Editor's choice paper

Homogeneously catalyzed epoxidation of α,β-unsaturated ketones using simple aluminum salts and aqueous H₂O₂—Is it possible?

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ABSTRACT

Simple aluminum salts activate hydrogen peroxide towards α,β-unsaturated ketones, affording as major products α,β-epoxyketones. The pathway of this reaction involves the interaction between $[Al(H_2O)_6]^{3+}$ and H_2O_2, through hydrogen bonds, in the second-coordination sphere. This interaction enhances the proton exchange between non-coordinated water and hydrogen peroxide, as detected by ^1H NMR experiments. By this means, the hydroperoxide anion, formed as reactive intermediate in the proton exchange between H_2O and H_2O_2, can be trapped by α,β-unsaturated ketones. Surprisingly, this pathway is not followed when diethylmaleate is used as substrate. In this case, the radical addition of THF to the C=C bond of diethylmaleate takes place with high selectivity, affording 2-(THF)-derivatives with high yields.

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1. Introduction

At a first glance, aluminium-assisted or -catalyzed oxidations seem to be something far to be possible. Typically, dioxygen and peroxides are activated by transition metals, in which charge transfer between metal and ligands plays a fundamental role to tune the reactivity of the activated oxo- or peroxo-species in the oxyfunctionalization of organic substrates [1]. Although aluminum cannot activate dioxygen or peroxides in the same way as transition metals, this does not mean that aluminum cannot play any role in oxidations at all.

In 1960s Davis and Hall investigated the preparation and properties of various organoaluminum peroxides [2]. These compounds are intermediates formed in the oxidation of alkylaluminum with alkylperoxides. Since R–O–O–Al species are rather unstable, only few examples of well-characterized organoaluminum peroxides are reported [3]. The reactivity of aluminum species/peroxide has been reported by several groups for many types of organic reactions along the last 50 years. Davis and Hall [2a] were the first to show that ketones are obtained in the stoichiometric reaction between aluminum alkoxides and alkylhydroperoxides by a rearrangement

of a cyclic transition state involving a four-coordinated aluminum species as shown in Scheme 1.

Oshima et al. [4] reported that the (t-BuO)₃Al/t-BuOOH system does stereoselective epoxidation of allylic alcohols and also dehydrogenative oxidation of secondary alcohols under mild reaction conditions. The yields reported for epoxides were higher than 70%, and for ketones above 90%. These reactions are proposed to proceed by a three-coordinated aluminum intermediate as shown in Scheme 2 [4]. More recently, Proto and co-workers [5] showed that aluminum alkyls and methylaluminoxane (MAO)/alkylhydroperoxide systems also convert efficiently saturated and unsaturated alcohols to the corresponding ketones and epoxy-alcohols via a four-coordinated intermediate (Scheme 1).

Aluminum alkoxides mediate the transfer of hydride from an alcohol to a ketone. This reaction is known by Meerwein–Pondorff–Verley reduction or by Oppenauer oxidation as this approach can be used either to reduction of ketones or to oxidation of alcohols [6]. The hydride transfer proceeds through a six-member cyclic transition state (Scheme 3), in which both alcohol and ketone O-sites are coordinated to the metal. Hydride donation usually takes place from the less hindered face of the carbonyl group. Al(III) shows slow ligand exchange rate, thus its efficient use in catalytic amounts is not feasible [6]. The utilization of lanthanides catalysts, in which the metal centre shows more favorable ligand

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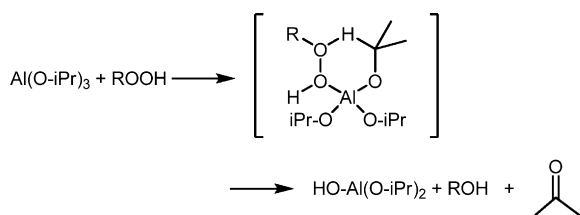
Scheme 1. Stoichiometric reaction between aluminum alkoxides and alkylhydroperoxides [2].
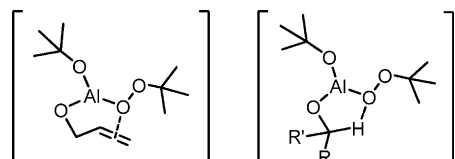
Scheme 2. Intermediates proposed for stereoselective epoxidation of allylic alcohols (left) and dehydrogenative oxidation of secondary alcohols (right) [4,5].

exchange kinetics, expanded the scope of synthetic applications of Meerwein–Pondorff–Verley and Oppenauer reactions [6].

Dodonov and co-workers explored the synthetic possibilities of the $(t\text{-}BuO_3)Al/t\text{-}BuOOH$ system in the oxidation of tri- and tetrasubstituted alkenes [7a], unsaturated ethers [7b,c], and phenylalkenes [7d]. In these reports, radicals are proposed to participate in the oxidation of the substrates.

For organic synthesis, however, the applicability of aluminum alkyls, aluminum alkoxides or MAO/alkylhydroperoxide systems is limited. Firstly, these reagents are expensive and should be used in stoichiometric amounts [4–6]. Additionally, the stability and the safety of these systems are also important issues, since organoaluminum compounds are typically very reactive. Fairly recently, we reported that a simple hexaaquoaluminum salt (2 mol% of $Al(NO_3)_3 \cdot 9H_2O$) is able to catalyze the epoxidation of cis-cyclooctene at high yield (87% at 12 h) using aqueous 70 wt.% hydrogen peroxide in THF [8]. However $[Al(H_2O)_6]^{3+}$, is quite prone to deactivation under the reaction conditions [8].

Baeyer-Villiger oxidation of ketones using $AlCl_3$ dissolved in ethanol and 30 wt.% H_2O_2 was recently reported by Lei et al. [9] The authors showed that cyclic ketones and acyclic ketones are transformed almost quantitatively into the corresponding lactones or esters with very high selectivity (99%). However, the reaction mechanism involving the oxygen transfer from H_2O_2 to ketones needs elucidation [9].

Mandelli et al. [10] reported that aluminum nitrate in acetonitrile can catalyze the hydroperoxidation of alkanes. The authors reported that a yield of 31% cyclooctane hydroperoxide could be attained at 70 °C after 32 h. The oxidation is proposed to occur with the participation of hydroxyl radicals, as suggested by the parameters of selectivity for the oxidation of linear and branched alkanes.

Nowadays there are some hypotheses that aluminum could also take place in oxidative processes in biological systems. Exley [11] has revised the pro-oxidant activity of aluminum in biological systems, showing that there are provoking evidences for a "pro-oxidant" role of aluminum both in vitro and in vivo preparations.
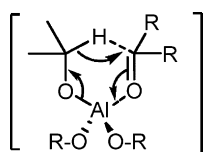
Scheme 3. Proposed transition-state of the Meerwein–Pondorff–Verley–Oppenauer reactions [6].

