Fe(III) Complexes in Cyclohexane Oxidation: Comparison of Catalytic Activities under Different Energy Stimuli

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Abstract: In this study, the mononuclear Fe(III) complex $[Fe(HL)(NO_3)(H_2O)_2]NO_3$ (**1**) derived from N'-acetylpyrazine-2-carbohydrazide (H_2L) was synthesized and characterized by several physicochemical methods, e.g., elemental analysis, infrared (IR) spectroscopy, electrospray ionization mass spectrometry (ESI-MS), and single crystal X-ray diffraction analysis. The catalytic performances of **1** and the previously reported complexes $[Fe(HL)Cl_2]$ (**2**) and $[Fe(HL)Cl(\mu\text{-OMe})]_2$ (**3**) towards the peroxidative oxidation of cyclohexane under three different energy stimuli (microwave irradiation, ultrasound, and conventional heating) were compared. **1-3** displayed homogeneous catalytic activity, leading to the formation of cyclohexanol and cyclohexanone as final products, with a high selectivity for the alcohol (up to 95%). Complex **1** exhibited the highest catalytic activity, with a total product yield of 38% (cyclohexanol + cyclohexanone) under optimized microwave-assisted conditions.

Keywords: Fe(III) complex; *N,O* donor; X-ray analysis; alkane oxidation; microwave irradiation

1. Introduction

The functionalization of alkanes should provide convenient methods for building a range of valuable organic products [1–9]. However, due to their inertness, such processes are difficult and, e.g., the catalytic oxidation of alkanes remains one of the most challenging fields of chemistry.

The selective oxidation of cyclohexane to cyclohexanol and cyclohexanone has a significant relevance in terms of industrial and economical viewpoints, because these products are used as precursors of adipic acid which, among other applications, is used in the manufacturing of Nylon-6,6 [1–14]. In industry, that reaction is currently performed using a cobalt(II) naphthenate catalyst [15] at 160 °C and 15 bar with very low yields (4%), in order to achieve a good selectivity (80%) [1,2,9,14,15]. The search for more efficient catalytic systems through the development of novel metal-based catalysts and single-pot methodologies for the mild oxidation of alkanes is thus a challenging task [1–3,7,16–23], involving new catalysts with cheap and abundant metals, namely copper [24–27] and iron [28–33]. Microwave irradiation has also been shown to assist with the reaction in various cases [28–33].

In continuation of our work on the catalytic oxidation of alkanes and related species with metal-hydrazone catalysts [24–27,34–44], herein, we report the synthesis and characterization of the new mononuclear Fe(III) complex $[Fe(HL)(NO_3)(H_2O)_2]NO_3$ (**1**) obtained

from *N′*-acetylpyrazine-2-carbohydrazide (H$_2$L), and a comparison of its catalytic activity with those of the related compounds [Fe(HL)Cl$_2$] (**2**) and [Fe(HL)Cl(μ-OMe)]$_2$ (**3**) [45]. The catalytic activity of these complexes in the oxidation of cyclohexane was evaluated by conventional heating and under microwave (MW) or ultrasound (US) irradiations. MW and US irradiations were applied to activate the proposed catalytic system, eventually enhancing the yield, selectivity, and/or rate in comparison with conventional heating [46,47], but their application in alkane functionalization is still rather underexplored [48–50].

2. Results and Discussion

The reaction between Fe(NO$_3$)$_3$·9H$_2$O and the pro-ligand *N′*-acetylpyrazine-2-carbohydrazide (H$_2$L) in methanol results in the formation of the mononuclear Fe(III) complex [Fe(HL)(NO$_3$)(H$_2$O)$_2$]NO$_3$ (**1**) (Scheme 1). Complexes **2** and **3** were synthesized according to the literature [45]. These complexes were characterized by elemental analysis, infrared (IR) spectroscopy, and electrospray ionization mass spectrometry (ESI-MS) and, for **1**, also by X-ray single crystal diffraction analysis. The expected characteristic stretching bands of HL$^-$ in **1** are shifted to lower wavenumbers relative to those in the pro-ligand (see the experimental section), specifically the ν(NH) at 3136 cm^{-1} and the ν(C=O) detected at 1678 and 1646 cm^{-1}; the band for nitrate ions occurs at the typical value of 1383 cm^{-1} [51]. The molecular ion was not observed in the ESI-MS analysis (see the experimental section), but instead, the species [M-(NO$_3$)]$^+$ resulting from the loss of the nitrate counter-ion was detected.
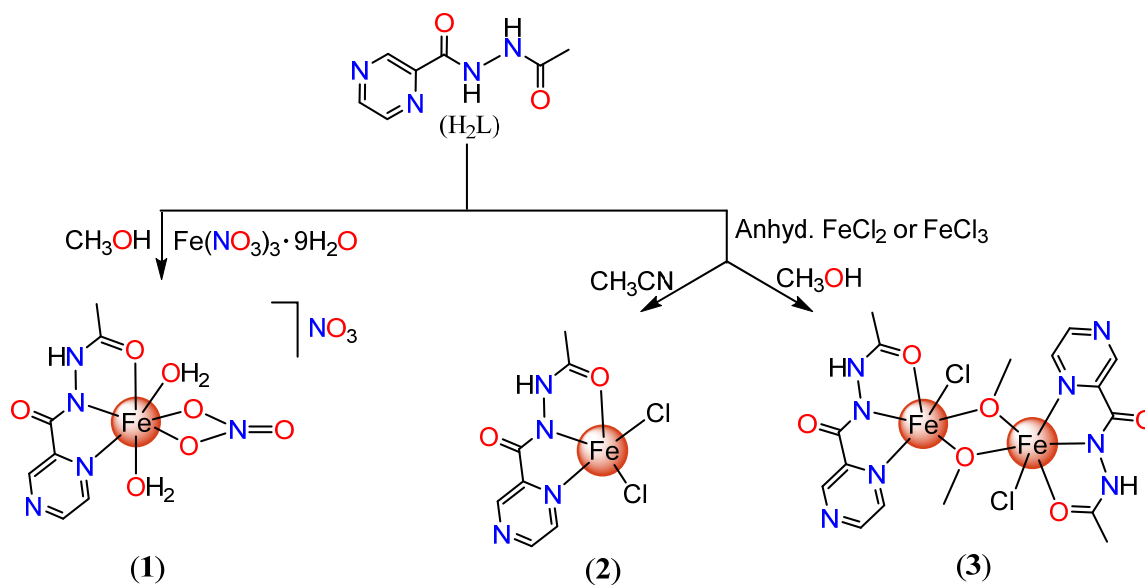

Scheme 1. Syntheses of **1**–**3**.

