Journal of Molecular Catalysis A: Chemical 335 (2011) 24–30

Contents lists available at ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Hydrocarbon chlorination promoted by manganese and iron complexes with methylated derivatives of bis(2-pyridylmethyl)-1,2-ethanediamine

Christian R. Goldsmith*, Cristina M. Coates, Kenton Hagan, Casey A. Mitchell

Department of Chemistry & Biochemistry, Auburn University, Auburn, AL 36849, United States

ARTICLE INFO

Article history:
Received 2 September 2010
Received in revised form 4 November 2010
Accepted 5 November 2010
Available online 13 November 2010

Keywords:
Chlorination
Regioselectivity
C–H activation

ABSTRACT

Non-heme iron halogenases, such as SyrB2 and CytC3, catalyze the regioselective chlorination and bromination of aliphatic C–H bonds. Reported here is the hydrocarbon chlorination promoted by manganese and iron complexes with methylated derivatives of bis(2-pyridylmethyl)-1,2-ethanediamine (bispicen). The reactions between these coordination compounds and *meta*-chloroperbenzoic acid generate oxidants capable of oxidizing weak C–H bonds to C–Cl bonds. This chemistry is regioselective, with a strong preference for activating C–H bonds on secondary carbons over weaker C–H bonds on tertiary carbons. The reactivity is consistent with the methyl groups on the ligands preventing more sterically encumbered substrates from accessing the reactive portions of a $[M^{IV}(L^{Me}n)(O)Cl_2]$ oxidant. The iron compounds promote more hydrocarbon chlorination than their manganese analogs.

1. Introduction

The conversion of chemically inert C–H bonds to more useful functional groups remains a significant challenge in synthetic chemistry [1–8]. A large amount of effort has been devoted to finding conditions and reagents that (1) halt the oxidation at a product that can potentially be further oxidized and (2) activate C–H bonds within a substrate molecule selectively.

The conversion of aliphatic C–H bonds to C–Cl or C–Br bonds commonly proceeds through radical processes [9]. The best known method, free radical halogenation, relies on halogen atom radicals to oxidize the hydrocarbon substrate. These oxidants are small and highly symmetric, and they thereby lack the means to enable either regio or stereosymmetric C–H activation at levels suitable for preparative synthetic chemistry [10–12]. Due to the inherent lack of selectivity and the high reactivity of chlorine and bromine radicals, free radical halogenations often yield polyhalogenated compounds as byproducts unless the substrate is present in excess [13,14]. Isolating desired monohalogenated products from these reactions can thereby be labor-intensive. An additional problem is that halogen radicals are capable of multiple modes of reactivity. With allylic substrates, for instance, the radical oxidants can either halogenate the C–H bonds α to the olefin or add across the olefin to yield dihalogenated alkanes [9,15]. Halogenation of aromatic C–H bonds has also been observed [16,17]. Alternative halogenation systems have also displayed a similar lack of chemoselectivity [18–20].

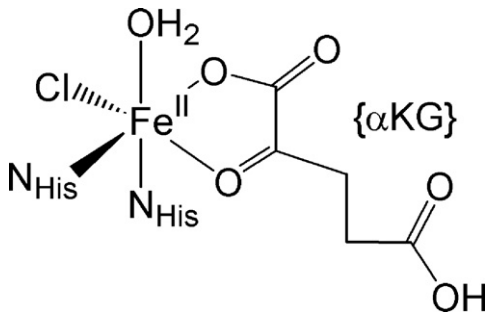
Halogenase enzymes, conversely, chemo- and regioselectively activate C–H bonds without over-oxidation [21–24]. The active oxidants in the enzymatic cycles are more geometrically complex than halogen radicals, which enables them both to differentiate their substrate from other compounds and to distinguish inequivalent C–H bonds within the same molecule. One class of halogenases contain mononuclear non-heme iron metal centers in their active sites [21,25–27]. The non-heme iron halogenases are notable for using O_2 as a terminal oxidant and being capable of oxidizing aliphatic C–H bonds. Haloperoxidases, in contrast, use H_2O_2 as a terminal oxidant and typically react with electronically activated C–H bonds [21,24].

The non-heme iron halogenase SyrB2 has been structurally characterized in its Fe(II) state (Scheme 1) [27]. The coordination sphere around the iron ion in the active site includes two histidine residues, a water molecule, a halide ligand, and α-ketoglutarate (αKG), which serves as a sacrificial reductant in the enzymatic cycle. The oxidant that reacts with the hydrocarbon substrate in the enzymatic cycle is believed to be a ferryl species, Fe(IV)(Cl)(O), which abstracts a hydrogen atom from the substrate to yield an organic radical and Fe(III)(Cl)(OH) [25,27,28]. A formal chlorine atom transfer from the ferric species to the organic radical yields the organochloride and Fe(II). The ferryl oxidants have recently been characterized by Mössbauer and X-ray absorption spectroscopies [28,29] but the ferric species have not been observed.

Reported in this manuscript are the chlorination activities of two series of metal complexes with bis(2-pyridylmethyl)-1,2-ethanediamine (L, bispicen) and five methylated derivatives ($L^{Me}n$,

* Corresponding author at: Department of Chemistry & Biochemistry, 179 Chemistry Building, Auburn University, Auburn, AL 36849, United States.
Tel.: +1 334 844 6463.
E-mail address: crgoldsmith@auburn.edu (C.R. Goldsmith).

1381-1169/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2010.11.006



Scheme 1. Active site of SyrB2.