Aluminum seems to facilitate both superoxide- and iron-driven biological oxidation by mechanisms that remain to be resolved [11].

In this report, we show that catalytic amounts of $[Al(H_2O)_6]^{3+}$ strongly enhance the nucleophilicity of H_2O_2, activating it towards epoxidation of α,β-unsaturated ketones. The previous problems related to catalyst deactivation [8] are not observed in the reactions with α,β-unsaturated ketones or with α,β-unsaturated diesters. The mechanism for the activation of H_2O_2 by $[Al(H_2O)_6]^{3+}$ was studied by ^1H NMR experiments. Herein we show that $[Al(H_2O)_6]^{3+}$ act catalyzing the exchange of protons between H_2O_2 and H_2O. In this process the reactive intermediate HOO^- is formed, which is then easily trapped by electrophilic substrates. Although the ionic pathway involving HOO^- species is prevailing in the epoxidation of α,β-unsaturated ketones, the radical pathway is revealed as the exclusive route followed in the reaction with diethylmaleate.

2. Experimental

Warning: the concentration of hydrogen peroxide in organic solvents should not be higher than to 25 wt.%. Mixtures of peroxides and THF can be explosive by shock or friction!

2.1. Epoxidation of (R)-carvone

A solution containing (R)-carvone (25 mmol, Merck) and di-n-butylether (12.5 mmol, internal standard (IS), Fluka) in THF (p.a., Merck) was prepared to give a total volume of 25 mL. The reaction was started adding 2 mL of a fresh solution of $Al(ClO_4)_3 \cdot 9H_2O$ (0.50 mmol, Fluka) dissolved in 70 wt.% H_2O_2 (56 mmol, Peroxidos do Brasil, Solvay) into the solution of (R)-carvone at 80 °C under reflux. For the reactions using 30 wt.% H_2O_2, 5 mL of oxidant were used. Samples were taken at different reaction times and analyzed by GC using a HP 6890 gas chromatograph, equipped with a Zorbax 1 column (28 m). The temperature program used in all analyses was: 40 °C (6 min), 180 °C (18 min), 280 °C (5 min) and 350 °C (isothermal, 5 min). The retention times (min) were: IS 5.3, (**1**) 13.5, (**1a**) 14.2, and (**1b**) 13.93. The epoxide was quantified using a calibration curve obtained with standard solutions of **1a**. An authentic sample of **1a** was prepared as described in Ref. [23]. Products were identified by GC–MS using EI and CI modes. The amount of byproducts was estimated considering that their FID responses are the same as that of epoxide **1a**. Selectivity is always given with respect to converted substrate. MS Spectrum: **1a** (CI, M$^{+\bullet}$ 166), EI m/z 166 (1), 123 (39), 85 (50), 67 (55), 55 (29), 43 (100); **1b** (CI, M$^{+\bullet}$ 168), EI m/z 150 (2), 108 (68), 95 (26), 82 (66), 67 (55), 54 (34), 43 (100).

2.2. Epoxidation of isophorone

The reaction using isophorone (25 mmol, Acros) was carried out at 60 °C following the procedure described for (R)-carvone. The epoxide **2a** was quantified by GC using a calibration curve obtained with standard solutions. The retention times (min) of the components were: (**2**) 10.4, (**2a**) 9.8, (**2b**) 12.2, (**2c**) 12.9, (**2d**) 13.6, (**2e**) 12.6. An authentic sample of **2a** was prepared using an alkaline H_2O_2 solution as described in Ref. [24]. Mass spectrum: **2a** (CI, M$^{+\bullet}$ 154), EI m/z, 154 (6), 139 (20), 126 (11), 97 (21), 83 (100), 69 (48), 55 (44); **2b** (CI, M$^{+\bullet}$ 154), EI m/z, 154 (3), 136 (3), 125 (6), 111 (16), 82 (100), 72 (30); **2c** (CI, M$^{+\bullet}$ 172), EI m/z, 158 (1), 140 (5), 125 (5), 112 (10), 101 (13), 83 (27), 70 (10), 58 (40); **2d** (CI, M$^{+\bullet}$ 172), EI m/z, 172 (7), 154 (10), 139 (6), 114 (23), 99 (100), 83 (23), 71 (13), 57 (23); **2e** (CI, M$^{+\bullet}$ 156), EI m/z, 156 (1), 138 (13), 123 (1), 100 (43), 82 (90), 70 (100), 58 (33).

2.3. Epoxidation of cyclohexenone

The reaction using cyclohexenone (25 mmol, Acros) was carried out at 25 °C following the procedure described for (R)-carvone. The epoxide **3a** was quantified by GC using a calibration curve obtained with standard solutions. The retention times (min) of the components were: (**3**) 5.68, (**3a**) 7.6, (**3b**) 9.7. An authentic sample of **3a** was prepared using an alkaline H_2O_2 solution as described in Ref. [25]. MS Spectrum: **3a** (CI, M$^{+\bullet}$ 112), EI m/z 112 (27), 96 (7), 83 (17), 71 (30), 55 (100); **3b** (CI, M$^{+\bullet}$ 130), EI m/z 130 (1), 112 (53), 101 (6), 86 (70), 70 (70), 57 (100).

