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Counterion-Directed Regioselective Acetylation of Octyl β-D-Glucopyranoside

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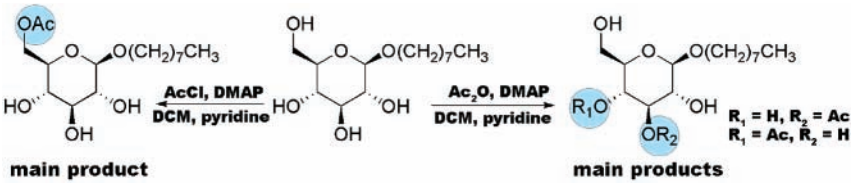
ABSTRACT



The DMAP-catalyzed acetylation of octyl β-D-glucopyranoside with a series of acetylating agents has been investigated. The nature of the counterion of the catalytic DMAP-acetyl complex dramatically influences the outcome of the reaction, indicating that the deprotonation of the transition state is controlling the reaction. Noncovalent interactions of the acetate ion with the substrate seem to direct the acetylation toward secondary hydroxyl groups.

The regioselective manipulation of polyfunctional molecules is one of the major challenges in organic chemistry. Carbohydrates, as protagonists in the rising field of glycobiology, represent an excellent playground for studying selective reactions. Due to the biological significance of this important class of compounds, a strategy, which facilitates a regioselective derivatization of sugars with minimal preparative efforts, would be highly desirable.[1]

One of the most studied reactions is the acetylation of alcohols. There are numerous reports on attempts to improve the selectivity and efficiency of this transformation. After the discovery of the beneficial role of DMAP (4-(dimethylamino)pyridine) as a nucleophilic catalyst for this reaction,[2] a series of equally or even more reactive nucleophilic catalysts has been reported.[3] The activation of the acylating agent by Lewis acids represents an alternative to the basic/nucleophilic catalysis. In addition to metal-based homogeneous catalysts[4] some heterogeneous systems have been found to be efficient, easily removable promoters for acetylations.[5]

Currently, one of the major goals in the design of catalysts consists of finding asymmetric derivatives, which allow for an enantioselective acetylation of racemates. The main body of work is related to the variation of the DMAP structure in a chiral environment.[6] Other systems are based on chiral

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trialkyl phosphines,[7] tertiary amines,[8] or imidazoles.[9] In contrast to the large amount of literature dealing with structural variations of catalysts for the acetylation there are only a few reports that are (partly) concerned with the role of the acetylating agent.[2b,10] The commonly used acetyl donors acetic anhydride and acetyl chloride, respectively, are supposed to react with DMAP to build a covalent, ionic intermediate (**A**, Figure 1). Subsequently, this reactive species

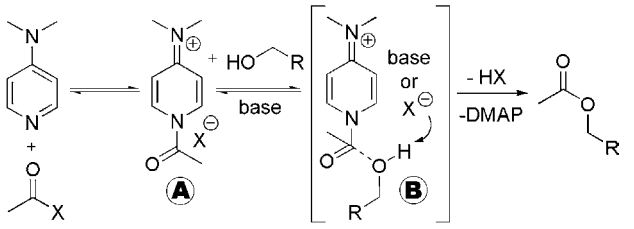

Figure 1. Mechanism of the DMAP-catalyzed acetylation.

reacts with the alcohol (**B**, Figure 1). Deprotonation of this complex gives rise to the formation of the ester and regenerates the catalyst. NMR and IR studies have shown that the equilibrium of the reaction of acetyl chloride and DMAP is shifted completely to the right, whereas acetic anhydride only gives 5−10% of the corresponding ionic complex (**A**) at room temperature.[1b] The concentration of this active complex is believed to control the reaction rate (Figure 1). However, it was noted by several groups that DMAP-catalyzed acetylations with acetyl chloride as acetyl donor are slower than those with acetic anhydride.[2b,3a] A given explanation for that is based on structural differences in catalytically active ion pairs. Mesomerically stabilized anions such as acetates exist as wider ion pairs compared to those with anions such as chloride. The attack of the nucleophile to wider ion pairs should be facilitated. Additionally, the acetate ion can act as a general base catalyst by deprotonating the nucleophile in the transition state. Though this explanation seems to be plausible no experiments have been carried out to support this notion. Recently, Yoshida et al. disclosed some surprising results on the DMAP-catalyzed acetylation of different octyl glycopyranosides.[1a] By using Ac_2O in the presence of a heterogeneous base (K_2CO_3), mainly the secondary hydroxyl groups at positions 3 and 4 were acetylated, the primary group at C-6 remained almost unaffected. These contraintuitive results were attributed to a complex hydrogen bond network and to the catalytic activity of DMAP.

In this paper we want to communicate our results, which indicate that the deprotonation of the transition state has a pronounced impact on the reaction rate for primary and secondary alcohols. Depending on the auxiliary base, the relative reactivities of acetyl chloride and acetic anhydride can be reversed, which was shown by kinetic measurements with simple alcohols. Octyl β-D-glucopyranoside can be acetylated with high selectivity either on the primary or on secondary OH groups by using different acetylation agents under otherwise identical conditions.

