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***In-situ* Dimanganese Catalyst for Fast Screening of Molecular Recognition Catalysts for Regioselective Oxygenation of an sp^3 C–H Bond**

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Abstract

We report a rapid method for assembling our di- μ -oxo dimanganese catalyst, verified by ESI-MS and EPR, assessing its water oxidation activity by a Clark electrode O_2 -assay study and its regioselective C–H activation activity by product analysis in catalytic runs.

Introduction

Synthesis and isolation of suitable high valent catalysts as well as finding a suitable catalyst-substrate combination have presented major challenges in research directed toward biomimetic regioselective C–H bond oxygenation.[1–3] In the absence of molecular recognition, a typical catalyst brings about oxygenation of a substrate at the most reactive site.[4–9] While this approach is of significance, it is of limited use for bringing about reaction at a less reactive site. Chelate control has been used in a number of cases, but this causes activation only at a neighbouring site.[10–12] The use of a molecular recognition unit at a remote location on a ligand to bind the substrate prior to reaction can provide high selectivity. When the target reaction is the oxygenation of a saturated C–H bond, this presents several complications in the design of ligand. As most of the bonds are more oxidation prone than saturated C–H bonds, all the groups in the ligand have to be highly oxidation resistant. Moreover, once such a ligand has been designed and synthesized, the isolation of a high valent metal catalyst bearing the ligand is time-consuming.

The di- μ -oxo dimanganese $[Mn^{III}(\mu-O)_2Mn^{IV}]$ core has been proved to be an exceptionally active oxidation catalyst. But isolation of an intact $[LMn^{III}(\mu-O)_2Mn^{IV}L]X_3$ (X: anion) complex with a ligand L has proved to be tedious and has only been achieved with limited success. Other than the complex with the molecular recognition ligand, **L_{MR}**, shown in Scheme 1, high valent di- μ -oxo dimanganese complexes, even those bearing much simpler ligands, were only isolated in low yield.[13,14] With change of ligand, the solubility, stability, selectivity and activity of $[LMn(\mu-O)_2MnL]^{3+}$ change in an unpredictable fashion.

Recent studies by our group indicate that $[L_{MR}Mn^{III}(\mu-O)_2Mn^{IV}L_{MR}]^{3+}$ can function as an efficient catalyst for oxygenation of saturated C–H bonds with high regio-(>98%) and stereoselectivity (>99%) and with hundreds of turnovers (total turnover >700).[15] Our molecular recognition ligand, **L_{MR}**, can lead to selective oxygenation at a remote unactivated site. We found that for regioselective catalysis, steric exclusion of unbound substrate by bound substrate is an important requirement.[16] This prevents the unselective

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reaction of unbound substrate molecules at the active site and puts another constraint on the design.

These difficulties have led us to look for an easier method to screen ligands. In the present study, we have used ligand substitution to prepare the catalyst *in situ* (Scheme 1). This *in-situ* catalyst has an activity comparable to the isolated catalyst with the molecular recognition ligand (**L_{MR}**) suggesting that this strategy can be used as a fast screening method for catalysts that are otherwise difficult to synthesize.[15] Once initial data have been obtained in a screen of this type, the successful system can be isolated and fully characterized for definitive studies.

Experimental section

Materials

Ibuprofen, tetrabutyl ammonium oxone (used as primary oxidant), dipy, HPLC grade acetonitrile were bought from Sigma-Aldrich and were used without further purification. $[(\text{dipy})_2\text{Mn}(\text{O})_2\text{Mn}(\text{dipy})_2](\text{ClO}_4)_3$ was synthesized according to literature procedure.[24]

Physical measurements

^1H and ^{13}C NMR spectra were recorded in deuterated solvents (Cambridge Isotope Laboratories) at 25°C on a Bruker 400 or Bruker 500 spectrometer at the Yale Department of Chemistry Instrument Center. Electrospray ionization-mass spectroscopy (ESI-MS) was done on a Waters ZQ LC-MS instrument. Gas chromatography-mass spectroscopy (GC-MS) was done on an Agilent 5973 GC-MS instrument.

