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N-Hydroxyphthalimide (NHPI)/lead tetraacetate reactions with cyclic and acyclic alkenes

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The reactions between phthalimide *N*-oxyl (PINO) radical and cyclohexene, cyclooctene, and *trans*-3-hexene were carried out. The PINO radical has been *in situ* generated from its hydroxylimide parent, *N*-hydroxyphthalimide (NHPI), applying two approaches: using metallic salts, such as lead tetraacetate and cerium (IV) ammonium nitrate (CAN), and a "metal free" system in which the role of metallic species has been undertaken by antraquinone. In the former case, the strong influence of lead tetraacetate (or CAN) on the NHPI's reactivity, induce two different channels for the reaction pathway, radical and non-radical, a complex mixture of both saturated and unsaturated diadducts together with the corresponding monoadduct being formed. This behavior will not occur in the case of PINO generation in non-metallic systems, in this case the reaction pathway proceed exclusively *via* radical mechanism, with the formation of monoadducts as sole products. Copyright © 2008 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this paper.

Keywords: *N*-hydroxyphthalimide (NHPI); phthalimide *N*-oxyl (PINO) radical; lead tetraacetate; adducts formation; oxidation

INTRODUCTION

The development of efficient catalytic system for selective organic transformation is currently one of the challenging tasks in synthetic organic chemistry.

In recent years, *N*-hydroxyphthalimide (NHPI) has been recognized as a valuable catalyst for the aerobic oxidation of various organic compounds under mild conditions.[1] It is generally assumed that these oxidations proceed *via* intermediate phthalimide *N*-oxyl (PINO) radical, able to abstract a hydrogen atom from the organic substrate.[2] The newly formed carbon centered radical then readily reacts with dioxygen, to give ultimately oxygenated compounds, Scheme 1.

The generation of the PINO radicals from its precursor NHPI, can be achieved by using various methods, including the well-known "Ishii catalytic system" which implies the use of Co(II) or Mn(II) salts.[3] However, in the last years, due to metallic toxicity and high expense, researchers have been concentrated on developing non-metallic systems, which becomes frequently used. These metal free systems able to generate NHPI includes compounds such as: α,α-azoisobutyronitrile,[4] peracids,[5] dioxirane,[6] NO_2,[7] anthraquinones,[8] and others.

Among the metallic salts used for the PINO radical generation, lead tetraacetate was used for the first time, early on 1964 by Lemaire and Rassat,[9] using EPR spectroscopy, Scheme 2. PINO presents a triplet signal with a hyperfine coupling constant in *t*-BuOH of $a_N = 4{,}36\,G$, which is smaller than the constants of other nitroxyl radicals.[10] The *g*-factor in PINO is larger than that of other nitroxyl radicals; one explanation could be due to the presence of acyl groups linked to the nitrogen atom.

Koshino *et al.*,[2] reported that the molar absorptivity of PINO generated from $NHPI/Pb(OAc)_4$ in acetic acid, is $1.36 \times 10^3\,L\,mol^{-1}\,cm^{-1}$ at λ_{max} 382 nm, Fig. 1.

We have carried out further explorations into NHPI's chemistry, particularly in the PINO's reactions with cyclic and acyclic alkenes. To check if NHPI/lead tetraacetate presents indeed a particular behavior in reaction with alkenes, we have used different systems to generate PINO radical, either metallic [by using cerium (IV) ammonium nitrate (CAN)] and non-metallic (by using antraquinone). On the other hand, lead tetraacetate has been used to generate besides PINO (**1**), see Scheme 3, another nitroxyl radical that is, benzotriazole-*N*-oxyl (**2**; BTNO), Scheme 3, from its parent hydroxylamine (1-hydroxybenzotriazole, HBT) then reacting with alkenes, **4**, **5**, and **6**, Scheme 3.