2.1. Crystal Structure

Crystals of **1** (Figure 1) were obtained from methanol upon slow evaporation, at room temperature. A summary of the crystallographic data and processing parameters is presented in Table 1. Complex **1** (Supplementary Materials: CCDC number 2019464) crystallized in the monoclinic *P*2$_1$/*c* space group, with the asymmetric unit containing an iron cation with *N′*-acetylpyrazine-2-carbohydrazide acting as a mononegative *N*$_{pyrazine}$*N*$_{amido}$*O*$_{keto}$ chelate ligand and a *OO′*-donor nitrate anion sharing the equatorial binding region. The axial sites were engaged with two water ligands, and a cationic pentagonal bipyramidal iron complex was thus formed, with its charge being balanced by a nitrate counter anion. The unit cell of **1** contains five non-coordinated and disordered water molecules. The *NN′O* coordination mode of HL$^-$ was observed in other cases [45,51] and differs from that found in complexes with ligands derived from *N*-acetylsalicylhydrazide [34,52,53]. The HL$^-$ ligand in **1** is slightly twisted, as measured by the distance between the least-square plane defined by the pyrazine

ring and the C_{methyl} atom (0.539 Å); in **3**, that distance is shorter (0.388 Å) and in **2**, such moieties are coplanar [45]. Due to the water ligands and non-coordinated water molecules, compound **1** is involved in extensive H-bond interactions, which extend the structure to the third dimension. This contrasts with what was found in **2** and **3**, resulting from the kind of contact [45], with the former being assembled in dimers and the latter giving rise to 1D chains.
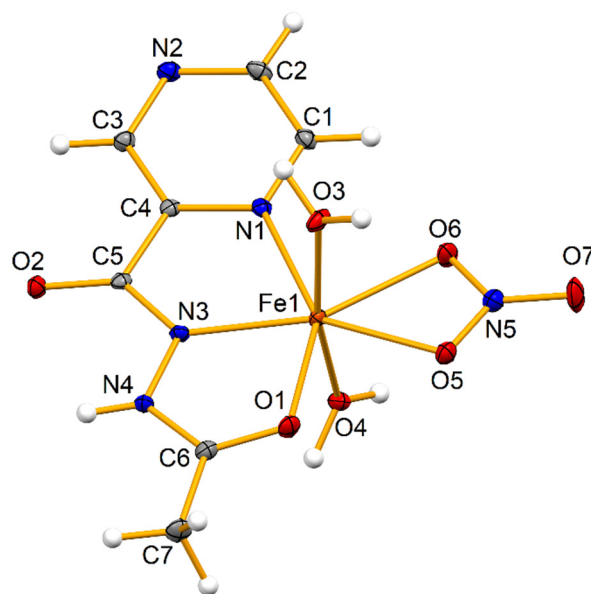
Figure 1. Ellipsoid plot of the complex cation in **1** (drawn at a 30% probability level) with an atom labeling scheme. Selected bond distances (Å) and angles (°): N3–N4 1.389(3); C5–O2 1.241(3); C6–O1 1.266(3); N1–Fe1 2.2547(19); N3–Fe1 2.034(2); O1–Fe1 2.0707(17); O3–Fe1 1.9998(17); O4–Fe1 1.9910(17); O5–Fe1 2.1163(17); O6–Fe1 2.2508(18); O4–Fe1–O3 167.97(8); O1–Fe1–N1 146.91(7); N3–Fe1–N1 72.68(7); N3–Fe1–O1 74.29(7); and O3–Fe1–N3 95.88(7).

**Table 1.** Crystallographic parameters and structure refinement data for complex **1**.

	1
Empirical formula	$C_7H_{11}FeN_6O_{11.25}$
Formula weight	415.04
Crystal system	Monoclinic
Space group	$P2_1/c$
Temperature/K	150(2)
a/Å	7.2541(4)
b/Å	14.4633(8)
c/Å	14.7415(9)
β/°	93.275(2)
V (Å^3)	1544.13(15)
Z	4
D_{calc} (g cm^{-3})	1.785
F000	844
μ(Mo Kα) (mm^{-1})	1.052
Rfls. collected/unique/observed	22957/2837/2385
R_{int}	0.0478
Final $R1^a$, $wR2^b$ ($I \geq 2\sigma$)	0.0319, 0.0711
Goodness-of-fit on F^2	1.051

^{a} R = $\Sigma||F_o|-|F_c||/\Sigma|F_o|$; ^{b} wR(F^2) = $[\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w|F_o|^4]^{\frac{1}{2}}$.

The catalytic properties of **1-3** were investigated and compared for the peroxidative oxidation of cyclohexane, and the effect of the type of activating energy input on the catalytic output was also studied.

2.2. Peroxidative Oxidation of Cyclohexane

Using aqueous *tert*-butylhydroperoxide (*t*-BuOOH, 70% aqueous solution) as an oxidant in acetonitrile (NCMe) at 50 °C, the homogeneous **1-3** were screened for the microwave-assisted (MW) oxidation of cyclohexane (CyH) to cyclohexanone (Cy=O) and cyclohexanol (CyOH) as the final products (Scheme 2). The detection of no other products by Gas Chromatography–Mass Spectrometry (GC-MS) analysis suggests that the catalytic oxidation is very selective. The mechanism involved in the cyclohexane oxidation, involving the generation of cyclohexyl hydroperoxide (CyOOH) as a primary product, was corroborated by the method proposed by Shul'pin [54] and the reaction mixture injected in the gas chromatograph before and after treatment with triphenylphosphine (PPh$_3$). The amount of CyOH had increased significantly after the addition of PPh$_3$ to the reaction mixture, due to the reduction of CyOOH to CyOH and formation of phosphine oxide (PPh$_3$O) (Scheme 2). The results are reported in Table 2 (yield values refer to the samples after treatment with an excess of PPh$_3$).
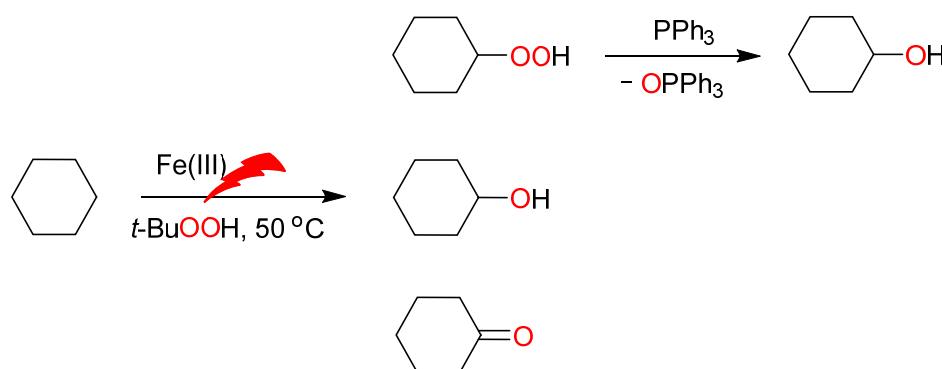
Scheme 2. Microwave (MW)-assisted oxidation of cyclohexane (CyH).