To compare the reactivity of different acetylating agents, we started a series of experiments with 1-propanol and 2-propanol. K_2CO_3 served as a heterogeneous or pyridine as a homogeneous base in our experiments with $CDCl_3$ as solvent. DMAP was used as a catalyst in all cases. Acetyl chloride, being the reagent with the highest carbonyl reactivity among the tested reagents, is converted very fast in the presence of pyridine (2 equiv) as auxiliary base in $CDCl_3$ as solvent and 5 mol % of DMAP as catalyst. ^{1}H NMR kinetics indicate a half-life for the reaction with both 1-propanol as well as 2-propanol of less than 10 s. In correlation with the lower carbonyl reactivity, the reaction rate for acetic anhydride was significantly slower for both 1- and 2-propanol ($t_{1/2}$ = 11 and 120 min, respectively). With K_2CO_3 as the heterogeneous, auxiliary base the relative order of reaction rates was *reversed* and the half-life times for both reactions with acetyl chloride were rather slow ($t_{1/2}$ = 35 and 200 min). This observed low reactivity is consistent with previous reports (vide supra).[2b,3a] In contrast to that, the reactions with acetic anhydride were considerably faster under these conditions ($t_{1/2}$ = 3.2 and 18 min).[11] Though these results, in view of marked differences in carbonyl activity, might be surprising at first sight, the reversed reaction rates may be contributed to the basicity of the counterion of the catalytically active ionic complex (**A**, Figure 1). In the presence of a homogeneous base the deprotonation of the transition state (**B**, Figure 1) can be performed by the auxiliary base or the counterion. By using a base such as K_2CO_3, which is insoluble in the reaction system, the deprotonation has to be carried out by the acetate or chloride counterion. This implies that the proton-transfer step influences the reaction rate. To support this notion experiments with the labeled compounds

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(11) In contrast to the acetylation with 2 equiv of pyridine (Table 1, entry 2), the solvent environment is less polar, thereby accelerating the reaction: see refs 2b and 10.

1-propanol-d_1 and 2-propanol-d_1 were conducted. Primary kinetic isotope effects under basic conditions in the range 1.1−1.9 reflect the impact of the deprotonation step on the reaction rate. Since primary kinetic isotope effects of >2 have to be expected for general base catalysis and of 1−1.5 for nucleophilic catalysis,[12] no stringent conclusion about the operating mechanism can be drawn.

Although acetyl cyanide is prone to homodimerization under basic conditions,[13] it can be used as an acetyl transfer reagent under nucleophilic catalysis.[14] Acetyl cyanide differs from acetic anhydride and acetyl chloride, since the released anion CN^- represents a rather strong base with a pK_a of 9.4 for the conjugated acid. As can be seen from Table 1, acetyl cyanide rapidly reacts with 1-propanol *independent* from the base in use. Due to the unwanted homodimerization, the preparative potential is narrowed; however, it underlines the important role of the counterion for DMAP-catalyzed acetylations.

Table 1. Experimental Half-Lives ($t_{1/2}$ (min)) and Primary Kinetic Isotope Effects (k_D/k_H in Parentheses) for the Reaction of 1- and 2-Propanol with Three Different Acetylating Agents

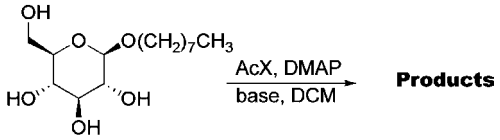
		base[a]	Ac_2O	AcCN	AcCl
1	1-propanol	K_2CO_3	3.2 (1.6)	1.3 (1.9)	35 (1.8)
2		pyridine	11 (1.4)	1.0 (1.4)	<0.2 (n.d.)[b]
3		none	30 (1.6)	1.5 (1.4)	33 (1.4)[d]
4	2-propanol	K_2CO_3	18 (1.3)	n.d. (1.3)[c]	200 (1.3)
5		pyridine	120 (1.6)	32 (1.1)	<0.2 (n.d.)[b]
6		none	350 (1.3)	n.d. (1.2)[c]	120 (0.9)[d]

[a] 4 equiv of K_2CO_3 and 2 equiv of pyridine. [b] n.d. = not determined; the reaction was too fast for an accurate determination of $t_{1/2}$ (100% conversion after 2 min). [c] The homodimerization of acetyl cyanide is faster than the acetylation (the conversion does not exceed 40% in any case). [d] Autocatalysis of the released HCl is assumed.

