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Mechanistic insight into the lanthanide (III) salt catalysed monoacylation of symmetrical diols from structural models†

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Model studies are presented that suggest the mechanism of the lanthanide(III) salt catalysed mono acylation of symmetrical diols proceeds *via* chelation of the diol and the anhydride to the lanthanide salt, followed by an 'intramolecular' acyl transfer.

We have recently reported that lanthanide salts LnX_3 (X = Cl, OTf) catalyse the selective mono acylation of symmetrical 1,2-, 1,3- and 1,4-diols with carboxylic acid anhydrides.[1–3] These reactions are all the more remarkable as catalyst loadings can be as low as 1 mol% ($YbCl_3$) or even 0.1 mol% ($Yb(OTf)_3$), while 10 equiv. of anhydride may be used without any detrimental effect on the selectivity of the mono acylation reaction. Previous to our work, the state-of-the-art in diol mono protection included cleavage of cyclic acetals[4] and continuous extraction procedures.[5] Lewis acid catalysts from the d- and p-block are non-selective for this acylation. Herein, we propose a possible mechanistic pathway, and present studies using sterically encumbered substrates and complexes that model proposed intermediates, which provide support for this hypothesis.

A number of observations have lead us to postulate a mechanism for this reaction: (1) The acylation is faster, but equally as selective, in a non co-ordinating solvent such as CH_2Cl_2, compared with the standard THF solvent.[6] (2) *meso*-Diols or cyclic *cis*-1,2-diols are acylated at a reduced rate compared to their C_2-symmetric or cyclic *trans*-1,2-counterparts. (3) The rate of *bis* acylation is extremely slow. In general, reactions left for many hours after mono acylation is complete show only minimal *bis* acylation (< 5%).

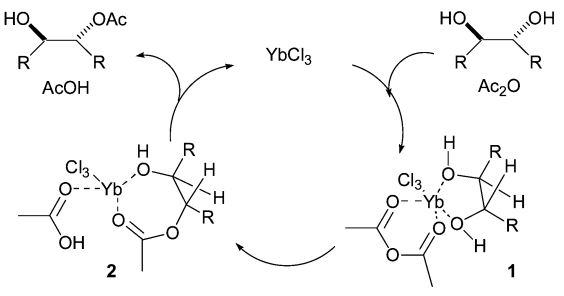
Our proposed reaction sequence, Scheme 1, shows both a diol and an anhydride co-ordinated to the lanthanide(III) salt, **1**. By conventional wisdom this diol is now less nucleophilic. However, co-ordination of the anhydride means that in **1** the 'intra-molecular' transfer of an activated acyl group is facilitated. The resultant 7-member chelate **2** is less stable than the 5-membered chelate originally formed by the substrate diol, so the mono-acylated product dissociates, to be replaced by diol, thus regenerating **1**.

This proposed mechanism invokes homogeneous catalysis by the lanthanide(III) salt. However, the halides are only poorly soluble, and solid $LnCl_3$ is always seen during the course of the reaction. To rule out the possibility of heterogeneous catalysis at the surface of the undissolved lanthanide(III) salt, we prepared a saturated THF solution of $CeCl_3$ (conc. 0.018 M, 5 mol% w.r.t. diol)[7] and filtered it to remove any undissolved $CeCl_3$. This solution catalysed the mono acylation of *meso*-hydrobenzoin‡ equally effectively, implying that the catalysis is homogeneous. The absence of competing donor solvent would lead to a rate acceleration if the substrates bind to the metal before reacting, and in CH_2Cl_2 solvent, this has been observed.

If the Ln(III) cation catalyses the reaction by chelating the diol before acylation, then bound substrate would be acylated at a much greater rate than any non-chelated substrate. The observation that C_2 diols are acylated faster than *meso*-diols supports a mechanism where the substrate diol binds to the metal catalyst in a bidentate fashion. The chelation of a *meso*-diol to the metal salt might result in an unfavourable eclipsing interaction between the R groups which is not present in the case of the C_2 diol. This interaction would slow the rate of chelation and hence the rate of acylation (Fig. 1).

