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Carbohydrate Research 342 (2007) 1998–2002
Carbohydrate RESEARCH

Chelation-controlled regioselectivity in the lanthanum-promoted monobenzoylation of monosaccharides in water

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Received 28 March 2007; received in revised form 16 May 2007; accepted 19 May 2007
Available online 2 June 2007

Abstract—Monosaccharides are selectively converted to monobenzoates in a base-catalyzed reaction with benzoyl methyl phosphate (BzMP) and a lanthanum salt in water. Yields are reported in terms of formation of the ester, which competes with hydrolysis of BzMP, to give an estimate of the efficiency of the conversion of the sugar. Higher conversions can be achieved using excess reagent. Regioselectivity is influenced by the structure of the glycoside. For example, the reaction leads to different product distributions from α- and β-anomers of the glycosides. The reaction combination provides a basis for efficient ester formation in specific geometric situations, providing a means of identification as well as modification.

Keywords: Benzoyl methyl phosphate; Lanthanide; Catalysis; Water; Regioselective monoacylation; Aqueous reaction and recognition

1. Introduction

The formation of esters in water involves an inherent competition for the acyl donor between the reacting hydroxyl group and solvent water. We have found that acyl phosphate monoesters are useful in these reactions because ester formation occurs by coordination of a lanthanide ion to these molecules along with a vicinal diol. It was proposed that this reaction proceeds as a specific base-catalyzed process via a bis-bidentate chelated lanthanide in which both the acyl phosphate and diol are ligands. This pattern suggests that the combination of lanthanum and an acyl phosphate monoester could lead to selective monoacylation of carbohydrates in water. The selectivity would be based on the extent of chelate formation and reactivity within the chelate. Such a pattern has precedent in metal–carbohydrate interactions that lead to regioselective acylation[1–10] That anticipation was borne out by the demonstration that lanthanum salts promote the monobenzoylation of several monosaccharides in water (with benzoyl methyl phosphate, BzMP[11]). The pattern of the reaction is consistent with the proposed formation of a bis-bidentate chelate of lanthanum from two hydroxyls of the carbohydrate and the anhydride within BzMP. This is also consistent with observations of lanthanide catalysis of monoacylation of diols in organic solvents.[12,13]

Efforts to extend the selective, metal-directed acylation reactions to carbohydrate modifications from organic solvents to water have been hindered by competitive occupation of the metal ion coordination sphere by water molecules[7,14] Furthermore, carbohydrates have strong hydrogen bonding interactions with water. These compete with intramolecular hydrogen-bond networks that effectively control the relative reactivity of hydroxyl groups in organic solvents[15–17] This contrasts with the specific recognition of glycosides in water[18–20] We have now examined the reaction patterns of a range of related glycosides in water with lanthanum–BzMP, giving monobenzoylation. The results present a combination of sufficient reactivity and selective recognition to make this method one that should be of interest for specific applications that require reactions to be conducted in water.

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doi:10.1016/j.carres.2007.05.024

2. Experimental

2.1. General methods

Reagent grade chemicals were used as received. High-resolution mass spectrometry was performed at the QStar Chemistry Mass Spectral Facility, the University of Toronto. HPLC analysis and preparation were performed with C18 reversed phase analytical columns (3.9 mm × 300 mm) and preparative columns (7.8 mm × 300 mm). Samples were eluted with water and acetonitrile. Solvents were filtered and degassed before use. BzMP was readily prepared by the reported procedure.[21] Ester formation was followed by HPLC and detected at 230 nm upon elution from the analytical column. Reactions were usually complete within 20 min. The products remained stable in the reaction solution so the samples were usually left for 2 h to assure completion. The sample was eluted with 80:20 (v/v) water–acetonitrile containing 0.1% trifluoroacetic acid (TFA) with a flow rate of 1.5 mL/min. The relative yields of products obtained in the reactions were determined by integration of the areas of the HPLC peaks for the esters (from glycosides) and acid (from hydrolysis) formed from BzMP in the presence of each glycoside. HPLC (preparative column) was used to separate the esters resulting from the reaction, with the effluent monitored at 230 nm. The collected material was freeze-dried and stored at −20 °C. Confirmation of ester formation was established by high-resolution mass spectral analysis of parent peaks.

2.2. Lanthanum-catalyzed reactions of BzMP and glycosides

General procedure: 1–2 equiv of the glycoside and lanthanum trichloride were combined in 100 mM pH 8 *N*-(2-hyroxyethyl)piperazine-*N*′-(3-propanesulfonic acid (EPPS) buffer solution. BzMP (1.0 equiv) was added and the solution was stirred at room temperature. The reaction was monitored periodically by HPLC analysis. Each aliquot was quenched with a solution of pH 8 EDTA. Reactions were complete within 1 h and the products remained stable once formed.

