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Mechanism of Acyl Group Migration in Carbohydrates

Robert Lassfolk*[a] and Reko Leino[b]

Abstract: Acyl group migration has been the subject of several studies. Such migration processes may cause problems during synthesis, isolation, and purification of different acyl-bearing compounds, and have biological relevance, for example, in the metabolism of pharmaceuticals. Considering the recent evidence of acyl group migration being possible even over glycosidic bonds, it could be hypothesized to be involved also in the regulation of biological activity of natural polysaccharides in the host cells. Migrations are mostly observed in carbohydrates, typically having several hydroxyl groups near each other. Several studies have investigated the migration in a single or only a few different carbohydrate molecules, providing different suggestions for the mechanisms of migration, seldom supported by comprehensive computational investigations. In this concept article we discuss the recent progress on the mechanistic aspects of acyl group migration, with carbohydrates in particular focus.

Introduction

Acyl groups are commonly used for protection of hydroxyl groups in organic synthesis, in linear sequences, and for orthogonal protection, particularly in carbohydrate chemistry.[1] They are prone to intramolecular migration,[2] which can cause problems in synthesis, purification and isolation of organic compounds. The migration may take place in any compound containing hydroxyl groups, thiols, and amines, with acyl moieties, but is most prominent in carbohydrates due to several hydroxyl groups being present in close proximity. It was Fischer who first observed the migration phenomenon,[3] and several studies on the subject have been reported since his work.

Understanding the acyl group migration is crucial, not only because of the potential problems in preparative laboratory work, but also for its potential biological relevance. Pharmaceuticals and other compounds containing carboxylic acid moieties are metabolized to acyl glucuronides in the liver.[4] Consequently, migrations in glucuronic acid have been thoroughly studied in the literature.[5] Many polysaccharides in nature, such as xylans, glucans and mannans, are acetylated to various degrees, and these polysaccharides often display biological activities.[6] Bacterial polysaccharides, and vaccines based them, form another group of partially acetylated polysaccharides.[7] Interestingly, studies suggest that the acetyl groups rearrange within the saccharide unit of bacterial polysaccharides after the biosynthesis,[8] which could imply that such migration is crucial for the biological activity of these polysaccharides. Acetyl groups are also found in sialoglycoproteins,[9] gangliosides[10] and their constituents, including *N*-acetylneuraminic acid.[11] Acyl groups, therefore, play a key role in not only synthetic chemistry but also in biological systems, and by understanding the mechanism of migration, further knowledge on its potential biological role could be gained. Acetyl groups, specifically, may play a role in more complex biological regulation and recognition processes, including cell signaling events in biomolecules.[12]

The mechanism of acyl group migration has been investigated in several studies, some under acidic conditions,[13] some under basic[3,14,15] and some utilizing Lewis acids and bases.[16] Earlier reported computational studies have typically not included all parts of the migration process, making it difficult to evaluate and verify the more general validity of the suggested mechanisms. For example, until recently, the deprotonation step in the base catalyzed mechanism has not been included in the computational models. In this concept article, based on both literature by others and our recent own work in the subject,[15,17] we address the current understanding of the acetyl group migration mechanism, in carbohydrates in particular, and the acyl group migration process on more general level.

The Migration

Discussion of the mechanism starts here from the general features of the migration process. In monosaccharides, the acyl group typically migrates between two adjacent hydroxyl groups. Direct migrations across the same ring, between two non-adjacent hydroxyl groups, have been tested in both myoinositol[18] and mannose[19] derivatives, but without success. The preferred position for an acyl group, in general, is the primary hydroxyl, if present (Scheme 1).[11,15,20] However, when

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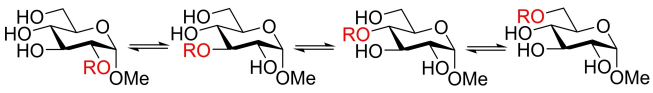