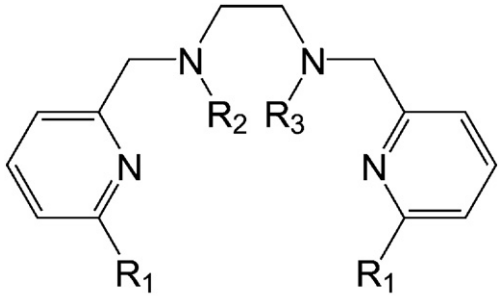
Scheme 2). The N-donor ligands are meant to approximate the endogenous coordination provided by the SyrB2 enzyme [27] and are also electronically similar to ligands that have previously supported analogous hydrocarbon hydroxylation [30,31]. The bispicen framework, while certainly an imperfect reproduction of the enzymatic coordination sphere, is attractive due to the ease of its synthesis and modification. The methyl groups installed on the pyridines and secondary amines allow us to assess the impact of ligand sterics on the oxidative reactivity of the associated metal complexes.

One series contains iron(II) ([Fe(L^{Me}n)Cl_2]); whereas, the other contains manganese(II) ([Mn(L^{Me}n)Cl_2]). Manganese has previously substituted for iron in hydrocarbon oxidations with equal or superior activity [32–36], but has not been systematically investigated for its ability to chlorinate hydrocarbon C–H bonds. Reaction of the M(II) compounds with *meta*-chloroperbenzoic acid (MCPBA) generates oxidants that are capable of chlorinating hydrocarbon substrates with weak C–H bonds.

2. Experimental

2.1. Materials

Acetonitrile (MeCN), iron(II) chloride tetrahydrate ($FeCl_2$•$4H_2O$), and manganese(II) chloride ($MnCl_2$) were bought from Sigma–Aldrich and used as received. Anhydrous diethyl ether (ether) was purchased from Fisher Scientific, degassed, and stored over 4 Å molecular sieves. Cyclohexene and chlorocyclohexane were purchased from Sigma–Aldrich and stored in a glovebox free of moisture and oxygen. Toluene, cumene, and ethylbenzene were bought from Sigma–Aldrich and distilled prior to use. *Meta*-chloroperbenzoic acid (MCPBA) was acquired from Sigma–Aldrich and stored in a refrigerator until needed. Chloroform-*d* and acetonitrile-d_3 were purchased from Cambridge Isotopes and used without further purification. The syntheses of *N,N*-bis(2-pyridylmethyl)-1,2-ethanediamine (bispicen, L) [37], *N,N′*-dimethyl-*N,N′*-bis(2-pyridylmethyl)-1,2-ethanediamine (L^{Me}2) [38], *N,N′*-bis(2-pyridylmethyl)imidazolidine [39], *N*-methyl-*N,N′*-bis(2-pyridylmethyl)-1,2-ethanediamine (L^{Me}1) [39,40], *N,N′*-bis(6-methyl-2-pyridylmethyl)-1,2-ethanediamine (L^{Me}2′) [41] and *cis*-(*N,N*-bis(2-pyridylmethyl)-1,2-ethanediamine)-dichloromanganese(II) ([Mn(L)Cl_2]) [42] have been reported previously by others. We are detailing the syntheses of the other ligands and metal complexes in another manuscript that focuses on the conformational flexibility and dynamics of the bispicen framework [43].



$R_1 = R_2 = R_3 = H$: L {bispicen}
$R_1 = R_2 = H$, $R_3 = CH_3$: $L^{Me}1$
$R_1 = H$, $R_2 = R_3 = CH_3$: $L^{Me}2$
$R_1 = CH_3$, $R_2 = R_3 = H$: $L^{Me}2'$
$R_1 = R_2 = CH_3$, $R_3 = H$: $L^{Me}3$
$R_1 = R_2 = R_3 = CH_3$: $L^{Me}4$

Scheme 2.

2.2. Instrumentation

All ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a 400 MHz AV Bruker NMR spectrometer at 294 K; internal standards were used to reference all NMR resonances. Gas chromatography (GC) was performed on either a ThermoScientific Trace GC Ultra or a Hewlett Packard 5890 gas chromatograph with a flame ionization detector (FID). Tanden GC/mass spectrometry (GC–MS) was performed on either a Hewlett Packard 5890 gas chromatograph with a Fissons Instruments electrospray mass spectrometry detector or an Agilent 6890N gas chromatograph with a Trio-2000 mass spectrometer. Optical spectroscopy data were acquired on a Cary 50 spectrophotometer.

2.3. Mass spectrometry

Samples were analyzed using an Ultra Performance LC Systems (ACQUITY, Waters Corp., Milford, MA, USA) coupled with a quadrupole time-of-flight mass spectrometer (Q-TOF Premier, Waters) with electrospray ionization (ESI) in positive ESI-MS and ESI-MS/MS modes operated by the Masslynx software (V4.1). The ion source voltages were set at 3 kV, the sampling cone was set at 37 V and the extraction cone was at 3 V. The source and desolvation temperature was maintained at both 80 °C with the desolvation gas flow at 200 L/h.

Samples containing the metal oxidant generated from [Fe(L^{Me}2)Cl_2] were directly injected into the ESI source at a flow rate of 100 μL/min with a 50% acetonitrile, 0.1% formic acid mobile phase. The sample spent 6 s at 12 °C before it was ionized into gas phase. The TOF MS scanning was from 350 to 450 *m/z* at 1 s with 0.1 s inter-scan delay using extended dynamic range acquisition with centriod data format. For real time mass calibration, direct infusion of sodium formate solution (10% formic acid/0.1 M NaOH/aceonitrile) at a ratio of 1:1:8 at 1 s/10 s to ion source at 2 μL/min was used for a single point mass calibration.

Ions of interest were analyzed for their elemental composition using accurate mass (less than 5 ppm error) and isotope modeling to identify the formula. Collision-induced dissociation (CID) by argon on precursor ions resulted in structural fragments that further assisted the identification.

