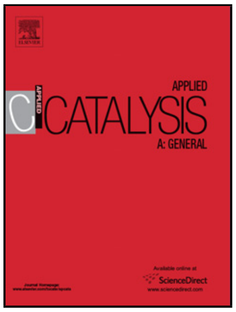

Title: Experimental and theoretical studies of a greener catalytic system for saturated hydrocarbon chlorination composed by trichloroisocyanuric acid and a copper(II) compound

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Experimental and theoretical studies of a greener catalytic system for saturated hydrocarbon chlorination composed by trichloroisocyanuric acid and a copper(II) compound

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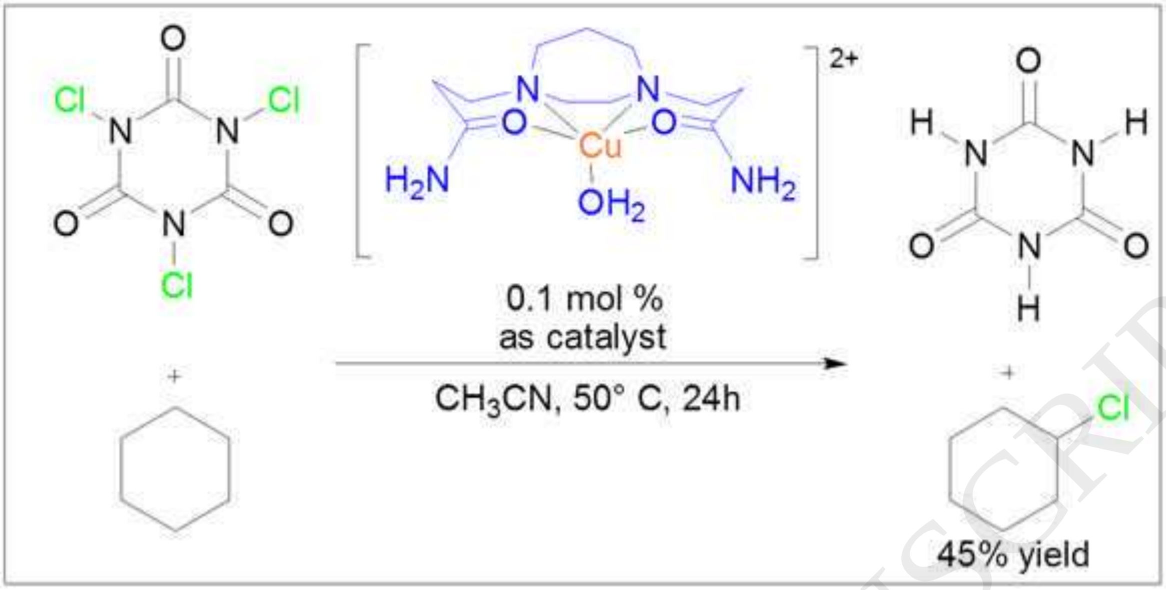
Graphical abstract



Highlights

- A new catalytic system composed by a copper(II) catalyst and trichloroisocyanuric acid promoted the cyclohexane chlorination.
- The catalytic system also promoted the monochlorination of n-hexane and adamantane.
- The system showed 100% selectivity for chlorocyclohexane, reaching a convertion of 44% at 50°C.
- A Cu(II)-hypochlorite intermediate species is proposed in the catalytic cycle, which is supported by theoretical calculation, ESI-(+)-MS and EPR studies.

Abstract

We are describing herein a new environmentally friendly catalytic system able to convert cyclohexane to chlorocyclohexane with 100 % selectivity. The method was also applied to the chlorination of n-hexane and adamantane. The catalytic system employs thichloroisocyanuric acid (TCCA) as halogenating agent and a mononuclear copper(II) complex $[Cu(BPAH)(H_2O)](ClO_4)_2$, **1**, as catalyst (BPAH = 1,4-bis(propanamide)homopiperazine), whose molecular structure was solved by monocrystal X-ray diffraction. For cyclohexane, at a ratio catalyst:substrate:TCCA of 1:1000:333, the system reached a conversion of 32.0±1% at 25^{o}C and 44.7±0.4% at 50^{o}C, with 100% selectivity for chlorocyclohexane. With n-hexane, a similar conversion was observed at 50 ^{o}C, resulting in mixture of monochlorides. Employing adamantane as substrate, the isomers 1-chloroadamantane and 2-chloroadamante were preferentially formed, together with traces of dichloroadamantane. EPR and ESI-(+)-MS analyses indicate the formation of a Cu-hypochlorite intermediate species, which is supported by theoretical calculations.

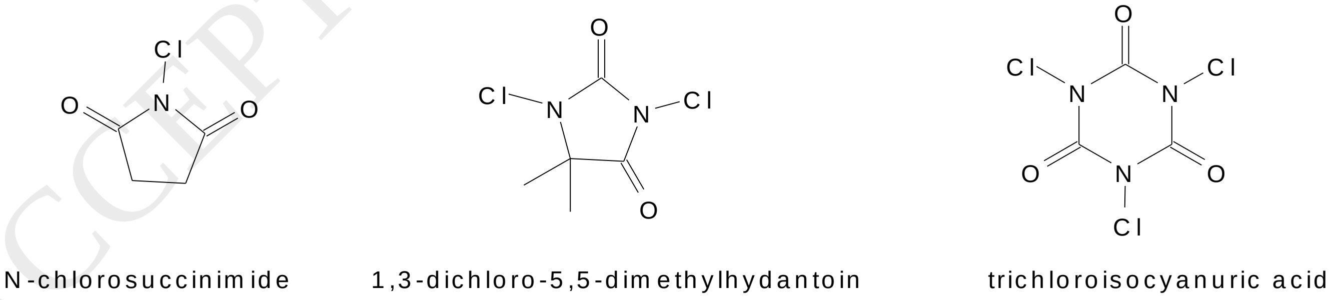
Keywords: Copper catalyst; thichloroisocyanuric acid, chlorocyclohexane, copper(II)-oxyl species, chlorohexane, chloroadamantane

1. Introduction

Hydrocarbons obtained from petroleum and natural gas are yet largely employed as feedstock of more valuable chemicals [1, 2] This may be illustrated by the conversion of benzene to cyclohexane, which is the key precursor to prepare cyclohexanol and cyclohexanone (KA oil). These molecules can be oxidized to adipic acid and caprolactam, monomers employed in the synthesis of Nylon-6 and Nylon-6,6. Industrially, the preparation of KA oil is carried out in the presence of a cobalt catalyst and molecular oxygen at a temperature between 150^{o}C and 160^{o}C and pressure about 0.9 MPa [3]. The low yield (4%) shown by this reaction illustrates the difficulty associated with the oxidation of saturated hydrocarbons and is explained by the similarity in the electronegativity of the carbon and hydrogen atoms [4], which result in C-H bonds thermodynamically strong and kinetically inert [5]. Therefore the KA oil system is one of the 10 challenges of the modern chemistry [6, 7].