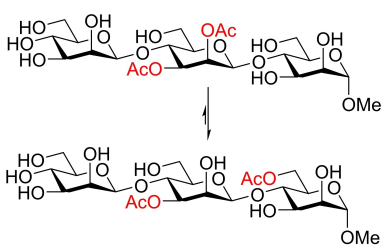
Scheme 1. Acyl group migration in methyl-α-glucopyranoside.

the primary position is lacking or blocked, a more even spread between the acylated secondary hydroxyl groups is often observed.[5a,15,21] The ratio commonly depends on both the nature of the acyl group and the stereochemical configuration of the carbohydrate ring.[15] One such example involves the comparison of the acetyl group migration in Me β-xylo-, Me β-arabino- and Me β-ribopyranoside. In ribopyranoside, O3 is the preferred position by a small margin over O4, in xylopyranoside the O3 and O4 positions are approximately equally preferred, and in the arabinopyranoside O4 position is the most preferred position.[15]

Most of the earlier studies on acyl group migration have been performed in monosaccharides.[2] Recently, however, also investigations on acyl group migration in oligo- and polysaccharides have been reported.[17,22] These studies have demonstrated that an acetyl group may also migrate across the glycosidic linkage, from a secondary to a primary hydroxyl group in both oligosaccharides (Scheme 2) and a native polysaccharide. These studies were carried out on hemicellulose model compounds, where the glycosidic linkage is β-(1→4). The observations could potentially be related to a biological role of the migration in acetylated hemicelluloses.

Several factors, including the reaction conditions and the structures of both the acyl group and the carbohydrate in question, influence the overall migration process. In particular, the stereochemical relationship between the hydroxyl groups participating in the migration will significantly affect the phenomenon. Migration over *cis*-hydroxyl groups is much faster than the migration over hydroxyl groups in *trans*-relationship,[15,20b] which can be observed when comparing the O2⇌O3 migration in Me α-gluco-, and Me α-mannopyranosides, where the O2⇌O3 migration is eight times faster in the mannopyranoside.[15] The underlying reason is likely associated with the favorable five-membered transition state. On the other hand, the migration from a secondary to a primary position in carbohydrates forms a six-membered ring in the transition state, where the preferred orientation of the primary hydroxyl group determines how close it lies to the secondary, and therefore also the rate of migration. Comparing the O4→O6 migration in Me α-gluco- and Me α-galactopyranoside shows that the migration is four times faster in the glucopyranoside.[15] In cases where the migration of an acyl group takes place over secondary hydroxyl groups sharing a *trans* relationship, configuration of the anomeric position will influence the rate of migration.[15] When the anomeric substituent is axial, the rate of migration is slowed down compared to when the anomeric substituent is equatorial. An example is the comparison between the O2⇌O3 and O3⇌O4 acetyl group migrations in Me β- and α-glucopyranosides, where the migration in the β-anomer is on average two times faster.[15] The underlying reason is the anomeric effect. When the anomeric position is axial, the bond between the ring-O and C1 is shortened, resulting in more strain in the ring and, consequently, also in the transition state of the migration.

The acyl groups themselves influence the migration in two ways: through steric hindrance and by their electronic properties. By increasing the electron withdrawing properties of the substituent, the rate of acyl group migration also generally increases.[23] Steric hindrance is a more frequently investigated factor influencing the rate of migration. By blocking the carbonyl carbon, the nucleophilic attack is more hindered, as investigated in several earlier studies.[15,20b,23] Stereochemistry of



Scheme 2. Acetyl group migration across the glycosidic bond in a mannan trisaccharide.