2.4. Reactivity studies

All oxidation reactions were run in MeCN at 23 °C under N_2. For the reactions with cyclohexene, 10 mM of the metal complex, 10 mM of MCPBA, and 400 mM of cyclohexene were mixed at once. After stirring for 30 min, the solutions were filtered through a plug of silica gel to remove the metal complex and analyzed through GC. Products were identified both through GC–MS and by comparison of their retention times with those of commercially available standards, such as cyclohexene oxide and 3-chlorocyclohexene. Yields were calculated through comparison to an internal standard, chlorocyclohexane, which was found to be unreactive under these conditions. Parallel reactions in MeCN-d_3 corroborated the identities and ratios of the products.

The reactivity assays with the benzylic substrates proceeded in an analogous fashion. In the first set of experiments, the starting concentrations of MCPBA, the metal complex, and the benzylic substrate were set at 10 mM. In the second set of reactivity assays, the starting concentrations of MCPBA and hydrocarbon were 100 mM and 400 mM, respectively. The reaction times with the benzylic substrates were extended to 60 min. All reactions were repeated at least three times to ensure reproducibility; all reported product yields are the averages of the results of these independent reactions.

3. Results

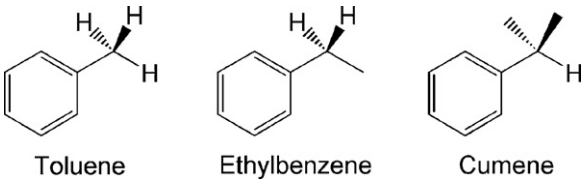
The oxidative reactivities of the manganese and iron complexes were investigated, with a focus on their abilities to promote the chlorination of hydrocarbon substrates. The M(II) complexes are unstable in the presence of excess chloride, as assessed by optical spectroscopy. In order to simplify the analysis, the present studies are therefore limited to stoichiometric chlorination, with no additional chloride ion present beyond the two equivalents initially associated with the metal complex.

3.1. Selection of oxidant

Meta-chloroperbenzoic acid (MCPBA) was selected as the terminal oxidant. Hydrogen peroxide, *tert*-butylhydroperoxide, oxone, and iodosobenzene were also investigated but were not found to be competent terminal oxidants for hydrocarbon chlorination by these metal complexes. Although commercially available peracetic acid was found to promote hydrocarbon oxidation to a greater extent than MCPBA, the reactivity was found to be non-discriminate, and the organic products included many compounds that are not readily identifiable. The reactivity assays with MCPBA, conversely, led to fewer organic products, all of which were easily identified. In the absence of an organic substrate, the L^{Me}n ligands undergo oxidative degradation, as indicated by both thin layer chromatography and NMR analysis.

3.2. Cyclohexene reactivity

The reactivity was initially screened using cyclohexane and cyclohexene as substrates. Cyclohexane was found to be completely inert under the investigated conditions, in contrast to similar systems previously reported by Que and Comba [44,45]. When 400 mM cyclohexene reacts with 10 mM of a [M(L^{Me}n)Cl_2] metal complex and 10 mM MCPBA in MeCN, the product mixtures include cyclohexene oxide, 3-cyclohexenol, 3-cyclohexenone, and 3-chlorocyclohexene (Table S1). Cyclohexene is a poor substrate for these systems in that the oxygenated products form readily from the reaction of MCPBA with the olefin, even in the absence of metal ions. Furthermore, oxygenated products continue to form during the reaction workup, and the yields of these products sometimes exceed the theoretical maxima based on the amount of MCPBA present. A recent report from Fukuzumi and Nam's groups found that cyclohexene could initiate the generation of a ferryl oxo oxidant from Fe(II) species and O_2 [46]. A similar reaction involving the [M(L^{Me}n)Cl_2] complexes and cyclohexene could explain the additional oxygenated products in Table S1, given that the reaction workup was done under air.



Scheme 3.

Despite these two complications, three observations are noted from the cyclohexene data. First, 1,2-dichlorocyclohexane is never found as an oxidation product. Second, iron consistently promotes chlorination to a greater extent than manganese, at parity of ligand. Third, the bispicen derivative with methyl groups installed on the two amines, L^{Me}2, leads to the most chlorinated product for both iron and manganese, with further methylation reducing the yield of 3-chlorocyclohexene.

3.3. Reactivity of benzylic substrates

The chlorination chemistry was subsequently investigated with three substrates containing benzylic C–H bonds: toluene, ethylbenzene, and cumene (Scheme 3). In these substrates, the C–H bonds most thermodynamically susceptible to oxidative attack are on primary, secondary, and tertiary carbons, respectively. The different steric environments around the benzylic C–H bonds provide a means of assessing the regioselectivity of the chlorination reactions. The bond dissociation energies of the benzylic C–H bonds are 88 (±1) kcal mol^{-1} for toluene [47], 85 (±1) kcal mol^{-1} for ethylbenzene, and 83 (±1) kcal mol^{-1} for cumene [48]. Based on these bond dissociation energies, cumene would be anticipated to be the most active substrate. Unlike cyclohexene, these substrates do not react extensively with MCBPA. In the control experiments, ethylbenzene, and cumene react with MCPBA to form 1-hydroxyethylbenzene and 1-hydroxycumene in less than 10% yield (Table 1).

