



# Oxidation of cyclohexane by transition-metal complexes with biomimetic ligands

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## ABSTRACT

This work reports the catalytic activity, in homogeneous phase, of transition-metal complexes of the first-row (V(IV), Mn(III), Fe(III), Co(III) and Cu(II)) with biomimetic Schiff base ligands with N<sub>2</sub>O<sub>2</sub> coordination sphere, as well as an N<sub>4</sub> (Fe(II)), in the room-temperature oxidation of cyclohexane using environmentally benign reagents: hydrogen peroxide (30 wt%) as the oxygen source and acetonitrile as the solvent. Nitric acid is also used as promoter of the oxidation reaction. The structure of the ligands is confirmed by FTIR, <sup>1</sup>H NMR and high-resolution ESI mass spectrometry. The corresponding transition metal complexes are characterized by elemental analysis, high resolution ESI mass spectrometry, FTIR and UV–vis. Cyclohexanone and cyclohexanol are the main products of the oxidation of cyclohexane, obtained when the following complexes are used as homogeneous catalysts in only 1 mol% based on the substrate: VO(IV), Fe(III) and Cu(II) complexes with the N<sub>2</sub>O<sub>2</sub> Schiff base, new Fe(II) complex with the Schiff base with N<sub>4</sub> coordination sphere and commercial [VO(acac)<sub>2</sub>] with O<sub>4</sub> coordination sphere. The Fe(III) complex with N<sub>2</sub>O<sub>2</sub> Schiff base ligand ([Fe(salhd)Cl]) is the homogeneous catalyst with highest activity, which could be further enhanced by the addition of methyl electron donating groups to the N<sub>2</sub>O<sub>2</sub> Schiff base aldehyde fragment (reaching 46% oxygenate yields and 45 turnover numbers). Cyclooctane and *n*-hexane could also be oxidized to the corresponding ketones and alcohols with higher turnover numbers than cyclohexane by the Fe(III) complex with N<sub>2</sub>O<sub>2</sub> Schiff base ligand.

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## 1. Introduction

The functionalization of relatively abundant and low-cost feedstock, such as alkanes, into more valuable products, such as alcohols, ketones and aldehydes, is still a scientific challenge [1–4]. On the other hand, the alkane-functionalized products are more reactive than the parent alkane; when their concentration approaches the remaining alkane, the target products will be involved in a substantial over-oxidation to produce undesirable compounds, reducing therefore their yield [3].

The oxidation of cyclohexane is a reaction of great industrial relevance as the main products, cyclohexanol and cyclohexanone, are used as precursors to the synthesis of added-value products, such as Nylon-6 and Nylon-6,6 [1,5]. In the industry, the reaction is currently performed using a cobalt(II) naphthenate catalyst [6] at 160 °C and 15 bar with very low yields and good selectivities [3,5,6]: 4% conversion into oxidized products with 80% selectivity towards cyclohexanol and cyclohexanone [5]. Therefore, catalysis by transition-metal complexes is a promising route to the selective functionalization of alkanes under mild conditions [1–4].

Certain enzymes already perform this reaction efficiently with molecular oxygen under mild conditions constituting the state-of-the-art in alkane oxidation. They are, however, expensive and easily deactivated, while inspiration on nature, specifically on the active centre of enzymes, may lead to better catalytic systems for the C–H activation [4]. Several biomimetic ligands have been described as models for the *heme*-containing cytochrome P450 enzyme including metalloporphyrins [7] and metallosalen [8–10]. These systems mediate the transference of oxygen atoms to hydrocarbons promoting their oxidation. The later, however, have the advantage of being more stable in strongly oxidizing reaction media and are easily synthesized in high yields from readily available and inexpensive precursors [8–10]. Their electronic properties may also be easily tuned by introduction of electron withdrawing or donating groups in the aldehyde fragment [10].

Several non-heme iron catalysts with tetradentate nitrogen-based ligands are also selective in the oxidation of alkanes with hydrogen peroxide. Kinetic isotope effects indicate that the active oxidant in these systems is a high-valent iron(V)oxo species suggesting a mechanism analogous to that of Cytochrome P-450 [5,11]. On the other hand, iron salts in 1 mol% are known to be highly-active catalysts in the oxidation of cyclohexane at 50 °C in acetonitrile using hydrogen peroxide [5]. Furthermore, the addition of a tridentate Schiff-base ligand with N<sub>3</sub> coordination sphere increases selectivity towards cyclohexanol and cyclohexanone [5].

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The mechanism of the reaction was attributed to be the competing radical pathways involving hydroxyl radicals and more selective non-radical high valent iron species pathways, as the major problem with Fenton chemistry is the lack of selectivity in alkane oxidation [5]. This conclusion is also supported by experiments using other systems where a radical inhibitor was added to the reaction after which oxygenated products were still obtained [12].

One of the most active catalysts for the mild oxidation cyclohexane is a copper(II) triethanolamine complex, whose activity is drastically accelerated by the presence of nitric acid additive (co-catalyst) leading to 39% yield of oxygenates in a single batch based on the substrate [4,13].

Several heterogenized metallosalen systems have been reported as heterogeneous catalysts for the alkane oxidation [8,14–16]. To the best of our knowledge, however, a comprehensive study is not available of alkane oxidation at room temperature by these transition-metal complexes in homogeneous phase and the effect of the addition of additives to the reaction. In this context, here we wish to present a systematic study on the catalytic activity of sustainable first-row transition metal complexes (Fe, V, Cu, Co, Mn) with biomimetic salen-type polydentate ligands with  $N_2O_2$  or  $N_4$  coordination sphere, in homogeneous phase, in the oxidation of cyclohexane at room temperature, using environmentally-benign reactants: hydrogen peroxide as the oxygen source and acetonitrile as the solvent. The use of catalysts based on more abundant transition metals is also desirable as it would decrease costs and increase sustainability. Therefore the best metal catalyst was identified and the effect of the different co-catalysts and temperature in the reaction studied. Other oxidants, such as  $H_2O_2$ -urea and iodosylbenzene, were also tested.