In the presence of **1** and after 3 h under MW-irradiation at 50 °C, 14.9% of cyclohexane was converted into ketone-alcohol (KA) oil (cyclohexanol and cyclohexanone mixture), with cyclohexanol as the major product (selectivity up to 86% relative to KA oil after treatment with PPh$_3$), in the absence of any co-catalyst (entry 5, Table 2), with a turnover number of 75 per Fe atom. There was always an increase in the amount of alcohol when the reaction mixture was analyzed after the addition of triphenylphosphine with respect to the existing amount before this treatment. This fact suggests the formation of cyclohexyl hydroperoxide (CyOOH) as a primary product which, after treatment with PPh$_3$, is reduced to cyclohexanol (CyOH). As an example, entries 4 and 5 from Table 2 are presented, and from an initial CyOH yield of 7.5% (before PPh$_3$ treatment), an increment to 13.2% was detected (after PPh$_3$ treatment). Furthermore, a decrease in the amount of cyclohexanone (Cy=O) was observed, although with a less pronounced difference. For iron complexes **2** and **3**, and for the same reaction conditions, total yields of 10.4% and 14.4% were obtained, with selectivities of 88% and 85% for the alcohol, respectively (Table 2, entries 22 and 25).

The oxidation reaction of cyclohexane was attempted under solvent-free conditions (in the absence of acetonitrile) in the presence of **1** (Table 2, entry 3), without success (the yield did not go beyond 0.74%, despite the high selectivity for the alcohol of 95%). The replacement of compounds **1-3** by their precursor salts, Fe(NO$_3$)$_3$.9H$_2$O and FeCl$_2$, resulted in much lower conversions, with total yields not exceeding 5% (Table 2, entries 28 and 29, respectively), denoting the significance of the *NN'O*-donor ligand *N'*-acetylpyrazine-2-carbohydrazide (HL$^-$) in the Fe coordination sphere in the promotion of the catalytic performance of complexes **1-3**. The free pro-ligand did not exhibit any activity. Blank tests

were performed in the absence of any of the Fe(III) compounds **1-3**, but no noteworthy conversion was observed.

Table 2. Data [a] for the MW-assisted oxidation of cyclohexane by catalysts **1-3** using TBHP (70% aqueous) as an oxidant.

Entry	Catalyst	Catalyst Amount (mol)	Reaction Time (h)	Yield (%) [b]			Selectivity to Cyclohexanol (%) [d]
				CyOH	Cy=O	TOTAL [c]	
1		10	0.5	1.6	0.1	1.7	94
2		10	1	6.7	0.7	7.4	91
3 [e]		10	1	0.7	0.04	0.74	95
4 [f]		10	3	7.5	3.1	10.6	71
5		10	3	13.2	1.7	14.9	86
6		10	6	14.2	2.7	16.9	84
7 [g]		10	3	7.6	1.1	8.7	87
8 [h]		10	3	16.7	4.8	21.5	78
9		2.5	3	3.6	0.2	3.8	95
10		5	3	8.4	0.9	9.3	90
11	**1**	20	3	15.7	3.7	19.4	80
12 [i]		10	3	17.1	4.3	21.4	80
13 [j]		10	3	22.6	6.1	28.7	79
14 [k]		10	3	24.8	12.9	37.7	66
15 [l]		10	3	27.5	9.7	37.2	74
16 [k]		10	1	9.9	1.7	11.6	85
17 [k]		10	6	24.7	12.9	37.6	66
18 [k]		10	9	23.5	13.6	37.1	63
19 [m]		10	3	7.7	1.1	8.8	88
20 [n]		10	3	21.8	6.5	28.3	77
21 [o]		10	3	1.3	0.4	1.7	76
22		10	3	9.1	1.3	10.4	88
23 [k]	**2**	10	3	9.8	0.9	10.7	92
24 [o]		10	3	2.5	0.2	2.7	93
25		10	3	12.3	2.1	14.4	85
26 [k]	**3**	10	3	16.3	1.9	18.2	90
27 [o]		10	3	1.9	0.4	2.3	83
28	Fe(NO$_3$)$_3$.9H$_2$O	10	3	3.8	1.5	5.3	72
29	Anhy. FeCl$_2$	10	3	3.3	0.9	4.2	79

[a] Reaction conditions (unless stated otherwise): cyclohexane (5.0 mmol); 2.5-20 µmol of catalyst; acetonitrile (3 mL); TBHP 70% aqueous solution (10 mmol); 1-9 h; 50 °C; microwave irradiation (5 W); yield and Turnover number (TON) determined by gas chromatography upon treatment with PPh$_3$ (see text). [b] Molar yield (%) based on substrate, i.e., moles of product [cyclohexanol (CyOH) or cyclohexanone (Cy=O)] per 100 moles of cyclohexane after PPh$_3$ treatment. [c] Total yield = moles of products [cyclohexanol (CyOH) + cyclohexanone (Cy=O)]/100 moles of cyclohexane. [d] Selectivity to cyclohexanol relative to KA oil mixture, i.e., moles of CyOH/(100 moles of CyOH + Cy=O). [e] Solvent-free conditions. [f] Without PPh$_3$ treatment. [g] Oxidant:substrate = 1:1. [h] Oxidant:substrate = 4:1. [i] n(HNO$_3$)/n(catalyst) = 5. [j] n(HNO$_3$)/n(catalyst) = 10. [k] n(HNO$_3$)/n(catalyst) = 25. [l] n(HNO$_3$)/n(catalyst) = 50. [m] n(HPCA)/n(catalyst) = 25. [n] n(TFA)/n(catalyst) = 25. [o] n(TEMPO)/n(catalyst) = 25.