EXPERIMENTAL

General information

High-resolution mass spectroscopy was carried out on a Jeol SX 102 instrument, used for both electron ionization (EI) and fast atom bombardment (FAB) ionization techniques. Nuclear magnetic resonance spectra were acquired using a Bruker DPX 400 instrument. The spectra were calibrated where possible to the signals of tetramethylsilane or the small quantity of $CHCl_3$ present in $CDCl_3$, typically used as the standard solvent for these

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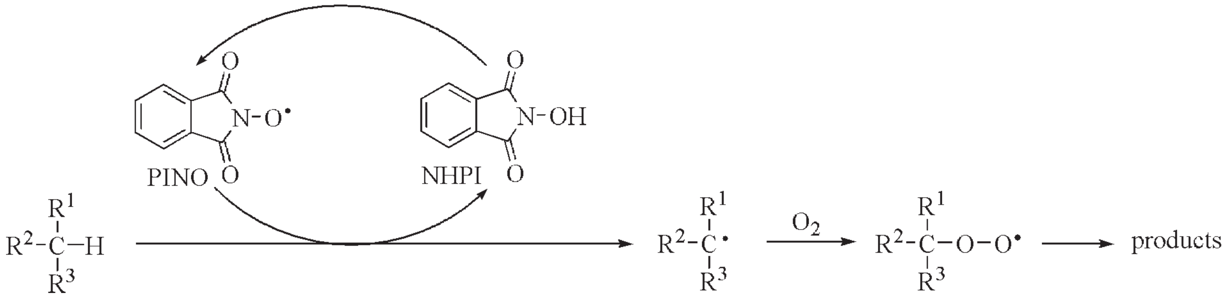
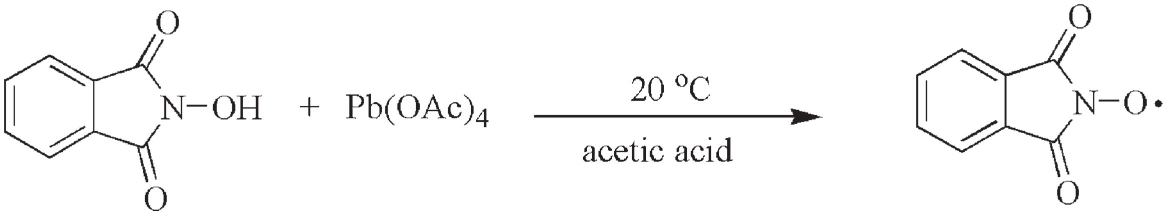


Scheme 1.



Scheme 2.

experiments. All ^{2}H NMR spectra were obtained in CHCl$_3$. The T_1 relaxation times of the ^{2}H signals were ~100 ms and the delay time between pulses was therefore chosen to be 2 s ($>> 5 \times T_1$) to ensure accurate integration of these signals. Flash column chromatography on silica was used as a standard purification procedure using Fluka Kieselgel 60, 0.04–0.063 mm particle size. Thin layer chromatography was used where possible as a standard procedure for monitoring the course and rate of a given reaction. TLC plates used were Merck aluminum backed sheets with Kieselgel 60 F254 silica coating.

trans-3,4-Dideuteriohex-3-ene was prepared following a modified literature method.[11] In a round-bottom flask fitted with a reflux condenser slurry of LiAlD$_4$ (1.4 g, 33.6 mmol) in 30 mL anhydrous diglyme was prepared. To the slurry, 3-hexyne (2.4 g, 28.6 mmol) was added dropwise via syringe. The heterogeneous mixture was heated to 150 °C for 6.5 h. The mixture was allowed to cool to room temperature, the flask was placed in an ice-bath, and then carefully quenched by dropwise addition of D$_2$O (7 mL), D$_2$O/DCl (20% DCl, 3 mL) and finally HCl (6 N, 10 mL). The dideuterated compound was extracted into hexadecane, and the hexadecane layer was washed with water (5×8 mL), dried with Na$_2$SO$_4$ and filtered. Distillation gave 1.24 g (14.4 mmol, 50% yield) of the title compound as a clear, colorless liquid. ^{1}H NMR (CHCl$_3$) δ 1.99 (q, 4H, CH$_2$), 1.00 (t, 6H, CH$_3$); ^{13}C NMR (CHCl$_3$) δ 130.4 (t), 25.4, 13.9. Deuterium incorporation at the vinylic site was >99% as determined by ^{1}H NMR.

