Lanthanum-catalyzed aqueous acylation of monosaccharides by benzoyl methyl phosphate[1]

Ian James Gray, Rui Ren, Bernhard Westermann, and Ronald Kluger

Abstract: It was previously reported that diols dissolved in water (pH 8, EPPS buffer) react with benzoyl methyl phosphate (BMP) in the presence of lanthanide ions to form monobenzoyl esters. We have investigated the possibility of extending this process to include formation of esters of monosaccharides in water from lanthanide-catalyzed reactions with BMP. The combination of methyl-α-D-glucopyranoside and BMP in the presence of lanthanum trichloride gave selective monoacylation of the 2- and 6-hydroxyl groups in a ratio of 2:1. The likely mechanism involves preferential bisbidentate coordination of BMP and the diol to lanthanide ion (which explains how an ester forms when water is in enormous excess) followed by base-catalyzed intramolecular acyl transfer. The method should be generally applicable where a selective acylation reaction in water as solvent is desirable.

Key words: benzoyl methyl phosphate, lanthanide, catalysis, water, monoacylation, selective.

Résumé : Il a été rapporté antérieurement que les diols dissous dans l'eau (pH de 8 et tampon « EPPS ») réagissent avec le phosphate de benzoyle et de méthyle (PBM), en présence d'ions de lanthanide, pour conduire à la formation d'esters monobenzoylés. On a examiné la possibilité d'étendre cette méthode de façon à inclure la formation d'esters de monosaccharides, par des réactions en milieu aqueux avec du PBM et catalysées par des lanthanides. La combinaison de l'α-D-glucopyranoside de méthyle et du PBM, en présence de trichlorure de lanthane, conduit à la monoacétylation sélective des groupes hydroxyles en positions 2 et 6, dans un rapport de 2 : 1. Le mécanisme probable implique la coordination bisbidentate préférentielle du PBM et du diol à l'ion lanthanide (qui explique comme un ester peut se former en présence d'un énorme excès d'eau), qui est suivie d'un transfert de groupe acyle intramoléculaire catalysé par la base. La méthode devrait être applicable d'une façon générale quand il est désirable d'effectuer une réaction d'acétylation sélective en utilisant l'eau comme solvant.

Mots clés : phosphate de benzoyle et de méthyle, lanthanide, catalyse, eau, monoacétylation, sélective.

[Traduit par la Rédaction]

Introduction

We are reporting our work in conjunction with the production of an issue of the *Canadian Journal of Chemistry* honoring Walter Szarek, whose work in the field of biological carbohydrate chemistry exemplifies his insight, perspective, and creativity. In addition, Walter's outstanding personal qualities match his science.

Reactions that accomplish selective monoacylation of carbohydrates take advantage of differences in the inherent reactivity of individual hydroxyl groups (1, 2). For example, monobenzoates result from reactions of *N*-benzoyl imidazole and benzoyl cyanide with protected monosaccharides, provided that the combination of regioselection and product stability is sufficient (3). Subtle differences in the reactivity of hydroxyls and the catalysis of group migration add to the complexity of possible outcomes (4).

Benzoyl methyl phosphate (BMP) is an acyl phosphate monoester, a class of materials that resists hydrolysis and is inherently unreactive toward alcohols (5). Yet, acyl phosphates are anhydrides that have a high chemical potential for acyl transfer and are utilized in diverse biochemical acylation, including the formation of aminoacyl tRNAs. It was recently reported that BMP can form monobenozyl esters from diols in water in the presence of lanthanide ions (6). It is likely that bidentate coordination is the key to the selective acylation reaction since under similar conditions there is only a modest acceleration of base-catalyzed hydrolysis and formation of methyl esters (in methanol–water mixtures) (7). The likely mechanism is consistent with Clarke et al.'s (8) observations of lanthanide-promoted monoacetylation of diols in nonhydroxylic solvents. They reported NMR data that characterized an intermediate bisbidentate-coordinated complex of the lanthanide with a diol and an anhydride. Ionization of a coordinated hydroxyl in such an intermediate leads to Lewis acid promoted intramolecular attack on the adjacent carbonyl of the coordinated anhydride to form the ester (7).

Based on this background, we have been interested in extending the utility of BMP as a water-stable benzoylating agent whose inherent specificity would be associated with

Received 8 September 2005. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 10 May 2006.