## 2. Materials and methods

### 2.1. Materials and solvents

The reagents used in the synthesis of the ligands were used as received. In the synthesis of the ligands and corresponding complexes 1,2-cyclohexanediamine (99%), salicylaldehyde (98%), 5-bromosalicylaldehyde (98%), 2-hydroxymethylbenzaldehyde (98%), 2-pyridinecarboxaldehyde (99%), iron(III) chloride hexahydrate (p.a.), manganese(II) chloride dehydrate (p.a.), vanadyl(IV) sulphate pentahydrate (97%), vanadyl(IV) acetylacetonate (95%) and deuterated solvents were purchased from Sigma–Aldrich. Cobalt(II) chloride hexahydrate (p.a.), copper(II) acetate monohydrate (p.a.) and ethanol were from Panreac.

In the catalytic tests cyclohexane ( $\geq 99.5\%$ ), chlorobenzene ( $\geq 99.5\%$ ), hydrogen peroxide 30% wt in water, hydrogen peroxide–urea adduct (p.a.), nitric acid (p.a.) and triphenylphosphine (99%) were purchased from Sigma–Aldrich; acetonitrile was HPLC grade and from Romil. *n*-Hexane (99.8%) was from Fisher Scientific. For the FTIR potassium bromide was used spectroscopic grade.

### 2.2. Synthesis of the ligands

The synthesis of the ligands was performed according to the process described by Holm et al. [17]; ethanolic solutions of salicylaldehyde, or its derivatives or 2-pyridinecarboxaldehyde, were refluxed for 1–2 h with cyclohexanediamine in the proportion of 2:1 with vigorous magnetic stirring. Typically 0.015 mmol of diamine were refluxed with 0.03 mmol of salicylaldehyde in 20 ml of ethanol for 1 h. The solution was kept in the freezer overnight and the precipitated ligand was collected after filtration under vacuum. All synthesized ligands were yellow and yields were between 55 and 95%. The ligand structure is represented in Scheme 1 where

$H_2$ salhd is (a) with  $Y=H$ ,  $H_2$ (Brsalhd) is (a) with  $Y=Br$ ,  $H_2$ (Mesalhd) is (b) with  $Y=CH_3$  and pyhd is (b).

**$H_2$ salhd**,  $N,N'$ -bis(salicylaldehyde)-cyclohexanodiamine:  $C_{20}H_{22}N_2O_2$ .  $^1H$  NMR ( $CDCl_3$ , 300 MHz, 297 K)  $\delta$ /ppm: 13.5, 13.3 (s, 2H, HO), 8.4, 8.3 (s, 2H, N=CH), 7.2–7.1 (m, 4H, aromatic), 6.9–6.7 (m, 4H, aromatic), 3.6, 3.3 (m, 2H,  $CH_2$ ), 2.0–1.5 (m, 8H,  $CH_2$ ). EA, %: calculated C 74.51, N 6.88, H 8.69, experimental C 73.96, N 7.09, H 8.68. FTIR,  $\nu/cm^{-1}$ : 2933 m, 1629 vs, 1579 m, 1280 s. UV–vis,  $\lambda_{max}/nm$ : 262, 357, 410.

**$H_2$ Brsalhd**,  $N,N'$ -bis(5-bromosalicylaldehyde)-cyclohexanodiamine:  $C_{20}H_{20}Br_2N_2O_2$ .  $^1H$  NMR ( $CDCl_3$ , 300 MHz, 297 K)  $\delta$ /ppm: 13.4, 13.2 (s, 2H, HO), 8.3, 8.2 (s, 2H, N=CH), 7.4–7.3 (m, 4H, aromatic), 6.8 (m, 2H, aromatic), 3.6, 3.3 (m, 2H,  $CH_2$ ), 2.0–1.5 (m, 8H,  $CH_2$ ). FTIR,  $\nu/cm^{-1}$ : 2925 m, 1631 vs, 1567 m, 1475; s, 1500 m, 1280 s, 827 m.

**$H_2$ Mesalhd**,  $N,N'$ -bis(5-methylsalicylaldehyde)-cyclohexanodiamine:  $C_{22}H_{26}N_2O_2$ .  $^1H$  NMR ( $CDCl_3$ , 300 MHz, 297 K)  $\delta$ /ppm: 13.2, 13.1 (s, 2H, HO), 8.3, 8.2 (s, 2H, N=CH), 7.1–6.9 (m, 4H, aromatic), 6.8 (m, 2H, aromatic), 3.6, 3.3 (m, 2H,  $CH_2$ ), 2.3, 2.2 (m, 6H,  $CH_2$ ), 1.9–1.6 (m, 8H,  $CH_2$ ). FTIR,  $\nu/cm^{-1}$ : 2927 m, 1631 vs, 1589 m, 1494 s, 1280 s.