Alkene reaction with PINO and BTNO radicals

In our first investigation of the mechanism of reaction of PINO with three alkenes, we oxidized the NHPI with lead tetraacetate or CAN, at room temperature in deoxygenated acetonitrile, one of

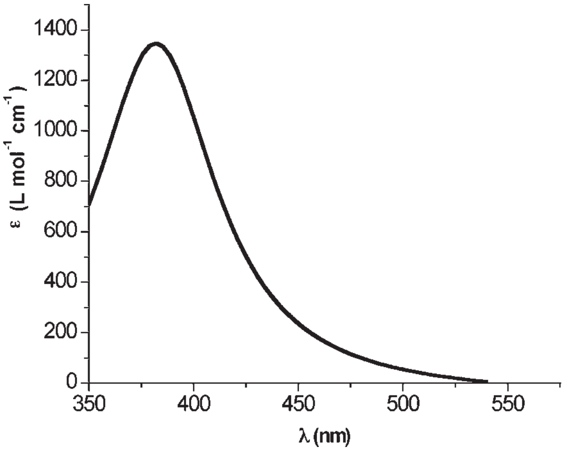
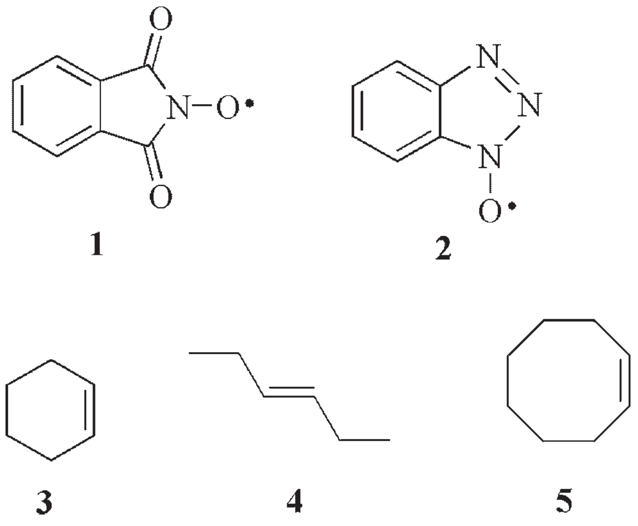
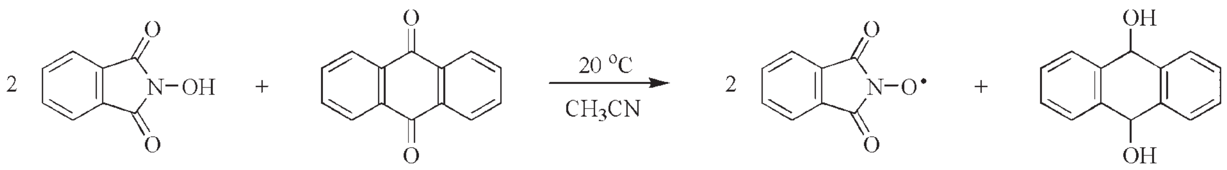


Figure 1. UV/Vis spectrum of PINO (generated from NHPI and lead tetraacetate) radical in acetic acid



Scheme 3.



Scheme 4.

the most suitable solvent for these reagents, which provide both reasonable solubilities for NHPI and $Pb(OAc)_4$ and easy product workup. The alkene, NHPI, and $Pb(OAc)_4$ (or CAN) were always reacted together at molar ratios of 10:2:1. The alkene (0.50 mM) and NHPI in 5 mL of acetonitrile were added to 5 mL of acetonitrile solutions of $Pb(OAc)_4$ (or CAN). Shorter after mixing (less than 15 min), the acetonitrile and excess alkene were removed under reduced pressure. The mono- and di-PINO alkene adducts were separated and purified by preparative TLC using hexane/ethyl acetate (2:1, v/v) as an eluent.

The same procedure was followed in the case of BTNO (generated from its parent hydroxylamine with lead tetraacetate) reactions with alkenes, **3**, **4**, and **5**.

The next step to generate PINO radical was to employ a "metal free" system. We have chosen to use antraquinone, a chemical system which was shown to form PINO radicals,[8] according with the Scheme 4.

The antraquinone/NHPI/alkene experiments were carried out under oxygen-free conditions, the molar ratio between reagents: 1:4:10. The products were separated in the usual way.

RESULTS AND DISCUSSION

In our previous work,[12] we have used the TEMPO, di-*tert*-butyliminoxyl, and PINO radicals, to investigate the competition between the two possible reaction mechanisms on the three symmetric alkenes that is, abstraction–addition or addition–abstraction mechanisms as the first step in these reactions.

The reaction mechanism was identical for all the studied reaction systems, except the NHPI/$Pb(OAc)_4$/alkene system, when it was found that the major product was a diadduct in which two PINO moieties had added across the double bond of the alkene, Scheme 5. Interestingly, the diadduct formation was found only in the case of the reaction when PINO was generated by lead tetraacetate.