2.4. Radical addition of THF to diethylmaleinate

The reaction using diethylmaleinate (25 mmol, Merck) was carried out at 80 °C following the procedure described for (R)-carvone. The reaction yields a mixture of diasteroisomers, **4a**, as main products. In the GC analysis, the retention times (min) of the components were: (**4**) 11.6, (**4a**) 21.7 and 22.09, (**4b**) 23.4 and 23.6, (**4c**) 30.2, 30.3 and 30.4. The diasteroisomers **4a** were isolated using preparative GC at the GC facilities of the Max-Plank-Institut für Kohlenforschung. Mass spectrum: diasteroisomers **4a** (CI, M$^{+\bullet}$ 244), EI m/z 199 (7), 157 (15), 111 (6), 97 (3), 71 (100). Diasteroisomer **4a** with a shorter retention time: ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.10 (dq, J = 7.1, 2.2, 2H), 4.05 (dq, J = 7.2, 1.8, 2H), 3.92 (q, J = 7.0, 1H), 3.77–3.60 (m, 2H), 2.80 (ddd, J = 9.2, 7.3, 4.8, 1H), 2.69 (dd, J = 16.6, 9.2, 2.61, 1H), 2.61 (dd, J = 16.6, 4.8, 1H), 1.98–1.73 (m, 3H), 1.72–1.62 (m, 1H), 1.19 (t, J = 7.1, 3H), 1.17 (t, J = 7.1, 3H), ^{13}C NMR (100 MHz, CDCl$_3$): 173.2, 172.5, 79.1, 68.4, 61.1, 60.9, 47.2, 33.9, 30.0, 26.0, 14.5. HRMS [M+Na$^+$] = 267.120294 (calc. C$_{12}$H$_{20}$O$_5$Na, 267.120012). Diasteroisomer **4a** with a longer retention time: ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.11 (dq, J = 7.3, 7.1, 2H), 4.05 (q, J = 7.1, 2H), 4.00 (q, J = 7.1, 1H), 3.79 (dt, J = 6.5, 1H), 3.66 (m, 1H), 2.99 (dd, J = 10.2, 4.4, 1H), 2.66 (dd, J = 10.2, 16.5, 1H), 2.38 (dd, J = 16.5, 4.4, 1H), 1.93–1.73 (m, 3H), 1.68–1.52 (m, 1H), 1.19 (t, J = 7.1, 3H), 1.17 (t, J = 7.1, 3H), ^{13}C NMR (100 MHz, CDCl$_3$): 173.2, 172.5, 79.1, 68.4, 61.1, 60.9, 47.2, 33.9, 30.0, 26.0, 14.5. HRMS [M+Na$^+$] = 267.120294 (calc. C$_{12}$H$_{20}$O$_5$Na, 267.120012); diasteroisomers **4b** (CI, M$^{+\bullet}$ 260), EI m/z 243 (1), 187 (2), 157 (15), 111 (6), 97 (3), 71 (100); diasteroisomers **4c** (CI, M$^{+\bullet}$ 416), EI m/z 371 (20), 325 (30), 283 (100), 243 (63), 197 (82), 169 (30), 123 (26), 101 (24), 81 (23).

2.5. ^{1}H NMR studies of the $[Al(H_2O)_6]^{3+}/H_2O_2$ system

The ^{1}H NMR spectra of the solutions of H_2O_2, H_2O_2/H_3O^+, $[Al(H_2O)_6]^{3+}$, and $[Al(H_2O)_6]^{3+}/H_2O_2$ in THF-d_8 were recorded at 60 °C using a Varian Inova 500 spectrometer operating at 500 MHz. For each spectrum 64 transients were accumulated. The solutions were prepared in THF-d_8 (Cambridge Isotope Laboratories Inc.). The concentrations of H_2O_2 and $[Al(H_2O)_6]^{3+}$ were always 0.14 and 0.003 mol L^{-1}, respectively. For the spectrum of the H_2O_2/H_3O^+ solution, the concentration of H_3O^+ was 0.005 mol L^{-1}. In variable-temperature ^{1}H NMR experiment the range −75 to 65 °C was investigated for the system $[Al(H_2O)_6]^{3+}/H_2O_2$ in THF-d_8.

2.6. Electronic structure calculation

The DFT calculations were done with the software package Gaussian 03 using the B3LYP method with the 6-31G* basis set [26].

3. Results and discussion

3.1. Reactivity of the $[Al(H_2O)_6]^{3+}/H_2O_2$ system

Table 1 shows the results of the catalytic epoxidation of (R)-carvone, cyclohexenone and isophorone using the
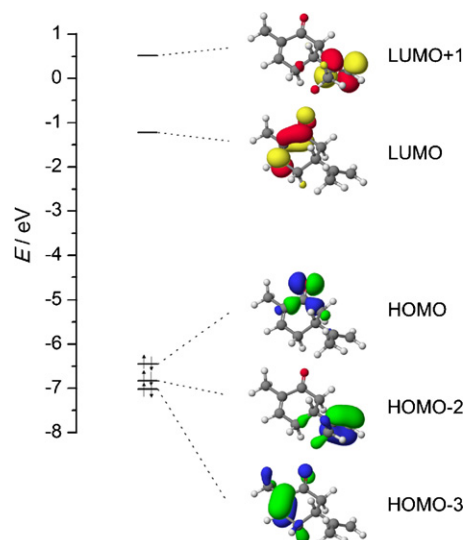

Fig. 1. Energy of some molecular orbitals of (R)-carvone predicted according DFT calculation using the B3LYP method with the 6-31G* basis set.
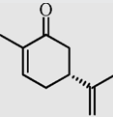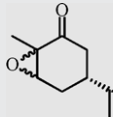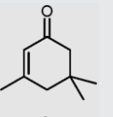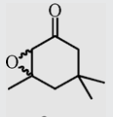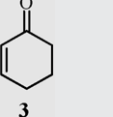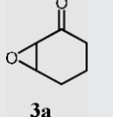
$[Al(H_2O)_6]^{3+}/H_2O_2$ system. Al(ClO$_4$)$_3$·9H$_2$O was employed as source of $[Al(H_2O)_6]^{3+}$. For all substrates, the conversions are from moderate to high after 5 h. The main products obtained in these reactions are epoxides. However, longer reaction times resulted in a strong decrease of selectivity for epoxides due to the formation of a complex mixture containing several minor byproducts, formed by acid-catalyzed rearrangements, ring-opening reactions, oligomerization, and radical oxidation. Interestingly, only for (R)-carvone both high conversion (78%) and high selectivity (81%) for epoxide using 70 wt.% H_2O_2 are achieved. Reactions are faster and much more selective for epoxides when 70 wt.% instead of 30 wt.% H_2O_2 was used.

In the absence of $[Al(H_2O)_6]^{3+}$ conversions ranging from 2 to 5% after 24 h, using 70 wt.% H_2O_2, are obtained. However, the selectivity for epoxides is near to zero for all substrates in these blank reactions. Furthermore, similar low conversion and low selectivity are obtained for reactions in which Al(ClO$_4$)$_3$·9H$_2$O or Al(NO$_3$)$_3$·9H$_2$O is replaced by NaClO$_4$ or NaNO$_3$. Consequently, the oxygen transfer to the electron-deficient C=C bonds is surely not assisted by the anion, but indeed by $[Al(H_2O)_6]^{3+}$.

The results shown in Table 1 are not expected starting from the experience gained with heterogeneously alumina-catalyzed epoxidation [12,13]. Alumina catalyzes the oxygen transfer from H_2O_2 almost exclusively towards the most nucleophilic C=C bond [12,13]. The activation of H_2O_2 by the alumina surface occurs by the reaction between the weak type Ia Brønsted acid sites and H_2O_2, forming Al–OOH surface species [13]. In these species the O–O bond is polarized, facilitating the oxygen transfer to nucleophilic olefins [13] or even, to apparently deactivated substrates, such as cyclohexanone, yielding ε-caprolactone [14]. Although alumina surface can mutually activate ketones and H_2O_2 allowing Baeyer-Villiger oxidation, electrophilic functionalities such as α,β-unsaturated ketones, aldehydes or allylic alcohols cannot be oxidized by the alumina/H_2O_2 system [13b].