The chemistries of the best chlorinating agents in the cyclohexene studies, [Fe(L^{Me}2)Cl_2] and $FeCl_2$ were compared to that of the bulkiest iron complex, [Fe(L^{Me}4)Cl_2]. The reactivities of $MnCl_2$, [Mn(L^{Me}2)Cl_2], and [Mn(L^{Me}4)Cl_2] were also further explored in order to corroborate the second observation noted in the cyclohexene reactivity. In the first series of reactivity runs, 10 mM of the metal complex was mixed with 10 mM of MCPBA and 10 mM of the benzylic substrate. The only reaction that produces an oxidized product in more than trace (0.5%) quantities is that between ethylbenzene and [Fe(L^{Me}2)Cl_2], which produces 1-chloroethylbenzene in 15% yield (Scheme 4). No oxygenated or polychlorinated benzylic products are observed in any of the reactions using 1 equiv. of terminal oxidant.

In the second series of reactivity runs, excesses of oxidant and substrate were used in attempts to increase the yields of the chlorinated products. Although the yields of the chlorinated benzylic compounds do increase, the reactions become much less selective with the excess oxidant and generate more oxygenated side-products. As was observed in the cyclohexene reactivity assays, $FeCl_2$ is the most active benzylic chlorinating agent when MCPBA is present in excess (Table 1). The manganese complexes continue to produce fewer chlorinated organic products than their iron analogs at parity of the other reaction conditions. Mixtures of MCPBA with

Table 1
Reactivity of [M(L^{Me}n)Cl_2]-derived oxidants with benzylic susbstrates.

Substrate	Complex	Oxygenated products	Chlorinated products
Toluene	None	None	None
	$MnCl_2$	Benzyl alcohol (0.3 mM) Benzaldehyde (0.3 mM)	Benzylchloride (0.4 mM)
	$FeCl_2$	Benzaldehyde (0.8 mM)	Benzylchloride (9.1 mM)
	[Mn(L^{Me}2)Cl_2]	None	Benzylchloride (0.7 mM)
	[Fe(L^{Me}2)Cl_2]	Benzaldehyde (0.9 mM)	Benzylchloride (2.0 mM)
	[Mn(L^{Me}4)Cl_2]	None	None
	[Fe(L^{Me}4)Cl_2]	Benzyl alcohol (0.9 mM) Benzaldehyde (1.0 mM)	Benzylchloride (2.0 mM)
Ethylbenzene	None	1-Hydroxyethylbenzene (7.7 mM)	None
	$FeCl_2$	1-Hydroxyethylbenzene (6.0 mM)	1-Chloroethylbenzene (17.7 mM)
	[Mn(L^{Me}2)Cl_2]	1-Hydroxyethylbenzene (0.4 mM)	1-Chloroethylbenzene (0.2 mM)
	[Fe(L^{Me}2)Cl_2]	1-Hydroxyethylbenzene (3.3 mM)	1-Chloroethylbenzene (8.3 mM)
	[Mn(L^{Me}4)Cl_2]	1-Hydroxyethylbenzene (0.3 mM)	1-Chloroethylbenzene (0.3 mM)
	[Fe(L^{Me}4)Cl_2]	None	1-Chloroethylbenzene (6.0 mM)
Cumene	None	1-Hydroxycumene (5.0 mM)	None
	$FeCl_2$	1-Hydroxycumene (42.0 mM)	1-Chlorocumene (9.0 mM)
	[Mn(L^{Me}2)Cl_2]	None	None
	[Fe(L^{Me}2)Cl_2]	None	None
	[Mn(L^{Me}4)Cl_2]	None	None
	[Fe(L^{Me}4)Cl_2]	None	None

The initial concentrations of reagents are as follows: metal complex (if present), 10 mM; MCPBA, 100 mM; benzylic substrate, 400 mM. All reactions were run for 60 min at 23 °C in MeCN under N_2.

[Fe(L^{Me}2)Cl_2] and [Fe(L^{Me}4)Cl_2] chlorinate toluene to the same extent, although the iron complex with the tetramethylated ligand does tend to promote the formation of more oxygenated products (Table 1). When ethylbenzene is used as a substrate, the iron compound with the dimethylated ligand leads to more 1-chloroethylbenzene than that with the tetramethylated ligand, reminiscent of what was observed with cyclohexene (Table S1). The additional methyl groups in [Fe(L^{Me}4)Cl_2] appear to hinder the ability of the oxidant to activate C–H bonds on secondary carbons. When cumene is employed as a substrate, only $FeCl_2$ promotes the formation of any oxidized products above the lower limit of detection; the oxidants derived from [M(L^{Me}n)Cl_2] precursors do not react with cumene, despite this substrate having the weakest C–H bond in the series.

In each case, the yield of *meta*-chlorobenzoic acid (MCBA), the reduced form of the terminal oxidant, exceeds the yields of oxidized benzylic products. In the reaction between $FeCl_2$ and ethylbenzene, the yield of MCBA is twice that of 1-chloroethylbenzene. This demonstrates that alternate pathways for MCPBA reduction are operable. These pathways include ligand oxidation when a [M(L^{Me}n)Cl_2] complex is present.

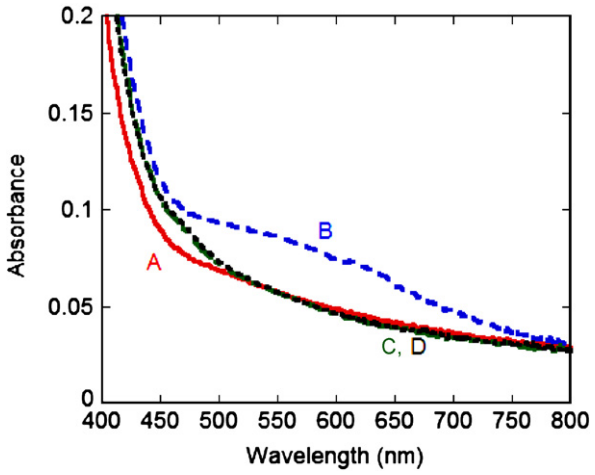
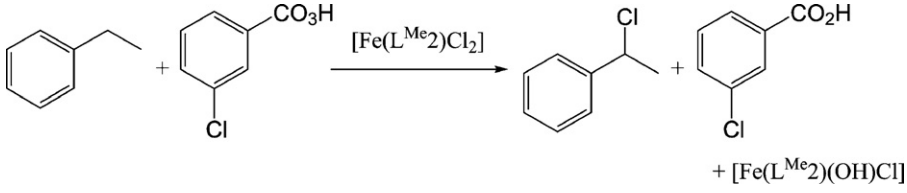