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Prof. Reko Leino (born 1969) studied chemical engineering at Åbo Akademi University, Turku, Finland, receiving his M.Sc. in 1994 and Dr.Sc. (eng) in 1998 with Prof. Jan H. Näsman. After a post-doctoral period at Stanford University with Prof. Robert M. Waymouth in 1998/1999, he also briefly worked in the biopharmaceutical start-up business, before being appointed to a professorship in synthetic organic chemistry in 2003 at his alma mater, where he currently, since 2022, acts as vice-rector for research affairs. His research has focused on various aspects of chemical synthesis technology, from organic, organometallic and polymer chemistry to homogeneous and heterogeneous catalysis, carbohydrate chemistry and chemical biology, drug development and discovery.

the α-carbon, likewise, has an effect. Depending on the configuration,[23,24] different migration transition states will be preferred due to steric hindrance from one side of the carbonyl moiety (Scheme 3).[24a]

Most of the earlier studies have been carried out in buffer solutions, due to the potential biological importance of some acyl glucuronides, while investigations of the migration process in other solvents have been lacking. In some studies, influence of solvent polarity on the rate of migration has been observed.[25] A more polar solvent may stabilize the charges, giving the hydroxyl group longer time to undergo a nucleophilic attack at the carbonyl carbon, thereby increasing the rate of migration. Deeper experimental and computational studies of how the solvent influences the migration are still needed to establish how much the properties of the solvents affect the acyl group migration.

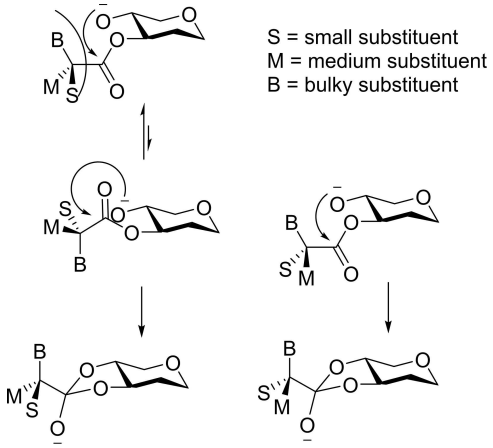
The Mechanism

The most suggested mechanism of acyl group migration is the base catalyzed, supported by both experimental evidence and computational studies. The base catalyzed mechanism is usually investigated in water, commencing with deprotonation of the hydroxyl group, followed by nucleophilic attack at the carbonyl carbon, forming an orthoester acid (Scheme 4). The former C–O bond is then broken, followed by protonation. The orthoester acid has been observed as a stable intermediate during the migration of a pivaloyl group in a galactose derivative.[26] The difference between the rates over *trans* and *cis* hydroxyl groups serves as further evidence for the orthoester intermediate.[15]

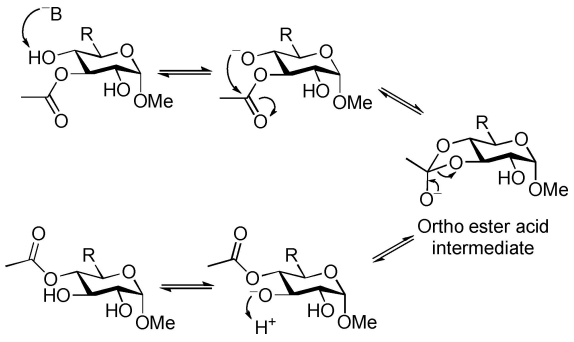
Since most of the earlier migration studies have been investigated in buffers, migrations under different pHs have been performed. Several studies demonstrate that the migration is faster at higher pH.[5b,20b,24d,27] In one study, a relationship between the rate constants and the pH was observed.[15] By using pHs in the range of 6–9 a linear dependence between the concentration of [OH^-] and the rates of migration was established. Such linear relationship further supports the base catalyzed mechanism prevailing under aqueous conditions.

Investigations on the primary kinetic isotope effect have also been performed.[22a] Clear evidence for the $^1H/^2H$ kinetic isotope effect has been gained, while not supporting a $^{13}C/^{12}C$ kinetic isotope effect. The observed $^1H/^2H$ kinetic isotope effect suggests that deprotonation is a key step in the migration process.