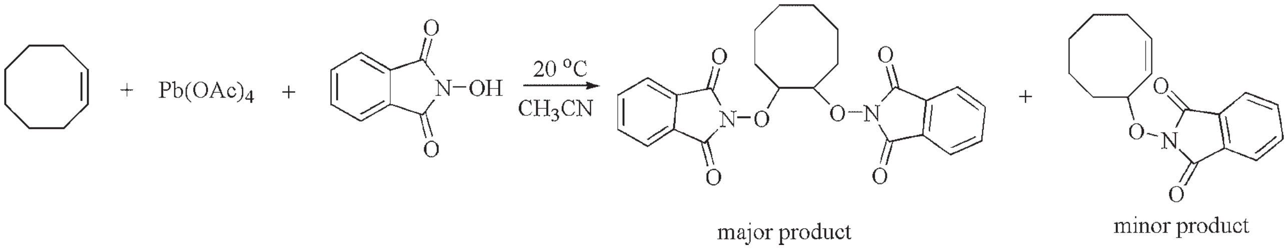
In this paper, we extend the study of PINO radical reactions with the three alkenes, by comparison the mechanisms when PINO was generated either in the presence or absence of metallic species as cocatalyst. Moreover, further information on the reaction mechanisms involved in these reactions could be acquire by analyzing the products composition when instead PINO radical, another nitroxyl radical, BTNO (generate by using lead tetraacetate) has been employed, and comparing with those identified in the case of NHPI/lead tetraacetate system.

In one set of experiments, we have synthesized the *trans*-3,4-dideuteriohex-3-ene by the lithium aluminum deuteride ($LiAlD_4$) reduction of 3-hexyne, and then react with NHPI/$Pb(OAc)_4$ system. Deuterium label was chosen because, for both potentially mechanisms involved, there would be no primary deuterium kinetic isotope effect, and would considerable simplify the interpretation of the ^2H NMR spectra of the resulted products. The deuterium labeled alkene, NHPI, and $Pb(OAc)_4$ were used at molar ratio 10:2:1, at room temperature in deoxygenated acetonitrile. Products yield based on NHPI were (**a**) 12%, (**b**) 10%, (**c**) 2.5% (NHPI reacted $= 12 + 2 \times 10 + 2 \times 2.5 = 37\%$), Scheme 6.

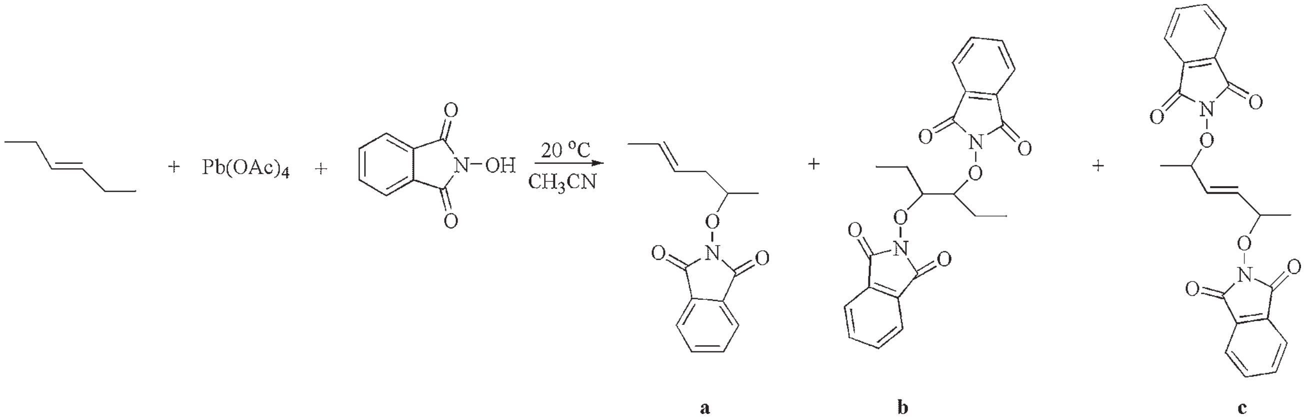
In another set of experiments, to ensure that the diadduct **c** (Scheme 6) is indeed present in the reaction mixture, a larger scale reaction was performed, employing unlabeled alkene, *trans*-hex-3-ene in reaction with NHPI/$Pb(OAc)_4$ system, in sufficient quantity to obtain X-ray crystallographic structure of the unexpected unsaturated diadduct, see Supporting Information. The crystallographic structure for the diadduct **c** has been deposited to the Cambridge Crystallographic Data Centre, deposition number CCDC 669756.