Complex **1** was chosen for optimizing the reaction conditions and several parameters were explored. The effect of the reaction time is shown in Figure 2a, for the period between 0.5 and 6 h, without any additive and at 50 °C (Table 2, entries 1, 2, 5, and 6). There was a gradual increase over time in the amount of KA oil formed, achieving a total yield of ca. 15 and 17% after 3 and 6 h, respectively. During the first hour, the formation of cyclohexanone was not significant (94 and 91% of selectivity for the alcohol, after 0.5 and 1 h reaction, respectively). The yield of cyclohexanone increased (from 0.1 to 1.7%, after 0.5 and 3 h, respectively) and the selectively to the alcohol decreased to 86%, possibly due to the partial oxidation of cyclohexanol.
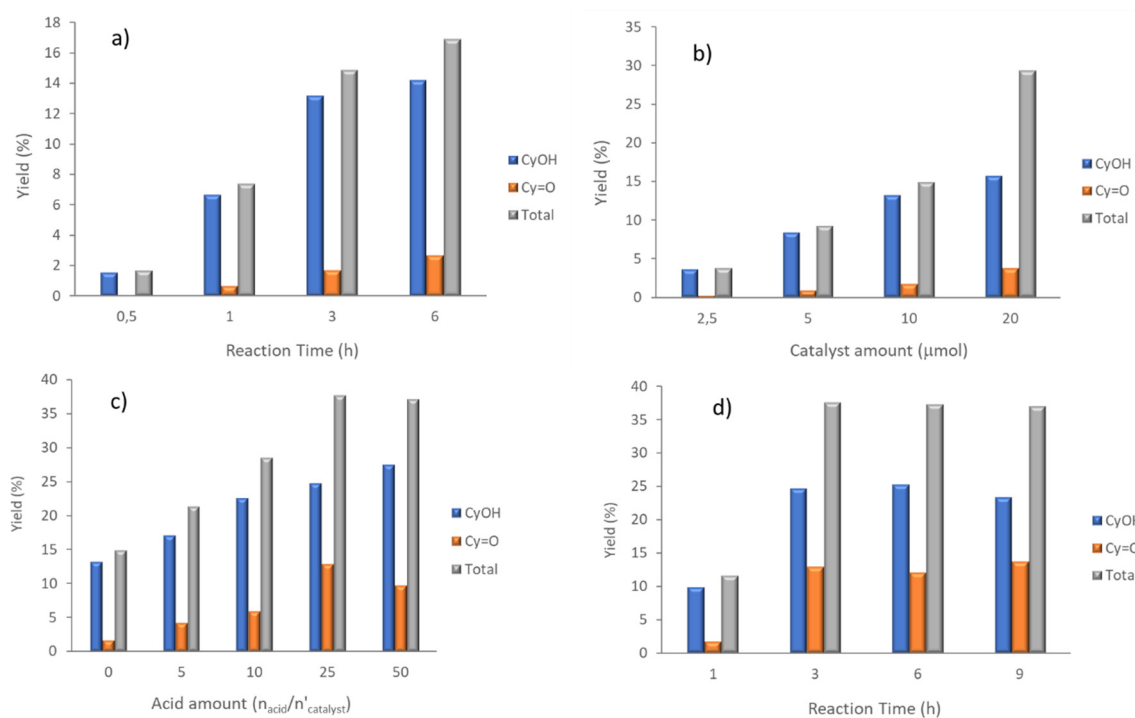
Figure 2. Oxygenated product yield of cyclohexane (CyH) oxidation [cyclohexanol (CyOH) + cyclohexanone (Cy=O)] with respect to the following: (**a**) reaction time (10 µmol of **1**); (**b**) catalyst amount (3 h reaction time); (**c**) acid amount (10 µmol of **1** and 3 h reaction time); and (**d**) reaction time in the presence of acid additive [10 µmol of **1** and $n(HNO_3)/n'$(catalyst) = 25]. Other reaction conditions: CyH (5 mmol); NCMe (3 mL); TBHP (70% aqueous) (10 mmol); 50 °C; under MW-irradiation (5 W); and GC analysis after the addition of PPh_3.

The amount of catalyst varied between 2.5 and 20 µmol (Figure 2b), and a maximum yield of 19.4% of KA oil was verified for an amount of 20 µmol of **1** (entry 11, Table 2). This parameter does not affect only the yield, which increases from 3.8 to 19.4% with the indicated range amount of catalyst, but also the selectivity which, for cyclohexanol, decreases from 95 to 80% (entries 1 and 9-1, Table 2). In this way, we can conclude that both the increase of the reaction time and the increase in the amount of catalyst favor the formation of ketone.

When performing the oxidation reactions under the typical conditions (3 h, 50 °C, and 10 µmol of **1**), the variation in the oxidant/substrate molar ratio also has an important effect on the oxidized product yields (Table 2, entries 5, 7, and 8). The yield of KA oil increased from 8.7 to 14.9 and afterwards to 21.5% when the oxidant/substrate molar ratio was changed from 1:1 to 2:1 and then to 4:1, respectively.

The effect of various additives on the peroxidative microwave-assisted oxidation of cyclohexane was also investigated. In the presence of nitric acid (HNO_3), complex **1** exhibited a highly promising effect. The $n(HNO_3)/n'$(catalyst) molar ratio changed from 5 to 50 (Figure 2c). The total yield increased to 37.7%, for $n(HNO_3)/n'$(catalyst **1**) = 25, relative to 14.9% obtained in the absence of any additive (Table 2, entries 5 and 14, respectively). Going beyond this molar ratio does not lead to a significant yield change (37.2% for $n/n' = 50$) (Table 2, entries 14 and 15).

To investigate the effect of the acid additive over time, catalytic oxidation was performed in the presence of this acid additive ($n/n' = 25$) for several time periods (1, 3, 6, and 9 h). Firstly, for both cases, in the absence and presence of HNO_3 ($n/n' = 25$) (Figure 2a,d), the quantity of oxygenated products (CyOH + Cy=O) practically reached the maximum after 3 h and then seemed to stabilize.

The positive effect of nitric acid has been observed for other catalytic systems involving the oxidative transformation of alkanes [26,27,55–57]. The presence of a certain amount of acid can promote

the catalytic process, either by catalyst activation through the protonation of ligands and unsaturation of the metal center, or by promoting the properties of the oxidant.