Also, computational investigations have been performed in several studies. Many of the computational investigations are consistent with the base catalyzed mechanism. These investigations typically presume the formation of an anion from the beginning, inferring the first step of the migration process rate determining (Figure 1).[24a,25a,28] Petkov and co-workers[25a] investigated the migration phenomenon in 2′(3′)-formyl nucleosides computationally. Both a neutral and an anionic mechanism were studied. The results suggest that after deprotonation, the migration is spontaneous. Typically, hydroxyl groups are not easily deprotonated, making deprotonation the rate limiting step, which was not considered in the calculations. Stachulski and co-workers[24a] also assumed complete deprotonation while only calculating the first transition structures of the migration



Scheme 3. Stereochemical interactions during acyl group migration.



Scheme 4. The base catalyzed acyl group migration mechanism.

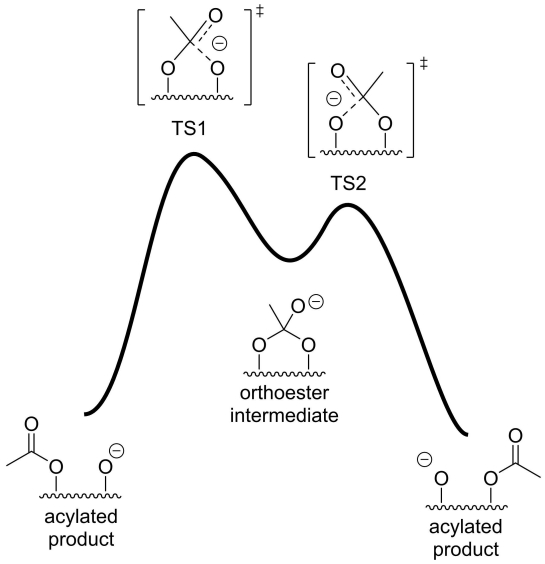


Figure 1. Mechanism of acyl migration assuming preceding deprotonation and the first step as the rate-limiting transition stage.

processes leading to the orthoester intermediate. The connection between the acylated compounds and the orthoester cannot be assessed properly since complete studies were not reported. Stachulski and co-workers also studied the intramolecular transacylation of acyl glucosides.[28] The main uncertainty in such computational studies is that the fully deprotonated species is assumed, which is not the case when the reaction is carried out in water or neutral solvents that do not fully deprotonate the hydroxyl groups. Complete deprotonation of all hydroxyl groups involved would require a very high pH, which most often is not the case. To establish the concentration of the deprotonated species, the pK_a of the hydroxyl groups should be considered.