In addition to cyclohexanol and cyclohexanone, halocyclohexanes are also intermediates that show important industrial application. They have been used in the rubber industry to prepare cyclohexylthiophthalimide and in the synthesis of pharmaceuticals (trihexyphenidyl) and pesticides (azocyclotin) [8]. Furthermore, alkyl halides have a broad chemical versatility, since they can be transformed into other functional groups (alcohols, ethers, ester, amines, nitriles) [9]. Traditionally, alkyl halides are produced in large scale by reactions between an alkane and halogens in their elemental forms (X_2) or by oxyhalogenation (O_2 + HX) [9], which are reactions that present many drawbacks from the green chemistry point of view. Halogens are toxic, corrosives and need special equipment for proper handling and manipulation. Additionally, these reactions usually involve toxic halogenated solvents, hazardous acids are generated (HX) as byproducts and the reactions are not selective, since polyhalogenated compounds are usually produced due to the reactivity of free-radical intermediates[10]. Alternatively, halocyclohexane can be prepared by substitution of cyclohexanol by hydrogen halides (HX) or by the addition reaction between cyclohexene and HX [11-14], with both routes employing more expensive substrates and harmful acids.

A category of halogenating agents that has shown high efficiency in promoting the insertion of halogen atoms and the oxidation of hydrocarbons, especially the unsaturated ones, are the haloamides, which include N-chlorosuccinimide, 1,3-dichloro-5,5-dimethylhydantoin and trichloroisocyanuric acid (Figure 1). Considering chloramides, trichloroisocyanuric acid (TCCA) deserves special attention. It is a stable solid compound with powerful bactericide and algaecide activities, which make it a first choice for swimming pool treatment [15]. It has also been used for dishwashing, laundry bleach and in the food industry [16]. It is considered a safe chemical and therefore an attractive reagent within the perspective of green chemistry. Moreover, it can donate three chlorine atoms to the substrate (45 % of its mass), which is very relevant concerning atom economy [16]. Also of importance is the fact that the product generated after reaction, cyanuric acid, can be used to prepare TCCA again [17].



N-chlorosuccinimide 1,3-dichloro-5,5-dimethylhydantoin trichloroisocyanuric acid

Figure 1. Examples of chloroamines employed as halogenating agents.

It has been demonstrated that TCCA is also very useful in organic synthesis. It can promote the chlorination of alkenes, alkynes, arenes, ketones, cyclic ethers, the oxidation of ethers, aldehydes, acetals, alcohols, sulfide, oximes, and the dehydrogenation of amines [15-17]. Only recently, we and others have shown that TCCA can be useful to halogenate saturated hydrocarbons [18, 19]. In view of developing a more robust catalytic system for hydrocarbon halogenation, we report an experimental and theoretical study of the first copper catalyst able to promote the insertion of chlorine atom into the cyclohexane structure in the presence of TCCA, reaching a 100 % selectivity for chlorocyclohexane. Furthermore, the system was also tested with n-hexane and adamantane, aiming to evaluate the selectivity associated with the stability of the carbon-centered radical.

2. Experimental

Elemental (C, H, N) analysis was performed on a Thermo Scientific Flash 2000 CHN analyzer. The IR analyses, ranging from 4000 to 400 cm^{-1}, was recorded in KBr disks on a Shimadzu IRAffinity-1 instrument. The electronic spectra (400–1000 nm) were recorded in DMSO, H_2O and CH_3CN on a UV–vis Cary 50 Bio Varian. The NMR (^1H and ^{13}C) spectra were recorded on an Ascend 500 Advance III HD Bruker instrument operating at 500 MHz for ^1H and 125 MHz for ^{13}C in D_2O or CD_3CN . The electrospray ionization mass spectra [ESI-(+)-MS] were acquired using a Bruker MicroTOF spectrometer, employing CH_3CN as the solvent, with the collision cell RF set to 650.0 Vpp, the capillary set to 4500 V, the nebulizer set to 0.4 bar, the dry heater set to 180 ^oC, and the dry gas set to 4.0 dm^3 min^{-1}. The EPR spectra were obtained in a Bruker E500 spectrometer with a high sensitivity cylindrical cavity operating at X-band (9 GHz) at 100 K with a microwave power of 5 mW, modulation frequency of 100 kHz, modulation amplitude of 2 G, receiver gain of 60 dB, in acetonitrile. MgO:Cr(III) was used as a reference and was attached to each sample (g = 1.9797). Computer simulated spectra were performed using the Qpow program.

Synthesis: The ligand 1,4-bis(propanamide)homopiperazine (BPAH) was prepared as described in the literature [20]. The catalyst $[Cu(BPAH)(H_2O)](ClO_4)_2$ (**1**) was synthesized in a reaction (25 ^oC) employing stoichiometric amounts of $Cu(ClO_4)_2.6H_2O$ (1 mmol, 0.370 g) and the ligand BPAH (1 mmol, 0.242 g) in methanol (20 cm^3), which resulted in a blue solution. After 30 min, a blue solid precipitated, which was filtered, washed with cold propan-2-ol and ether, and dried under vacuum. After standing for some days at room temperature, blue crystals were isolated from the mother liquor. Infrared and CHN analyses indicated that both amorphous and crystalline samples are the same compounds.

Yield: 0.333 g, 79%. Elemental (CHN) analysis found (%): C, 25.28; H, 4.67; N, 10.64. Calcd. for $[Cu(C_{11}H_{24}N_4O_3)](ClO_4)_2$: C, 25.27; H, 4.11; N, 10.72.

X-ray: The single-crystal X-ray diffraction data for **1** was collected on a Bruker APEX II DUO diffractometer using graphite-monochromated MoKα radiation (0.71073) from a sealed tube. All frames were recorded with the φ and ω scan methods using APEX2 software [21]. All data were corrected for Lorentz and polarization effects and for absorption using the SADABS semi-empirical multi-scan method. The structure was solved by direct methods and refined by applying the full-matrix least-squares method using the SHELX package [22]. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed at their idealized positions. Hydrogen atoms of the amide groups and coordinated water molecules were identified in the Fourier difference map and refined with the riding model. Selected crystallographic data are summarized in Table SI1, as supporting information.

Theoretical study: The study was carried out to evaluate the energies involved in the catalytic system containing cyclohexane, TCCA and the copper catalyst. Optimizations and frequency calculations were performed for each intermediate, in order to obtain thermochemical data. All calculations were performed with Gaussian 09 software [23], using 6-31+G** or 6-31++G** basis sets [24-28] with the LANL2 [29] pseudopotential for copper. The basis system used in this work was the pure set (5d and 7f). Both PBE0 [30] and TPSSh [31] exchange-correlation functionals were employed for the electronic structure calculations, together with the IEFPCM [32-35] model to account for solvent effects (acetonitrile), and the ultrafine grid for integral evaluation. The starting coordinates for compound **1** were taken from the X-ray structure. The starting geometries for the intermediates **(A)**, **(B)** and **(C)** (see Figure 5) were built using a pre optimized structure for compound **1** or for a preceding intermediate. All copper species shown in Figure 5, except for compound **(B)**, have an odd electron number; hence, their lowest multiplicity is 2. The chlorine atom and the cyclohexyl radical were assumed to be doublets, consistent with their radical nature. Both singlet and triplet multiplicities were tested for compound **(B)**. All other compounds were modeled as singlets.