The presence of HNO_3 affects, apart from the total yield, the product distribution. In the case of **1**, the selectivity for the alcohol was lower in the presence of acid, with the prolongation of time accentuating this effect. In the presence of acid, there was a clear preferential formation of CyOH (selectivity of 85%) in the first hour; a decrease of CyOH selectivity accompanied by an increase of Cy=O selectivity in the 1-3 h period; and beyond 3 h, the ratio between both products seemed to stabilize (Figure 2d).

In the presence of **1,** the influences of the 2-pyrazine carboxylic acid (HPCA), trifluroacetic acid (TFA), and stable free radical 2,2,6,6-tetramethylpiperidin-l-oxyl (TEMPO) were also explored (Figure 3). After 3 h at 50 °C under MW-irradiation, the total yield of products dropped in the presence of HPCA (8.8%) and TEMPO (drastically to 1.7%), whereas in the presence of TFA, it increased from 14.9% to 28.3% (Table 2, entries 14, 19, 20, and 21), although not as effectively as for HNO_3.
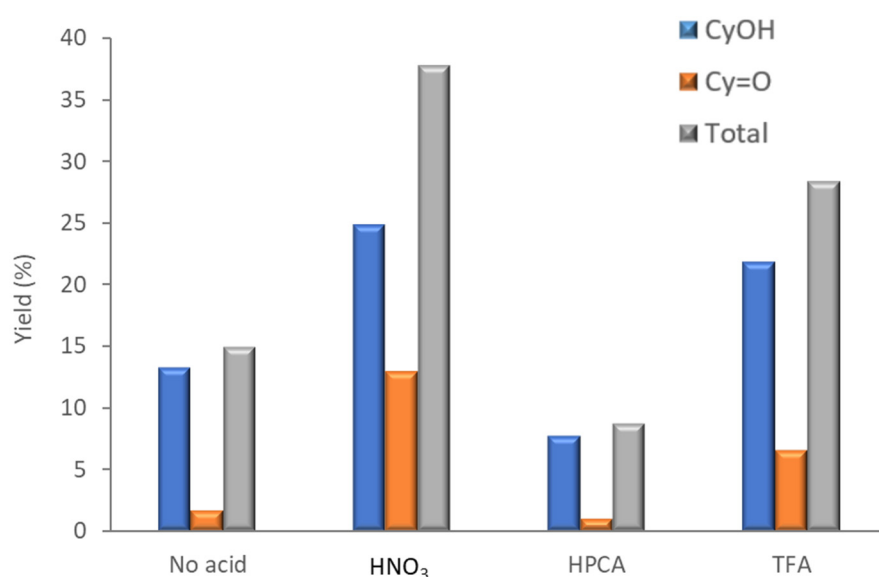
Figure 3. Effects of different additives on the oxidation of cyclohexane catalyzed by **1**. Reaction conditions: CyH (5 mmol); **1** (10 μmol); TBHP (70% aq.) (10 mmol); NCMe (3 mL); 50 °C; 3 h; under MW-irradiation (5 W).

The effects of the presence of HNO_3 ($n(HNO_3)/n'$(catalyst **2** or **3**) = 25) and TEMPO additives were also analyzed for compounds **2** and **3**. In the case of the acid additive, although an increase in the amount of oxygenated products was observed, this effect was not so accentuated for these catalysts as for **1** (Table 2, entries 23 and 26, for **2** and **3**, respectively). The presence of the TEMPO radical resulted, for both catalytic systems, as in the case of **1**, in a drastic decrease in the yields (Table 2, entries 24 and 27, for **2** and **3**, respectively).

The peroxidative oxidation of cyclohexane was also performed, for comparative purposes, using different types of energy inputs, apart from microwaves, namely conventional heating and ultrasound (US) irradiation. Reactions were performed for compounds **1-3**, during 3 h at 50 °C and in the presence of HNO_3 as an additive ($n(HNO_3)/n'$(catalyst) = 25), and in the case of compound **1**, for different periods of time.

If we consider the period of 3 h, compounds **1-3** responded differently to the different energy stimuli. It can be observed that **1** exhibits a better performance when the reaction is promoted by microwave radiation (Table 3, entry 8), conceivably due to its ionic character and larger dipole, which promote microwave energy absorption [31,48,58–60]. Accordingly, the effect of MW irradiation (in comparison with conventional heating) in the case of catalyst **3**, with a symmetrical apolar molecule,

is negligible (Table 3, entries 17 and 18). In this case, a different driving force, i.e., acoustic cavitation in sonochemistry, shows a more effective role (Table 3, entry 19), which is consistent with the known ultrasonic cleavage of a metal-ligand bond [61]. For the dinuclear catalyst **3**, this can lead to the formation of more active mononuclear catalytic species. The reaction catalyzed by **2** does not seem to be favored by any of the radiations (MW and US), which may be due to its possible decomposition into less active or inactive species when it is under these energy inputs. It is also noteworthy to mention that, for the same period, the selectivity does not vary much when we compare the catalytic activity of **1-3** under the effect of different energy inputs (Table 3). For example, for the period of 3 h, and in the presence of **1**, the selectivity for cyclohexanol varies between 66 and 69% for different energy sources. In the case of **2** and **3**, only the MW stands out and the selectivities reach values higher than 90%.

Table 3. Effect of different energy inputs for the oxidation of cyclohexane by catalysts **1-3** using TBHP (70% aq.) as an oxidant [a].

Entry	Catalyst	Method	Reaction Time (h)	Yield (%) [b]			Selectivity to Cyclohexanol (%) [d]
				CyOH	Cy=O	TOTAL [c]	
1			0.5	16.5	5.1	21.6	76
2			1	16.9	6.2	23.1	73
3		CONV	3	18.9	8.6	27.5	69
4			6	19.8	7.8	27.6	72
5			24	28.8	11.8	40.6	71
6	**1**		0.5	11.6	2.9	14.5	82
7 [e]		MW	1	15.2	4.6	19.8	77
8 [e]			3	24.8	12.9	37.7	66
9 [e]			6	24.7	12.9	37.6	66
10			0.5	16.4	4.9	21.3	77
11		US	1	16.2	6.5	22.7	71
12			3	15.4	7.7	23.1	67
13			6	14.9	9.7	24.6	61
14		CONV	3	15.2	6.9	22.1	69
15	**2**	MW	3	9.8	0.9	10.7	92
16		US	3	7.3	4.0	11.3	65
17		CONV	3	13.3	4.4	17.7	75
18	**3**	MW	3	16.3	1.9	18.2	90
19		US	3	20.9	9.1	29.9	70