To identify the coordination of substrates in solution, we prepared solutions of *meso*-hydrobenzoin and its mono ester at reaction concentrations in an NMR tube and added solid $CeCl_3$ (10 mol%). Unfortunately, we were unable to detect, by chemical shift changes, any co-ordination of substrate to $CeCl_3$ using ^1H or ^{13}C NMR spectroscopy. However, addition of soluble $[Eu(tfc)_3]$ (10 mol%), affords sizable ^1H NMR resonance shifts of the carbinol (C*H*(OH)) protons in both *meso*-hydrobenzoin (from 4.85 ppm to 5.22 ppm) and the mono-acetate (5.81 and 4.96 ppm to 6.55 and 5.42 ppm),[6,7] indicating that both the diol and the mono ester product can chelate. As a catalyst, $[Eu(tfc)]_3$ (10 mol%) does generate mono-acylated product in 90% yield.§

The use of a β-diketonate was considered a suitable anhydride mimic for a model study, since it is structurally similar to an anhydride. Treatment of $[Pr(thd)_3]$, (thd = tetramethylheptanedioate, $[Bu^tC(O)CHC(O)Bu^t]^-$) with an equivalent of *meso*-hydrobenzoin, afforded a pale green solid after isolation and recrystallisation from diethyl ether, which was characterised as **3**, eqn. (1).† The ^1H NMR spectrum of **3** reveals strongly paramagnetically shifted and broadened enantiotopic carbinol and hydroxyl protons (μ_{eff} Pr^{3+} (f^2) = 3.58), providing strong evidence for the formation of a praseodymium diol chelate complex in solution. This complex may be a valid model of an intermediate **1**.



Scheme 1 Mechanistic hypothesis.

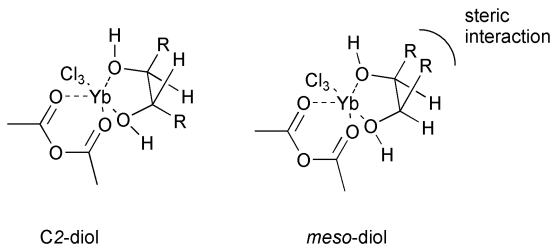


Fig. 1 Diol co-ordination.

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b308171k/

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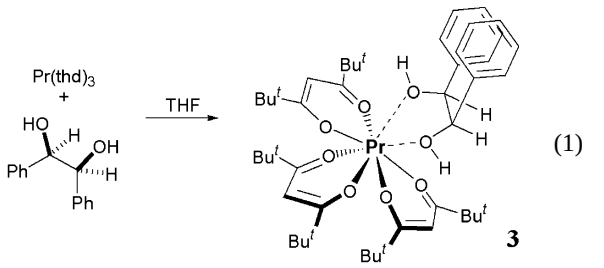
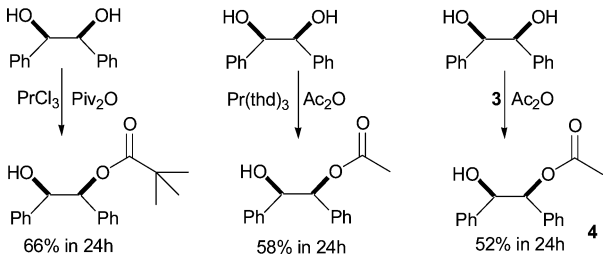


(1)

Praesodymium complexes (10 mol%) were shown to catalyse the pivolyation ($PrCl_3$), and acylation ([$Pr(thd)_3$] and **3**) of *meso*-hydrobenzoin Scheme 2. This shows that **3** is an effective precatalyst as it is clearly capable of generating a species that can catalyse the acylation reaction to the same extent as the free lanthanide salt. To provide a structural as well as functional model of the proposed transition state in which both substrates are coordinated, crystals of **3** suitable for X-ray structural analysis were grown from diethyl ether.¶

The solid-state molecular structure of **3**, Fig. 2, reveals a monomeric 8-coordinate Pr(III) centre, in which the rare earth ion is ligated by both O atoms of *meso*-hydrobenzoin, forming an approximate dodecahedral cation geometry. This is a rare example of a structurally characterised lanthanide(III) polyol adduct.[7] Importantly, the *meso*-hydrobenzoin phenyl substituents are eclipsed with respect to one another, with a dihedral angle of 43.5°, implying a significant steric interaction in the solid state. A weak chelation to the metal is evidenced by C_{ipso}–OH bond lengths that are not significantly elongated upon complexation. The HO–Pr and other distances are as anticipated.[7]

The *meso*-hydrobenzoin hydroxyl protons were located on the difference fourier map. The O62 hydroxyl proton participates in a hydrogen-bonding interaction with O41 of the closest β-diketonate ligand (close contacts are H62···O41 2.43(3)Å, O62···O41 2.745(3) Å and < (O62–H61–O41) 104.2(2)°). This



Scheme 2 Evaluation of praesodymium complexes.

