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Metal free in situ formation of phthalimide *N*-oxyl radicals by light-induced homolysis of *N*-alkoxyphthalimides

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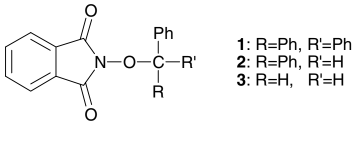
Abstract—Irradiation of *N*-triphenylmethyloxy- or *N*-diphenylmethyloxy phthalimide is reported to result in the formation of phthalimide *N*-oxyl radical (PINO), which is able to initiate and propagate oxidative radical chain reactions of hydrocarbons.

Selective catalytic oxidation of hydrocarbons with molecular oxygen is a primary essential tool in organic synthesis and in industrial chemistry.[1] In the past years it has been shown that *N*-hydroxyphthalimide (NHPI) is an efficient catalyst for the oxidation of organic compounds by molecular oxygen under mild conditions.[2] This reaction occurs via the intermediacy of carbon-centered radicals from the substrate produced by the phthalimide *N*-oxyl radical (PINO), which must be formed in situ from NHPI in order to initiate the oxidative radical chains.[3] This is generally achieved by using Co(II) or Mn(II) salts (Ishii conditions).[4,5] The transition metal salt appears to have a two-fold function: it generates PINO radicals, which abstract hydrogen atoms from the hydrocarbon substrate thus initiating free-radical chains and, at the same time, it catalytically decomposes the hydroperoxide formed during the oxidation reaction. The main disadvantage in using transition metal catalysts concerns the potential adverse effects with regard to the environment. For this reason, metal-free NHPI-based oxidation of C–H bonds with dioxygen by using nonmetallic compounds, such as α,α-azoisobutyronitrile,[6] peracids,[7] dioxirane,[7a] NO_2,[8] and anthraquinones[9] have also been proposed. These nonmetallic mediators behave as the radical initiators by inducing the formation of PINO radicals and are, thus, are consumed during the reaction and are not recoverable.

It is well-known that *N*-alkoxylamines (TEMPO-R), derived from the combination of 2,2,6,6-tetramethyl-1-piperidinyloxyl with resonance stabilized alkyl radicals R, are unstable and undergo thermal fragmentation at the carbon–oxygen bond affording the starting radicals. This is due to the weakness of the C–O bond that in the case of $R\equiv C(CH_3)Ph_2$ has a bond dissociation enthalpy (BDE) value of only 21 kcal/mol.[10]

Based on this, we explored the viability of *N*-alkoxylamines derived from NHPI as radical initiators to form PINO radicals in order to promote the oxidation of hydrocarbons using molecular oxygen as terminal oxidant and oxygen atom source. It is known that *N*-alkoxyphthalimides can afford alkoxy radicals under standard radical conditions (Bu_3SnH/AIBN).[11] In no cases, however, formation of the PINO radical by cleavage of C–O bond has been documented. We turned our attention to three different PINO-R, namely, *N*-triphenylmethyloxy- (**1**), *N*-diphenylmethyloxy- (**2**) and *N*-benzyloxyphthalimide (**3**) in which the oxygen atom is bound with resonance stabilized alkyl groups (see Scheme 1).[12]



Scheme 1.

Keywords: Oxidation; Nitroxide; Free radical; EPR; Catalysis.

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Warming up to 100 °C, inside the cavity of an EPR spectrometer, *tert*-butyl benzene solutions of compounds **1**–**3** (0.1 M), both in the presence and absence of oxygen, did not lead to the appearance of any EPR signals. These results are not unexpected considering that acyl hydroxylamines have a higher O–H bond strength than the corresponding alkyl hydroxylamines[13] (e.g., BDE(O–H) is 87 kcal/mol in NHPI and 70 kcal/mol in TEMPOH), and the strengths of the O–C bonds are conceivably parallel to those of the corresponding O–H bond.

On the other hand, room temperature irradiation with filtered light ($\lambda > 300$ nm)[14] of a mercury lamp of an aerobic benzene solution containing **1** or **2** gave rise to the formation of a strong EPR signal of the PINO radical ($a_N = 4.3$ G, $a_{2H} = 0.45$ G, $g = 2.0073$, see Fig. 1). Thus, these two *N*-alkoxyphthalimides, in their photoexcited state, easily undergo cleavage of the O–C bond even at room temperature.[15] Compound **3**, instead, does not show any EPR signal under irradiation; this suggests that the photostability of *N*-alkoxyphthalimides is strongly dependent on the nature of the alkyl moiety attached to the oxygen atom.