[a] Reaction conditions (unless stated otherwise): cyclohexane (5.0 mmol); 10 μmol of catalyst; acetonitrile (3 mL); TBHP 70% aqueous solution (10 mmol); $n(HNO_3)/n'$(catalyst) = 25; 0.5-6 h; 50 °C; microwave irradiation (5 W); yield and TON determined by gas chromatography upon treatment with PPh_3. [b] Molar yield (%) based on substrate, i.e., moles of product [cyclohexanol (CyOH) or cyclohexanone (Cy=O)] per 100 moles of cyclohexane after PPh_3 treatment. [c] Total yield = moles of products [cyclohexanol (CyOH) + cyclohexanone (Cy=O)]/100 moles of cyclohexane. [d] Selectivity to cyclohexanol relative to KA oil mixture, i.e., moles of CyOH/(100 moles of CyOH + Cy=O). [e] Data from Table 2 (entries 14, 16, and 17). CONV = under conventional heating with oil bath; MW = under MW-assisted condition; US = under ultrasound irradiation.

In addition, compound **1** was exposed to different types of energy input for different reaction times and, in all of the cases, a maximum selectivity for cyclohexanol was observed in the first 30 min of the reaction (Figure 4, Table 3). Thereafter, the selectivity decreased, conceivably due to the conversion of the cyclohexanol into cyclohexanone.
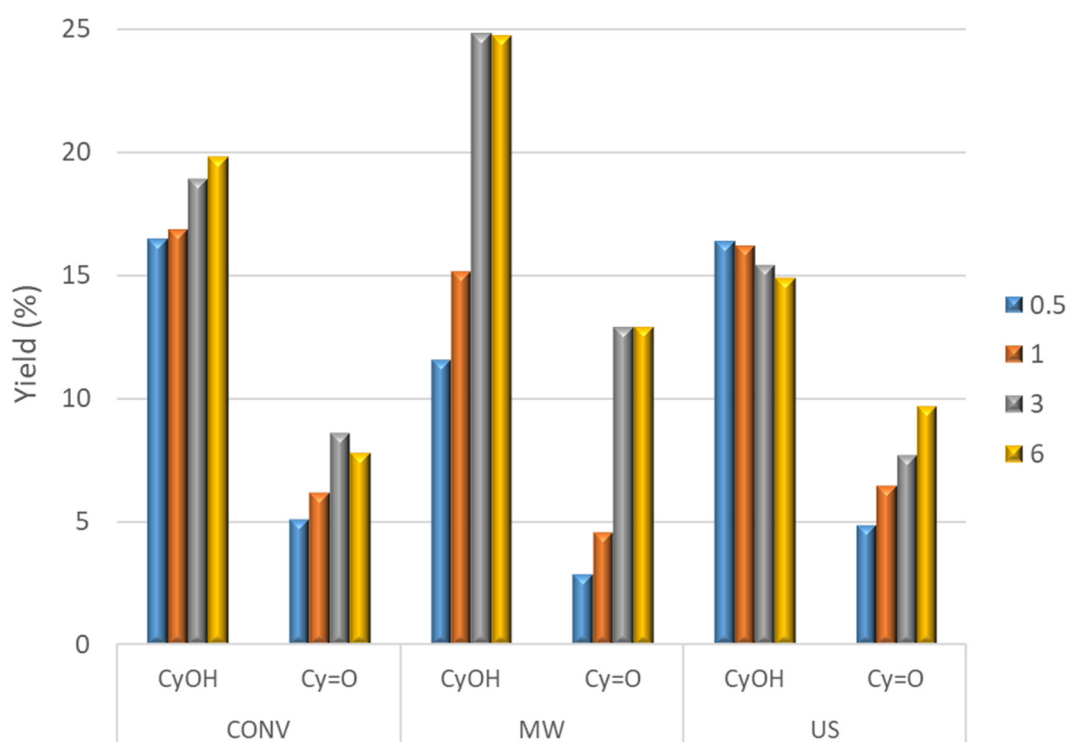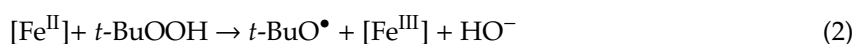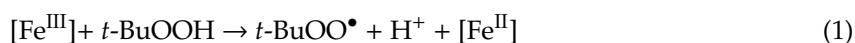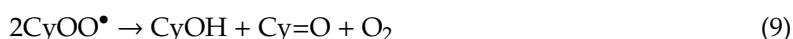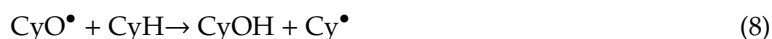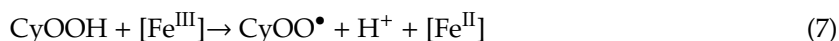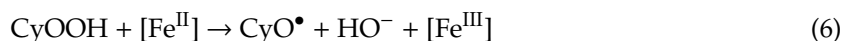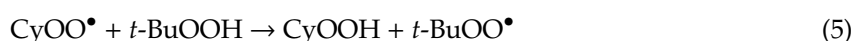
Figure 4. Effect of different energy stimuli on the oxidation of cyclohexane catalyzed by **1**. Reaction conditions: CyH (5 mmol); **1** (10 μmol); TBHP (70% aqueous) (10 mmol); NCMe (3 mL); n(HNO_3)/n′(catalyst) = 25; 50 °C; 0.5-6 h. CONV = under conventional heating with oil bath; MW = under MW-assisted condition; US = under ultrasound irradiation.

The present Fe(III) catalytic system is more effective for the oxidation of cyclohexane under MW conditions in terms of yields, compared to Cu(II) or V(V) catalytic systems with hydrazone-based ligands [27,35,42]. In the presence of an additive (HNO_3), the current Fe(III) catalytic system shows significant increase in the total yield, whereas the V(V) systems are effective under additive-free conditions [27,42]. The total yield under US conditions is also higher than that shown by a hydrazone Cu(II) catalytic system under MW conditions [27]. The selectivity towards CyOH of the current catalytic system is moderate in comparison with the hydrazone V(V) system [35,42].

