Magnesium ion enhances lanthanum-promoted monobenzoylation of a monosaccharide in water†

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Received 23rd December 2009, Accepted 3rd March 2010
First published as an Advance Article on the web 15th March 2010
DOI: 10.1039/b926851k

Magnesium ion combines selectively with the methyl phosphate by-product in the lanthanum-promoted biomimetic reaction of benzoyl methyl phosphate with monosaccharides.

Introduction

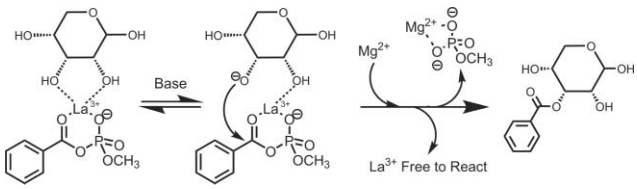
Reagents that acylate alcohols in water must distinguish a hydroxyl group of the reactant from a functionally similarly solvent. This distinction is often a challenge in the development of "green chemistry".[1] A biomimetic approach to the problem utilizes the reaction of acyl phosphate monoesters with diols in the presence of lanthanum salts in water, producing esters through chelation-directed selectivity.[2,3] Acyl phosphate monoesters are functional analogues of biological acylation agents, acyl adenylates.[4] The latter are formed in the enzyme-catalyzed reactions of carboxylic acids with ATP. Examples include intermediates in aminoacyl-tRNA synthetases[5] as well as reactions involving ubiquitin-adenylates.[6]

Acyl phosphate monoesters are inherently unreactive towards oxygen-centred nucleophiles but are very reactive towards amines in water, rapidly producing amides.[7] In a recent example the reaction was used to create peptide bonds derived from phosphorylated amino acids in the synthesis of phospho-peptides.[8] Another important application has been in the identification of kinases in proteomics by reactions with biotin carboxyl derivatives of ATP and ADP.[9]

Directing acyl phosphate monoesters to react with oxygen nucleophiles requires a fundamental change in their inherent reactivity from attack by an amino group to attack by a hydroxyl group. This has been achieved by coordination of the reactant to lanthanide ions as a bis-bidentate chelate of the acyl phosphate monoester and a *cis* diol. At the same time, lanthanide coordination facilitates ionization of a coordinated hydroxyl group, selectively targeting acylation at the other coordinated hydroxyl group of the diol. The mutual coordination of the reactant and reagent at the lanthanide also produces a significant entropic advantage for reaction of the tethered bifunctional reactant compared to the singly-coordinated water molecules.[2,3] The proposed mechanism is consistent with structures and mechanisms presented by Clarke and co-workers for lanthanum-promoted acylation of diols by acetic anhydride in organic solvents, where there is no reaction with the solvent to compete with the reactants.[10]

A critical operational drawback to a biomimetic process based on the reaction of lanthanum-coordinated acyl phosphate monoesters is that the alkyl phosphate by-product combines with the lanthanide, resulting in formation of a salt that removes the lanthanide ion from solution, requiring stoichiometric amounts of lanthanide for the reaction.[11,12] Furthermore, the presence of the voluminous lanthanide phosphate gel interferes with product isolation.

We investigated the use of magnesium salts to provide a sacrificial ion that would combine selectively with the alkyl phosphate by-product to produce a solid precipitate (Scheme 1). This would allow lanthanum to be involved in the acylation process without being removed, allowing for true lanthanide catalysis while easily separating the by-product.



Scheme 1 Synergistic metal ions: Mg^{2+} scavenges byproduct to establish La^{3+} catalysis.

We note that magnesium ions combine readily with alkyl phosphate dianions but do not coordinate well with either of the reactants or esters.[13] We report here the effects of added magnesium salts on the lanthanum requirements of the monoacylation reactions of carbohydrates with benzoyl methyl phosphate (BMP).

Results and discussion

The acyl phosphate reagent is unique as it can repel oxygen based nucleophiles due to its anionic character. The addition of a lanthanide ion activates the reagent towards all oxygen nucleophiles but is selective for vicinal diols. This provides simultaneous activation towards both esterification and hydrolysis. The reagent is therefore susceptible to decomposition because of the hydrolysis pathway but this does not interfere with formation of the desired product as excess reagent is used and is readily available. Similar approaches with expendable reagents in combination with valuable substrates is a necessary and common practice as exemplified in carbohydrate peracetylation/deacetylation,[14] peptide synthesis[15] and nucleotide coupling.