Catalytic study: The halogenation reaction of cyclohexane was prepared by adding catalyst **1** (1.8 mg) dissolved in CH_3CN (4.62 cm^3), cyclohexane (0.38 cm^3) and TCCA (0.27 g). The reactions were carried out during 24 h at 25ºC or 50ºC. A sample (0.4 cm^3) was taken from this solution and 0.02 cm^3

of 1-chloropropanol (internal standard) was added. The products were quantified in a Varian GC-430-FID equipped with a 30 m×0.25 mm (0.25 μm i.d.) CP-WAX 58 column. Product identification was performed by injecting a real sample of chlorocyclohexane purchased for Sigma-Aldrich. The reactions were done in triplicate. Similar reactions were also carried out employing $Ca(ClO)_2$ (0.25 g) instead of TCCA.

The n-hexane and adamantane chlorination reactions were evaluated by NMR^1H. The reactions were conducted in CD_3CN (1 cm^3) at 25 and 50^o C, during 24 h, employing a ratio catalyst:substrate:TCCA of 1:1000:333. The conversions and the obtained products were also confirmed by mass spectrometry. The reaction with n-hexane was prepared with CD_3CN (1 cm^3) containing **1** ($7x10^{-4}$ mol dm^{-3}), TCCA (0.233 mol dm^{-3}) and n-hexane (0.7 mol dm^{-3}). For the reaction with adamantane, the amounts of the components were decreased, since adamantane shows low solubility in CD_3CN. The final solution contains **1**, TCCA and adamantane at concentrations of $5.8x10^{-5}$, $1.9\ x10^{-2}$ and $5.8x10^{-2}$ mol dm^{-3}, respectively.

3. Results and Discussion

The catalyst employed in this study is the mononuclear Cu(II) compound $[Cu(BPAH)(H_2O)](ClO_4)_2$, **1**, where BPAH = 1,4-bis(propanamide)homopiperazine. The synthesis of the BPAH ligand was published recently by us and a similar copper complex, $[Cu(BPAH)(H_2O)](Cl)_2$, **2**, containing chloride counter ions as well [20].

The X-ray analysis reveals that **1** crystallizes in a monoclinic (P21/c) system. Compound **1** shows a square pyramidal geometry (Figure 2) in which the donor atoms from the ligand BPAH form the base and the water molecule is in the apical position. Although the copper center in **1** shows the same coordination environment than in **2**, their bond lengths are slightly shorter than **2**. For example, the distances Cu1-O11, Cu-N1 and Cu-O1W observed in **1** are around 1.95, 1.98 and 2.21 Å (see Figure 2 Caption and Supporting Information), respectively, whereas **2** shows bond lengths for these same coordinating atoms of 1.96, 2.00 and 2.25 Å. The bond angles involving the BPAH ligand are similar in both complexes. The X-ray analysis also revealed that **1** is disordered, showing molecules with two different orientations that are rotated 180^o with respect to each other. Form A shows a site occupancy factor of 0.904(2) whilst for B this value is 0.096(2).

The spectroscopic characterization of **1** revealed that its infrared spectrum is dominated by strong absorptions at 1088 (ν ClO_4), 1587 (δ NH), 1652 (ν C=O), 3143 (ν N-H) and 3304 cm^{-1} (ν N-H), which confirm mainly the presence of the perchlorate anion and the amide group in the compound. The UV-Vis analysis showed that **1** present a symmetric absorption band typical of d-d transition at 661 nm (ε = 160 $dm^3\ mol^{-1}\ cm^{-1}$) in water, 645 nm (ε = 215 $dm^3\ mol^{-1}\ cm^{-1}$) in acetonitrile and 662 nm (ε = 188 $dm^3\ mol^{-1}\ cm^{-1}$) in DMSO. These values are in the range (550-700 nm) observed for copper complexes showing pseudo-octahedral geometry and N_2O_2 coordination environment in the equatorial plane [36], indicating that the tested solvents are interacting with the copper center, resulting in a compound with a geometry different from that observed in the solid state.

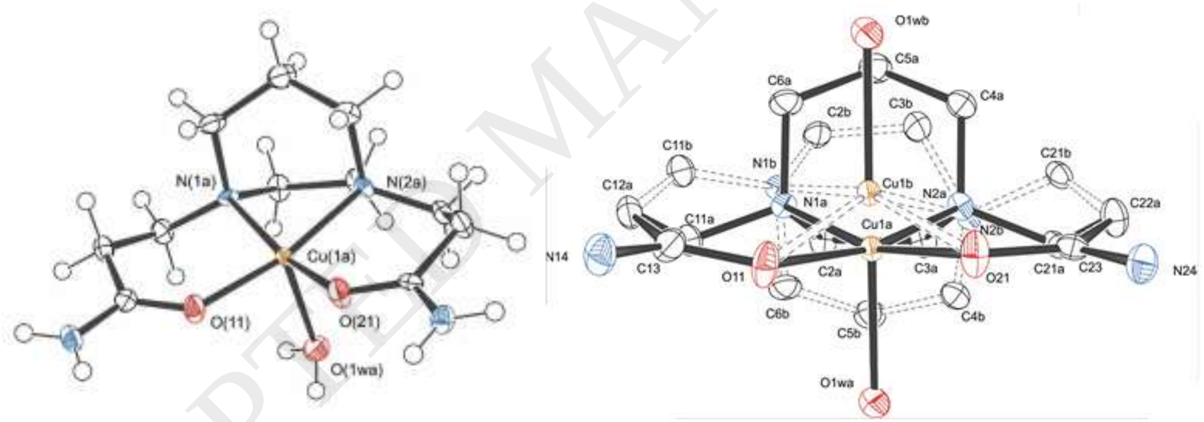


Figure 2. Ortep diagram showing the molecular structure of **1** (left) and the two projections (right) observed in the X-ray analysis, with occupancy sites of 0.904(2) for form A and 0.096(2) for B. Perchlorate ions were omitted for clarity. Main bond lengths (Å): Cu(1a)-O(11) = 1.954 (5); Cu(1a)-O(21) = 1.955 (5); Cu(1a)-N(2a) = 1.976 (7); Cu(1a)-N(1a) = 1.985 (7); Cu(1a)-O(1Wa) = 2.215 (5); Cu(1b)-O(1Wb) = 2.16 (3); Cu(1b)-N(2b) = 2.37 (10); Cu(1b)-N(1b) = 2.26 (10); Cu(1b)-O(11) = 2.025 (10), Cu(1b)-O(21) = 2.019 (10).

The catalytic assay was carried out during 24 h, employing acetonitrile as solvent and a ratio **1**:cyclohexane:TCCA of 1:1000:333, since TCCA can donate 3 chlorine atoms. The study was performed at two different temperatures (25 and 50° C) and blank reactions in the absence of catalyst were also carried out (Table 1).