(R)-Carvone is an interesting substrate to trace the oxidizing species involved in the oxidations. This molecule has two C=C bonds with rather different reactivities. DFT calculations using the B3LYP method and 6-31G(d) basis set give a quantitative view on the energy of the molecular orbitals of these C=C bonds (Fig. 1). The higher energy of the external C=C bond molecular orbital (−6.83 eV, HOMO-2) indicates that this alkene site is the most nucleophilic. On the other hand, the lower energy of the

Table 1
Epoxidation of α,β-unsaturated ketones using $[Al(H_2O)_6]^{3+}/H_2O_2$ system.

Substrate	Main product	T (°C)	Oxid.	1 h		3 h		5 h		24 h	
				C (%)	S (%)	C (%)	S (%)	C (%)	S (%)	C (%)	S (%)
1	**1a**	80	H_2O_2 30%	13	26	15	60	21	74	75	45
			H_2O_2 70%	47	93	69	88	78	81	93	56
2	**2a**	60	H_2O_2 30%	6	33	11	16	13	13	21	3
			H_2O_2 70%	19	50	33	33	38	30	49	29
3	**3a**	25	H_2O_2 30%	3	46	12	40	29	33	79	22
			H_2O_2 70%	47	32	70	28	82	22	88	1

C: conversion, S: selectivity. Reaction conditions: substrate (25 mmol), di-n-butylether (internal standard, 12.5 mmol), 70 wt.% H_2O_2 (56 mmol), $Al(ClO_4)_3 \cdot 9H_2O$ (0.5 mmol), THF (solvent), at the temperature indicated in this table.

vacant molecular orbital related to the α,β-unsaturated ketone moiety, −1.22 eV (LUMO), clearly shows that this C=C bond is much more electrophilic than the external C=C bond (0.52 eV, LUMO+1). Therefore, reactions involving a nucleophilic oxidant, such as HOO^-, should take place at the α,β-unsaturated ketone site, while reactions involving electrophilic peroxo-species, e.g. M–OOH or $M(\eta^2-O_2)$, should happen at the C=C external bond of (R)-carvone [13a,b].

Fig. 2 shows the comparison between γ-alumina and $[Al(H_2O)_6]^{3+}$ in the catalyzed epoxidation of (R)-carvone using aqueous 70 wt.% H_2O_2 as oxidant. The epoxidation using $[Al(H_2O)_6]^{3+}/H_2O_2$ proceeds exclusively on the electron-deficient C=C bond, indicating that the oxidizing species involved in this reaction is a nucleophile, such as HOO^-. On the other hand, the
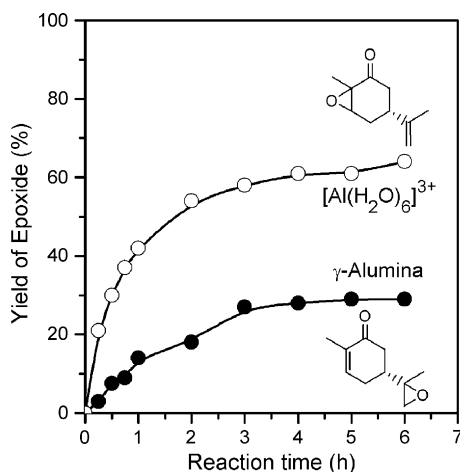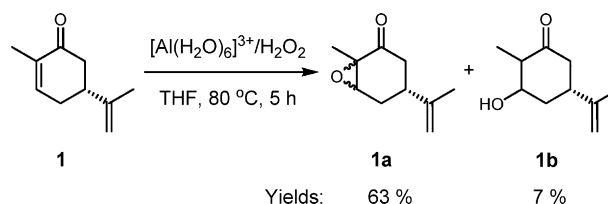
epoxidation of (R)-carvone employing the γ-alumina/H_2O_2 system occurs exclusively at the external and most nucleophilic C=C bond, involving indeed the electrophilic Al–OOH surface species [12,13].

The epoxidation of (R)-carvone using the $[Al(H_2O)_6]^{3+}/H_2O_2$ system is followed by the formation of the hydroxylated byproduct **1b** (Scheme 4). This product is formed by the Markownikoff addition of HO• or HOO• radicals to the α,β-unsaturated ketone moiety. Other minor byproducts are also detected in the epoxidation of (R)-carvone. The concentration of these byproducts was not high enough to ensure high-quality mass spectra for proper molecular elucidation.

Epoxidation of isophorone (Scheme 5) is followed by the formation of a much more complex mixture of byproducts. We have detected products from acid-catalyzed rearrangement of the isophorone oxide (**2b** and **2c**), ring-opening reaction (**2d**), and radical oxidation (**2e**). The optimal yield and selectivity of isophorone oxide (**2a**) are achieved carrying out the reaction at 60 °C. Apparently, two factors make the selectivity for epoxides, in the case of isophorone, lower than that observed for (R)-carvone. First, isophorone possesses a tertiary carbon at position 3. This facilitates radical addition, as well as nucleophilic addition at this site, due to the high-stability of the resulting tertiary radicals or ionic species conjugated with the ketone site. Moreover, the isophorone oxide is very sensitive to acid-catalyzed rearrangements [15]. In fact, the possibility to rearrange the isophorone oxide is proven to be an interesting method of preparing relevant and useful aldehydes for the synthesis of fragrances and synthetic flavors [15c].