Fig. 1. Reaction between 0.32 mM [Fe(L^{Me}2)Cl_2] and 0.36 mM MCPBA in MeCN at 23 °C. Four scans shown: (A) [Fe(L^{Me}2)Cl_2] prior to addition of oxidant, (B) Fe(II) complex plus MCPBA 5 s after addition, (C) reaction mixture 30 s after addition, and (D) reaction mixture 60 s after addition. An expanded version of this figure is available in the supporting information.

3.4. Mechanistic analysis

Reactions were performed in the absence of substrate in order to gain insight into the nature of the active oxidant. The reaction between [Fe(L^{Me}2)Cl_2] and MCPBA at 23 °C generates a short-lived species, with heighted absorbance in the 550–650 nm region (Fig. 1), where optical features associated with Fe(IV) species often appear [28,49–51]. The absorbance quickly drops, signifying that the species completely vanishes by 30 s. Parallel studies using mass spectrometry detect a transient species with a peak *m*/*z* ratio of 412.0538 (Fig. 2); this feature matches that predicted for



Scheme 4.

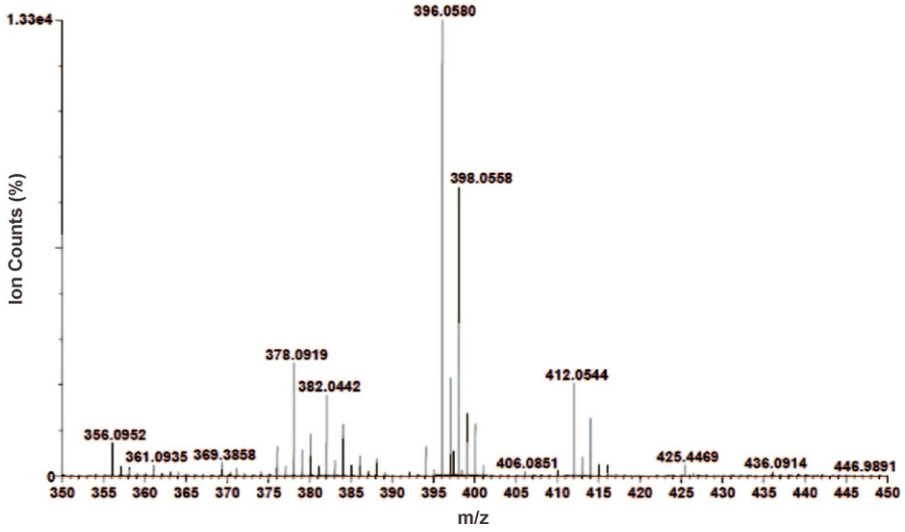


Fig. 2. Mass spectrum of [Fe(L^{Me}2)Cl_2]/MCPBA reaction mixture at 6 s. Identified species include [Fe(L^{Me}2)Cl_2] at 396.0580, [Fe(L^{Me}2)(OH)Cl] at 378.0920, and [Fe(L^{Me}2)(O)Cl_2] at 412.0544. A mass spectrum of the same sample acquired 5 min after the start of the reaction is included in the supporting information.

[Fe^{IV}(L^{Me}2)(O)Cl_2]. As with the optical feature in Fig. 1, the intensity of the 412.0538 feature decreases quickly with time.

4. Discussion

The reactivity of the [M(L^{Me}n)Cl_2] complexes was investigated with a focus on the chlorination chemistry. Hydrocarbon oxygenation reactions with metal chloride compounds often generate traces of organochlorides as by-products [52]. In certain cases, stoichiometric [45,53] or catalytic halogenation [19] has been observed. Our primary aim with the methylated bispicen ligands and their metal complexes was to investigate the factors that modulate halogenation chemistry, in particular to determine whether manganese is capable of substituting for iron as it does in other oxidative systems. A secondary aim was to determine whether the chlorination chemistry could be made regiospecific through the incorporation of modest steric bulk onto the ligand framework.

4.1. Reactivity with cyclohexene

For each metal compound, the oxidation reaction with cyclohexene yields a mixture of cyclohexene oxide, 3-cyclohexenone, 3-cyclohexenol, and 3-chlorocyclohexene. The chlorinated product is a minor component in the product distributions of most of the reactions (Table S1). Much of the oxygenated products likely results from the direct interaction of MCPBA with the olefin. The lack of 1,2-dichlorocyclohexane in the product mixtures, however, is notable since this is the major product in the free radical halogenation of cyclohexene [15]. The observed chlorination in this system is more consistent with a metal-based oxidant than chlorine radicals.

4.2. Reactivity with benzylic substrates

4.2.1. Reactivity with a stoichiometric amount of terminal oxidant

The oxidation chemistry was subsequently investigated with benzylic substrates (Scheme 3), which display less background reactivity with the MCPBA oxidant (Table 1). With these substrates, the studies focused on the complexes with L^{Me}2, which showed the most extensive chlorination activity in the cyclohexene assay, and L^{Me}4, which should be the bulkiest ligand. The benzylic substrates provide a means to assess the regioselectivity of the metal-based oxidants, given that the weak C–H bonds in toluene, ethylbenzene, and cumene are on primary, secondary, and tertiary carbons, respectively. When the concentration of MCPBA is limited to 1 equiv. relative to the metal complex, only the reaction between ethylbenzene and the iron complex with the dimethylated ligand and with L^{Me}2, leads to any substrate oxidation (Scheme 4). The yield of the reaction, which converts ethylbenzene exclusively to 1-chloroethylbenzene, is relatively low. As in the cyclohexene assays, iron outperforms manganese as a chlorination agent and the iron complex with L^{Me}2 outperforms that with L^{Me}4.