From radical trapping experiments (addition of 2,2,6,6-tetramethylpiperidin-l-oxyl free radical to the reaction medium), in the presence of **1**, **2**, or **3** (Table 2, entries 21, 24, and 27, respectively), an extensive product yield inhibition (over 80%), relative to the total yield obtained when the reactions were carried out without any additive (Table 2, entries 5, 22, and 25, respectively), was observed. This suggests that the cyclohexane oxidation catalysed by complexes **1-3** proceeds through a radical mechanism, as proposed in other cases, depicted in Equations (1)–(9) [27,35,36,54,62]. Firstly, the reaction proceeds through the iron-catalyzed decomposition of the oxidant, leading to the formation of *t*-BuOO• and *t*-BuO• radicals upon the reduction of Fe(III) and oxidation of Fe(II) species, according to reactions (1) and (2), respectively. Then, cyclohexyl radical (Cy•) formation takes place due to H-abstraction from CyH by *t*-BuO• (reaction (3)). Upon the reaction with dioxygen, Cy• forms CyOO• (reaction (4)), and then upon H-abstraction from TBHP by CyOO•, CyOOH is formed (reaction (5)). In the reactions (6) and (7), the Fe-assisted decomposition of CyOOH produces CyO• and CyOO•, which leads to the formation of cyclohexanol (CyOH) and cyclohexanone (Cy=O) (the desired products), according to reactions (8) and (9).

$$[Fe^{III}] + t\text{-BuOOH} \rightarrow t\text{-BuOO}^\bullet + H^+ + [Fe^{II}] \tag{1}$$

$$[Fe^{II}] + t\text{-BuOOH} \rightarrow t\text{-BuO}^\bullet + [Fe^{III}] + HO^- \tag{2}$$

$$t\text{-BuO}^{\bullet} + \text{CyH} \rightarrow \text{t-BuOH} + \text{Cy}^{\bullet} \tag{3}$$

$$\text{Cy}^{\bullet} + \text{O}_2 \rightarrow \text{CyOO}^{\bullet} \tag{4}$$

$$\text{CyOO}^{\bullet} + t\text{-BuOOH} \rightarrow \text{CyOOH} + t\text{-BuOO}^{\bullet} \tag{5}$$

$$\text{CyOOH} + [\text{Fe}^{\text{II}}] \rightarrow \text{CyO}^{\bullet} + \text{HO}^{-} + [\text{Fe}^{\text{III}}] \tag{6}$$

$$\text{CyOOH} + [\text{Fe}^{\text{III}}] \rightarrow \text{CyOO}^{\bullet} + \text{H}^{+} + [\text{Fe}^{\text{II}}] \tag{7}$$

$$\text{CyO}^{\bullet} + \text{CyH} \rightarrow \text{CyOH} + \text{Cy}^{\bullet} \tag{8}$$

$$2\text{CyOO}^{\bullet} \rightarrow \text{CyOH} + \text{Cy=O} + \text{O}_2 \tag{9}$$

3. Experimental

3.1. General Materials and Procedures

The syntheses were performed in air. Reagents and solvents were obtained from commercial sources and used as received, without further purification or drying. $Fe(NO_3)_3.9H_2O$ was used as the source of metal ion for the synthesis of **1**. Anhydrous $FeCl_2$ was used for the syntheses of **2** and **3**.

C, H, and N elemental analyses were carried out by the Microanalytical Service of the Instituto Superior Técnico. Infrared spectra (4000–400 cm^{-1}) were recorded on a Bruker Vertex 70 instrument (Bruker Corporation, Ettlingen, Germany) in KBr pellets; wavenumbers are given in cm^{-1}. Mass spectra were run in a Varian 500-MS LC Ion Trap Mass Spectrometer (Agilent technologies, Amstelveen, The Netherlands) equipped with an electrospray (ESI) ion source. The drying gas and flow rate were optimized (for electrospray ionization) according to the particular sample, with a 35 p.s.i. nebulizer pressure. Scanning was performed from *m/z* 100 to 1200 in methanol solution. The compounds were observed in the positive mode (capillary voltage = 80–105 V).

3.2. Synthesis of the Pro-Ligand H_2L

N'-acetylpyrazine-2-carbohydrazide (H_2L), the pro-ligand, (Scheme 1), was synthesized as described in the literature [45], by the acetylation of pyrazine-2-carbohydrazide.

Yield: 86.0%. Anal. calc. for ($C_7H_8N_4O_2$): C, 46.67; H, 4.48; N, 31.10; found: C, 46.62; H, 4.43; N, 31.06%. IR (KBr pellet, cm^{-1}): 3324 ν(NH), 3216 ν(NH), 1698 ν(C=O), 1670 ν(C=O). ^{1}H NMR (DMSO-d_6, δ): 9.18-8.86 (m, 3H, $C_4H_3N_2$), 8.74 (s, 2H, NH), 1.91 (s, 3H, CH_3).

3.3. Syntheses of Fe(III) Complexes of N'-acetylpyrazine-2-carbohydrazide

3.3.1. [Fe(HL)(H_2O)_2(NO_3)]NO_3 (**1**)

In this study, 0.404 g (1.00 mmol) of $Fe(NO_3)_3.9H_2O$ was added to a 30 mL methanol solution of H_2L (0.180 g, 1.00 mmol). Then, at room temperature, the reaction mixture was stirred for 30 min, in open air. The resultant reddish brown solution was filtered and the filtrate was kept in air. Single crystals of **1** were isolated after 3 days, washed twice with cold $CHCl_3$, and dried in open air.

Yield 66%. Anal. Calcd. for $C_7H_{11}FeN_6O_{10}$: C, 21.28; H, 2.81; N, 21.27. Found: C, 21.20; H, 2.72; N, 21.18. IR (KBr pellet, cm^{-1}): 3136 ν(NH), 1383 ν(NO_3)$^-$, 1678 ν(C=O), 1646 ν(C=O), 1032 ν(N–N). ESI-MS (+): *m/z* 333 [M-(NO_3)]$^+$ (100%).

3.3.2. [Fe(HL)Cl_2] (**2**) and [Fe(HL)Cl(μ-OMe)]_2 (**3**)

Both **2** and **3** were synthesized according to the literature [45].
[Fe(HL)Cl_2] (**2**)
Yield 70%. Anal. Calcd. for $C_7H_7Cl_2FeN_4O_2$: C, 27.48; H, 2.31; N, 18.31. Found: C, 27.42; H, 2.28; N, 18.25. IR (KBr pellet, cm^{-1}): 3134 ν(NH), 1702 ν(C=O), 1668 ν(C=O), 1037 ν(N–N). ESI-MS (+): *m/z* 306 [M+H]$^+$ (100%).