**pyhd**,  $N,N'$ -bis(2-pyridinealdehyde)-cyclohexanodiamine:  $C_{18}H_{20}N_4$ .  $^1H$  NMR ( $CDCl_3$ , 300 MHz, 297 K)  $\delta$ /ppm: 8.6, 8.5 (s, 2H, N=CH), 8.3, 8.2 (m, 2H, aromatic), 7.9–7.8 (m, 4H, aromatic), 7.4 (m, 2H, aromatic), 3.7, 3.5 (m, 2H,  $CH_2$ ), 1.8–1.5 (m, 8H,  $CH_2$ ). ESI-HRMS,  $m/z$ : calculated ( $C_{20}H_{21}N_4^+$ ) 293.17607, experimental 293.17618. FTIR,  $\nu/cm^{-1}$ : 2927 s, 2854 s, 1644 vs, 1585 s, 1564 s, 1467 s, 1436 s, 788 m, 771 m.

### 2.3. Synthesis of the metal complexes

The transition-metal complexes of vanadyl(IV), manganese(III), iron(III), cobalt(III) and copper(II) were synthesized by procedures described in the literature [10,17]; equimolar solutions of ligand and metal salt (17 mmol) were refluxed for 1–2 h under magnetic stirring. After precipitation of the solids they were collected by vacuum filtration and dried under reduced pressure during several days. The yields were between 49 and 62% and their structure is represented in Scheme 1c and d. The complexes were characterized by FTIR, UV–visible, C, N and H elemental analysis and high resolution mass spectrometry.

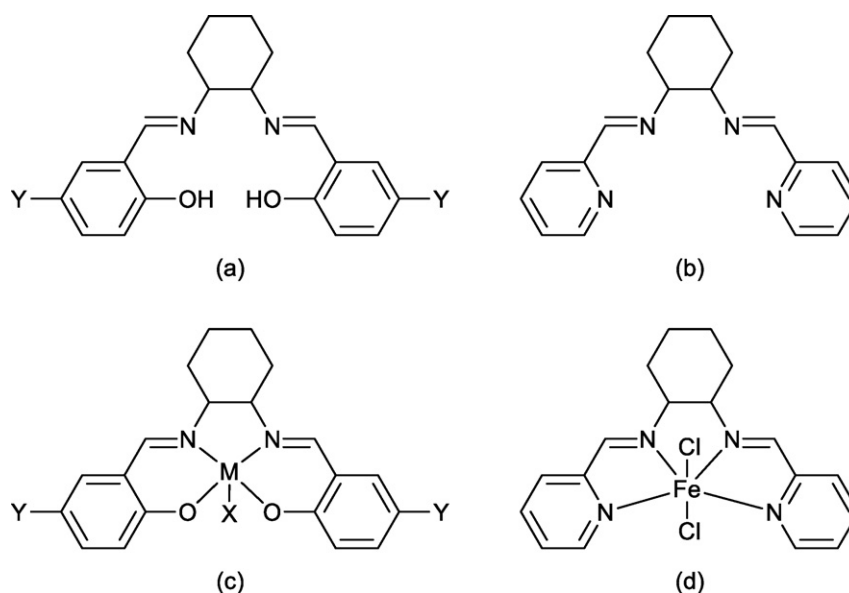
**[VO(salhd)]**, [ $N,N'$ -bis(salicylaldehyde)-cyclohexanodiamine] vanadyl(IV):  $VC_{20}H_{20}N_2O_3$ . ESI-HRMS,  $m/z$ : calculated ( $VC_{20}H_{20}N_2O_3^+$ ) 387.09081, experimental 387.09053. EA, %: calculated C 62.02, N 7.23, H 5.20, experimental C 61.63, N 7.30, H 5.38. FTIR,  $\nu/cm^{-1}$ : 2933 m, 1614 vs, 1311 s. UV–vis,  $\lambda_{max}/nm$ : 262, 397, 458 (i), 597, ~650 (i).

**[Mn(salhd)Cl]**, chloro-[ $N,N'$ -bis(salicylaldehyde)-cyclohexanodiamine] manganese(III):  $MnC_{20}H_{20}N_2O_2Cl$ . ESI-HRMS,  $m/z$ : calculated ( $MnC_{20}H_{20}N_2O_2^+$ ) 375.08998, experimental 375.08948. FTIR,  $\nu/cm^{-1}$ : 2931 m, 1621 vs, 1598 vs, 1311 s, 1278 s. UV–vis,  $\lambda_{max}/nm$ : 264, 412, 455 (i), ~686 (i).

**[Fe(salhd)Cl]**, chloro-[ $N,N'$ -bis(salicylaldehyde)-cyclohexanodiamine] iron(III):  $FeC_{20}H_{20}N_2O_2Cl$ . ESI-HRMS,  $m/z$ : calculated ( $FeC_{20}H_{20}N_2O_2^+$ ) 376.0869, experimental 376.0864. EA, %: calculated C 58.35, N 6.80, H 4.90, experimental C 58.34, N 6.76, H 4.99. FTIR,  $\nu/cm^{-1}$ : 2937 m, 1625 vs, 1608 vs, 1311 s. UV–vis,  $\lambda_{max}/nm$ : 256, 475.

**[Fe(Brsalhd)Cl]**, chloro-[ $N,N'$ -bis(5-bromosalicylaldehyde)-cyclohexanodiamine] iron(III):  $FeC_{20}H_{18}N_2O_2Br_2Cl$ . ESI-HRMS,  $m/z$ : calculated ( $FeC_{20}H_{18}N_2O_2Br_2^+$ ) 531.90796, experimental 531.90549. FTIR,  $\nu/cm^{-1}$ : 2937 m, 2859 m, 1644 vs, 1625 vs, 1625 vs, 1608 vs, 1460 s, 1384 s, 1314 s. UV–vis,  $\lambda_{max}/nm$ : 266, 394, 534.

**[Fe(Mesalhd)Cl]**, chloro-[ $N,N'$ -bis(5-methylsalicylaldehyde)-cyclohexanodiamine] iron(III):  $FeC_{22}H_{24}N_2O_2Cl$ . ESI-HRMS,  $m/z$ : calculated ( $FeC_{22}H_{24}N_2O_2^+$ ) 404.11817, experimental 404.11686.