Using cyclohexane as substrate, at 25°C, compound **1** reached a conversion of 32.0±1% (based on cyclohexane), which is about 800 % higher than the result presented by the blank reaction (Table 1). Catalyst **1** showed at 25°C a similar conversion obtained at 50°C by the iron catalyst $[Fe^{III}(L)(Cl)_2]$ recently described by us [18]. The reaction presented an impressive 100 % selectivity for chlorocyclohexane. At 50°C, the yield is further extended to 44.7±0.4% while maintaining 100% selectivity to chlorocyclohexane. On the other hand, the uncatalysed reaction showed a yield around 15%. Interestingly, at 50 °C, a white precipitate was formed and isolated. Subsequent analysis indicated that this precipitate is isocyanuric acid [38], the product of TCCA hydrolysis [39]. It decomposes around 325 °C (lit. = 330°C) [37] and presents a ^{13}C NMR (DMSO-d6) spectrum with only one signal at 150.34 ppm.

Similar reactions were carried out employing $Ca(ClO)_2$ as chlorination reagent, but in this case, employing a ratio catalyst:substrate:oxidant of 1:1000:500. The best yield was obtained at 50 °C, showing a conversion of 8.70%, which establish that TCCA is a better chlorine donor than $Ca(ClO)_2$.

Due to the high conversion and selectivity for the monochlorination product shown by the catalytic system on cyclohexane, experiments were carried out on other substrates (n-hexane, adamantane) aiming to evaluate the preference of the system by primary, secondary or tertiary carbon atoms.

For n-hexane, only monochlorides were observed, resulting in a total conversion of 46.8% at 50°C, which is similar to the one observed for cyclohexane (44.7%). However, at 25 °C, the conversion (12%) was almost 3 times lower than the observed for cyclohexane. At both temperatures, the uncatalised reaction resulted in conversions lower than 6%. However, differently than cyclohexane, three distinct isomers were obtained in both temperatures. 1-chlorohexane, 2-chlorohexane and 3-chlorohexane were detected at 50°C at a ratio 1:5:3, respectively (Table 1), which represent a selectivity methylene:methyl of 10.4. At 25°C the ratio was aroud 1:5:4, increasing the selectivity to 13. Interesting is the fact that the reaction occurs preferentially on C2 than C3.

The catalytic system was also tested with adamantane. The best conversion (28%) was achieved at 50°C, rendering preferentially the isomer 1-chloroadamantane (19.6%) than 2-chloroadamantane (8.4%), which represents a selectivity tertiary:secondary carbon of 7. A small amount of dichloroadamantane was also observed (< 2 %). The smaller adamantane conversion in comparison with cyclohexane and n-hexane may be due to the lower substrate concentration employed in the process. Once more, the presence of the copper catalyst increase the yield of the chlorination reaction significantly when compared with the uncatalised reaction. The total conversion was slightly higher than that described by Schreiner (23% at 30°C after 4 h, selectivity C1:C2 = 4), but the selectivity for C1 was higher [19].

Table 1. Chlorination of hydrocarbons at 25 and 50 °C.

System	Substrate (T)	Product yield (%)						Conversion (%) (TON/TOF (h^{-1}))
		Cl-cyhex	1-Cl-hex	2-Cl-hex	3-Cl-hex	1-Cl-adam	2-Cl-adam	
1 + TCCA[a]	Cyclohexane (50 °C)	44.7±0.9						44.7(447/18.6)
1 + TCCA[a]	Cyclohexane (25 °C)	32.0±1						32.0 (320/13.4)
1 + $Ca(ClO)_2$[a]	Cyclohexane (50 °C)	8.70±1.0						8.70 (87/3.6)
1 + $Ca(ClO)_2$[a]	Cyclohexane (25 °C)	< 1						< 1
TCCA[a]	Cyclohexane (50 °C)	15.3±1.2						15.3
TCCA[a]	Cyclohexane (25 °C)	4.0±0.4						4.0
$[Fe^{III}(L)(Cl)_2]$[b] + TCCA[a]	Cyclohexane (50 °C)	34.4±1.8						34.4(344/14.3)
$[Fe^{III}(L)(Cl)_2]$[b] + TCCA[a]	Cyclohexane (25 °C)	8.3±1						8.3(83/3.4)
1 + TCCA	n-hexane (50 °C)		5.3±1.1	25.7±1.8	15.8±1.4			46.8 (468/19.5)
1 + TCCA	n-hexane (25 °C)		1.1±0.3	6.0±1.8	4.9±1.8			12.0 (120/5.0)
TCCA	n-hexane (50 °C)		< 1	2.8±0.4	1.9±0.4			
TCCA	n-hexane (25 °C)		< 1	2.0±0.4	1.5±0.4			
1 + TCCA	adamantane[c] (50 °C)					19.6±1.7	8.4±0.7	28.0(280/11.6)
1 + TCCA	adamantane (25 °C)					2.1±0.3	<1	~3(30/1.2)
TCCA	adamantane (50 °C)					8.8±0.8	3.7±0.4	

TCCA	adamantane (25 °C)		1.2	<1

[a] The reactions showed 100% selectivity for chlorocyclohexane. [b] reference [18]. [c] 1.4% of 1,3-dichloroadamantane was detected. L = N-(2-hydroxybenzyl)-N-(2-pyridylmethyl)(3-chloro)(2-hydroxy)propylamine. Cl-cyhex = clorocyclohexane. 1-Cl-hex = 1-chlorohexane. 2-Cl-hex = 2-chlorohexane. 3-Cl-hex = 3-chlorohexane. 1-Cl-adam = 1-chloroadamantane. 2-Cl-adam = 2-chloroadamantane.

A few studies aiming the halogenation of cyclohexane employing metal compounds have been described in the literature. Khusnutdinov *et. al.* reported a study employing vanadium, manganese, molybdenum, and iron compounds as catalysts and CCl_4 as the source of chlorine, at temperature between 130-200°C. The best result was obtained with $Mn(acac)_3$, reaching 100% of conversion and selectivity of 88% for chlorocyclohexane [40]. Wu and coworkers reported a system containing chloride salts (Mn, Zn, Co, Ni, Sn, V, Cu and Fe) which under UV light induce the cyclohexane chlorination [8]. The best yield was obtained with copper chloride (~67 %) with a selectivity of 54 % for chlorocyclohexane. The reaction was carried out at a ratio cyclohexane:metal salt of 1:1. Although the conversions presented by these systems were better than the one described here, the employed conditions are environmentally less friendly.

Concerning mimetic compounds of halogenases, Comba and Wunderlich investigated the cyclohexane oxidation promoted by the compound $[Fe^{II}(L)X_2]$ (X = Br, Cl), where L = 3,7-dimethyl-9-oxo-2,4-bis(2pyridyl)-3,7-diazabicyclo[3.3.1]nonane-2,5-dicarboxylate methyl ester in the presence of H_2O_2, tert-butylhydroperoxide (TBHP) or iodosylbenzene [41]. Under stoichiometric conditions (catalyst:TBHP), halocyclohexane and cyclohexanol were obtained at a ratio close to 1:1, with 100 % yield based on the oxidant. A reaction mechanism was proposed and $Fe^{IV}=O$ species or even $Fe^{V}=O$ might take part in the reaction. Liu and Groves have shown that Mn(III)-porphyrins/hypochlorite system also can promote the cyclohexane chlorination, through a mechanism that involves the oxidation of Mn(III), resulting in Mn(V)=O and Mn(IV)-OCl intermediates [42, 43].