All the unlabeled alkenes were afterwards reacted with the PINO and BTNO radicals, generated *in situ* by using different cocatalysts. The percentages of monosubstituted and disubstituted adducts are shown in Table 1.

The reactions of both **1** and **2** radicals (when generated in a "metal free" system) with alkenes **3**, **4**, and **5** are forming exclusively monoadducts (Table 1, entries 1, 5, 7, 10, 12, and 15). The diadducts are formed after the reaction of PINO [when generate by using $Pb(OAc)_4$ or CAN] with the alkenes **3**, **4**, and **5** (Table 1, entries 3, 4, 8, 9, 13, and 14). BTN radical behave similarly with PINO, when it is generate within a metallic system



Scheme 5.



Scheme 6.

Table 1. Percentages of monosubstituted and disubstituted adducts

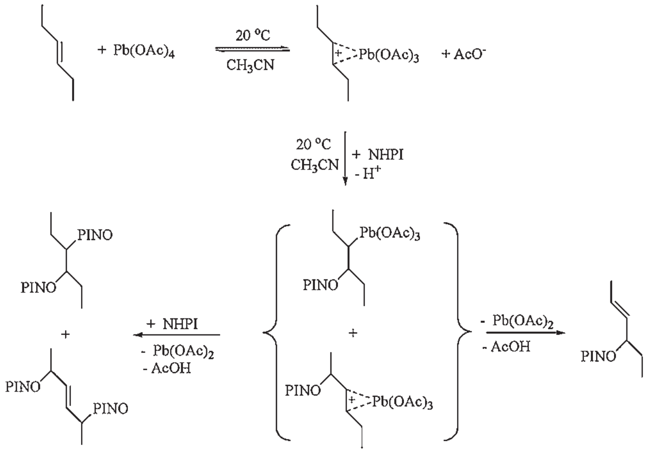
No.	Radical	Alkene	% Monosubstituted adduct	% Disubstituted adduct
1	**1** (antraquinone)	3	100	0
2	**1** (CuCl)*	3	100	0
3	**1** ($Pb(OAc)_4$)	3	97	3
4	**1** (CAN)	3	98	2
5	**2** (antraquinone)	3	100	0
6	**2** ($Pb(OAc)_4$)	3	97	3
7	**1** (antraquinone)	4	100	0
8	**1** ($Pb(OAc)_4$)	4	60	40
9	**1** (CAN)	4	68	32
10	**2** (antraquinone)	4	100	0
11	**2** ($Pb(OAc)_4$)	4	76	24
12	**1** (antraquinone)	5	100	0
13	**1** ($Pb(OAc)_4$)	5	40	60
14	**1** (CAN)	5	43	57
15	**2** (antraquinone)	5	100	0
16	**2** ($Pb(OAc)_4$)	5	88	12

* Data from Ref.[13]

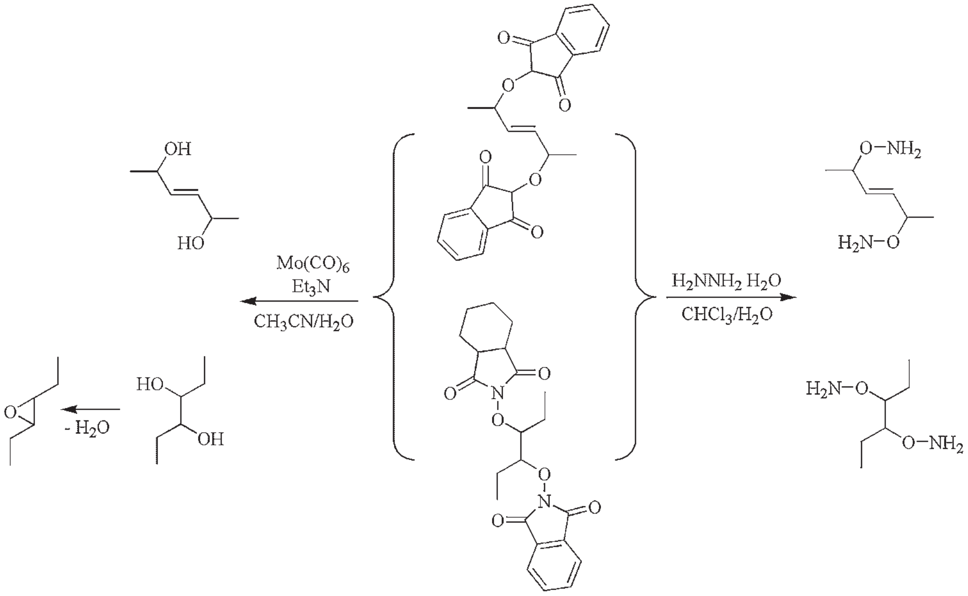
($Pb(OAc)_4$), Table 1, entries 6, 11, and 16. However the yields of the diadducts formation in this case are slightly lower. The diadducts formation, which is evident in the NHPI/$Pb(OAc)_4$ or NHPI/CAN cases, could be explained by considering the coexistence of both radical and non-radical mechanisms, in sharp contrast with the NHPI/antraquinone reaction with alkenes, when only the radical mechanism is operative.