The steric environments around substrate C–H bonds have been found to impact the ability of moderately bulky oxidants to access and activate them [54]. Of the three substrates, toluene has the highest benzylic C–H bond dissociation energy (BDE), with most estimates of the bond strength at approximately 88 kcal mol^{-1} [47]. The BDE of the benzylic C–H bonds in ethylbenzene are estimated to be 85 kcal mol^{-1}; whereas, that of the weak C–H bond in cumene is approximately 83 kcal mol^{-1} [48]. If neither substrate nor oxidant sterics are important, one would expect cumene to be oxidized to the greatest extent. The results suggest that the oxidant generated from [Fe(L^{Me}2)Cl_2] and MCPBA is sufficiently sterically hindered to preclude the activation of C–H bonds on tertiary carbons, yet the oxidant is not strong enough for toluene oxidation. The oxidant derived from [Fe(L^{Me}2)Cl_2] shows the best reactivity with ethylbenzene, which is intermediate with respect to both the strength and accessibility of the benzylic C–H bonds. The lack of reactivity with [Fe(L^{Me}4)Cl_2] suggests that the additional methyl groups may discourage the activation of C–H bonds on secondary, as well as tertiary, carbons.

4.2.2. Reactivity with an excess of terminal oxidant

Chlorinated products result from the other metal complex/substrate mixtures when large excesses of MCPBA and substrate are used. In most cases, the chlorination product is formed in under 40% yield (0.8 turnovers), given the maximum of 20 mM that can be formed with the chloride present in solution. This activity is rather modest relative to previously reported systems [19,45]. As with these systems, the increase in the amount of terminal oxidant added heightens the overall oxidation activity at the cost of selectivity, as evident by the increased incidence of oxygenated products [44,45]. Consistent with the other reactivity assays reported in this manuscript, the oxidants derived from the manganese chloride complexes chlorinate benzylic substrates to a much lesser degree than their iron analogs. Although manganese

has proven superior to iron in other oxidation reactions [32–34,55], this does not appear to be the case with chlorination, at least with the reaction conditions investigated thus far.

Ethylbenzene continues to be the most active substrate with respect to chlorination. Notably, even with the excess terminal oxidant, ethylbenzene is not oxidized past 1-chloroethylbenzene. We speculate that the additional steric bulk provided by the installed chlorine atom precludes further reactivity. The iron compound with the tetramethylated ligand enables chlorination of the ethylbenzene to 1-chloroethylbenzene to a lesser degree, but with no oxygenated byproducts. When cumene and toluene are used as substrates, however, the yields of the chlorinated products associated with the two discrete iron complexes are equivalent within error. Even with excess oxidant, neither of the systems containing [Fe(L^{Me}2)Cl_2] or [Fe(L^{Me}4)Cl_2] can oxidize cumene, despite this substrate having the weakest C–H bond in the series of hydrocarbons.

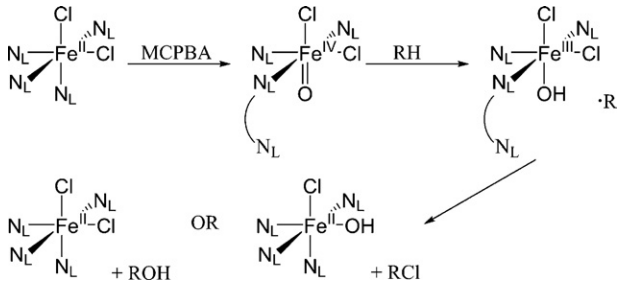
With the excess MCPBA, the oxidant(s) formed from $FeCl_2$ are the most active chlorination agents for each benzylic substrate. Unlike the oxidants generated from the [Fe(L^{Me}n)Cl_2] complexes, the $FeCl_2$/MCPBA mixture is capable of activating benzylic C–H bonds on primary, secondary, and tertiary carbons (Table 1). With cumene, $FeCl_2$ catalyzes the oxygenation of the substrate to 1-hydroxycumene, achieving 0.9 turnovers with respect to the chlorination and 4.2 turnovers with respect to the hydroxylation. Given the high conversion of MCPBA to MCBA (Scheme 4), the active species is likely an iron complex with one or more equivalents of deprotonated MCBA. One possibility is that the more anionic coordination sphere provided by these carboxylate ligands may promote chlorination. Increasing the negative charge around the metal ion should weaken the bonds between the metal and monodentate anionic ligands, such as hydroxide and chloride. Another factor that could explain the superior chlorination activity of $FeCl_2$ is its lack of an organic ligand. The bispicen deriviatives act as competing substrates and decompose during the reactions. Elimination of ligand degradation pathways may direct more of the MCPBA into substrate oxidation.

Subtle modifications in the ligand structure thereby appear to modulate the regiospecificity of the iron-mediated chlorination. In the absence of a tetradentate ligand, the oxidants formed can activate weak allylic or benzylic C–H bonds, regardless of the substrate's steric character. With $FeCl_2$, the extent to which the hydrocarbon is oxidized scales with the BDE of its weakest C–H bond(s). As methyl groups are installed on the ligand, the oxidants' abilities to chlorinate C–H bonds on tertiary and secondary carbons are curtailed. Ethylbenzene is most susceptible to chlorination by [Fe(L^{Me}2)Cl_2] and [Fe(L^{Me}4)Cl_2]-derived oxidants partly due to its weakened C–H bonds, relative to toluene, and partly due to the greater accessibility of these bonds, relative to cumene.