This marked counterion effect prompted us to (re)-investigate the reaction with a more complex substrate, namely octyl β-D-glucopyranoside. Monosaccharidic glycosides are endowed with three secondary hydroxyl groups of comparable reactivity and one primary, slightly more reactive OH group. Selective acetylation of the primary hydroxyl group is supposed to be predominant.[15] However, as demonstrated by Yoshida et al. in a comprehensive study,[1a] the hydroxyl groups at C-3 and C-4 preferentially react with Ac_2O in $CHCl_3$ in the presence of DMAP and K_2CO_3 as auxiliary base.

In our experiments, to accurately determine the product distribution, mild (0 °C) reaction conditions and a stoichiometric amount (1.0 equiv) of the acetylating agents were employed. CH_2Cl_2 as a nonpolar solvent should allow efficient intra- and intermolecular hydrogen bonding. Acetyl group migrations could be avoided by careful temperature control (0 °C) during the reaction.[16] By using K_2CO_3 as auxiliary base the results of Yoshida et al. could be reproduced with minor deviations due to slightly varied reaction conditions (Table 2, entry 1). However, AcCl gave, albeit in moderate yield, mainly the 6-acetate (entry 5). Since both reactions have been conducted under the same reaction conditions, the altered regioselectivity has to be attributed to the counterions, assuming that a quaternary ammonium salt (structure **A**, Figure 1) represents the reactive species in both cases.

Table 2. Product Distribution and Isolated Yields of the Acetylation of Octyl β-D-Glucopyranoside under Varying Conditions



	conditions[a]	2-OAc	3-OAc	4-OAc	6-OAc	yield[b]
1	Ac_2O, K_2CO_3		0.50	0.46	0.04	47%
2	Ac_2O, pyridine		0.57	0.23	0.20	60%
3	AcCN, K_2CO_3		0.15	0.08	0.77	44%
4	AcCN, pyridine		0.16	0.08	0.76	46%
5	AcCl, K_2CO_3	0.06	0.17	0.03	0.74	44%
6	AcCl, pyridine		0.12	0.03	0.85	73%
7	$AcOCO_2tBu$, K_2CO_3	0.06	0.44	0.25	0.25	59%
8	$AcOCO_2tBu$, pyridine		0.48	0.18	0.34	83%

[a] All reactions were performed in the presence of 5 mol % of DMAP and 1 equiv. of auxiliary base. [b] The yield refers to isolated monoacetylated sugars.

This effect has also been observed when pyridine was used as a homogeneous base (entries 2 and 6). The reaction with AcCl is fast and gives monoacetylated sugars in 73% yield, with predominant formation (85%) of the 6-acetate. A possible explanation for this phenomenon is given in Figure 2. In contrast to the chloride ion, the acetate ion can interact with two OH groups by forming a noncovalently linked cyclic transition state. The primary OH group directs the deprotonation toward the secondary OH groups at positions 3 and 4. The deprotonation of the secondary OH groups in

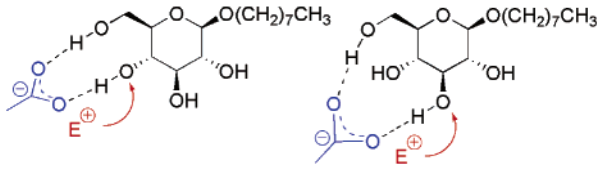


Figure 2. Directed acetylation of secondary OH groups.

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proximity is thereby facilitated. This is not possible for chloride as counterion. To support this notion, AcCN was submitted to the reaction with octyl β-D-glucopyranoside. Similar to the chloride ion, cyanide should not be able to direct the acetylation toward the secondary OH groups. A pronounced selectivity for the primary OH group was found under the applied conditions (entries 4 and 5). Contrarily, acetyl *tert*-butyl carbonate,[17] despite steric demands of the released *tert*-butyl carbonate anion, preferentially acetylates the secondary OH groups at position 3 and 4 with a ratio of 3 to 1 (entry 7).

A prerequisite for the participation of the counterion consists of the formation of a quaternary ammonium salt. Depending on the nature of the acylating agent and the tertiary amine the formation of such a species is possible, thereby enabling nucleophilic catalysis. Brittain et al. showed by ^{1}H NMR experiments that quinuclidine, though to a lesser extent than DMAP, can give quaternary ammonium salts.[12a] Pyridine, however, as a rather poor nucleophile does not give such a reactive intermediate with Ac_2O. By using the latter as catalyst and auxiliary base (1.05 equiv), the reaction with Ac_2O was slow and the 6-acetate was formed as the major product, indicating a general base catalysis of pyridine. By using quinuclidine as catalyst (0.05 equiv), K_2CO_3 as auxiliary base (1 equiv), and Ac_2O as reagent the product distribution was comparable to that obtained with DMAP with 3- and 4-acetates as major products.

In the present study we have shown that the rate and the selectivity of an acetylation reaction can be controlled by the counterion of the acetylating agent under nucleophilic catalysis. The team play of reagent, catalyst, and auxiliary base is responsible for the outcome of the reaction. Further studies dealing with other functional (e.g. chiral) counterions will be reported in due course.

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Supporting Information Available: Experimental procedures and selected spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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