[Fe(HL)Cl(μ-OMe)]$_2$ (**3**)

Yield 65%. Anal. Calcd. for $C_{16}H_{20}Cl_2Fe_2N_8O_6$: C, 31.87; H, 3.34; N, 18.58. Found: C, 31.84; H, 3.33; N, 18.54. IR (KBr; cm^{-1}): 3138 ν(NH), 1664 ν(C=O), 1641 ν(C=O), 1038 ν(N–N). ESI-MS (+): *m/z* 604 [M+H]$^+$ (100%).

3.4. X-ray Measurements

A crystal of **1** was immersed in cryo-oil, mounted in a Nylon loop, and measured at 150 K. Intensity data were collected using a Bruker AXS-KAPPA APEX II diffractometer (Bruker AXS Inc., Madison, WI, USA) with graphite monochromated Mo-Kα (λ 0.71073) radiation. Omega scans of 0.5° per frame were used for data collection and a full sphere of data was obtained. Cell parameters were retrieved using Bruker SMART [63] software and the data were refined using Bruker SAINT [63] on all the observed reflections. SADABS was used for absorption corrections [64]. Direct methods were employed by using SHELXS97 [65] and refined with SHELXL2018/3 [66]. Calculations were conducted using WinGX version 2018.3 [67]. The H-atoms bonded to carbon and nitrogen were introduced in the model at geometrically calculated positions and refined using a riding model, with U_{iso} defined as $1.2U_{eq}$ of the parent carbon atoms for aromatic residues and for nitrogen, and $1.5U_{eq}$ for the methyl group. The hydrogen atoms of water ligands were found in the difference Fourier map and allowed to refine with distance restrains. The non-coordinated water molecule was disordered over two positions and refined with the use of PART instruction, with the occupancy of O1W and O2W at a ratio of 74% and 26%, respectively. After this strategy, the remaining electron density was considered as being due to another water molecule (O3W), which was refined with an occupancy of 0.25, flanked by PART -1, and the structure finalized normally. The hydrogen atoms of O1W, O2W, and O3W could be neither located nor inserted in the calculated positions (the use of the CALC-OH routine in WinGX proved to be unsuccessful). Least square refinements were carried out with anisotropic thermal motion parameters for all of the non-hydrogen atoms.

3.5. Catalytic Studies

The microwave-assisted peroxidative oxidation of cyclohexane was carried out in G10 Pyrex tubes (10 mL capacity reaction tube with a 13 mm internal diameter) in a focused Anton Paar Monowave 300 reactor (Anton Paar GmbH, Graz, Austria) fitted with a rotational system and an IR temperature detector.

The test was performed under the following conditions: The desired amount of catalyst **1**, **2**, or **3** (2.5–20 μmol); cyclohexane (5 mmol); acetonitrile (3 mL) and oxidant (1, 2, or 4 equivalent vs. substrate, *t*-BuOOH, 70% aqueous solution) were added into an Pyrex tube, which was introduced in the MW reactor and stirred under irradiation (5—10 W) at 50 °C. After completion of the desired reaction time, the reaction mixture was cooled to room temperature, whereafter 90 μL of cycloheptanone (internal standard) and 10 mL of diethyl ether (for substrate and organic product extraction) were added. The reaction mixture was stirred and centrifuged. A sample was taken from the mixture and analyzed by gas chromatography (GC) after the addition of an excess of triphenylphosphine, in order to reduce cyclohexyl hydroperoxide to cyclohexanol, following a method developed by Shul'pin [54]. The composition of products was confirmed by Gas Chromatography-Mass Spectrometry (GC-MS).

For the ultrasound-assisted oxidation reactions, a reaction tube was immersed in an ATU ultrasonic thermoregulated bath (40 kHz, 600 W) equipped with an automatic temperature heating-cooling circulatory system, which kept the bath temperature at ca. 50 °C for all of the trials.

GC measurements were carried out using a FISONS Instruments GC 8000 series gas chromatograph (Agilent Technologies, Santa Clara, CA, USA) with an FID detector and a capillary column (DB-WAX, column length: 30 m; internal diameter: 0.32 mm), using helium as a carrier gas and the Jasco-Borwin v.1.50 software (Jasco, Tokyo, Japan). The samples were injected at 240 °C, whereas the initial temperature was maintained at 100 °C for 1 min, increased to 180 °C at the rate 10 °C/min, and then hold for 1 min.

The samples were analysed by GC-MS using a Perkin Elmer Clarus 600 C instrument (Shelton, CT, USA) (He as the carrier gas). The ionization voltage was 70 eV. Gas chromatography was guided in the temperature-programming mode, using an SGE BPX5 column (30 m × 0.25 mm × 0.25 µm).

Retention times of all identified reaction products were compared with those of the commercially available samples. Reaction products' mass spectra were compared to fragmentation patterns obtained from the NIST spectral library stored in the computer software of the mass spectrometer.

4. Conclusions

Three Fe(III) compounds (**1-3**) derived from *N*′-acetylpyrazine-2-carbohydrazide were successfully applied for the peroxidative oxidation of cyclohexane under different energy stimuli (microwave irradiation, ultrasound, and conventional heating). In order to improve the catalytic performance, the effects of different reaction parameters were studied, namely the reaction time, catalyst amount, substrate:oxidant ratio, and presence of additives. Compounds **1-3** catalyzed the oxidation of cyclohexane via a radical mechanism, yielding cyclohexanol and cyclohexanone as the main products; the former with a high selectivity upon the reduction of the primary product cyclohexylperoxide (up to 95%). Complexes **1** and **3** exhibited similar catalytic activities, with 14–15% yields of cyclohexanol and cyclohexanone under 3 h of microwave irradiation at 50 °C, whereas complex **2** reached a total product yield of 10.4%.

Apart from being undertaken under microwaves, the peroxidative oxidation of cyclohexane was also performed using other types of energy inputs, i.e., conventional heating and ultrasound irradiation. The catalysts responded differently to the various energy stimuli, with the best performance of **1** being observed under microwave radiation, whereas complex **2** showed the maximum activity under conventional heating and compound **3** under ultrasounds. However, in all cases, the highest selectivity to cyclohexanol was verified when the reaction was assisted by microwave radiation.

In the case of **1,** a significant increase of the total yield was observed from 15 to 38% in the presence of an additive (HNO_3), although such an influence was not found for **2** and **3**. Therefore, the combined use of nitric acid and the mononuclear cationic Fe(III) compound **1** plays a crucial role in accelerating the catalytic oxidation process.

This study can help to foster the fruitful use of the environmentally acceptable oxidant aqueous TBHP and the application of microwave heating or ultrasounds to promote catalysis, which have significant environmental implications.

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