I.J. Gray, R. Ren, and R. Kluger.[2] Davenport Chemistry Laboratory, Department of Chemistry, University of Toronto, Toronto, ON M5S 3H6, Canada.
B. Westermann. Department of Bioorganic Chemistry, Leibniz Institute for Plant Biochemistry, Halle, Germany.

[1]This article is part of a Special Issue dedicated to Professor Walter A. Szarek.
[2]Corresponding author (e-mail: rkluger@chem.utoronto.ca).

 doi:10.1139/V06-047

the formation of lanthanide chelates from adjacent hydroxyls of the reactant, a description that could find useful applications in the carbohydrate field. Applications of lanthanide catalysis of reactions by acyl phosphate monoesters would be expected to provide for selection among hydroxyl groups based on the properties of their lanthanide chelates, rather than on the inherent differences of reactivity among the hydroxyl groups of the substrate. We have now investigated the reactions of typical monosaccharides with BMP and lanthanide ions and find that this combination can introduce chelation-based selectivity in monobenzoylation reactions conducted in water.

Experimental

Reagent grade chemicals were used as received. High-resolution mass spectrometry was performed at the QStar Chemistry Mass Spectral Facility, University of Toronto. HPLC analysis and preparation were performed with C18 reversed-phase analytical columns (Waters μBondapak™ C18 3.9 mm × 300 mm) and preparative columns (Waters μBondapak™ C18 7.8 mm × 300 mm). Samples were eluted with purified water and HPLC grade acetonitrile. Benzoyl methyl phosphate (BMP) was prepared by the previously reported procedure (6, 9). Acylation of the carbohydrates was followed by HPLC, detected at 230 nm on a C18 reverse-phase analytical column, and eluted with 75:25 (*v*/*v*) water–acetonitrile containing 0.1% trifluoroacetic acid (TFA). The flow rate was 1.5 mL/min. Solvents were filtered and degassed before use. The ratio of acylation and hydrolysis from BMP was determined from the relative molar amounts of reactants (carbohydrate:water) to their corresponding products (ester:acid), according to eq. [1]. The ratio of products was obtained from the areas of the HPLC peaks for the resulting esters and benzoic acid.

$$[1] \qquad k_{rel} = (\text{Area}_{ester}/\text{Area}_{acid}) \times ([H_2O]/[\text{carbohydrate}])$$

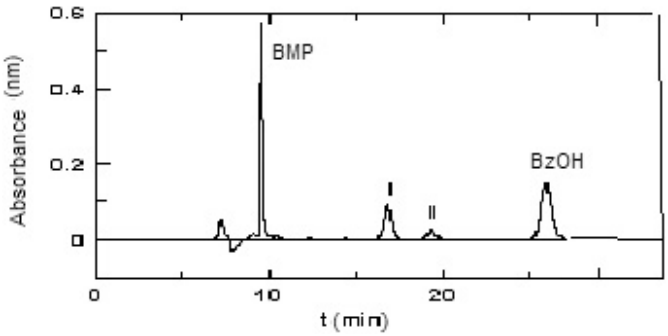
Separation of the ester products by was performed by HPLC. The effluent was continuously monitored at UV 230 nm on a C18 reverse-phase preparative column. The material in each product peak was freeze-dried and stored at –20 °C. The general structure was ascertained from the mass spectrum and refined by NMR analysis.

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was obtained commercially. Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside was prepared by the published method (10, 11).

Benzoylation of methyl-α-D-glucopyranoside (1) using BMP

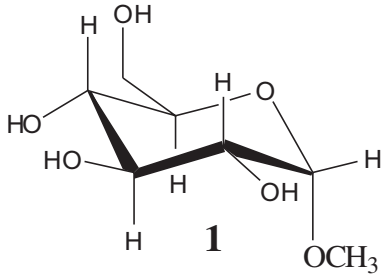
One equivalent of **1** and 2 equiv. of lanthanum trichloride were dissolved in 100 mmol/Lof EPPS buffer at pH 8. Freshly prepared BMP (1 equiv.) was added to this solution and stirred at room temperature. The reaction was monitored by HPLC (quenched with buffer (pH 8) containing EDTA at time points) and was complete within about 2 h. The disappearance of the BMP peak signified its conversion into benzoic acid and benzoyl ester products. Relative yields were calculated using internal standards.

Fig. 1. HPLC output for lanthanum-promoted reaction of BMP and **1**.