2.3. Measurement of yields

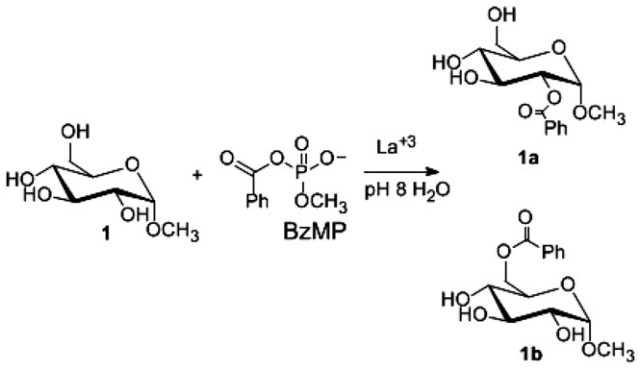
BzMP reacts with water as well as with the hydroxyl groups of the glycosides in this study. The yields are based on the net amount of benzoate ester produced compared to the reagent added.

3. Results and discussion

The lanthanum-promoted reaction of BzMP with methyl α-D-glucopyranoside (**1**) yields two products, 2-*O*-benzoate ester (**1a**) and 6-*O*-benzoyl ester (**1b**), as summarized in Scheme 1. Similarly, the reaction of methyl β-D-glucopyranoside with BzMP and lanthanum produces the corresponding 2-*O*-benzoyl and 6-*O*-benzoyl esters. In reactions of the methyl α-D-glucopyranoside, the 2-*O*-benzoate ester is formed to a larger extent than the 6-*O*-benzoate ester (Table 1). The reaction of the β-glycoside gives the 6-*O*-benzoate ester in a 2.5:1 ratio over the 2-*O*-benzoate ester. No products with more than one ester group were detected. Our reported yields are based on the amount of the reagent BzMP we added, which was equimolar with the carbohydrate. Yields are reported to provide a measure of the observed rate of benzoylation competing with hydrolysis of the reagent. Because water is the solvent, it is necessarily present in great excess. For practical conversions, we note that the remaining glycoside can be reacted with additional reagent and the unreacted glycoside can be recovered. Reagents that function in organic solvents will not be subject to this competition, so that reported yields should not serve as a basis for comparison.

Our observation that reaction of 1 equiv of BzMP with a methyl glycoside produces two monoesters is consistent with formation of a chelated intermediate in which the subsequently modified hydroxyls are coordinated to lanthanum. For the esters to be produced, BzMP must also form a second bidentate chelate on lanthanum, permitting the reaction to occur in a bis-bidentate array with the conjugate base of a hydroxyl group.

As a probe of the origins of the observed regiospecificity, we reacted methyl β-D-xylopyranoside and 1,6-anhydro-D-glucopyranose with BzMP and lanthanum chloride. Based on the proposed coordination scheme, the xylopyranoside should not be esterified as it cannot form a chelate with its terminal hydroxyl, which is incorporated as an ether into the acetal function at C-1 (Table 1). While the 1,6-anhydro-β-D-glucopyranose cannot react at the C-6 hydroxyl, it can nonetheless coordinate to lanthanum at that position via a non-bonded electron pair of the oxygen atom, in addition to coordinating and



Scheme 1. Lanthanum-promoted benzoylation of methyl α-D-glucopyranoside by BzMP.

Table 1. Esters from the reaction of BzMP with monsaccharides and lanthanum

Reactant[a]	Ester products[b]	Molar ratio[c]	Yield[c] (%)
Methyl α-D-glucopyranoside	2-*O*-Bz, 6-*O*-Bz	2.8:1	33
Methyl β-D-glucopyranoside	2-*O*-Bz, 6-*O*-Bz	0.1:2.5	13
Methyl α-D-galactopyranoside	2-*O*-Bz, 3-*O*-Bz, 6-*O*-Bz	1:1.5:1.5	50
Methyl β-D-galactopyranoside	2-*O*-Bz, 3-*O*-Bz, 6-*O*-Bz	0.1:1:1.1	41
Methyl α-D-mannopyranoside	2-*O*-Bz, 3-*O*-Bz, 6-*O*-Bz	2:1:1	25
1,6-Anhydro-β-D-glucopyranose	2-*O*-Bz		37
D-Ribose	2-*O*-Bz, 3-*O*-Bz, 4-*O*-Bz	5:1:3	91
Methyl D-ribopyranoside (anomeric mixture)	2-*O*-Bz, 3-*O*-Bz, 4-*O*-Bz	8:1:1	80
Methyl β-D-xylopyranoside	0		0
2-Hydroxy-tetrahydropyran	0		0
D-Glucal	0		0

[a] Reaction conditions: substrate (1 equiv), BzMP (1 equiv), $LaCl_3$ (2 equiv), pH 8 EPPS 20 °C.
[b] Determined by ^{13}C NMR , MS and HPLC after reaction.
[c] HPLC analysis based on the reagent (benzoylation competes with hydrolysis).

reacting with the conjugate base derived from the hydroxyl at C-2. This observation is consistent with our finding that for this example, the 2-*O*-benzoate ester forms exclusively (Table 1). A depiction of the proposed mechanism is presented in Scheme 2.