**Scheme 1.** Molecular structure of the biomimetic ligands and corresponding first-row transition-metal complexes: (a)  $H_2(salhd)$  ( $Y=H$ ),  $H_2(Brsalhd)$  ( $Y=Br$ ) and  $H_2(Mesalhd)$  ( $Y=CH_3$ ); (b)  $pyhd$ ; (c)  $[VO(salhd)]$  ( $M=V$ ,  $X=O$ ,  $Y=H$ ),  $[Cu(salhd)]$  ( $M=Cu$ ,  $Y=H$ ),  $[Co(salhd)Cl]$  ( $M=Co$ ,  $X=Cl$ ,  $Y=H$ ),  $[Fe(salhd)Cl]$  ( $M=Fe$ ,  $X=Cl$ ,  $Y=H$ ),  $[Fe(Mesalhd)Cl]$  ( $M=Fe$ ,  $X=Cl$ ,  $Y=CH_3$ ) and  $[Fe(Brsalhd)Cl]$  ( $M=Fe$ ,  $X=Cl$ ,  $Y=Br$ ) (d)  $[Fe(pyhd)Cl_2]$ .

FTIR,  $\nu/cm^{-1}$ : 2930 m, 2857 m, 1620 vs, 1600 vs, 1542 s, 1473 s, 1380 s, 1308 s. UV–vis,  $\lambda_{max}/nm$ : 266, 528.

**[Co(salhd)Cl]**, chloro- $[N,N'$ -bis(salicylaldehyde)-cyclohexanodiminate] cobalt(III):  $CoC_{20}H_{20}N_2O_2Cl$ . ESI-HRMS,  $m/z$ : calculated ( $CoC_{20}H_{20}N_2O_2^+$ ) 379.0851, experimental 379.0846. FTIR,  $\nu/cm^{-1}$ : 2935 m, 1633 vs. UV–vis,  $\lambda_{max}/nm$ : 256, 409, 542.

**[Cu(salhd)]**,  $[N,N'$ -bis(salicylaldehyde)-cyclohexanodiminate] copper(II):  $CuC_{20}H_{20}N_2O_2$ . ESI-HRMS,  $m/z$ : calculated ( $CuC_{20}H_{21}N_2O_2^+$ ) 384.08936, experimental 384.08908. EA, %: calculated C 62.57, N 7.30, H 5.25, experimental C 62.20, N 7.32, H 5.27. FTIR,  $\nu/cm^{-1}$ : 2931 m, 1631 vs. UV–vis,  $\lambda_{max}/nm$ : 269, 343, 392, 552.

**[Fe(pyhd)Cl<sub>2</sub>]**, dichloro- $[N,N'$ -bis(2-pyridinealdehyde)-cyclohexanodiminate] iron(II):  $FeC_{18}H_{18}N_4O_2Cl_2$ . ESI-HRMS,  $m/z$ : calculated ( $FeC_{20}H_{20}N_4Cl^+$ ) 283.07208, experimental 283.07197. FTIR,  $\nu/cm^{-1}$ : 2941 m, 1651 m, 1639 m, 1597 s, 1475 m, 1448 m, 1300 m, 1036 vs, 783 s, 496 s. UV–vis,  $\lambda_{max}/nm$ : 265 (i), 420, 520, 595 (i).

#### 2.4. Catalytic experiments

The homogeneous phase catalytic studies were performed using 5.00 mmol of cyclohexane, 0.05 mmol of homogeneous catalyst (1 mol% relative to cyclohexane), 0.5 mmol of nitric acid and 25 mmol of hydrogen peroxide as sustainable oxidant in 20.00 ml of acetonitrile in batch reactors at room temperature, atmospheric pressure and under constant stirring (1300 rpm) (Scheme 2). Therefore, the ratio of cyclohexane/catalyst/ $HNO_3/H_2O_2$  was, respectively, 100/1/10/500 [18]. The reactions were performed



**Scheme 2.** Oxidation of cyclohexane into cyclohexanol (OH) and cyclohexanone (=O).

at least twice. As the homogeneous catalysts may present dismutase activity [4,19], hydrogen peroxide was added slowly to the reaction using a syringe pump in order to prevent its degradation [11]. Reactions at 40 and 65 °C were also performed with the  $[Fe(salhd)Cl]$  homogeneous catalyst to check the effect of the temperature on the catalytic parameters. In a typical procedure, an aliquot of 150  $\mu$ l was withdrawn from the reaction mixture, the alkylhydroperoxides were reduced with excess of triphenylphosphine (0.0330 g), according to a method described in the literature [18–20], and then chlorobenzene was added as external standard prior to the GC analysis (44.0  $\mu$ l of a 0.135 mol  $dm^{-3}$  solution in acetonitrile). Cyclohexanol and cyclohexanone were identified by comparison of their retention times with commercially available samples and their quantification by interpolation into multipoint calibration curves. Other oxygenated products were identified by a Finnigan Trace GG–MS. It is noteworthy that no alkane oxidation products were detected in control experiments using the same experimental conditions but without addition of homogeneous catalyst.

#### 2.5. Physical measurements

$^1H$  NMR spectra were recorded on a Bruker Avance 300 spectrometer at 297 K, using tetramethylsilane as internal reference. FTIR spectra were obtained as KBr pellets in a FT Mattson 7000 galaxy series in the range 400–4000  $cm^{-1}$ , and ultraviolet diffuse reflectance spectra on a Jasco V-560 in the range 800–200 nm using barium sulfate as reference. Elemental analysis and ESI-HRMS were performed at CACTI, Universidade de Vigo (Spain).