Results and discussion

Our initial studies focused on the monobenzoylation of methyl-α-D-glucopyranoside (**1**) with the intention of establishing a general procedure that extends to the monobenzoylation of other monosaccharides.



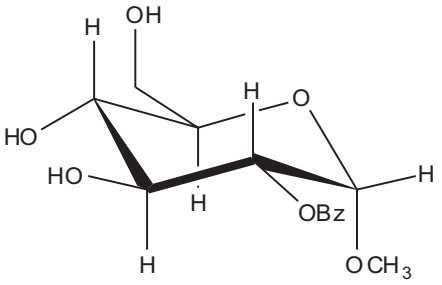
As expected, combining **1** with BMP in 100 mmol/L of EPPS (pH 8) without added lanthanum ion produces no reaction. Under the same conditions with added lanthanum, three new HPLC peaks are observed within 1 min (Fig. 1). We optimized reaction conditions by varying the concentration and found that 2 equiv. of lanthanum trichloride and 1 equiv. each of BMP and carbohydrate in 100 mmol/L of EPPS buffer at pH 8, produced a 33% conversion to the product esters within 2 h, while the remaining substrate could be recovered and BMP was hydrolyzed.

Each product was separated by preparative HPLC. ESI-MS analysis revealed two of the peaks to be monobenzoyl esters of **1**, while the third was that of benzoic acid from the hydrolysis of BMP.

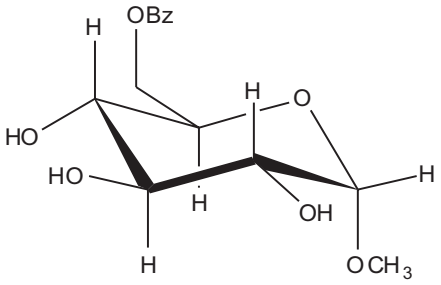
The stability of the esters in the reaction solution was observed over several days in the reaction solution. Product ratios were invariant, indicating that the hydrolysis of the benzoate esters is not promoted by the metal ions in the solution under these conditions. We have noted that lanthanum ions promote formation of monoesters from cis-diols by BMP in water (6). In **1**, the geometry of adjacent diols is constrained by the ring and this will affect coordination as well as the reactions of the coordinated species. The primary hydroxyl (6-position) and equatorial hydroxyl groups at positions 2, 3, and 4 are all potential candidates for benzoylation. Each of the products peaks was isolated to determine the pattern of the reaction.

Table 1. ^{13}C NMR chemical shifts for the monobenzoyl esters of **1** in DMSO.

Carbohydrate	C-1	C-2	C-3	C-4	C-5	C-6
1	99.23	71.21	73.08	69.55	71.56	60.56
Ester A	96.81	**74.68**	71.01	70.63	73.18	61.05
Ester B	99.59	71.62	73.18	70.15	69.59	**64.33**



Ester A



Ester B

Table 2. Relative rates of acylation and hydrolysis in EPPS buffer (pH 8) with 50 mmol/L of lanthanum trichloride, 25 mmol/L of BMP, and 25 mmol/L of carbohydrate.

Carbohydrate	Time (min)	k_{rel} (25 °C)	k_{rel} (0 °C)
Methyl-α-D-mannopyranoside	60	50	100
Methyl-α-D-glucopyranoside	60	370	730
Methyl-β-D-galactopyranoside	60	800	1 310
D-Ribose	60	8800	11 330

Analysis of the ^{13}C NMR spectra of the products (Table 1) indicate that reaction occurs at 2-OH and 6-OH preferentially.

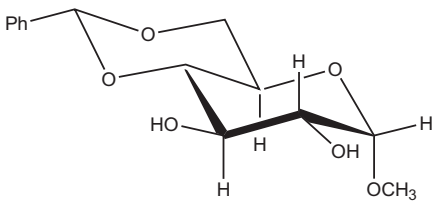
Due to competition with water, used as a solvent for the reaction, it is inevitable that BMP hydrolysis accompanies the monoacylation reaction. We found that hydrolysis was significantly less competitive at low temperatures (Table 2). The same carbohydrate reaction preferences hold at the lower temperatures, with ester formation being the major process.

