reactivity of the reactants. Cooling was found to be beneficial in all cases, in the case of carbohydrate thiols the optimal temperature was between -40 and -80 °C while in the case of alkyl thiols the optimal temperature was at 0 °C. The reaction can be performed on a disaccharide glycal and thiol as well.

Additions of thioacetic acid were special cases because no conditions that had been optimal for the addition of similar thiols led to acceptable conversions. The expected products were not thioglycosides but α-*S*-acetyl compounds, that could be selectively deacetylated and then used as starting materials in the 1-thiotrehalose analogue syntheses. For the examined glycals we successfully designed conditions with which the desired 1,2-*cis*-α-*S*-acetyl derivatives can be synthesized with good yield. We have observed that it was beneficial in all cases to increase one irradiation time to 60 min, and giving 4-methoxyacetophenone or acridine orange as co-initiator further increased the conversion in most cases. With the exception of the 2-acetamido-D-glucal the optimal temperature was found to be -80 °C.

Following selective *S*-deacetylation the newly formed α-1-thiosugars were used to form homo- and heterodimer structured α,α-thiodisaccharides. These reactions, similarly to the reactions of β-carbohydrate thiols, completed with high conversions and yields with full regio- and stereoselectivity.

We also examined various *O*-, *C*- and *N*-glycosides, studying the effects of the anomeric heteroatom on the radical mediated thiol-ene addition reaction. We have found that the photoinitiated thiol-ene addition reactions of 2,3-unsaturated *O*-glycosides formed the desired C-2 axially linked products with high or complete regio- and full axial stereoselectivity. The D-*erythro* configured 2,3-dideoxy-2,3-unsaturated *O*-ethyl, phenyl, allyl and 2-bromoethyl glycosides gave the D-*arabino* configured, C-2 thioalkylated or thioglyosylated products with complete regio- and stereoselectivity. Lowering the temperature was beneficial in most cases. Reactions with the D-*threo* configurated 2,3-unsaturated glycosides showed complete axial selectivity, however, the thiols were added to C-2 and C-3 positions as well. Both the conversion and the selectivity could have been improved by cooling. In the case of the C-2 substituted derivatives the addition showed lesser regioselectivity and conversion, which could be attributed to the steric congestion. The stereoselectivity was mainly defined by the reactivity of the thiols, the two additions showed full but opposite stereoselectivity. The reactivity of the *N*-glycoside was significantly lower than the one of *O*-glycosides, we observed yields lower than 20%. The absence of the anomeric oxygen atom lowered the reactivity of the terminal double bond in the *C*-allyl glycoside, and completely prevented the addition to the endocyclic bond.

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7. List of scientific publications

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Candidate: Viktor Kelemen
Doctoral School: Doctoral School of Pharmacy

List of publications related to the dissertation

1. **Kelemen, V.**, Csávás, M., Hotzi, J., Herczeg, M., Poonam,, Rathi, B., Herczegh, P., Jain, N., Borbás, A.: Photoinitiated Thiol-Ene Reactions of Various 2,3-Unsaturated O-, C- S- and N-Glycosides: scope and Limitations Study.
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3. Nemes, D., Kovács, R. L., Nagy, F., Tóth, Z., Herczegh, P., Borbás, A., **Kelemen, V.**, Pfliegler, V. P., Rebenku, I., Hajdu, P., Fehér, P., Ujhelyi, Z., Fenyvesi, F., Váradi, J., Vecsernyés, M., Bácskay, I.: Comparative biocompatibility and antimicrobial studies of sorbic acid derivates.
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Total IF of journals (all publications): 28,818
Total IF of journals (publications related to the dissertation): 8,913

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

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