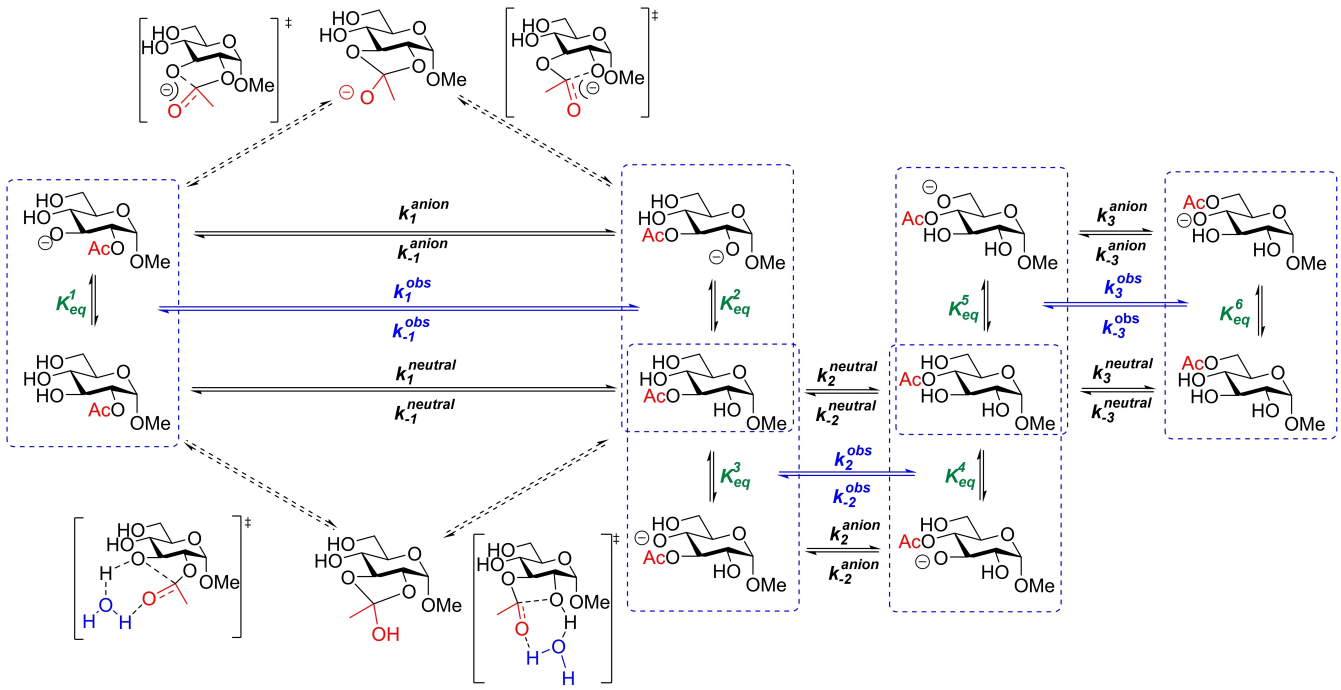
In a recent computational study, the pK_as were considered for acetyl group migration in several different carbohydrates.[15] It was concluded that two main paths influence the rate of migration: a neutral and an anionic path (Scheme 5). These two paths are in competition. The ratio of the neutral and anionic species was calculated based on the pK_as of the hydroxyl groups, which were determined computationally. The neutral path involves a water molecule for proton transfer, otherwise a highly strained four-membered ring would be formed. The anionic path requires three water molecules to stabilize the anions. It was observed that at $pH > 6$ the neutral mechanism could be disregarded, but at lower pH it should be included. Equation (1) could be used at $pH \leq 6$ and Equation (2) at $pH > 6$.

$$K^{obs} = k^{neutral} + \frac{k^{anion} \cdot K_{eq}}{[H]^+} \quad (1)$$

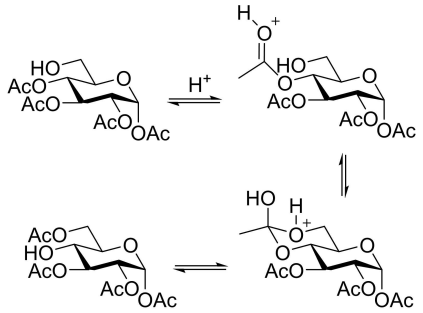
$$K^{obs} = \frac{k^{anionic} \cdot K_{eq}}{[H]^+} \quad (2)$$

Energies corresponding to the observed rate constants were obtained by considering the pK_as when calculating the energies of the acetyl group migration in several structurally different carbohydrate molecules. The same mechanism was applied to acetyl group migration over the glycosidic bond in both glycan and mannan trisaccharides, with good results considering the challenge of calculating the pK_as and the conformations of such flexible trisaccharides.[17]