Syntheses

Ligand **L_{MR}** and catalyst **C_{inact}** were synthesized following literature procedure.[15,24]

Catalytic conditions

To a solution of 7 mM (1 eq) of **S₁** in 20 ml acetonitrile, 0.03 eq of **C_{inact}** and 0.06 eq of **L_{MR}** or terpy were added. The solution was cooled in an ice bath and 5 ml CH_3CN solution of tetrabutyl ammonium Oxone®, TBAO (5 mmol) was added and the solution was stirred at room temperature, 0°C and -20°C . At room temperature, after 6 hours the reaction was quenched by addition of excess aqueous NaHSO_3 , acidified with 0.1N HCl solution and the products and unreacted substrate were extracted in ether. The ether extract was evaporated under vacuum and the residue was dried in vacuo in the presence of P_2O_5 . The products were analyzed by ^1H -NMR and GC-MS.

Results and Discussion

Synthesis and characterization of active *in-situ* dimanganese catalyst (**C_{in-situ}**)

$[(\text{dipy})_2\text{Mn}(\text{O})_2\text{Mn}(\text{dipy})_2](\text{ClO}_4)_3$ (**C_{inact}**) (dipy = 2,2'-dipyridyl) has a high valent di- μ -oxo dimanganese site. This complex has been found to be almost inactive catalytically because it lacks exchangeable terminal water ligands, so we do not expect a background oxidation from it. However, the Mn-dipy bonds in the Mn(III/IV) dimer are quite labile, allowing the bidentate dipy to be easily replaced by the tridentate **L_{MR}** to form the desired active catalyst (**C_{in-situ}**) *in situ*.

To an acetonitrile solution of **C_{inact}**, **L_{MR}** is added **C_{inact}**:**L_{MR}** in 1:2 molar ratio. After 5 minutes, the ESI-MS spectra of this solution gave a peak at $m/z = 1042$ with isotopic peaks closely matching the simulated isotopic distribution of $[(\text{L}_{\text{MR}})\text{Mn}^{\text{III}}\text{Mn}^{\text{IV}}(\text{O})_2(\text{dipy})(\text{ClO}_4)_2]^+$ showing the formation of the desired high valent dimanganese complex with **L_{MR}**

as a ligand (Figure 1). An EPR spectrum of the same solution gives the 16 line spectrum characteristic of the $\text{Mn}^{\text{III}}(\mu\text{-O})_2\text{Mn}^{\text{IV}}$ core (Figure 2). To demonstrate successful formation of an active catalyst, we used oxygen evolution from water oxidation with oxone as primary oxidant as an assay. While C_{inact} does not evolve O_2 from H_2O with oxone[®], the $\text{C}_{\text{inact}} + \text{L}_{\text{MR}}$ combination does indeed do so according to oxygen assay studies with Clark electrode (Figure 3). We therefore propose that the $\text{C}_{\text{inact}} + \text{L}_{\text{MR}}$ combination generates an active catalyst, $\text{C}_{\text{in-situ}}$, in which two dipyr ligands have been replaced by L_{MR} .

Design of substrate

Molecular models of a $\text{Mn}(\mu\text{-O})_2\text{Mn}$ complex with L_{MR} as the ligand were constructed by importing crystal structure parameters of ligand L_{MR} and the $\text{Mn}(\mu\text{-O})_2\text{Mn}$ core followed by energy minimization (MM2, CAChe 5).[15] The crystal structure of L_{MR} shows a $\sim 32^\circ$ angle between the -COOH and the plane of the imide group. Thus, an sp^3 carbon center is required α to the -COOH group to bring the remote C-H bond within $\sim 4\text{--}5 \text{ \AA}$ distance from the metal, a distance necessary for successful attack to take place by the high-valent metal site (Figure 4).[2,15,16]

Regioselective oxygenation of ibuprofen (S1)

Prediction from molecular modeling—Ibuprofen [2-(4-isobutyl-phenyl)-propionic acid] (S_1) was selected as the most suitable substrate. Ibuprofen is a rigid substrate with at least two alternate sites of attack: the benzylic C-H bonds remote from the -COOH group and the -COOH group itself. But, with molecular recognition, we expected selective oxidation at the remote benzylic C-H bond with $\text{C}_{\text{in-situ}}$ as the catalyst, as shown in Figure 4, giving P_1 as the major product, any initial -CH(OH) intermediate being rapidly oxidized to the ketone. Oxidation at the -COOH site is expected to give P_1' via oxidative decarboxylation under reaction and workup conditions (Scheme 2).[17–21] Without the molecular recognition both P_1 and P_1' are expected to form in comparable amount.