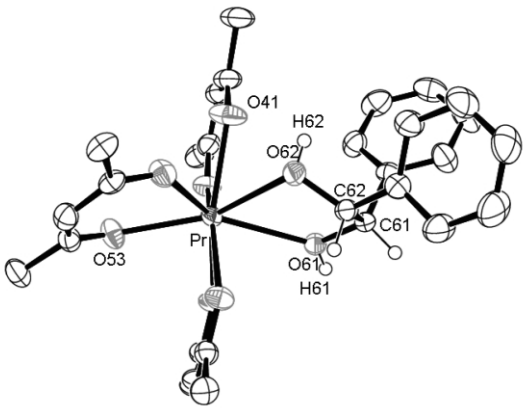


Fig. 2 Thermal ellipsoid drawing of **3** (50% probability). CH_3 groups, lattice solvent and H atoms other than diol OH and OCH omitted for clarity. Selected distances (Å) and angles (°): Pr–O(thd) range 2.368(2)–2.433(2), Pr–O61 2.579(2), Pr–O62 2.651(2), O61–C61 1.442(3), O62–C62 1.439(3), O61–Pr–O62 61.26(5), O53–Pr–O51 70.21(6).

single intramolecular H-bonding interaction must selectively weaken this OH and could, in principle, explain the selectivity for monoacylation. The other OH (O61) also forms a hydrogen bond, but to the lattice diethyl ether (O70); H61···O70 1.918(13) Å, O62···O70 2.707(2) Å and < (O62 H62 O70) 160.5(3)°. This could suggest an alternative, complex transition state in which the solvent intermolecular H-bonding controls the nucleophilic attack. However, the selectivity of this reaction in CH_2Cl_2, in which hydrogen bonding would be weaker, supports our confidence in the intramolecular hydrogen bonding as a controlling factor.

Analogously to the NMR solution study, the reaction of [$Pr(thd)_3$] with the monoacylated product **4** afforded a paramagnetically shifted adduct analogous to **2**, according to ^{1}H NMR spectroscopy, but only the two starting materials could ever be isolated upon crystallisation from a range of solvents. The 'transiency' of the Pr-ester adduct supports the proposed rapid replacement of product by diol substrate. If the chelated substrate is acylated at a much greater rate than any non-chelated substrate, this observation would account for both the rate enhancement and the mono-selectivity seen.

To conclude, we believe that the bidentate coordination of substrate diol to monoacylation catalysts of the form LnX_3 is a major factor in the control of selectively in diol desymmetrisation. We have shown that in solution both diol and monoester product bind to the metal, but only the diol binds well enough to form an isolable model complex. Structural characterisation of a model intermediate shows a significant, asymmetric hydrogen bond involving one of the diol hydroxyls.

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Notes and references

‡ *meso*-Hydrobenzoin was used in all of our studies as ultimately we hope to use the mechanistic insight gained to design asymmetric lanthanide (III) salts to use in desymmetrisation reactions.

§ We were unable to detect any enantioselectivity in the mono acylation of *meso*-hydrobenzoin with acetic anhydride using $Eu(tfc)_3$ as a catalyst.

¶ *Characterising data for* **3**: isolated from hexane in 24% yield, 0.1226 g. Anal. Calcd. for $C_{47}H_{71}O_8Pr$: C, 62.25; H, 8.06. Found: C, 62.34; H, 8.17%. *Crystallographic data for* **3**: C_{51} H_{81} O_9 Pr, fw 979.07, T = 150(2) K, triclinic, $P\bar{1}$, a 10.576(3), b 12.662(4), c 20.988(6) Å, α 79.191(7), β 81.482(6), γ 81.016(5)°. D_{calc} 1.201 mg m^{-3}, mu 0.948 mm^{-1}, F(000) 1036, S 1.019, $R1$ 0.0340, $w(R)2$ 0.0828. CCDC 215708. See http://www.rsc.org/suppdata/cc/b3/b308171k/ for crystallographic data in .cif or other electronic format.

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