Fig. 2. Comparison between $[Al(H_2O)_6]^{3+}$- and γ-alumina-catalyzed epoxidation of (R)-carvone. Reaction conditions: $[Al(H_2O)_6]^{3+}$ catalyzed epoxidation: (R)-carvone (25 mmol), di-n-butylether (internal standard, 12.5 mmol), 70 wt.% H_2O_2 (56 mmol), $Al(ClO_4)_3 \cdot 9H_2O$ (0.5 mmol), THF (solvent), 80 °C (reflux); γ-alumina-catalyzed epoxidation: (R)-carvone (25 mmol), di-n-butylether (internal standard, 12.5 mmol), 70 wt.% H_2O_2 (56 mmol), γ-alumina (200 mg), ethylacetate (solvent), 80 °C (reflux).
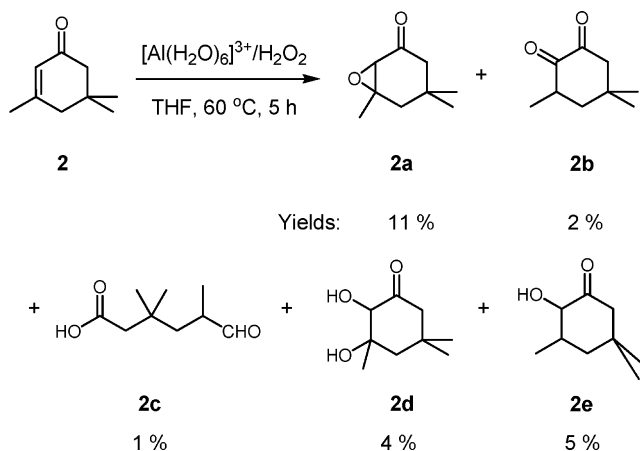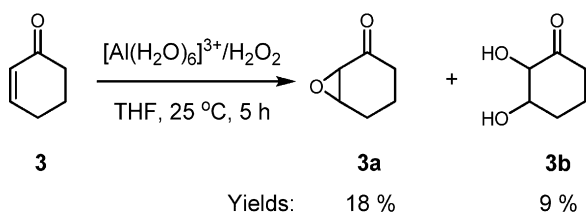
Yields: 63 % 7 %

Scheme 4. Oxidation of (R)-carvone.

Scheme 5. Oxidation of isophorone.

Scheme 6. Oxidation of cyclohexenone.

The epoxidation of cyclohexenone proceeds easily at 25 °C using $[Al(H_2O)_6]^{3+}/H_2O_2$. However, the epoxide **3a** is quite susceptive to acid-catalyzed hydrolysis, mainly because of the low steric hindrance to a nucleophilic attack on the oxirane ring site. As result, 2,3-diol **3b** is formed in large amount (Scheme 6).

Surprisingly, a totally different reactivity of the $[Al(H_2O)_6]^{3+}/H_2O_2$ system is observed when diethylmaleate – a compound containing a highly electron-deficient C=C double-bond – is used as substrate. The reaction yields no epoxide. Conversely, the main products isolated from this reaction are a mixture of diastereoisomers containing the tetrahydrofuran derivatives **4a**–**c**, as shown in Scheme 7. This reaction proceeds easily using the $[Al(H_2O)_6]^{3+}/H_2O_2$ system, achieving high conversion and high selectivity, even when 30 wt.% H_2O_2 is used (Table 2). The
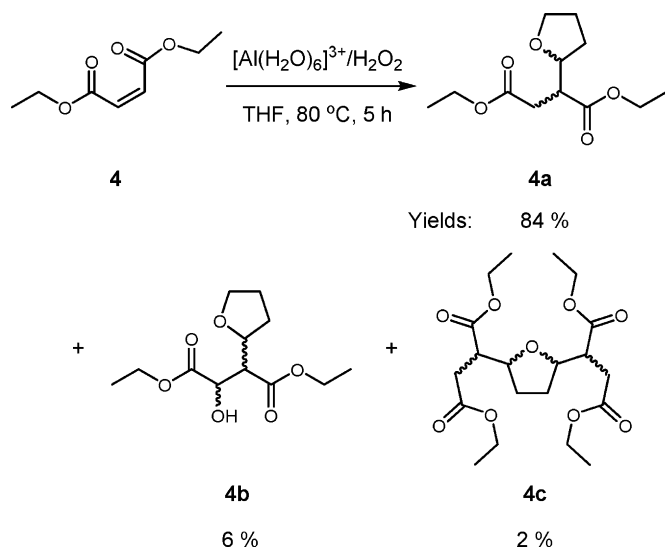
Scheme 7. Radical addition of THF to diethylmaleate.

Table 2
Reactivity of diethylmaleate towards the $[Al(H_2O)_6]^{3+}/H_2O_2$ system. Selectivity is given for **4a**.

t (h)	30 wt.% H_2O_2		70 wt.% H_2O_2	
	C (%)	S (%)	C (%)	S (%)
1	8	83	32	94
3	26	94	78	93
5	45	99	94	90
24	99	96	100	71

C: conversion, S: selectivity. Reaction conditions: diethylmaleate (25 mmol), di-n-butylether (internal standard, 12.5 mmol), 70 wt.% H_2O_2 (56 mmol), Al(ClO$_4$)$_3$·9H$_2$O (0.5 mmol), THF (solvent), 80 °C (reflux).

reaction in the absence of $[Al(H_2O)_6]^{3+}$ shows a conversion of 15% to **4a** and other products after 24 h.

A similar reaction involving the addition of THF, catalyzed by the $[Al(H_2O)_6]^{3+}/H_2O_2$ system, was also reported using dimethylzinc–air as radical initiator [16]. The dimethylzinc–air system promotes efficiently the addition of THF to several highly reactive radical acceptors, such as α,β-unsaturated N-aromatic aldehydes [16a], tosyl aldimines [16b], and α,β-unsaturated diesters [16c]. In these reactions, dimethylzinc is proposed to initiate radical reactions by forming a methyl radical, through reaction with air. The methyl radical is very energetic ($\Delta_D H = 429$ kJ mol^{-1}) and can abstract hydrogen at α-C in THF, forming the radical 2-tetrahydrofuranyl (2-THF)•. The abstraction of the hydrogen at α-C, instead of at β-C, is favored by the lower dissociation enthalpy of the α-C–H bond–$\Delta_D H$ (α-C–H) = 390 kJ mol^{-1} vs. $\Delta_D H$(β-C–H) = 405 kJ mol^{-1} [17]. The 2-tetrahydrofuranyl radical then adds to the substrate.

3.2. Mechanisms

The epoxidation of α,β-unsaturated ketones is a characteristic reaction of nucleophilic hydroperoxy or alkylperoxy anion species [18]. The site-selectivity of the $[Al(H_2O)_6]^{3+}/H_2O_2$ system for epoxidation of α,β-unsaturated ketones, as observed for (R)-carvone (Fig. 2), is then strong evidence that $[Al(H_2O)_6]^{3+}$ induce somehow nucleophilicity in H_2O_2. In a previous report [8], however, we proposed that the formation of electrophilic peroxo-species like $[Al(H_2O_2)_x(H_2O)_{6-x}]^{3+}$ activates H_2O_2 towards epoxidation of cis-cyclooctene [8]. Although the exchange of H_2O against H_2O_2 in $[Al(H_2O)_6]^{3+}$ can happen, the superior activity of the $[Al(H_2O)_6]^{3+}/H_2O_2$ system towards epoxidation of α,β-unsaturated ketones strongly suggest that this is not the preferential activation pathway for H_2O_2 in this system.