Gas chromatography experiments (GC) were performed with a Varian 450 GC chromatograph equipped with a FID detector and using helium as carrier gas and a fused silica Varian Chrompack capillary column VF-5ms (15 m, 0.15 mm id; 15 mm film thickness). The chromatographic conditions were: 60 °C (3 min), 5 °C/min, 170 °C (2 min), 20 °C/min, 200 °C (5 min); injector temperature, 230 °C; detector temperature, 250 °C. After reduction with triphenylphosphine ( $PPh_3$ ) of 150  $\mu$ l aliquots they were injected directly into the injector using a 1  $\mu$ l Hamilton syringe.

### 3. Results and discussion

#### 3.1. Synthesis of the biomimetic ligands and complexes

In this work two types of Schiff base ligands with  $N_2O_2$  ( $H_2salhd$ , Scheme 1a) and  $N_4$  ( $pyhd$ , Scheme 1b) coordination sphere were synthesized. For the  $N_2O_2$  Schiff base ligand bromine electron withdrawing substituent (Scheme 1a,  $Y=Br$ ) were also introduced in the aldehyde fragment, as well as a methyl electron withdrawing groups (Scheme 1b,  $Y=CH_3$ ) by varying the salicylaldehyde precursor. FTIR spectra of these ligands show the typical  $C=N$  stretching vibration around  $1630\text{ cm}^{-1}$ , besides the  $C-H$  stretching vibration of the cyclohexane in the diimine bridge at  $2930\text{ cm}^{-1}$ . Proton NMR is also typical of Schiff base ligands [10]. The structure of the ligands was also confirmed by elemental analysis and by high resolution mass spectrometry in the case of the  $pyhd$  (Scheme 1b).

With the  $N_2O_2$  type ligands the following first-row transition metal complexes were prepared as represented in Scheme 1c:  $VO(IV)$  ( $[VO(salhd)]$ ),  $M=V$ ,  $X=O$  and  $Y=H$ ),  $Mn(III)$  ( $[Mn(salhd)Cl]$ ),  $M=Mn$ ,  $X=Cl$  and  $Y=H$ ),  $Fe(III)$  ( $[Fe(salhd)Cl]$ ),  $M=Fe$ ,  $X=Cl$  and  $Y=H$ ),  $Co(III)$  ( $[Co(salhd)Cl]$ ),  $M=Co$ ,  $X=Cl$  and  $Y=H$ ) and  $Cu(II)$  ( $[Cu(salhd)]$ ),  $M=Cu$ ,  $Y=H$ ). Three more iron complexes were prepared:  $[Fe(Brsalhd)Cl]$  (Scheme 1c,  $M=Fe$ ,  $X=Cl$  and  $Y=Br$ ),  $[Fe(Mesalhd)Cl]$  (Scheme 1c,  $M=Fe$ ,  $X=Cl$  and  $Y=CH_3$ ) and  $[Fe(pyhd)Cl_2]$  (Scheme 1d). The structure of the complexes was confirmed by high-resolution mass spectrometry and/or by elemental analysis. To the best of our knowledge the  $[Fe(pyhd)Cl_2]$  complex is new.

The  $[Mn(salhd)Cl]$  and  $[Co(salhd)Cl]$  show brown colors, while the  $[Cu(salhd)]$ ,  $[Fe(salhd)Cl]$ ,  $[Fe(Brsalhd)Cl]$  and  $[Fe(Mesalhd)Cl]$  are dark red and the vanadyl(IV) complex is light green. The  $Fe(II)$  complex,  $[Fe(pyhd)Cl_2]$ , is orange. The solubility of all complexes is high in ethanol, while in acetonitrile solubility is only high for  $[Cu(salhd)]$ ,  $[Fe(salhd)Cl]$ ,  $[Fe(Mesalhd)Cl]$  and  $[VO(salhd)]$ , moderate for  $[Mn(salhd)Cl]$  and low for  $[Co(salhd)Cl]$  and  $[Fe(Brsalhd)Cl]$ .

The FTIR spectra of these complexes show the typical  $C=N$  stretching vibration between  $1614$  and  $1633\text{ cm}^{-1}$ . This value is shifted, in general, to lower wavenumbers when compared to the corresponding ligands in the case of the  $Mn(III)$ ,  $Fe(III)$ ,  $Co(III)$  and  $VO(IV)$  complexes, which is due to coordination to the metal (Scheme 1) [10].

#### 3.2. Catalytic oxidation of alkanes

The synthesized transition-metal complexes were tested as homogeneous catalysts (1 mol%) in the oxidation of cyclohexane in acetonitrile using excess of hydrogen peroxide as sustainable oxidant at room temperature. Acetonitrile is the reaction media often reported for the oxidation of alkanes [4–6,8,10–13,15,16,18,19,21–23]. Nitric acid was used as co-catalyst because it is described in the literature that acts as a promoter for this type of reactions [4,13]. Nevertheless, a control experiment without the addition of catalysts showed that the oxidation of cyclohexane does not occur.

The formation of alkylperoxides was confirmed by analyzing by GC the samples before and after reduction with triphenylphosphine ( $PPh_3$ ) giving rise to cyclohexanol and phosphane oxide, as described by Shul'pin et al. [19,20]. Therefore, the results presented in Table 1 are always after sample reduction and, consequently, only cyclohexanol and cyclohexanone were detected in the reaction mixture at short reaction times (3 h). Moreover, for comparison of the catalytic results shorter, rather than long, reaction times were chosen, as for 6 h of reaction over-oxidation products were detected by GC–MS in the reaction mixture [3].