In order to gain some insight on the reaction mechanism promoted by **1**, the interaction between the catalyst and TCCA was followed by ESI-(+)-MS and EPR. Figure 3 shows the ESI-(+)-MS spectrum of **1** in the absence (Figure 3A) and in the presence (Figure 3B) of TCCA. For pure **1**, the fragments observed at *m/z* 152.6 and 404.0 are attributed to $[Cu(BPAH)]^{2+}$ and $[(Cu(BPAH)(ClO_4)]^{+}$, respectively, as confirmed by comparing the experimental and simulated isotopic patterns spectra (see supplementary information). The spectrum obtained from the reaction between **1** and TCCA is more complex. A larger number of signals are observed and the base peak appears at *m/z* 220.5. The isotopic pattern for this signal indicates a double charged cation that agrees with the species $\{[Cu(BPAH) - 4H + 4Cl)]^{2+}\}$. To form this species, the amide groups ($-CONH_2$) were transformed to chloroamides ($-CONCl_2$). This process has been already described in the literature and can be induced by the reaction of amides with hypochlorite [44, 45]. Other signals that indicate the formation of chloroamides are observed at *m/z* 186.5 {[Cu(BPAH) – 2H + 2Cl)]$^{2+}$} and 420.7 {[Cu(BPAH) – NH_3 – 7H + 4Cl)]$^{+}$} (see supplementary information). Although with low intensity, the signal observed at 442.9 is of great relevance, since it agrees with the formation of an intermediate species (Figure 3B) containing hypochlorite (ClO^-). Hypochlorite is the species formed after TCCA hydrolysis [46]. The formation of an intermediate containing hypochlorite coordinated to a metal ion (iron) has been also identified by mass spectrometry in a model compound for iron chloroperoxidase [47]. Signals at *m/z* 539.9, 602.9 and 636.9 were identified as adducts containing the copper complex and TCCA derivatives (see supplementary information). ESI-(+)-MS spectrum of a solution containing **1**+TCCA+cyclohexane resulted in the same fragmentogram observed for the reaction between **1**+TCCA.

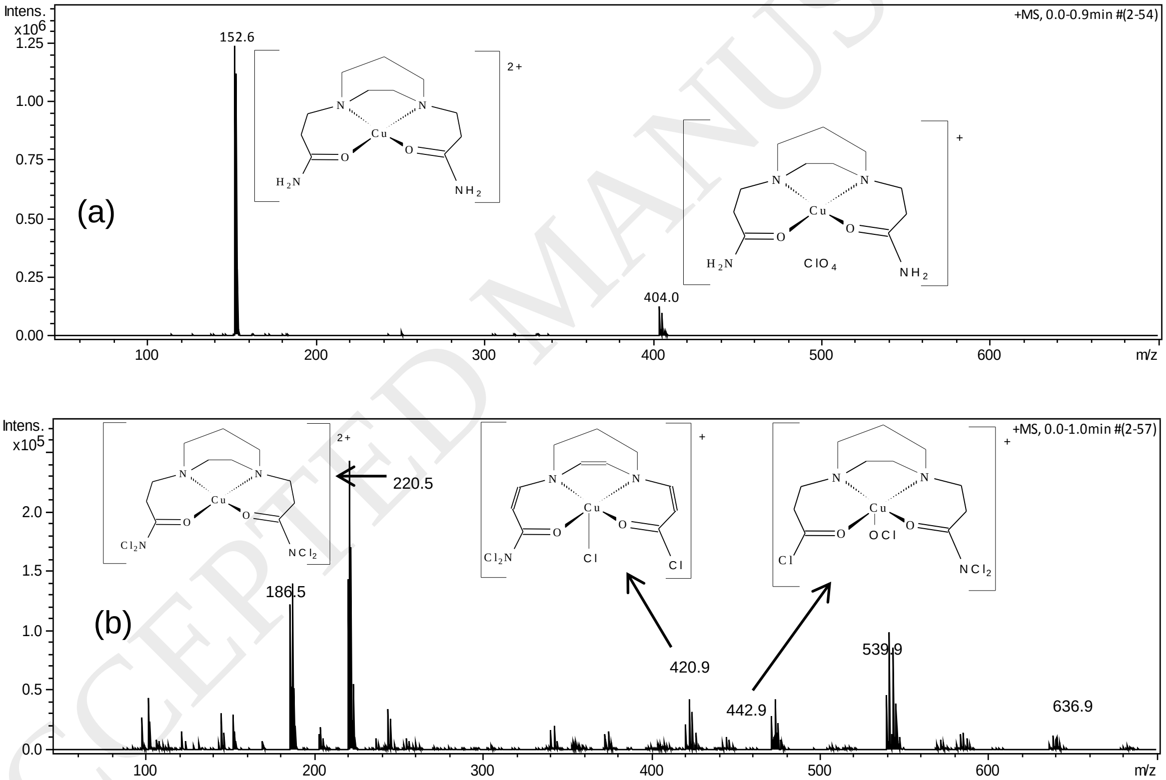


Figure 3. ESI-(+)-MS spectra of **1** in the absence (a) and in the presence (b) of TCCA. Proposals of structures for some ions are presented.

The EPR spectra corresponding to the mixture of **1** and TCCA is presented in Figure 4. An acetonitrile solution of the copper complex ($2.5x10^{-4}$ mol dm^{-3}) is dominated by an intense and broad line (ΔH = 350 MHz) at $g \approx 2$, as a result of the spin-spin interaction between Cu^{2+} ions close to each other (Figure 4 a). This signal could be partially resolved when a solution containing the copper compound ($2.5x10^{-4}$ mol dm^{-3}) was prepared in acetonitrile containing $LiClO_4$ (0.1 mol dm^{-3}) (Figure 4 b). Although it is still possible to see the broad line observed in (a), signals associated with isolated Cu^{2+} species were visible and allowed the simulation of the spectrum (Table 2). The simulated spectrum indicated the presence of a Cu^{2+} center with axial distortion.