In order for the reaction with BMP with the monosaccharide to compete with hydrolysis, the possibility of bidentate coordination must overwhelm the effect of overwhelmingly large excess of reaction sites in the water that serves as the solvent. To test this further, we proposed that no reaction would occur if the 6-hydroxyl is blocked, which would prevent the possibility of bidentate coordination. We used methyl-4,6-*O*-benzylidene-α-D-glucopyranoside and methyl-4,6-*O*-benzylidene-α-D-mannopyranoside. No ester formation occurs after 5 days with BMP and lanthanum trichloride under conditions where **1** reacts rapidly. This result supports the NMR-based analysis for reaction of **1**. More detailed product studies are in progress.

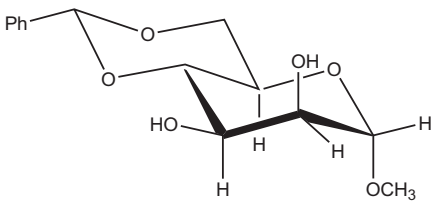
We have also done a preliminary survey of the reaction patterns of BMP and lanthanum trichloride with other monosaccharides (Table 3). From these results we see that the monobenzoylation process is applicable to a variety of species with varying efficacy: D-ribose > methyl-β-D-galactopyranoside > methyl-α-D-glucopyranoside > methyl-α-D-mannopyranoside.

For the reactants in Table 3, D-ribose gives the highest overall yield of ester products. However, we have not yet identified the individual monobenzoylated materials (there are three in all). The reaction of 2-deoxyribose leads to only two products, suggesting that one of the chelates involves the 2-OH. Two monobenzoylated esters were produced from uridine. There was no reaction with 2-deoxyuridine, as would be expected if 2,3-chelation is the major mode of reaction. The other aldohexose methyl pyranosides reacted similarly to the glucoside, giving two monobenzoylated products.

A probable mechanism, illustrated with methyl-α-D-glucopyranoside, is shown in Scheme 1. This involves internal addition from the conjugate base of the bisbidentate chelate of the lanthanide and the two reactants (7, 8), as has been shown in reactions of diol substrates.



Methyl-4,6-*O*-benzylidene-α-D-glucopyranoside



Methyl-4,6-*O*-benzylidene-α-D-mannopyranoside

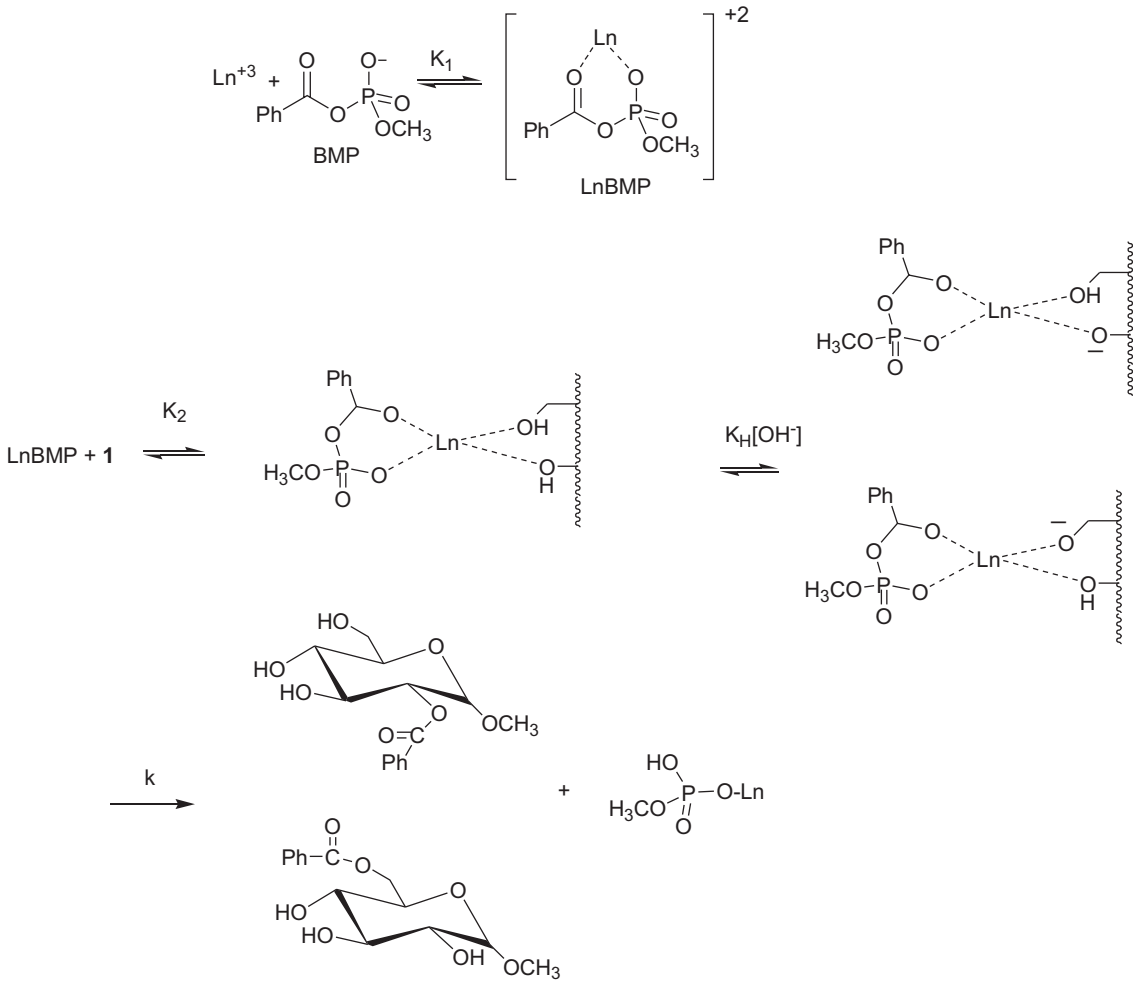
Table 3. Products of lanthanum-catalyzed monoacylation.