Cyclohexanol and cyclohexanone products were obtained in the presence of most of the transition-metal complexes studied

after 3 h of reaction (Table 1). As can be seen in Table 1, the most active catalyst was  $[Fe(salhd)Cl]$  and the cyclohexanone plus cyclohexanol TON and yields for the  $[M(salhd)X]$  series were:  $Fe(III)$  (entry 1) >  $VO(IV)$  (entry 4) >  $Cu(II)$  (entry 5). Complexes of  $Fe(II)$  [5,11,21,22],  $Fe(III)$  [5],  $VO(IV)$  [6,12,23] and  $Cu(II)$  [4,9] are known as homogeneous catalysts for the oxidation of cyclohexane using hydrogen peroxide as the oxidant, sometimes at elevated temperature [5,6,12].

On the other hand, the  $[Mn(salhd)Cl]$  (entry 6) and  $[Co(salhd)Cl]$  (entry 7) complexes were not selective for cyclohexanol and cyclohexanone, like already reported in the literature for  $Mn(II)$  and  $Co(II)$  complexes with  $N_4$  ligands [21]. Curiously, the  $[Mn(salhd)Cl]$  complex is a very efficient catalyst for the epoxidation of unfunctionalized alkenes at room temperature using, however, single-oxygen oxidants such as  $PhIO$  and  $NaOCl$  [10]. Moreover, taking into account that cobalt(II) naphthenate is the homogeneous catalyst for industrial oxidation of cyclohexane, albeit at high temperature and pressure [3,5,6], we were expecting that  $[Co(salhd)Cl]$  complex could be catalytically active in this reaction.

Another iron complex was synthesized with a Schiff base bearing a  $N_4$  coordination sphere, instead of  $N_2O_2$ , yielding a  $Fe(II)$  complex which was also active in the oxidation of cyclohexane, but with lower TON and yield than  $[Fe(salhd)Cl]$  (entry 2, Table 1). This complex was, however, more selective towards cyclohexanol showing a very high  $OH/O$  ratio, suggesting that hydroxyl radicals are not involved in the reaction and may implicate an iron-based oxidant [22].

Commercial vanadyl acetylacetonate ( $[VO(acac)_2]$ ) possessing an  $O_4$  coordination sphere, already reported in the literature as a homogeneous catalyst for the oxidation of cyclohexane using 70 wt% of hydrogen peroxide [6,12], was also tested under similar experimental conditions to those used for the other complexes. It showed lower catalytic performance than the  $[VO(salhd)]$  complex and, consequently, than  $[Fe(salhd)Cl]$ .

Since this reaction is normally performed at higher temperatures [5,6,12], two more reactions were performed at  $40^\circ\text{C}$  (entry 8, Table 1) and  $65^\circ\text{C}$  (entry 9, Table 1) in order to check the effect of the temperature with the best catalyst  $[Fe(salhd)Cl]$ . It was observed that the increase of temperature decreased the cyclohexanol plus cyclohexanone yields relatively to the reaction performed at room temperature (entry 1, Table 1). This may be due to the decomposition of hydrogen peroxide at higher temperature. With increase of the temperature, a change in the product distribution and an increase in the cyclohexanone relatively to cyclohexanol were also observed. Upon reduction of these samples with  $PPh_3$  the typical exothermic reaction did not occur suggesting that the amount of cyclohexylperoxide is much lower, resulting in the decrease in the cyclohexanol yield. Nevertheless oxidation of cyclohexanol to cyclohexanone at higher temperatures in excess of hydrogen peroxide is also likely to occur [11,21,22,24].

Experiments in the presence of microwaves (mostly 30 W at room temperature) were also performed, but only for the case of  $[VO(salhd)]$  a slight increase in the cyclohexanol and cyclohexanone yields were obtained, attributed to the increase of the reaction temperature which increased the oxygenate yields (not shown).

The oxidation of cyclohexane was also performed using the  $Fe(III)$  catalysts bearing electron withdrawing  $[Fe(Brsalhd)Cl]$  and electron-donating groups  $[Fe(Mesalhd)Cl]$  in the 5 position of the aldehyde fragment (Scheme 1c). The introduction of the methyl group increases the cyclohexanol and cyclohexanone yields, TON and  $OH/=O$  ratio (entry 10) relative to  $[Fe(salhd)Cl]$  (entry 1), whereas the introduction of the bromine decreases the cyclohexanol and cyclohexanone yield (entry 11). This suggests that there must be electronic effects on the  $Fe(III)$  salen catalyst and, therefore,

**Table 1**  
Catalytic oxidation of alkanes at room temperature with hydrogen peroxide by first-row transition metal complexes with biomimetic ligands.<sup>a</sup>