The importance of the presence of the anomeric oxygen in the reacting substrate was tested in the reactions of 2-hydroxy-tetrahydropyran and D-glucal. In both cases, no ester products were formed (Table 1). The mechanism in Scheme 2 is consistent with the combined preceding results.

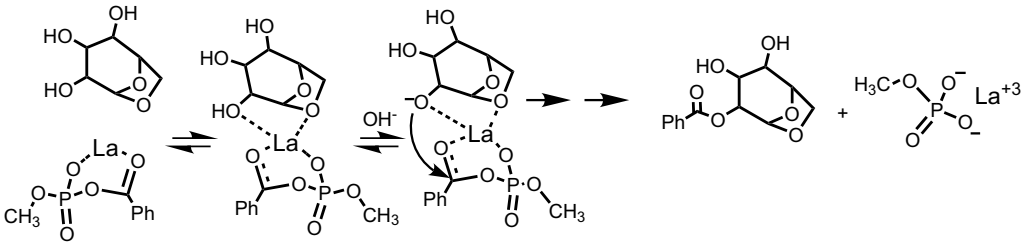
We also assessed the extent of esterification of galactose derivatives under the conditions we used with glucose derivatives. Methyl α-D-galactopyranoside and methyl β-D-galactopyranoside react with BzMP and lanthanum chloride to form esters at positions 2, 3, and 6 (respective product ratios: 0.1:3:4 and 1:1.5:1.5.). These results are consistent with chelation leading to ester formation via the 6-hydroxyl group and either the 2 or 3 hydroxyl groups as illustrated in Scheme 2. Molecular mechanics modeling (using Cambridge Software's Chem 3D) reveals that both modes are readily accessible.

We examined the reaction of a mixture of the α- and β-anomers of methyl ribopyranoside with BzMP and lanthanum chloride. This produced monobenzoate esters, predominantly at the O-2 position along with small amounts of the esters at O-3 and O-4. D-Ribose reacts to give a similar pattern of esters (Table 1). If reaction occurs through the pyranose from, the 2 and 3 hydroxyls most readily form a chelate of lanthanum. An alternative chelate that could form via the 4 and 3 hydroxyls can account for the additional ester formed at the 4 position.

We assessed the effectiveness of non-lanthanide metals in promoting ester formation. As expected from previous work, none gave a significant amount of an ester product (2% or less). On the other hand, all lanthanide metal ions promoted formation of esters with significant regioselectivity and yield (Table 2).

Our results suggest that the lanthanide ions promote ester formation through their ability to achieve the necessary highly coordinated state as well as Lewis acidity. Although lanthanides in general promote the reaction, each ion differs in its effect on the regioselectivity of the overall process. There is a relationship between the radius of the ion and the product ratio (Table 2 and Fig. 1), with the larger ions favoring formation of the ester at the 2-position while the smallest ion gives the opposite preference. In particular, lanthanum gave the highest ratio of the 2-*O*-benzoate ester to the 6-*O*-benzoate ester while dysprosium gave equal amounts (Fig. 1) and ytterbium ion yielded more of the 6-*O*-benzoate ester than the 2-*O*-benzoate ester.

The ability of the combination of an acyl phosphate monoester and lanthanum chloride to differentiate between glycosides based on their structure and conformation was assessed as a possible application for aqueous molecular recognition. The results summarized in Table 3



Scheme 2. Bis-bidentate chelation of lanthanum by 1,6-anhydro-β-D-glucopyranose and BzMP leads to regioselective ester formation. Reaction to form the ester at O-2 is shown.[22]

Table 2. Products from the reaction of BzMP and methyl α-D-glucopyranoside in the presence of lanthanide ions

Metal ion[a]	Product ratio[b]		Yield[c] (%)
	2-*O*-Bz	6-*O*-Bz	
La	2.8	1.0	32
Ce	2.7	1.0	14
Pr	2.4	1.0	20
Nd	2.2	1.0	28
Eu	1.4	1.0	34
Dy	1.1	1.0	24
Yb	1.0	1.6	28

[a] Conditions: methyl α-D-glucopyranoside (1 equiv), BzMP (1 equiv), Ln (1 equiv), pH 8 EPPS 20 °C.
[b] Determined by NMR, MS and HPLC.
[c] HPLC. Yield is based on BzMP (ester as a fraction of ester + acid).