Catalytic conditions—With $\text{-COOH} \dots \text{HOOC-}$ H-bonding as the source of the recognition, it was necessary to use a non-protic solvent. Acetonitrile is not only non-protic but also relatively oxidation resistant. For a typical run, the ratio of substrate: C_{inact} : L_{MR} :TBAO was set at 100:3:6:500 and the reaction was carried out at room temperature, 0°C and -20°C (See Experimental section).

Control experiments—Three control experiments were run under identical conditions i) with added terpy (instead of L_{MR}) to solutions of C_{inact} (terpy: [2,2';6',2'']terpyridine), ii) with used C_{inact} alone and iii) with the manganese catalyst omitted.

Product analysis—Products of ibuprofen oxidation were analyzed by ^1H NMR (CDCl_3) (Figure 5) and ESI-MS. As the carboxylic acids were found to be inappropriate for GC-MS, their methyl esters were prepared by addition of trimethylsilyldiazomethane in a methanol-benzene (2:7) solution of the residue.[22] Product P_1 was isolated as a pure compound by reversed phase HPLC using a C8 column. ^1H NMR (Figure 6) and ESI-MS (Figure 7) were used to identify the products unequivocally by comparison with the ^1H NMR of P_1 and GC-MS of both P_1 and P_1' , which are available in the literature.[15,17,23]

Catalytic results—We found that in the absence of manganese catalyst no oxidation takes place. With $\text{C}_{\text{in-situ}}$, P_1 is always formed in a higher percentage than in any of the control experiments. This is consistent with our molecular model with ibuprofen H-bonded to the proposed active complex (Figure 4). On lowering of temperature, the selectivity was enhanced, presumably due to the entropic factor with $\sim 96.5\%$ selectivity for P_1 at -20°C (Table 1). Turnovers of 20–27 were recorded with $\text{C}_{\text{in-situ}}$ catalyst combination indicating

the reversibility in substrate-catalyst binding. In our control experiments with ' $C_{inact}+terpy$ ', where the ligand -COOH group is absent, P_1' was always obtained in appreciable amounts and the $P_1:P_1'$ ratio remained practically unchanged at all temperatures.

Oxygenation of S_1 in presence of acetic acid

We attribute the high regioselectivity in oxidation of ibuprofen by $C_{in-situ}$ to molecular recognition via H-bonding to the -COOH group in L_{MR} , the ligand in $C_{in-situ}$. To test of the effect of H-bonding, experiments were performed by adding acetic acid to the catalytic solutions to disrupt the potential H-bonding leading to molecular recognition. With 4 equivs. acetic acid in the medium for each equiv. of substrate in the $C_{in-situ}$ system, the $P_1:P_1'$ ratio fell from ~7:1 to ~3:1 on adding acetic acid. Control experiments with ' $C_{inact}+terpy$ ' catalytic system gave the same 3:1 product mixture under identical conditions (Table 1). This is consistent with the proposed role of COOH...HOOC- H-bonding for high regioselectivity in the oxygenation of ibuprofen.

Time dependent study in the oxygenation of S_1

We were concerned about the potential degradation of P_1' leading to an apparent lower yield of P_1' versus P_1 , with the $C_{in-situ}$ catalytic system. A time course study was carried out to test this point. The $C_{in-situ}$ catalytic system at 0°C takes 24 hours to reach completion. We, therefore, began our product analyses at 0.5 hours followed by a series of measurements over 10 hours. The $P_1:P_1'$ ratio remained essentially constant throughout. A similar study with the control *in-situ* catalyst (' $C_{inact}+terpy$ ') also showed a constant $P_1:P_1'$ ratio throughout. This suggests that the high $P_1:P_1'$ ratio with the $C_{in-situ}$ catalytic system is, indeed, due to molecular recognition.