Our attempt to study $[Al(H_2O)_6]^{3+}/H_2O_2$ system in deuterated tetrahydrofuran (THF-d_8) by ^{1}H NMR spectroscopy showed that the proton exchange between H_2O and H_2O_2 is highly enhanced in the presence of catalytic amounts of $[Al(H_2O)_6]^{3+}$ (Fig. 3). The resonances of H_2O and H_2O_2 appear as a single, very wide and coalescent peak centered on 6 ppm for the spectrum acquired at 60 °C (Fig. 3). Table 3 summarizes the ^{1}H NMR signals observed for H_2O, H_2O_2, $[Al(H_2O)_6]^{3+}$ for the studied systems in THF-d_8 at 60 °C.

Table 3
Resonances found in ^{1}H NMR spectra of H_2O (0.14 mol L^{-1}), H_2O_2/H_3O^+ (0.14/0.05 mol L^{-1}), $[Al(H_2O)_6]^{3+}$ (0.03 mol L^{-1}) and $[Al(H_2O)_6]^{3+}/H_2O_2$ (0.14/0.03 mol L^{-1}) in THF-d_8 acquired at 60 °C.

System	δ H_2O (ppm)	δ H_2O_2 (ppm)	δ $[Al(H_2O)_6]^{3+}$ (ppm)
H_2O_2	2.49 (13.6)	9.27 (9.7)	–
H_2O_2/H_3O^+	2.50 (42.6)	9.27 (109.3)	–
$[Al(H_2O)_6]^{3+}$	2.44 (27.1)	–	9.21 (11.3)
$[Al(H_2O)_6]^{3+}/H_2O_2$	n.d.	n.d.	9.28 (25.3)

n.d.: not determined (peaks are coalescent); values between parentheses are the values of full-width at half-maximum, FWHM.
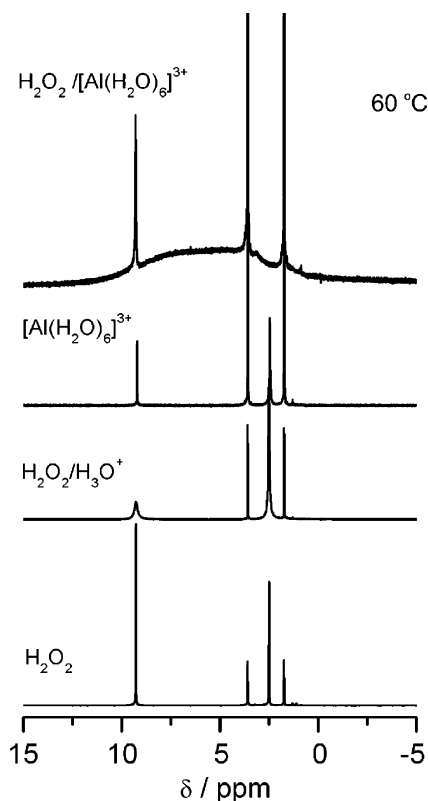
Fig. 3. ^{1}H NMR spectra of H_2O_2 (0.14 mol L^{-1}), H_2O_2/H_3O^+ (0.14/0.05 mol L^{-1}), [Al(H$_2$O)$_6$]$^{3+}$ (0.03 mol L^{-1}) and [Al(H$_2$O)$_6$]$^{3+}$/H$_2$O$_2$ (0.14/0.03 mol L^{-1}) in THF-d_8 acquired at 60 °C. The spectrum of the [Al(H$_2$O)$_6$]$^{3+}$/H$_2$O$_2$ system is 50 times magnified.

H_2O_2 dissolved in THF-d_8 shows a sharp resonance centered at 9.27 ppm (FWHM = 9.7 Hz) [19]. In this solution, the resonance of H_2O appears at 2.49 ppm (FWHM = 13.6 Hz). Addition of HNO_3 to the H_2O_2/THF-d_8 solution broadens the signals of H_2O_2 and of H_2O (FWHM = 109.3 and 42.6 Hz, respectively) due to the enhancement of proton exchanging between H_2O_2 and H_2O. The resonance of Al(III)-coordinated water appears at 9.21 ppm (FWHM = 11.3 Hz) for system [Al(H$_2$O)$_6$]$^{3+}$/THF-d_8, whereas the ^{1}H NMR signal for non-coordinated water is at 2.44 (FWHM = 27.1 Hz). When [Al(H$_2$O)$_6$]$^{3+}$ is added to the H_2O_2/THF-d_8 solution, the resonances assigned to H_2O_2 and non-coordinated H_2O appear as a very broad and coalescent resonance around 6 ppm. However, the resonance of Al(III)-coordinated water is only slightly affected. Variable-temperature ^{1}H NMR experiment (Fig. 4) clearly shows that H_2O_2 and non-coordinated H_2O are the species involved in the intermolecular proton exchange.

The presence of a well-defined resonance signal for water coordinated to Al(III) in the ^{1}H NMR spectra (Figs. 3 and 4) and the minor changes in the resonance signal of [Al(H$_2$O)$_6$]$^{3+}$ in the ^{27}Al NMR spectrum, as previously reported [8], show that the enhancement of the proton exchange between H_2O_2 and non-coordinated H_2O does not involve the first-coordination sphere.

Regarding the kinetics of octahedral ligand substitution, the exchange of water in the [Al(H$_2$O)$_6$]$^{3+}$ cation is slow. The rate constant of water exchanging is ca. 1 s^{-1} [20], which confers to [Al(H$_2$O)$_6$]$^{3+}$ a relative inertness to ligand exchange reactions. This inertness allows the water coordinated to Al(III) establishing hydrogen bond interactions with surrounding molecules in the second-coordination sphere. Although the second-coordination sphere of complexes is still not very explored in molecular chemocatalysis, several examples of its utilization in molecular recognition of molecules by biological receptors in solution, for
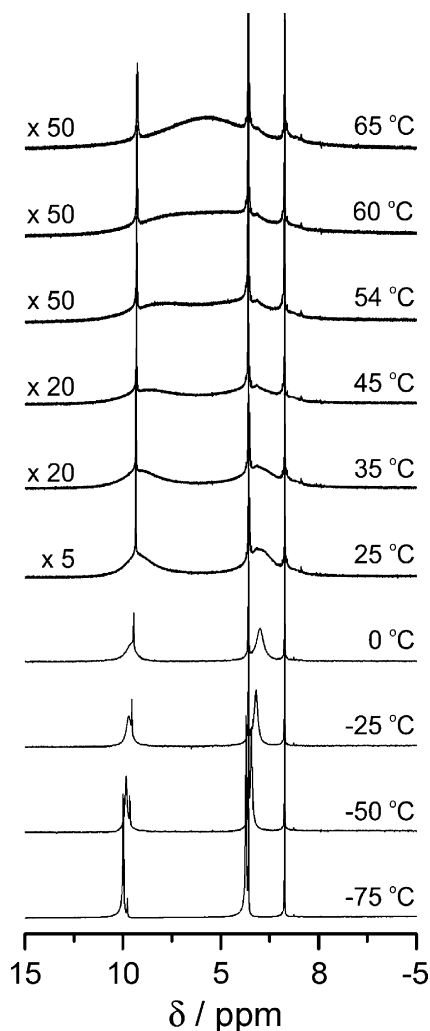