In order to verify if in situ formation of PINO radicals by light can be usefully employed to catalyze hydrocarbon oxidations, we measured the rate of oxygen consumption when **1** or **2** (3.0 mM) were photodecomposed in the presence of cumene 5.0 M (see Fig. 2). The reaction was followed by monitoring the oxygen uptake in a closed system with a method based on the determination of the EPR line width variation of a nitroxide spin probe dissolved in solution.[16]

While in the absence of light cumene (RH) was completely inert toward oxidation, irradiation ($\lambda > 300$ nm) resulted in a sudden increase of oxygen uptake, thus, indicating that the oxidation took place according to a mechanism whose putative steps are depicted in Scheme 2. Oxygen consumption was proportional to the intensity of incident light, on the concentration of both **1** and **2**, and was completely stopped when turning off the light.

Figure 2 also reports the recorded trace when using di-*tert*-butyl peroxide (3 mM) as photoinitiator. In this case oxygen consumption was significantly slower than found in the presence of **1** or **2**. The larger rate of oxidation observed when using the alkoxyamine photoinitiators can be attributed both to a more efficient initiation and to a faster propagation due to the presence of the NHPI catalyst formed during the continuous photolysis. Actually, addition of an equimolar amount of NHPI to di-*tert*-butylperoxide resulted in an acceleration of oxygen consumption; this, however, remained slower than found when either **1** or **2** was present.

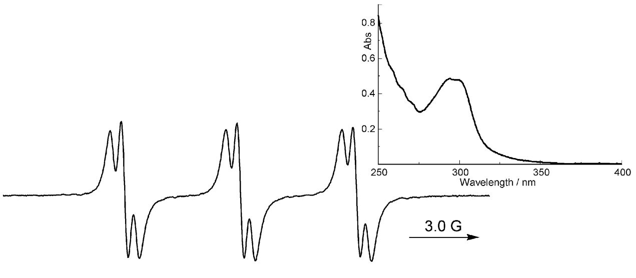


Figure 1. Room temperature EPR spectrum of the PINO radical produced by UV irradiation ($\lambda > 300$ nm) of **1** in benzene solution. Inset: UV–visible spectrum of **1** (0.22 mM in cyclohexane).

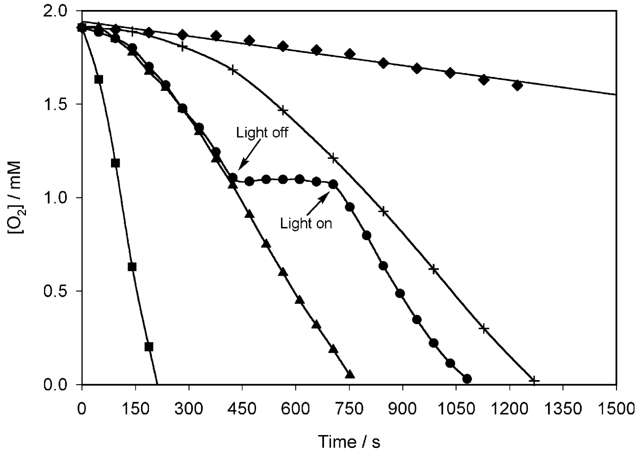
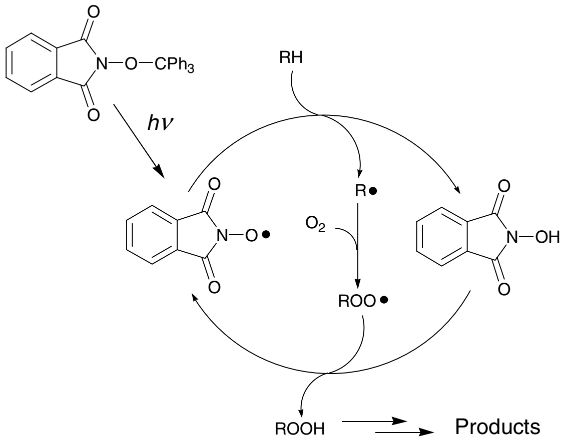


Figure 2. Oxygen consumption during photoinduced ($\lambda > 300$ nm) autoxidation of cumene 5 M (at 40 °C) in benzene: (◆) di-*tert*-butyl peroxide 3 mM; (+) di-*tert*-butyl peroxide 3 mM and NHPI 3 mM; (▲, ●) compound **1** 3 mM; (■) same conditions of the last two experiments but with a double intensity of incident light (similar results were obtained when using compound **2**; data not shown).



Scheme 2.