Carbohydrate	No. of ester products[a]	Ester ratios[a]	Total ester (%)[a]
Methyl-α-D-glucopyranoside	2	2.2:1	33.0
Methyl-β-D-galactopyranoside	2	1.1:1	41.0
Methyl-α-D-mannopyranoside	2	2.0:1	25.0
D-Ribose	3	5:1:3	91.0
2′-Deoxy-D-ribose	2	1:1.8	20.0
Uridine	2	1:1.8	76.0
2′-Deoxyuridine	0	0	0

Note: Reaction conditions: carbohydrate (1 equiv.), BMP (1 equiv.), $LaCl_3$ (2 equiv.), 100 mmol/L of EEPS buffer (pH 8) at room temperature.

[a]Relative yields were calculated from HPLC analysis.

Scheme 1. Proposed mechanism for the monobenzoylation of **1**.



Conclusions

We have for the first time shown that lanthanide-promoted monoesterification reactions of monosaccharides in water can be achieved by the reaction of an acyl phosphate monoester with lanthanum chloride. Products form from both hexoses and pentoses. NMR analysis indicated that the methyl-α-D-glucopyranoside (**1**) was benzoylated at the 2-oxygen and 6-oxygen in a ratio of 2:1. Since the 6-position is primary and the 2-position is secondary, it is clear that steric effects do not control the site of the reaction and that the geometry of the transition state is controlled by the coordination of the reacting complex. We intend to determine in further detail the scope, selectivity, and optimal conditions for this interesting new process. This approach should also be amenable to detection of species in complex mixtures and differential recognition, as well as for general synthetic applications.

Acknowledgements

We thank the Natural Sciences and Engineering Research

Council of Canada (NSERC) for support of this research through a Discovery Grant.

References

1. U.B. Gangadharmath and A.V. Demchenko. Synlett, **12**, 2191 (2004).
2. M. Nahmany and A. Melman. Org. Biomol. Chem. **2**, 1563 (2004).
3. S.A. Abbabs and A.H. Haines. Carbohydr. Res. **39**, 358 (1979).
4. G. Hu and A. Vasella. Helv. Chim. Acta, **86**, 4369 (2003).
5. R. Kluger, A.S.Grant, S.L. Bearne, and M.R. Trachsel. J. Org. Chem. **55**, 2864 (1990).
6. R. Kluger and L.L. Cameron. J. Am. Chem. Soc. **124**, 3033 (2002).
7. L.L Cameron, S.C.Wang, and R. Kluger. J. Am. Chem. Soc. **126**, 10721 (2004).
8. P.A. Clarke, P.L. Arnold, M.A. Smith, L.S. Natrajan, C. Wilson, and C. Chan. J. Chem. Soc. Chem. Commun. 2588 (2003)
9. L. Zervas and I. Dilaris. J. Am. Chem. Soc. **77**, 5354 (1955).
10. J.J. Patroni and R.V. Stick. Aust. J. Chem. **41**, 91 (1988).
11. O. Gronwald and K. Sakurai. Carbohydr. Res. **3**, 307 (2001).