Entry	Catalyst	Alkane	Co-catalyst/oxidant	% yield <sup>b</sup>			OH/=O ratio	TON
				OH <sup>c</sup>	=O <sup>d</sup>	Total		
1	[Fe(salhd)Cl]	C <sub>6</sub> H <sub>12</sub>	HNO <sub>3</sub> /HP	14.7	10.2	24.9	1.4	25.1
2	[Fe(pyhd)Cl <sub>2</sub> ]	C <sub>6</sub> H <sub>12</sub>	HNO <sub>3</sub> /HP	17.2	0.2	17.5	74.5	16.7
3	[VO(acac) <sub>2</sub> ]	C <sub>6</sub> H <sub>12</sub>	HNO <sub>3</sub> /HP	4.3	1.1	5.4	3.8	3.5
4	[VO(salhd)]	C <sub>6</sub> H <sub>12</sub>	HNO <sub>3</sub> /HP	16.9	4.6	21.5	3.6	21.1
5	[Cu(salhd)]	C <sub>6</sub> H <sub>12</sub>	HNO <sub>3</sub> /HP	0.5	0.2	0.7	2.4	0.7
6	[Mn(salhd)Cl]	C <sub>6</sub> H <sub>12</sub>	HNO <sub>3</sub> /HP	0	0	0	0	0
7	[Co(salhd)Cl]	C <sub>6</sub> H <sub>12</sub>	HNO <sub>3</sub> /HP	0	0	0	0	0
8	[Fe(salhd)Cl] <sup>e</sup>	C <sub>6</sub> H <sub>12</sub>	HNO <sub>3</sub> /HP	2.3	4.2	6.5	0.5	6.4
9	[Fe(salhd)Cl] <sup>f</sup>	C <sub>6</sub> H <sub>12</sub>	HNO <sub>3</sub> /HP	0.0	14.9	14.9	0.0	13.6
10	[Fe(Mesalhd)Cl]	C <sub>6</sub> H <sub>12</sub>	HNO <sub>3</sub> /HP	35.3	10.5	45.8	3.4	45.1
11	[Fe(Brsalhd)Cl]	C <sub>6</sub> H <sub>12</sub>	HNO <sub>3</sub> /HP	14.6	4.4	19.0	3.3	18.8
12	[Fe(salhd)Cl]	C <sub>6</sub> H <sub>12</sub>	None/HP	2.7	1.0	3.7	2.8	3.7
13	[Fe(salhd)Cl]	C <sub>6</sub> H <sub>12</sub>	HCl/HP	0.1	0.2	0.3	0.5	0.3
14	[Fe(salhd)Cl]	C <sub>6</sub> H <sub>12</sub>	MeCO <sub>2</sub> H/HP	3.8	2.4	6.2	1.6	6.1
15	[Fe(salhd)Cl] <sup>g</sup>	C <sub>6</sub> H <sub>12</sub>	HNO <sub>3</sub> /HP	3.8	2.9	6.7	1.3	3.6
16	[Fe(salhd)Cl]	C <sub>8</sub> H <sub>16</sub>	HNO <sub>3</sub> /HP	25.8	34.6	60.3	0.7	57.1
17	[Fe(salhd)Cl]	C <sub>6</sub> H <sub>14</sub>	HNO <sub>3</sub> /HP	25.9 <sup>h</sup>	70.2 <sup>i</sup>	96.1	0.4	97.0
18	[Fe(pyhd)Cl <sub>2</sub> ]	C <sub>6</sub> H <sub>14</sub>	HNO <sub>3</sub> /HP	51.5 <sup>j</sup>	34.9 <sup>k</sup>	86.4	1.5	86.7

<sup>a</sup> 5.00 mmol of alkane, 0.05 mmol of homogeneous catalyst (1 mol% relative to the alkane), 0.5 mmol of nitric acid and 25 mmol of hydrogen peroxide (HP) as oxidant in 20.00 ml of acetonitrile in batch reactors at room temperature and under constant stirring (1300 rpm) for 3 h of reaction – ratios of alkane/catalyst/HNO<sub>3</sub>/H<sub>2</sub>O<sub>2</sub>: 100/1/10/500; alkane=cyclohexane (C<sub>6</sub>H<sub>12</sub>), cyclooctane (C<sub>8</sub>H<sub>16</sub>) and *n*-hexane (C<sub>6</sub>H<sub>14</sub>).

<sup>b</sup> Yield based on the alkane.

<sup>c</sup> OH=alcohol.

<sup>d</sup> =O=ketone.

<sup>e</sup> Same reactions conditions but at 40 °C.

<sup>f</sup> Same reactions conditions but at 65 °C.

<sup>g</sup> Same reactions conditions but using 2.5 mmol of HP.

<sup>h</sup> 3-hexanol + 2-hexanol (ratio 1.4:1.0).

<sup>i</sup> 3-hexanone + 2-hexanone (ratio 1.4:1.0).

<sup>j</sup> 3-hexanol + 2-hexanol + 3-hexyl hydroperoxide + 2-hexyl hydroperoxide (ratio 4.0:2.1:1.2:1.0).

<sup>k</sup> 3-hexanone + 2-hexanone + 1-hexanone (ratio 6.2:5.0:1.0).

the oxidation of cyclohexane may be tuned by the introduction of electron withdrawing or donating groups in the 5 position of the aldehyde fragment, as observed in the efficient epoxidation of alkenes by Mn(III) *salen* complexes [10]. This similarity also indicates that there must be an analogy between the mechanisms of these two reactions.

Still using the best catalyst [Fe(salhd)Cl] but without adding nitric acid as co-catalyst to the reaction mixture, the yields and, consequently, the TON were much lower (entry 12, Table 1) than the reaction where it was used (entry 1, Table 1), confirming that nitric acid acts as an efficient promoter of the reaction, as previously described [4,18]. The effect of using other acid co-catalysts, such as hydrogen chloride and acetic acid, was also tested. Acetic acid had a promoting effect on the reaction almost doubling the cyclohexanol plus cyclohexanone yields (entry 14, Table 1), and TON, relatively to the reaction run without the addition of co-catalyst (entry 12, Table 1); it was, however, not as effective as nitric acid (entry 1, Table 1). Hydrogen chloride (entry 13, Table 1) had a detrimental effect on the course of the reaction lowering the yields of the oxygenated products.

Other oxygen sources were tested, such as urea–hydrogen peroxide, an anhydrous source of hydrogen peroxide, and iodosylbenzene, but no oxygenated products were obtained using the [Fe(salhd)Cl] catalyst.