Conclusions

We report a rapid screening method for testing ligands with a di- μ -oxo dimanganese catalyst. The activity of the catalysts formed by displacement of dipy by terpy or L_{MR} was confirmed by a Clark electrode O_2 -assay study (water oxidation activity) and the ligand displacement reaction itself was detected by an ESI-MS study. This indicated the formation of a new complex, $C_{in-situ}$, by replacement of dipy by L_{MR} . With $C_{in-situ}$, oxidation of ibuprofen (S_1) occurs with high selectivity (~97% at -20°C) at the benzylic C-H bond remote from the -COOH group, with 24 turnovers. This selectivity is attributed to anchoring and orientation of the substrate (S_1) via -COOH...HOOC- H-bonding between substrate -COOH group and the -COOH group of L_{MR} . Loss of selectivity after disruption of the H-bonding to the substrate with AcOH supports the proposed origin of the selectivity. The isolated di- μ -oxo dimanganese catalyst with L_{MR} as the ligand gave higher selectivity (>98%) and much higher turnovers (>500) so it is necessary to isolate the complexes to gain maximal activity.[15] Nonetheless, displacement studies may be useful in comparing a range of ligands for catalysis.

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Figure 1. ESI-MS of $[(\mathbf{L}_{\mathbf{MR}})\text{Mn}^{\text{III}}(\text{O})_2\text{Mn}^{\text{IV}}(\text{dipy})](\text{ClO}_4)_2]^+$ (solid green line) ($m/z = 1042$). Simulated spectrum is shown in broken black line.

Figure 2.
EPR spectrum of $[(L_{MR})Mn^{III}(O)_2Mn^{IV}(dipy)(ClO_4)_2]^+$.

Figure 3.

Oxygen assay with Clark electrode in H₂O:CH₃CN = 1:1 with C_{inact} (100 mM) + Dipy (400 mM) (black line) and C_{in-situ} [C_{inact} (100 mM) + L_{MR} (200 mM)] (red line). Primary oxidant: oxone (5 mM). Temperature: 25°C

Figure 4. Molecular model (Chem 3D) of ibuprofen (S_1) docked to one side of $C_{in-situ}$ via -COOH...HOOC- H-bonding. The other side of dimanganese complex might have L_{MR} as the ligand or might have one or two dipy. Due to the $\sim 32^\circ$ angle between the KTA - COOH group and the plane containing the imide group, the substrate needs a bent sp^3 carbon group after the -COOH group for the rest of the substrate to come into proximity with the active site (ideally 4–5 Å between target C atom and Mn).¹⁶

Figure 5. ^1H NMR (CDCl_3) of the product mixture after oxidation of ibuprofen by a) $\text{C}_{\text{in-situ}}$ and b) ' C_{inact} + terpy'

Figure 6.
 ^1H NMR (CDCl_3) of **P₁** (Inset: aromatic region)

Figure 7. ESI-mass spectrum of isolated P_1 ($m/z = 221$ corresponds to P_1H^+ ; $m/z = 242$ corresponds to tetrabutyl ammonium cation of TBAO, which was used as primary oxidant and was in excess)

Scheme 1.
Synthesis of **C_{in-situ}**

Scheme 2.

Possible products from oxidation of ibuprofen (S_1). Bold arrows indicate alternate sites of attack

Table 1

Product analysis of ibuprofen (**S**₁) oxidation

Temperatures	Catalysts	Total conversions versus substrate	P ₁	P ₁ ' versus total product	Turnover numbers
20°C	C _{in-situ}	72%	85%	13%	24
	'C _{inact} + terpy'	70%	69%	23%	23.3
	C _{inact}	<1%			~0
0°C	C _{in-situ}	65%	91%	6%	21.7
	'C _{inact} + terpy'	60%	73%	19%	20
	C _{inact}	35%	41.5%	54.5%	11.7
– 20°C	C _{in-situ}	82%	96.5%	2.2%	27.3
	'C _{inact} + terpy'	81%	73%	15%	27
	C _{inact}	48%	41.5%	42%	16
20°C	C _{in-situ} ^a	73%	73%	18%	24.3
	'C _{inact} + terpy' ^a	72%	72%	21%	24

Turnovers: mol. products per mol. catalysts;

^aCatalytic solutions contained excess acetic acid.