Fig. 4. Variable-temperature ^{1}H NMR spectra of [Al(H$_2$O)$_6$]$^{3+}$/H$_2$O$_2$ (0.14/0.03 mol L^{-1}) in THF-d_8.

enzymes, and for supramolecular assemblies are found [21]. In a seminal work, Wieghardt and co-workers [21] showed that the second-coordination sphere plays an import role for the recognition of several divalent cations of transition metals. Furthermore, they could also isolate and characterize the coordination compounds by single-crystal X-ray diffraction, in which the ligands were not directly bonded to the metal, but the ligand established non-covalent bonds with the water coordinated at the first-coordination sphere [21].

Fig. 5 shows the proposed mechanism for the [Al(H$_2$O)$_6$]$^{3+}$ catalyzed epoxidation of α,β-unsaturated ketones. Water coordinated to Al(III) exchanges slowly with the molecules in the second-coordination sphere, allowing then an effective interaction between [Al(H$_2$O)$_6$]$^{3+}$ and H_2O_2 through hydrogen bonds. As a result, the proton exchange H_a–O–H_a + H_b–O–O–H_b = $[(H_a)_2(H_b)O^+ + H_bOO^-]^{\ddagger}$ = H_a–O–H_b + H_a–O–O–H_b is enhanced. In the presence of α,β-unsaturated ketones, the reactive intermediate H_bOO^- is then trapped and affords α,β-epoxyketones.

The [Al(H$_2$O)$_6$]$^{3+}$/H$_2$O$_2$ system, however, does not only produce HOO$^-$ species. HO$^\bullet$ and HOO$^\bullet$ are also produced in a controlled fashion by the interaction between H_2O_2 and [Al(H$_2$O)$_6$]$^{3+}$ by a mechanism that remains to be elucidated. The main evidence of the formation of radicals is the catalyzed addition of THF to diethylmaleate (Scheme 7). Regarding the bond-formation free energies of these radical, HO$^\bullet$ is a much stronger radical than HOO$^\bullet$ (Scheme 8) [22]:
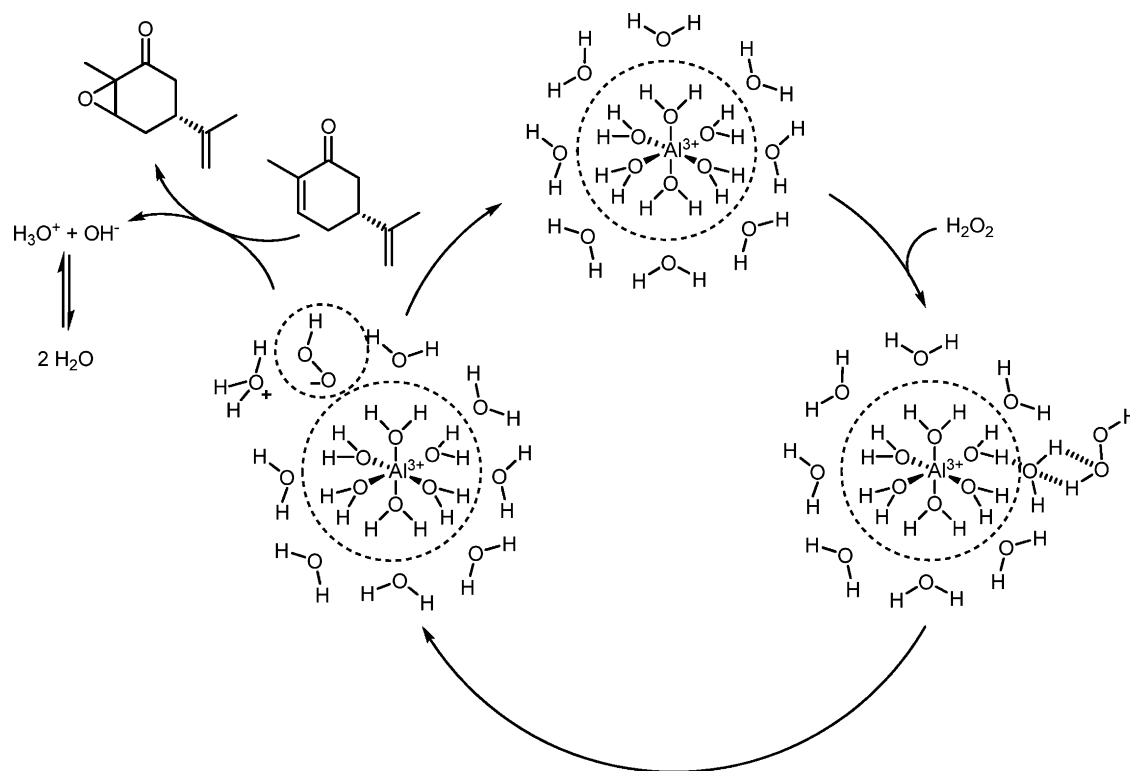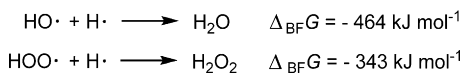
Fig. 5. Proposed mechanism of the $[Al(H_2O)_6]^{3+}$ catalyzed epoxidation of α,β-unsaturated ketones.

$$HO\cdot + H\cdot \longrightarrow H_2O \qquad \Delta_{BF}G = -464 \text{ kJ mol}^{-1}$$

$$HOO\cdot + H\cdot \longrightarrow H_2O_2 \qquad \Delta_{BF}G = -343 \text{ kJ mol}^{-1}$$

Scheme 8. Bond-formation free energies of $HO\bullet$ and $HOO\bullet$.