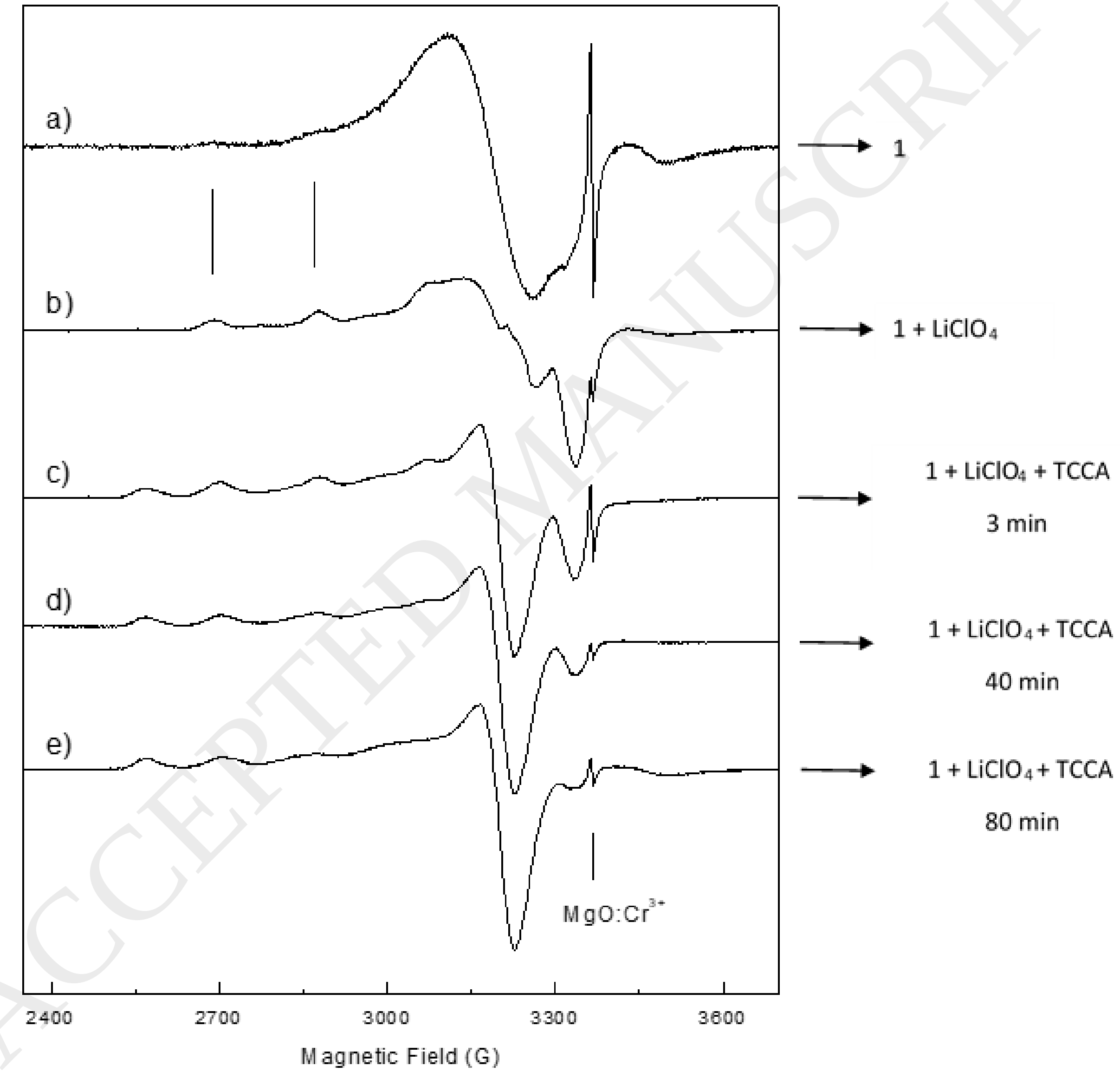


Figure 4. Experimental EPR spectra of **1** (a); **1 +** $LiClO_4$ (b); **1** + TCCA + $LiClO_4$ after 3 min reaction (c); **1** + TCCA + $LiClO_4$ after 40 min reaction (d); **1** + TCCA + $LiClO_4$ after 80 min reaction (e). All the spectra were obtained in frozen acetonitrile (100 K).

Table 2. EPR data obtained by the simulation of the spectra shown in Figure 4.

Sample/species	$g_{//}$	$g_{\perp}$	$A_{//}$ (MHz)	$A_{\perp}$ (MHz)	$g_{//}$ / $A_{//}$ (cm)
1 + LiClO4	2.242±0.002	2.05±0.003	575±5	50±10	117
1+ $LiClO_4$ +TCCA/S1	2.4±0.002	2.085±0.003	460±5	20±10	156
1+ $LiClO_4$ +TCCA/S2	2.24±0.002	2.051±0.003	575±5	60±10	117

The spectrum obtained immediately after the addition of TCCA (Figure 4 C) revealed the formation of a new Cu^{2+} species (named species S1 in Table 2), although, there is yet an intense signal associated with the original copper complex (named species S2 in Table 2). However the intensity of this latter signal decreases with the time, as can be observed by the decrease of the line close to the signal of the standard MgO:Cr (Figure 4 c, d and e), indicating that the reaction between the original copper complex and the product of TCCA hydrolyses (hypochlorite) is occurring slowly. The new species generated in the presence of TCCA shows signals shifted to lower magnetic field in comparison to the original copper complex, which is a feature of compounds presenting elongation in the z-axis.

All the spectra observed have $g_{//} > g_{\perp} > 2.0023$ e $A_{//} > A_{\perp}$, which is typical of copper center with tetragonal elongation and ground state $d_{x^2-y^2}$ ($^2B_{1g}$) [48, 49]. The ratio $g_{//}/A_{//}$ observed for **1** (117 cm) is in agreement with a square planar arrangement of the atoms that compose the plane of the molecule (N_2O_2). On the other hand, the product of reaction between **1** and TCCA shows higher $g_{//}/A_{//}$ ratio (156 cm), indicating a tetrahedral distortion [50].

Based on the ESI-(+)-MS and EPR data, and due to the fact that the catalytic system showed high selectivity in the cyclohexane chlorination reaction a putative reaction mechanism for this process in the presence of **1** and TCCA is presented in Figure 5 employing cyclohexane as substrate.

The initial step of reaction involves the hydrolysis of TCCA, generating the HClO/ClO^- system, which reacts with compound **1** resulting in an intermediate containing hypochlorite coordinated to the copper center (species **(A)** in Figure 5). This species was identified through ESI-(+)-MS analysis (*m/z* 442.9) and it is plausive that it accounts for the new species observed by EPR spectroscopy. The next step would involve the homolytic O-Cl cleavage, releasing the chlorine radical and the formation of a copper(III)-oxo/copper(II)-oxyl species (species **(B)**). This species has been suggested as reactive intermediate in enzymatic systems such as peptidylglycine α-hydroxylating monooxygenase [51, 52], and by theoretical and experimental data obtained with synthetic compounds [53, 54]. This species can abstract hydrogen atoms from alkanes [53, 54], rendering a cyclohexyl radical and a copper(II)-hydroxo intermediate (species **(C)**). The cyclohexyl radical can react, with the chlorine radical, for example, resulting in chlorocyclohexane, the product of reaction. The copper(II)-hydroxo species **(C)** can react with HClO, forming the species **(A)** again, restarting the catalytic cycle. Experiments to identify the chemical nature of the Cu(III)-oxo/Cu(II)-oxyl species were carried out without success. Similar species has been trapped only at -80 ^{o}C and characterized by UV-Vis spectroscopy [37], but, at a temperature of -60 ^{o}C, it was shown to be unstable [55]. However, theoretical calculation (see below) shows that the copper(II)-oxyl is more stable than the copper(III)-oxo species.