4.3. Mechanistic studies

When MCPBA is added to the [Fe(L^{Me}2)Cl_2] in the absence of substrate, a transient species is observed spectrophotometrically. At room temperature, the intermediate completely decays within 30 s. Parallel studies with mass spectrometry lead us to speculate that the transient species is [Fe^{IV}(L^{Me}2)(O)Cl_2] and that this intermediate is responsible for the hydrocarbon chlorination (Scheme 5). The presence of the second chloride in the oxidant distinguishes this system from another iron-based halogenation system recently reported by Comba, in which aliphatic chlorination is believed to proceed through an [Fe^{IV}(L)(O)Cl] species [44]. Results from Que's group suggest that the additional chloride may destabilize the Fe(IV) oxidation state [51].

The steric bulk provided by the methyl groups are believed to impede substrate access to the reactive portions of the oxidant and thereby prevent the oxidation of cumene. The lessened reactivity of [Fe(L^{Me}4)Cl_2] relative to [Fe(L^{Me}2)Cl_2] is consistent with the additional two methyl groups further impeding the substrate oxidation.



Scheme 5.

The primary obstacle to catalytic halogenation is that the ligands are themselves susceptible to oxidation, as indicated by NMR and TLC. The picolinylic C–H bonds have comparable bond dissociation energies to the benzylic substrates [56]. Other work from our group has found that the bispicen framework is much more dynamic than previously thought [57,58]. The flexibility of the ligand appears to correlate to a higher degree of self-oxidation, and consequently a lower degree of substrate oxidation, than those seen in systems using more constraining ligand backbones [44,45]. A rigid or oxidatively robust ligand therefore seems essential to efficient substrate chlorination.

5. Conclusion

The chlorination activity of manganese and iron complexes with methylated derivatives of the ligand bispicen is reported. The bispicen framework supports modest chlorination that is limited to benzylic and allylic C–H bonds. The identity of the metal and the extent of ligand methylation are found to have significant impacts on the reactivity. Iron appears to enable more extensive chlorination than manganese. The methylated bispicen ligands appear to discourage the chlorination of more sterically congested carbon centers, likely by restricting substrate access to the reactive portions of the generated [M^{IV}(L)(O)Cl_2] species. Although the changes to the ligand framework are ostensibly minor, they endow the chlorination reactions with a significant degree of regioselectivity.

Acknowledgements

This work was funded by Auburn University and a Doctoral New Investigator grant from the American Chemical Society-Petroleum Research Fund. K. H. was the recipient of a summer research scholarship provided by the Auburn University Cell and Molecular Biosciences Program (NSF EPS-0814103).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2010.11.006.

References

[1] M. Lersch, M. Tilset, Chem. Rev. 105 (2005) 2471–2526.
[2] H.M.L. Davies, R.E.J. Beckwith, Chem. Rev. 103 (2003) 2861–2904.
[3] D. Fiedler, D.H. Leung, R.G. Bergman, K.N. Raymond, Acc. Chem. Res. 38 (2004) 349–358.
[4] C. Jia, T. Kitamura, Y. Fujiwara, Acc. Chem. Res. 34 (2001) 633–639.
[5] D. Balcells, E. Clot, O. Eisenstein, Chem. Rev. 110 (2010) 749–823.
[6] C. Copéret, Chem. Rev. 110 (2010) 656–680.
[7] A. Gunay, K.H. Theopold, Chem. Rev. 110 (2010) 1060–1081.