The mechanism in aqueous media differs from those in other solvents, where the possibility for migration under acidic or neutral conditions becomes more viable. One such example was studied by Crout and co-workers.[13] They studied the migration in toluene in the presence of acetic acid to facilitate the migration process. The acetyl group migration took place mainly from O4→O6, which is fast compared to secondary-to-secondary hydroxyl group migrations. The study was performed at high temperature with O3→O4 migration observed in galactose but not in glucose, due to the *trans/cis* relationship of the hydroxyl groups. This mechanism commences with protonation of the carboxylic oxygen, followed by nucleophilic attack of the hydroxyl group at the carbonyl carbon (Scheme 6). Next, deprotonations and protonation of the hydroxyl groups take place to yield the final migration product. Currently, it is only in this single study where the acid catalyzed mechanism has been suggested, no other support has been published. Considering the high temperature and long experimental time needed for the migration, and that no migration took place over *trans*



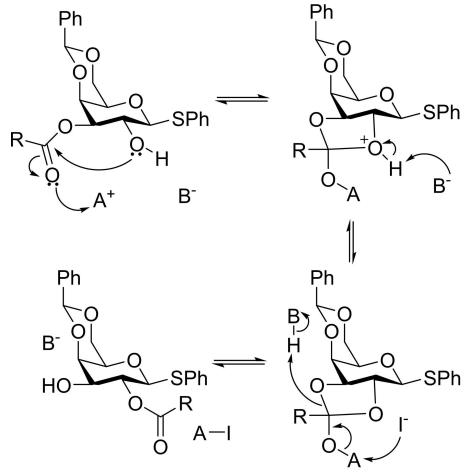
Scheme 5. Acetyl group migration in Me α-D-glucopyranoside.



Scheme 6. The mechanisms of the acid catalyzed migration paths.

hydroxyl groups, it appears conceivable that the mechanism under these conditions proceeds via a neutral mechanism, with acetic acid acting as a proton transferer. More studies are required to more accurately understand how the migration mechanism proceeds under these conditions.

Another example of a different mechanism involves both a Lewis acid and a base. This mechanism was suggested by Deng and co-workers, who studied the benzoyl migration in a galactoside derivative,[16] where iodine in combination with CsO_2CCF_3 or Ag_2O in DMF was applied. Interestingly, the suggested mechanism starts with a nucleophilic attack by the hydroxyl group at the carbonyl carbon, which is then stabilized by the Lewis acid, prior to deprotonation of the hydroxyl group (Scheme 7). Next, the Lewis acid is removed, and the carbonyl functionality is reformed by breaking the earlier C–O bond. It should be noted that no computational studies were performed. Conceivably, the described mechanism could commence by deprotonation prior to the nucleophilic attack, considering that the base catalyzed mechanism was favored over the neutral mechanism in our previous work.[15] It would be interesting to investigate further how important the base and acid are, backed up by computations.



Scheme 7. The mechanisms of Lewis acid and base catalyzed migration path.

Summary and Outlook

The experimental evidence and computational support on the migration processes in aqueous solution suggest that the migration proceeds via a basic or neutral reaction mechanism, depending on the pH. This conclusion is significant, since the migration might play a key role in the biological activity of several compounds, such as acyl glucuronides and polysaccharides. Consequently, it could become possible to evaluate and predict where migration processes are taking place in cells. In aqueous solutions, the use of different buffers should also be explored, as it has been shown that the buffer strength influences the rate of migration,[15] meaning that studies where different buffers have been used are not directly comparable. How the different counter ions can stabilize the anion has also not been explored in detail yet.

In anhydrous solutions the mechanism is not fully understood. Further investigations into the mechanism when the migration is not taking place in water should be performed. Such investigations would shed light on the migration mechanism under non-aqueous conditions. It would become easier to adjust the conditions and reagents to suppress or enhance the migration, if the mechanism were fully understood.

Migrations in furanosides have not been thoroughly explored. This is surprising, considering that both ribose and deoxy ribose are part of the fundamental molecules of life itself. Much remains to investigate also regarding the migration across the glycosidic bond in oligo- and polysaccharides. The surface of the possible combination of linkages and carbohydrates has just been touched.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: acetyl group · acyl group migration · carbohydrates · computational chemistry · reaction mechanisms

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