Moreover, in the case of using NHPI/$Pb(OAc)_4$ system, in reaction with acyclic alkenes, the diadduct formation is a more complex process. For this reaction system, the saturated diadduct is not the sole diadduct product, its formation is accompanied, surprisingly by the presence of unsaturated diadduct, which it is not found in the cyclic alkenes reaction with NHPI/$Pb(OAc)_4$.

Although, it is generally accepted that PINO radical is the active species resulted from NHPI activation, in the NHPI/$Pb(OAc)_4$ system, the intervention of some form of Pb(IV) in reaction introduces two quite different channels for product formation,



Scheme 7.



Scheme 8.

viz., radical and non-radical reactions. It was expected that PINO to generate even higher yields of monoadducts than BTNO, because at least two reasons.

PINO is known to be more stable,[14] an issue which matter if we take into account the limited stability of the aminoxyl radicals, and the second is the energy value of the O–H bond that the two aminoxyl radicals formed after H-abstraction. The BDE (O–H) of NHPI is larger than that of HBT, that is, 88 kcal mol^{-1} *versus* 85 kcal mol^{-1}, respectively, and therefore the H-abstraction with NHPI is thermodynamically more favored. The relative equal percents founded could be explained by the existence of "non-radical" route, dictated in fact by the presence of metallic species, that is, Pb and Ce, in detriment of "radical" route, responsible only for the monosubstituted product formation. Others,[15,16] signaled the ability of PINO radical to adds to the double bond, and the evidence for the saturated diadduct formation,[11] but the formation of the unsaturated diadduct which accompanied the saturated one, as far as we are concerned, is reported here for the first time. The proposed reaction mechanism for the *trans*-hex-3-ene reaction with NHPI/Pb(OAc)$_4$ which formed mono-, disaturated-, and diunsaturated diadducts is based on that proposed for the lead tetraacetate oxidation of cyclohexene to *cis*- and *trans*-1,2-diacetoxy-cyclohexanes and 3-acetoxycyclohexene[17,18] Scheme 7. The first step of this reaction involves the hex-3-ene/lead triacetate cation complex formation, then the reaction pathway follow the both routes, radical and non-radical, giving a mixture of monoadduct and diadducts, the entropic and enthalpic effects playing the crucial role for this kind of transformations. In the alkenes reactions, there is a partial "freeing" or a partial "freezing" of a bond rotation in the transition state, linked with the enthalpic effects. The alkene/lead triacetate cation complex formation is supported by the fact that the geometry of the molecules is the driving force that leads to the 1,2-disubstitued compounds, in the cyclic alkenes reactions, this adduct represent in fact the main product. The same route of the reaction is followed when NHPI/CAN is employed the Ce(IV) substituting the role of Pb(IV).

The resulted PINO diadducts could prove their synthetic utility, being readily converted into corresponding diols or dihydroxylamines species,[19] Scheme 8.

CONCLUSIONS

The reactions of alkene/NHPI/antraquinone systems, occurs via radical mechanism, the sole products being the corresponding monoadducts.

In sharp contrast, the alkene/NHPI/Pb(OAc)$_4$ and alkene/NHPI/CAN generates complex mixtures of mono- and diadducts, as an effect of interpenetration between radical and non-radical reaction mechanisms, caused by intervention of Pb(IV) and Ce(IV) species.

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