[8] I.A.I. Mkhalid, J.H. Barnard, T.B. Marder, J.M. Murphy, J.F. Hartwig, Chem. Rev. 110 (2010) 890–931.
[9] R.C. Larock, Comprehensive Organic Transformations, Wiley-VCH, New York, NY, 1999.
[10] G.A. Russell, J. Am. Chem. Soc. 79 (1957) 2977–2978.
[11] G.A. Russell, J. Am. Chem. Soc. 80 (1958) 4987–4996.
[12] C. Walling, M.F. Mayahi, J. Am. Chem. Soc. 81 (1959) 1485–1489.
[13] D.D. Tanner, J.E. Rowe, A. Potter, J. Org. Chem. 51 (1986) 457–460.
[14] S.R. Jensen, W.A. Brown, E. Heath, D.G. Cooper, Biodegradation 18 (2007) 703–717.
[15] M.L. Poutsma, J. Am. Chem. Soc. 87 (1965) 2161–2171.
[16] M.L. Alegre, M. Geronés, J.A. Rosso, S.G. Bertolotti, A.M. Braun, D.O. Mártire, M.C. Gonzalez, J. Phys. Chem. A 104 (2000) 3117–3125.
[17] D.O. Mátire, J.A. Rosso, S. Bertolotti, G.C. Le Roux, A.M. Braun, M.C. Gonzalez, J. Phys. Chem. A 105 (2001) 5385–5392.
[18] T. Hori, K.B. Sharpless, J. Org. Chem. 44 (1979) 4204–4208.
[19] D.T. Sawyer, J.P. Hage, A. Sobkowiak, J. Am. Chem. Soc. 117 (1995) 106–109.
[20] Y. He, C.R. Goldsmith, SynLett 21 (2010) 1377–1380.
[21] F.H. Vaillancourt, E. Yeh, D.A. Vosburg, S. Garneau-Tsodikova, C.T. Walsh, Chem. Rev. 106 (2006) 3364–3378.
[22] L.C. Blasiak, C.L. Drennan, Acc. Chem. Res. 42 (2009) 147–155.
[23] S. Keller, T. Wage, K. Hohaus, M. Hölzer, E. Eichhorn, K.-H. van Pée, Angew. Chem. Int. Ed. 39 (2000) 2300–2302.
[24] V.M. Martínez, G.D. Cremer, M.B.J. Roeffaers, M. Sliwa, M. Baruah, D.E. De Vos, J. Hofkens, B.F. Sels, J. Am. Chem. Soc. 130 (2008) 13192–13193.
[25] C. Krebs, D.G. Fujimori, C.T. Walsh, J.M. Bollinger Jr., Acc. Chem. Res. 40 (2007) 484–492.
[26] C. Wong, D. Galonić Fujimori, C.T. Walsh, C.L. Drennan, J. Am. Chem. Soc. 131 (2009) 4872–4879.
[27] L.C. Blasiak, F.H. Vaillancourt, C.T. Walsh, C.L. Drennan, Nature 440 (2006) 368–371.
[28] D.P. Galonić, E.W. Barr, C.T. Walsh, J.M. Bollinger Jr., C. Krebs, Nat. Chem. Biol. 3 (2007) 113–116.
[29] M.L. Matthews, C.M. Krest, E.W. Barr, F.H. Vaillancourt, C.T. Walsh, M.T. Green, C. Krebs, J.M. Bollinger, Biochemistry 48 (2009) 4331–4343.
[30] S.V. Kryatov, E.V. Rybak-Akimova, Chem. Rev. 105 (2005) 2175–2226.
[31] M. Costas, M.P. Mehn, M.P. Jensen, L. Que Jr., Chem. Rev. 104 (2004) 939–986.
[32] A. Murphy, A. Pace, T.D.P. Stack, Org. Lett. 6 (2004) 3119–3122.
[33] A. Murphy, T.D.P. Stack, J. Mol. Catal. A 251 (2006) 78–88.
[34] G. Dubois, A. Murphy, T.D.P. Stack, Org. Lett. 5 (2003) 2469–2472.
[35] R. Gupta, A.S. Borovik, J. Am. Chem. Soc. 125 (2003) 13234–13242.
[36] A.S. Borovik, Acc. Chem. Res. 38 (2005) 54–61.
[37] H. Toftlund, E. Pedersen, S. Yde-Andersen, Acta. Chem. Scand. A 38 (1984) 693–697.
[38] J. Glerup, P.A. Goodson, A. Hazell, R. Hazell, D.J. Hodgson, C.J. McKenzie, K. Michelsen, U. Rychlewska, H. Toftlund, Inorg. Chem. 33 (1994) 4105–4111.
[39] C. Baffert, M.-N. Collomb, A. Deronzier, S. Kjaergaard-Knudsen, J.-M. Latour, K.H. Lund, C.J. McKenzie, M. Mortensen, L.P. Nielsen, N. Thorup, Dalton Trans. (2003) 1765–1772.
[40] A.L. Nivorozhkin, E. Anxolabéhère-Mallart, P. Mialane, R. Davydov, J. Guilhem, M. Cesario, J.-P. Audière, J.-J. Girerd, S. Styring, L. Schussler, J.-L. Seris, Inorg. Chem. 36 (1997) 846–853.
[41] G.R. Newkome, Y.A. Frere, F.R. Fronczek, V.K. Gupta, Inorg. Chem. 24 (1985) 1001–1006.
[42] B. Chiswell, Inorg. Chim. Acta 12 (1975) 195–198.
[43] C. R. Goldsmith, C. M. Coates, K. Hagan,C. A. Mitchell, manuscript submitted.
[44] P. Comba, S. Wunderlich, Chem. Eur. J. 16 (2010) 7293–7299.
[45] R.A. Leising, Y. Zang, L. Que Jr., J. Am. Chem. Soc. 113 (1991) 8555–8557.
[46] Y.-M. Lee, S. Hong, Y. Morimoto, W. Shin, S. Fukuzumi, W. Nam, J. Am. Chem. Soc. 132 (2010) 10668–10670.
[47] J. Berkowitz, G.B. Ellison, D. Gutman, J. Phys. Chem. 98 (1994) 2744–2765.
[48] I.W.C.E. Arends, P. Mulder, K.B. Clark, D.D.M. Wayner, J. Phys. Chem. 99 (1995) 8182–8189.
[49] L. Que Jr., Acc. Chem. Res. 40 (2007) 493–500.
[50] N.D. Jabre, L. Hryhorczuk, J.J. Kodanko, Inorg. Chem. 48 (2009) 8078–8080.
[51] J.-U. Rohde, A. Stubna, E.L. Bominaar, E. Münck, W. Nam, L. Que Jr., Inorg. Chem. 45 (2006) 6435–6445.
[52] Y. Fujii, F. Ebina, M. Yanagisawa, H. Matsuoka, T. Kato, J. Inorg. Organomet. Polym. 4 (1994) 273–288.
[53] T. Kojima, R.A. Leising, S. Yan, L. Que Jr., J. Am. Chem. Soc. 115 (1993) 11328–11335.
[54] M.S. Chen, M.C. White, Science 327 (2010) 566–571.
[55] A. Murphy, G. Dubois, T.D.P. Stack, J. Am. Chem. Soc. 125 (2003) 5250–5251.
[56] J.S. Roberts, M. Szwarc, J. Chem. Phys. 16 (1948) 981–983.
[57] G.J.P. Britovsek, J. England, A.J.P. White, Dalton Trans. (2006) 1399–1408.
[58] C. Hureau, G. Blondin, M.-F. Charlot, C. Philouze, M. Nierlich, M. Cesario, E. Anxolabéhère-Mallart, Inorg. Chem. 44 (2005) 3669–3683.