The ability of compounds **1** or **2** to promote oxidation of hydrocarbons was evaluated by studying the oxidation of benzyl alcohol chosen as model substrate. Photoirradiation of benzyl alcohol (0.1 M) for 4 hours with the filtered light ($\lambda > 300$ nm) of a mercury lamp in *tert*-butyl benzene solution containing **1** or **2** 10 mol % at 25 °C under continuous oxygen flux, resulted in the formation of benzaldehyde in a 95 % yield.[17] Under aerobic conditions $Ph_3C^{\bullet}$ or $Ph_2C^{\bullet}$ radicals are expected to be trapped by O_2 to give oxygenated products.[18] Actually, GC analysis revealed the presence of triphenylmethyl alcohol or diphenylmethyl alcohol as byproducts, thus confirming the cleavage of O–C bond of the starting *N*-alkoxyphthalimides during the photoirradiation.

The main disadvantage of free radical processes involving NHPI as catalyst is represented by the self-decomposition of PINO under the reaction conditions, especially at the high temperatures (>80 °C) required for the oxidation of less reactive substrates. For this reason the determination of the life time of the PINO radical has been the object of several kinetic studies carried out under different conditions with the aim of understanding the factors responsible for its depletion. By using EPR spectroscopy, some of us reported that PINO decays by first order kinetics with a $k_d = 0.1\ s^{-1}$,[3a] presumably due to fragmentation at one of the carbonyl-nitrogen bonds, similarly to what previously suggested by Perkins et al. for another acyl-nitroxide.[19] This result is apparently in contrast with a previous paper by Masui et al.[20] who reported second order decay for electrochemically generated PINO radicals. Second order decay was also reported by Espenson et al.[21] when PINO was generated by oxidation of NHPI using a strong oxidant such as $Pb(OAc)_4$. However, the rate constant obtained $k_d = 0.6\ M^{-1}\ s^{-1}$ (both in acetic acid and in CH_3CN) was much smaller than that reported by Masui et al. ($k_d = 24.1\ M^{-1}\ s^{-1}$ in CH_3CN). Espenson attributed the short life time of the PINO radical found by us[3a] to some byproducts, formed during photodecomposition of dicumyl peroxide to acetophenone, with which PINO may react.[21]

In order to check this suggestion, we repeated the kinetic experiments by following the self-decay in benzene of the EPR signals of PINO produced by photolysis of compounds **1** or **2**, directly inside the EPR cavity (Fig. 3). This represents a cleaner reaction system since this does not require the use of peroxide radical initiators. Under these conditions, the decay of PINO recorded after stopping the sample irradiation, showed good first order kinetics both in absence and presence of oxygen,[22] with a rate constant, k_d, of $0.12\ s^{-1}$. This value is in excellent agreement with the one ($0.1\ s^{-1}$) measured previously by EPR when producing PINO photochemically from NHPI and dicumylperoxide.[3]

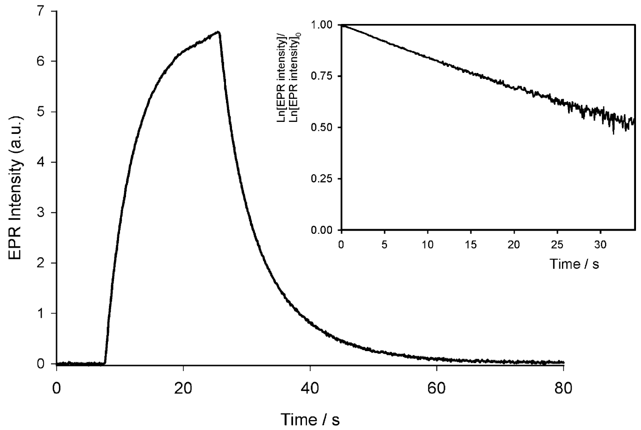


Figure 3. EPR trace of the growth and the decay of PINO photolytically generated from a 0.1 M solution of **2** in *tert*-butyl benzene, at 298 K. Insert: first order plot of the decay curve observed when shutting off the light.

In conclusion we have shown that irradiation of *N*-triphenylmethyloxy- (**1**) or *N*-diphenylmethyloxy phthalimide (**2**) results in the formation of PINO radicals capable of initiating and propagating oxidative radical chains of hydrocarbons.

Acknowledgments

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22. While in oxygen-free solvents the alkyl radicals R formed by the cleavage of the O–C bond could rapidly recombine with the nitroxide to give back the starting compound, thus reducing the life time of PINO, in the presence of O_2 the alkyl radicals are rapidly converted into peroxy radicals. The experimental observation that the life time of PINO is independent of the O_2 concentration present in the sample suggests that the decay process is not determined by the fate of the alkyl radical.