We utilized D-ribose as the test substrate for acylation as previous results demonstrated that monoacylation proceeds with

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† Electronic supplementary information (ESI) available: Experimental details, HPLC data for optimized small scale reactions and NMR data for preparative scale acylation of Me-α-glucopyranose. See DOI: 10.1039/b926851k

Table 1 Observed regioselectivity of acylation by BMP in the presence of lanthanum and magnesium triflates[20]

Monosaccharide	Esters obtained	Ratio
Me-α-Glucopyranose	2-OBz, 6-OBz	3 : 1
Me-β-Glucopyranose	2-OBz, 6-OBz	1 : 9
Me-α-Galactopyranose	2-OBz, 3-OBz, 6-OBz	1 : 5 : 5
Me-β-Galactopyranose	2-OBz, 3-OBz, 6-OBz	1 : 3 : 1
Me-α-Mannopyranose	2-OBz, 3-OBz, 6-OBz	2 : 1 : 1
D-Ribose	2-OBz, 3-OBz, 4-OBz	6 : 3 : 1

a high level of efficiency. The most stable carbohydrate-metal complexes form where the carbohydrate has three adjacent hydroxyl groups that are in an *ax-eq-ax* conformation through the pyranose form.[16] Solution and solid-state studies on ribose-lanthanide complexes clearly demonstrate the preponderance of this mode.[17] Coordination of the hydroxyl groups in this manner will also exclude water from the lanthanide core. The *ax-eq-ax* arrangement allows adjacent hydroxyl groups to assume the *cis* orientation that is most favourable for monoacylation to occur through necessary formation of a chelate.

It has been reported that the ionic strength of the reaction mixture has an impact on the effectiveness of lanthanide catalysis.[2] A prerequisite for this reaction is that the reactive components orient themselves about the lanthanide core prior to acyl transfer. An increase in ionic strength reduces the effect of lanthanide catalysis as it provides electrostatic stabilization of the dissociated components, precluding formation of the bis-bidentate array. This effect is observed in the acylation reaction; while a magnesium concentration of 0.1 M is optimal, we observe that the reaction rate is reduced at higher concentrations of the added salt.

The extent of migration of the acyl group in the initial ester product depends on the solvent and acidity/basicity of the medium.[18] Acyl groups tend to migrate under basic conditions. Our studies were carried out in solutions at pH = 8.0 but the mildly alkaline conditions do not affect the integrity or location of the benzoates during the course of product isolation. We observed the reaction products over 24 h and found that the distribution of the ester products is not altered, nor is there any hydrolysis of the resulting esters. In addition, the orientation of hydroxyl groups within a particular glycosidic geometry can also affect migration. However, as benzoyl groups have low migratory aptitudes[18] we cannot further generalize these results.

A critical issue in applying the lanthanum-promoted acylation reaction is the relationship of regioselectivity to the bis-bidentate array of the ligands. The only factors that should have significant impact on the regioselectivity would be the carbohydrate's reactive conformation in the transition state and its state of cyclization (*e.g.* pyranose or furanose, α or β *etc.*) as well as the energies of competing transition states from these chelates. Unless magnesium disrupts the bis-bidentate array on lanthanum, the reduction in the concentration of lanthanum will not affect regioselectivity. Indeed, we find that the relative regioselective preference is the same as in the absence of magnesium (Table 1).[11,12] We note that there are modest increases in the ratios of the esters obtained in some cases in the presence of both metal ions.

Reactions were also performed with reduced concentrations of lanthanum in the absence of magnesium in order to evaluate the role of magnesium. In these cases the acylation ceases prior to full consumption of the acyl phosphate, with both ribose and BMP remaining.[19] It is likely that the methyl phosphate by-product becomes bound to lanthanum, preventing both the carbohydrate from reacting and lanthanum promoted hydrolysis of the reagent. This result, alongside the observed regioselectivity, supports the designated role for magnesium in competing effectively for methyl phosphate.

Finally, in our choices for metal salts, we compared the effects of triflate and nitrate counterions in addition to chloride. Triflate enhances the Lewis acidity of lanthanum as evidenced by the increased rate of reaction. The use of magnesium triflate promotes complexation of the methyl phosphate by-product. We hypothesize that lanthanum is the optimal lanthanide for this reaction. We base this on the effect of the lanthanide contraction, where ions with an increasing atomic number also possess a higher charge relative to size.[21] One realistic consequence is that smaller lanthanides (*e.g.* Yb^{III}, Eu^{III}) will compete effectively with magnesium for binding to the phosphate by-product. Examining the effects of different lanthanides has been clearly demonstrated in our efforts towards acylation of RNA substrates.[22] Lanthanides with smaller ionic radii impart reduced efficiency of acylation as their charge-to-size ratio increases their selectivity for phosphates over diols.

In conclusion, we have observed synergistic metal-ion-promoted monoacylation of monosaccharides in water. The introduction of magnesium ions allows for the lanthanide to function as a true catalyst. This increases efficiency and permits the reaction to be done according to principles of "green" chemistry.[1]

Acknowledgements

We thank NSERC Canada for support through a Discovery Grant.

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