It may be suggested that the copper(II)-oxyl species may be the responsible by the higher chlorination at position C2 than C3 in the n-hexane molecule (ratio C1:C2:C3 of 1:5:3), since C3 is protected in the middle of the carbon chain and is less available to get contact with the copper(II)-oxyl intermediate. The higher selectivity on C2 shown by this system is in contrast with recently published data of a system composed by TCCA:Cu(OAc)$_2$ and phthalimido-*N*-oxyl employed as radical initiator, which resulted in the same ratio C2:C3 (13%), showing a conversion of 30% at 40^{o}C after 96 h [19]. Therefore, it may be proposed that steric effects in the interaction catalyst-substrate may drive the selectivity on C2.

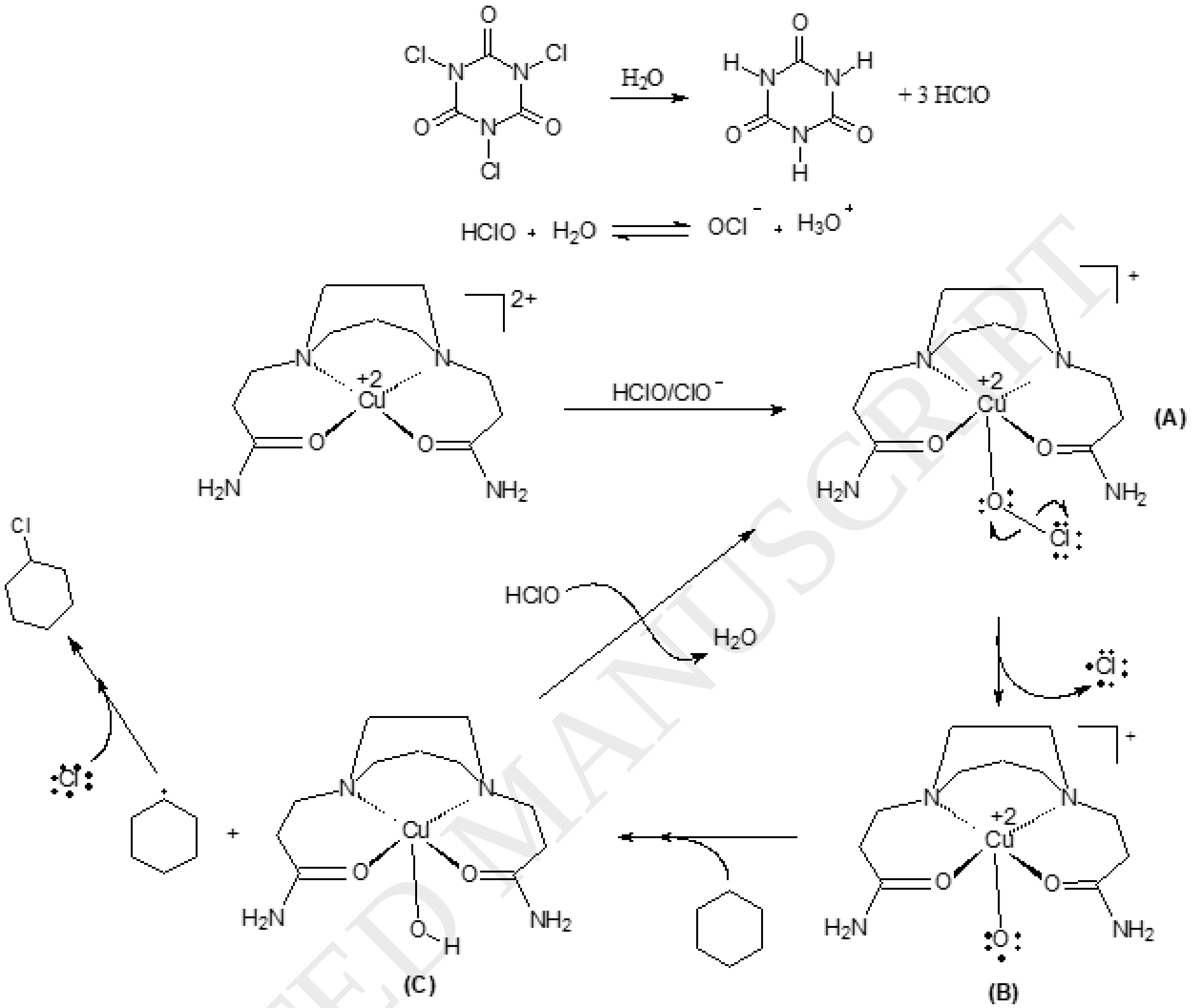


Figure 5. Proposed mechanism for the cyclohexane chlorination promoted by **1** in the presence of TCCA.

To provide further support to the mechanism proposed, we turned to DFT calculations. Four possible coordination schemes were tested for the creation of species **(A)**. The hypochlorite may coordinate above (opposite side to propanediamine backbone) or below the plane (same side to propanediamine) formed by the coordinated atoms from the ligand BPAH and the copper center (Figure 6 contains two examples to clarify), and it may do so through its oxygen or chlorine atoms. The basis set 6-31+G** was used and the results are summarized in Table 3. Both PBE0 and TPSSh estimate that coordination through oxygen and by the bottom (same side to propanediamine) is more stable (signalized by the positive entries). This was the route used to obtain thermochemical information, with 6-31++G** basis selected from this point forward.

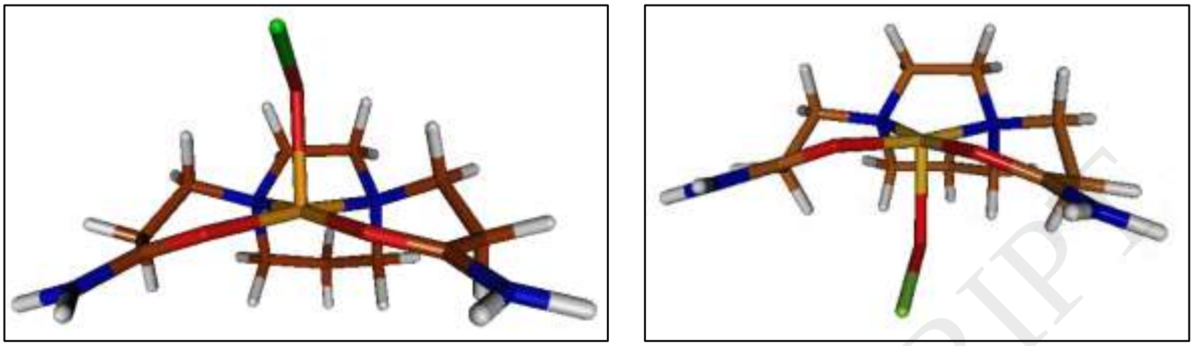


Figure 6. PBE0/6-31+G** optimized structures resulting from coordination of hypochlorite through oxygen atom by the top (left) and by the bottom (right). Color code: carbon (brown), oxygen (red), copper (yellow), hydrogen (light grey), nitrogen (blue).