The abstraction of hydrogen from the α-C–H bond of THF involves the radical $HO\bullet$. The homolytic cleavage of this C–H bond requires 390 kJ mol^{-1}, which is only energetically affordable by a reaction with $HO\bullet$ [22]. However, the radical 2-tetrahydrofuranyl can make a termination reaction with $HO\bullet$ or $HOO\bullet$, resulting in products such as 2-hydroperoxy-tetrahydrofuran and γ-butyrolactone, as detected by GC–MS. In this manner, the use of THF as solvent has the advantage to trap the $HO\bullet$ and $HOO\bullet$ radicals, since it is much easier statistically that $HO\bullet$ or $HOO\bullet$ attack solvent molecules than the substrates, as the substrate concentration is much lower than the solvent concentration.

In our previous report of the epoxidation of *cis*-cyclooctene using the $[Al(H_2O)_6]^{3+}/H_2O_2$ system [8], all reactions without catalyst show low conversions of the olefin after 1 h, however, after 12 h the conversions were considerable. For instance, yields of 39 and 18% of cyclooctene oxide for blank reactions, respectively, in MeOH and in THF, were achieved. In contrast, such high yields of epoxides are not obtained in the blank reaction with α,β-unsaturated ketones. As verified by ^{13}C NMR experiments [8], the reaction between the solvent and hydrogen peroxide produces activated species, i.e. peracids or other organoperoxo intermediates. These species react with *cis*-cyclooctene forming cyclooctene oxide. With the results presented in this report, it is clear that the $[Al(H_2O)_6]^{3+}/H_2O_2$ system is not directly involved in the epoxidation of *cis*-cyclooctene. However, the $[Al(H_2O)_6]^{3+}/H_2O_2$ system, through a radical pathway, does convert the solvents, in some extension, into peroxo-species, which are then responsible for the epoxidation of *cis*-cyclooctene (Scheme 9).

Fig. 6 shows a comparison of the energy for the molecular orbitals π^*_{O-O} and σ^*_{O-O} of H_2O_2, 2-hydroperoxy-tetrahydrofuran, performic acid and hydroperoxide anion. The quantitative view about the energy of the molecular orbitals π^*_{O-O} and σ^*_{O-O} allows ranking the electrophilicity and nucleophilicity of these molecules. Regarding the electrophilicity – ranked by the energy of the vacant molecular orbital σ^*_{O-O} – the following order can be established: performic acid > H_2O_2 > 2-hydroperoxy-tetrahydrofuran $\ggg$ HOO$^-$. On the order hand, when the nucleophilicity is addressed – ordered by the energy of the occupied molecular orbital π^*_{O-O} – the ranking is HOO$^-$ $\ggg$ H_2O_2 > 2-hydroperoxy-tetrahydrofuran > performic acid. The higher nucleophilicity of performic acid than 2-hydroperoxy-tetrahydrofuran explains our former results [8], in which higher yields of cyclooctene oxide were obtained in the blank reactions when using methanol instead of THF as solvent [8]. Actually, DFT calculation shows that 2-hydroperoxy-tetrahydrofuran is a weaker electrophile than performic acid. Therefore, 2-hydroperoxy-tetrahydrofuran is less reactive towards *cis*-cyclooctene epoxidation. Furthermore, this organic peroxide is also a slightly poorer nucleophile than H_2O_2. By this means, it is not
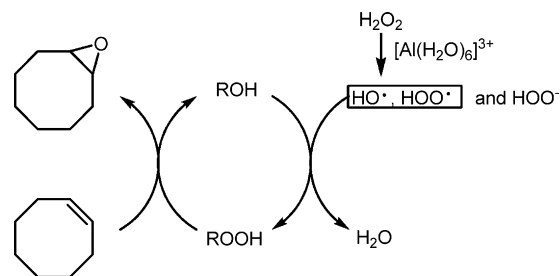
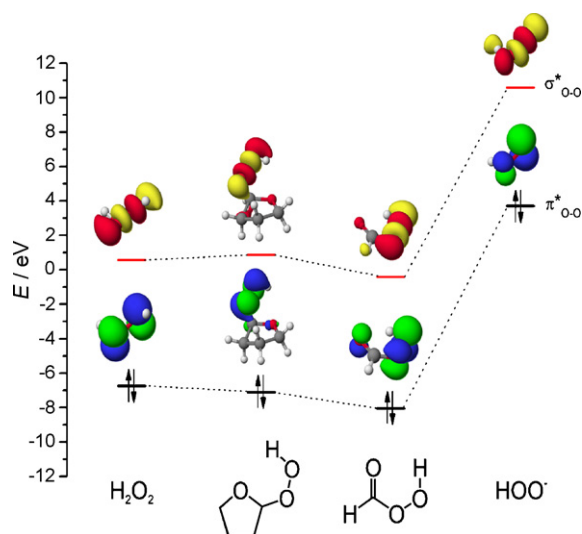**Scheme 9.** Mechanism for epoxidation of *cis*-cyclooctene by $[Al(H_2O)_6]^{3+}/H_2O_2$ system.

Fig. 6. Energies of the molecular orbitals σ^*_{O-O} and π^*_{O-O} calculated using DFT with B3LYP method and 6-31G* basis set.

expected that 2-hydroperoxy-tetrahydrofuran would play any role as oxidant in the epoxidation of α,β-unsaturated ketones.

4. Conclusions

Homogeneously catalyzed epoxidation of α,β-unsaturated ketones using simple aluminum salts and aqueous H_2O_2 is possible. $[Al(H_2O)_6]^{3+}$ induces H_2O_2 to act as a nucleophile towards α,β-unsaturated ketones, yielding α,β-epoxyketones as major products. The induction of nucleophilicity in H_2O_2 is a consequence of the enhance of proton exchange between H_2O and H_2O_2 in the second-coordination sphere of $[Al(H_2O)_6]^{3+}$. The induction of nucleophilicity in H_2O_2 by $[Al(H_2O)_6]^{3+}$ reveals that non-covalent interactions in the second-coordination sphere can be also used in molecular catalysis. In fact, these interactions are already known from enzymes and biological receptors. However, it is important to point out that this "exotic" induction caused by $[Al(H_2O)_6]^{3+}$ is only possible due to the non-redox chemistry of aluminum and the inertness of Al(III) to ligand exchange.

Surprisingly, for highly activated substrates, such as α,β-unsaturated diesters, radical addition of THF to the C=C bond takes place with high selectivity and high yield, providing 2-(THF)-derivatives. The solvent THF has a positive role as radical scavenger, since the attack of HO• or HOO• radicals is statistically prone to occur on THF molecules. This partially protects the substrates against radical oxidation, which allows the $[Al(H_2O)_6]^{3+}/H_2O_2$ system to provide epoxides as major products in the case of α,β-unsaturated ketones. The radical oxidation of the solvent affords electrophilic peroxo-species, which can act as an oxygen donor towards nucleophilic olefins, such as *cis*-cyclooctene, providing epoxides.

Acknowledgments

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