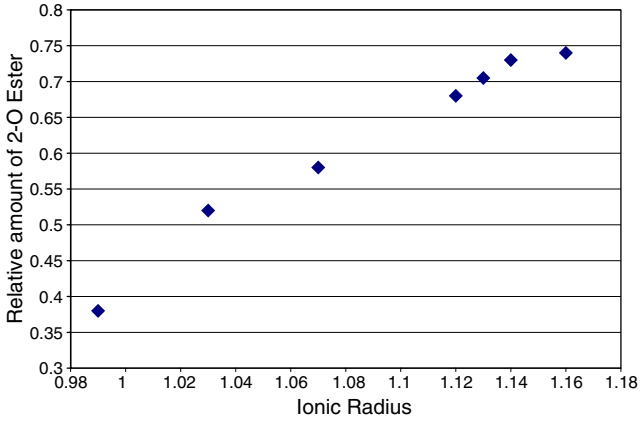


Figure 1. Relative amount of O-2 ester (as a fraction of combined O-2 and O-6 esters) in relation to the ionic radii (Å) of lanthanide^{+3} ions.

demonstrate this by showing the partial and distinct differences in product ratios for a series of hexopyranoside mixtures. Entry 4 demonstrates an 11:1 difference between the product ratios of methyl β-D-galactopyranoside and methyl β-D-glucopyranoside, which is in contrast to the result from their α analogs (entry 1). In addition the reaction demonstrates an ability to recognize the anomeric difference between the respective α and β-glucopyranosides and galactopyranosides (Table 3, entries 6 and 7). The reaction pattern for the respective α and β-hexopyranosides gives the following recognition sequence: methyl galactopyranoside > methyl mannopyranoside > methyl glucopyranoside. This implies that the galactopyranoside stereochemistry is more favorable for reaction under these conditions.

When the reaction was applied to the mixture of methyl α-D-glucopyranoside and D-ribose (Table 3, entry 11) a 1:15 product ratio was observed for the respective glycosides. This demonstrates the discrimination between the pentoses and hexoses. The reaction also distinguishes between methyl D-ribosides and D-ribose (entry 12). Therefore, the different structural geometries of the glycosides lead to differences in the stability of the glycoside–metal complex. This would suggest that the reaction recognizes subtle differences in glycoside structure.

In summary, our results show that coordination geometry is an important feature in controlling reaction products, consistent with the mechanism of reaction involving selective chelate formation. The yields of ester are variable and relate to the structure of the reactant. Competing hydrolysis of BzMP prevents the reaction from being highly efficient in terms of the use of the reagent. In addition the different reactivity patterns can help in identification of a reacting species.

Acknowledgment

We thank NSERC for support of this research through a Discovery Grant.

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Table 3. Product ratios from competitive reactions of BzMP with glycoside mixtures and La^{+3}

Reactants[a]	Entry number	Ester product ratio[b]
Methyl α-D-glucopyranoside, methyl α-D-galactopyranoside	1	1:3.0
Methyl α-D-glucopyranoside, methyl α-D-mannopyranoside	2	1:1.2
Methyl α-D-mannopyranoside, methyl α-D-galactopyranoside	3	1:1.9
Methyl β-D-glucopyranoside,methyl β-D-galactopyranoside	4	1:11.0
Methyl α-D-glucopyranoside: methyl β-D-galactopyranoside	5	1:1.4
Methyl β-D-galactopyranoside, methyl α-D-galactopyranoside	6	1:2.2
Methyl β-D-glucopyranoside, methyl α-D-glucopyranoside	7	1:3.5
Methyl β-D-galactopyranoside,methyl α-D-mannopyranoside	8	1.1:1
Methyl α-D-glucopyranoside, methyl α-D-galactopyranoside, methyl α-D-mannopyranoside	9	1.3:1:2.8
Methyl α-D-glucopyranoside, methyl β-D-galactopyranoside, methyl α-D-mannopyranoside	10	1:1.3:1.2
Methyl α-D-glucopyranoside, D-ribose	11	1:15
Methyl D-ribopyranoside, D-ribose	12	1:7

[a] Reaction conditions: substrate (1 equiv), BzMP (1 equiv), $LaCl_3$ (1 equiv), pH 8 EPPS 20 °C.
[b] Determined from HPLC analysis.

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