Concerning the electronic structure presented by species **(B)**, PBE0 predicts that the singlet state is higher by 11.37 kcal/mol in free energy and by 9.51 kcal/mol in electronic energy than the triplet state. Therefore, the triplet multiplicity was adopted for compound **(B)**. Both the oxygen atom and the copper center present large spin densities (Figure 7), showing that the electrons coupled in triplet can be considered to be distributed mainly along these two nuclei and, therefore, the presence of a copper(II)-oxyl species is proposed in the catalytic cycle. This biradicaloid structure is consistent with the proposed mechanism, since the electron in the oxygen center is readily available for abstracting one of cyclohexane's hydrogens. Furthermore, the stabilizations of a copper(II) center is in agreement with the EPR data, which indicated the formation of a new copper(II) species.

Table 3. Comparison between the four possible ways hypochlorite may coordinate to compound **1**, forming compound **(A)**. The reference used to calculate energy (ΔE), enthalpies (ΔH) and free energies (ΔG) differences is the coordination through oxygen and by the bottom as illustrate in Figure 6 (right). The unit is kcal/mol; temperature and pressure used were 298.15 K and 1 atm; basis set used was 6-31+G**.

PBE0 (kcal/mol)	Coordination through O		Coordination through Cl	
	Below the plane (reference)	Above the plane	Below the plane	Above the plane
ΔE	0.00	0.68	25.29	22.94
ΔH	0.00	0.63	25.20	22.62
ΔG	0.00	0.40	23.52	20.69

TPSSh (kcal/mol)	Coordination through O		Coordination through Cl	
	Below the plane (reference)	Above the plane	Below the plane	Above the plane
ΔE	0.00	1.01	25.28	23.07
ΔH	0.00	0.90	25.08	22.64
ΔG	0.00	0.69	23.03	20.39

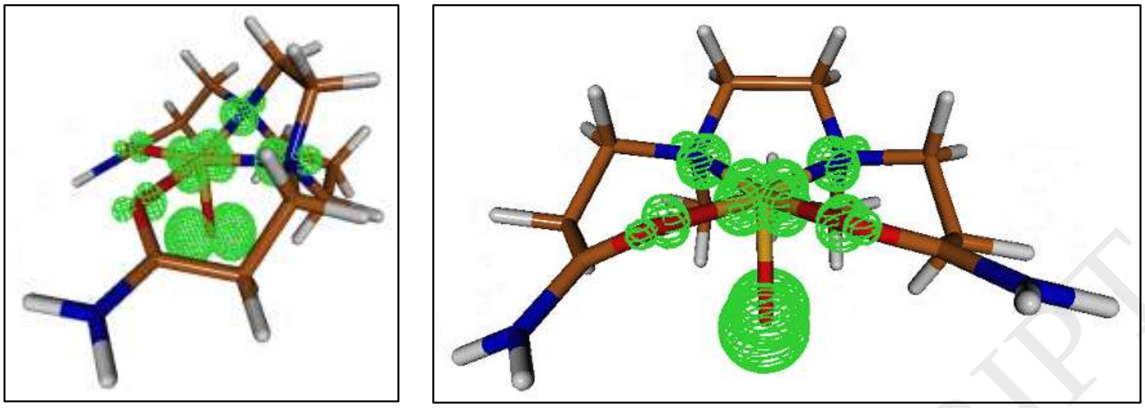


Figure 7. PBE0/6-31++G** Spin density for intermediate **(B)** triplet optimized structure. Color code: carbon (brown), oxygen (red), copper (yellow), hydrogen (light grey), nitrogen (blue), isodensity contour lines (light green, with value 0.01).

The predicted enthalpy (ΔH) and free energy (ΔG) of each reaction step are shown in Table 4. Steps 1, 4 and 2 amount to, respectively, formation of Cu-O and C-Cl bonds and breakage of O-Cl. Steps 3 and 5 encompass formation and breakage of several bonds and, as expected, have lower enthalpy variation. From Table 4, it is possible to deduce from the sum of steps 2 to 5 that there is at least one thermodynamically feasible route supporting the proposed mechanism. It can be inferred, as well, that step 2, due to its very large positive ΔG, should have a barrier at least that high and is likely to be the slow step of the reaction.

Table 4 Enthalpies (ΔH) and Free Energies (ΔG) of Reaction, in kcal/mol, at 298.15 K and 1 atm of pressure, from PBE0 and TPSSh calculations, using 6-31++G** basis set.

Reaction step	Reaction	ΔH (kcal/mol)		ΔG (kcal/mol)	
		PBE0	TPSSh	PBE0	TPSSh
1	**1** + OCl^- → **(A)**	-33.81	-32.83	-22.96	-21.56
2	**(A)** → **(B)** + Cl	61.67	60.79	52.98	51.47
3	**(B)** + C_6H_{12} → **(C)** + C_6H_{11}	-13.94	-12.13	-14.76	-13.14
4	C_6H_{11}+ Cl → $C_6H_{11}Cl$	-83.21	-80.59	-73.18	-70.63
5	**(C)** + HClO → **(A)** + H_2O	-18.58	-17.83	-18.23	-16.66
Sum of steps 2-5		-54.05	-49.76	-53.18	-48.95

Both theoretical and experimental data support that the copper center is not oxidized during the process. This is in controversy with the investigation carried out by us with an iron catalyst, whose experimental evidences suggested that the iron(III) center undergoes oxidation to iron(IV) or iron(V) [18]. Such results indicate that the catalytic process of hydrocarbon halogenation promoted by TCCA and coordination compounds can follow different ways and involve distinct intermediates. These facts suggest that studies with different metal ions need to be performed in order to better understand the mechanism of the reaction and increase the yield of this environmentally benign process.

4. Conclusions

We presented a new catalytic system based on a copper(II) compound that was able to convert cyclohexane to chlorocyclohexane with good yields (~45 % at 50°C) and excellent selectivity (100%). Similar yields were obtained with n-hexane (~47%), generating also only monochlorated products. In the presence of adamantane, the conversion was around 28%. In these cases, mixtures of isomers were obtained, rendering preferentially the product whose carbon-centered radical are more stable. A mechanism of reaction was proposed involving the Cu(II) species. Calculations suggest that the intermediate **B** is a biradical species, with the radical centers located in the copper and oxygen atoms. The described process may be considered environmentally benign, in comparison to traditional processes that involves harmful chemicals (Cl_2, HCl, halogenated solvents); it also operates at low temperature, generates cyanuric acid as residual product, which can be easily isolated by filtration and reused to prepare TCCA again. Furthermore, TCCA is a solid and stable compound that can be manipulated easily. In summary, the catalytic process presented here attains several goals associated with the green chemistry philosophy and paves the way for the development of environmentally friendly catalytic systems for the chemical transformation of saturated hydrocarbons.

5. Electronic Supplementary Information

Full crystallographic tables (including structure factors) for the complexes have been deposited with the Cambridge Crystallographic Data Center (n^o 1486426). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. Crystal data, main bond lengths and angles and ESI-(+)-MS data are presented as ESI.

6. Funding

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