Because alkanes are inexpensive compared with hydrogen peroxide, a reaction using excess of cyclohexane when compared to hydrogen peroxide was also performed using the [Fe(salhd)Cl] catalyst. However the yield based on the hydrogen peroxide was much lower than when it is used in excess, when compared to the alkane, probably due to the known hydrogen peroxide decomposition activity of iron complexes (dismutase activity) [4,19].

A larger cycloalkane, cyclooctane, was oxidized at room temperature using hydrogen peroxide and [Fe(salhd)Cl] as catalyst (entry

16, Table 1). Cyclooctanone and cyclooctanol were the main products with 95% conversion of alkane, with higher yields of the ketone than the alcohol. Hence much larger yield and TON were observed than in the oxidation of cyclohexane, but lower OH/O ratio. Other oxygenated products were, however, detected by GC–MS in 35% of yield, such as 1,2-cyclooctane epoxide and the over-oxidation products cyclooctanol epoxide and 1,4-cyclooctadione. Again, the reaction performed without the addition of nitric acid as co-catalyst only gave 34% of alkane conversion.

A linear alkane, *n*-hexane, was oxidized at room temperature using hydrogen peroxide and [Fe(salhd)Cl] as catalyst with 96% alkane conversion. A broader range of oxygenated products were detected by GC–MS due to the possibilities of oxidation in the 1, 2 and 3 carbons of the linear hexane: 3-hexanone and 2-hexanone were the major products, but 3-hexanol and 2-hexanol were also observed. Therefore much larger yield and TON of ketone and alcohol than in the oxidation of cyclohexane was obtained (entry 17, Table 1). The oxidation of the linear hexane only took place at the 3 and 2 carbons with the major formation of ketones, thus yielding OH/O ratio lower than 1. Again, the reaction performed without the addition of nitric acid as co-catalyst gave lower alkane conversion (52%).

The oxidation of *n*-hexane was also performed using the [Fe(pyhd)Cl<sub>2</sub>] complex as catalyst under similar experimental conditions (entry 18, Table 1). High alkane conversion (86.4%) was also observed with this catalyst, despite lower than using [Fe(salhd)Cl], but with higher amount of alcohols than ketones; 3-hexanol was the major product but 2-hexanol and unreduced 3-hexyl hydroperoxide and 2-hexyl hydroperoxide were also observed, whereas 3-hexanone, 2-hexanone and a smaller amount of 1-hexanone were also detected by GC–MS. Therefore by changing the ligand structure from N<sub>2</sub>O<sub>2</sub> to N<sub>4</sub> the selectivity towards alcohols can be tuned using this type of catalysts.

#### 4. Conclusions

There are several reports on attempts to selectively oxidize alkanes which can be divided in three types of processes: high temperature heterogeneous catalysis by metal oxides mediated by radicals, biological/biomimetic catalysis debatably mediated by selective high valent metal centres and organometallic activation [2]. The use of catalysts based on more abundant transition metals is also desirable as it would decrease costs and increase sustainability. Therefore herein a new systematic study on the catalytic activity of sustainable first-row transition metal complexes (Fe, V, Cu, Co, Mn) with biomimetic *salen*-type polydentate ligands with N<sub>2</sub>O<sub>2</sub> or N<sub>4</sub> coordination sphere, in homogeneous phase, in the oxidation of cyclohexane at room temperature, using environmentally-benign reactants was performed.

Functionalization of cyclohexane to cyclohexanol and cyclohexanone was selectively achieved with the Fe(III), Fe(II), VO(IV) and Cu(II) complexes with these biomimetic ligands in only 1 mol% at room temperature, using excess of hydrogen peroxide and nitric acid as co-catalyst. The TON and yields on cyclohexanone plus cyclohexanol for the N<sub>2</sub>O<sub>2</sub> Schiff base ligand complexes were in the order Fe(III) > VO(IV) > Cu(II). Negligible amounts of oxygenated products were obtained with the Mn(III) and Co(III) N<sub>2</sub>O<sub>2</sub> Schiff base complexes. The Fe(III) catalyst with the N<sub>2</sub>O<sub>2</sub> Schiff base ligand ([Fe(salhd)Cl]) was the best with a TON of 25, whereas the new Fe(II) complex with N<sub>4</sub> Schiff base gave lower (17) TON, but much higher cyclohexanol selectivity. Nevertheless, the cyclohexanol plus cyclohexanone yields and reaction TON could be further increased to 46% and 45%, respectively, by the introduction of electron donating groups (methyl) in the N<sub>2</sub>O<sub>2</sub> Schiff base ligand of the [Fe(salhd)Cl] catalyst. Furthermore, cyclooctane and a linear alkane, *n*-hexane, could also be efficiently oxidized mainly to the corresponding ketones by the [Fe(salhd)Cl] catalyst at room temperature with higher TON than for cyclohexane. Using the new Fe(II) catalyst in the oxidation of *n*-hexane gave slightly lower TON, but was selective towards the *n*-hexane alcohols. Therefore the advantage of this type of catalysts is that even linear alkanes can be selectively oxidized at room temperature towards alcohols or ketones by only changing the ligand structure from N<sub>2</sub>O<sub>2</sub> to N<sub>4</sub>.

Finally, higher cyclohexanol and cyclohexanone yields (46%) are obtained with the best catalytic system reported herein, at milder conditions, than in the industrial process for the oxidation of cyclohexane (3%) which occurs at high temperatures and pressures. The values are also slightly higher than the reported copper(II) MOF catalyst with 44 TON and 32% yield, which was tested under similar experimental conditions and analytical methods [18]. The comparison of the present results with reported ones for non-heme iron complexes at room temperature is, however, not straightforward and seldom turnovers are provided [11,21].

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