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Molecule-induced homolysis of *N*-hydroxyphthalimide (NHPI) by peracids and dioxirane. A new, simple, selective aerobic radical epoxidation of alkenes

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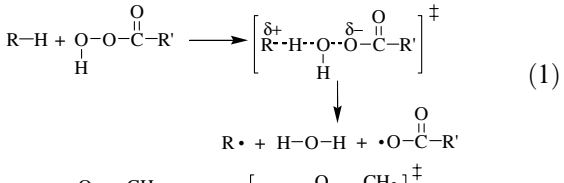
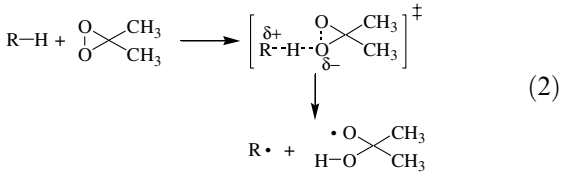
Abstract—Evidences are reported concerning the molecule-induced homolysis of NHPI by peracids and dioxirane; their combination can be utilized for the aerobic free-radical epoxidation of alkenes with selectivity quite different from the well-known epoxidation by peracids.

Some years ago we reported evidences that the oxidation of a variety of organic compounds (hydrocarbons, alcohols, ethers, aldehydes, etc.) by dioxiranes[1] and peracids[2] can be explained by radical mechanism in clear contrast with the widely accepted[3,4] mechanism of 'concerted oxenoid oxygen insertion'. Our interpretation[1,2] involves a 'molecule-induced homolysis' in which the transition states are related to the hydrogen abstractions leading to radical pairs (Eqs. 1 and 2).



(1)



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Keywords: *N*-Hydroxyphthalimide; Epoxides; Alkenes; Peracids.
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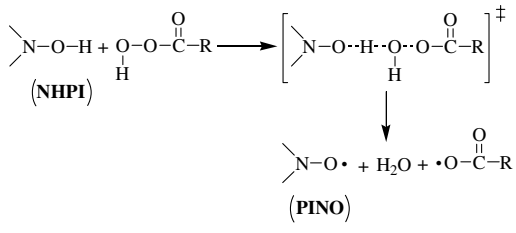
The controversial mechanisms, particularly with dioxiranes, are intriguing since the fast coupling of the radical pair in the solvent cage leads to the same reaction products of the oxygen insertion mechanism and only few radicals can escape from the cage giving typical free-radical reactions. Very recently this controversy has been resumed in the case of dioxiranes: one report[5] categorically states that 'a radical-type process has been experimentally and theoretically rigorously discounted', whereas another research group reports[6] that 'theoretical calculations support both alternative reaction mechanisms as feasible reaction pathways for the oxygenation of C–H bonds by dioxirane' and also the experimental results suggest that 'the process splits into two reaction pathways with different transition states leading to the O–O homolysis and the O-atom insertion, respectively, the incidence of each process depending on the structure of the dioxirane'.[6] What is not clear in this last interpretation is the reason why the coupling of the radical pair (Eq. 2), leading to the same products of the oxygen insertion mechanism, does not occur in the solvent cage.

We have ascribed the driving force for Eqs. 1 and 2 to the high bond dissociation enthalpies (BDE) of the O–H bonds formed in hydrogen abstraction, which are particularly effective with the weaker C–H bonds (tertiary alkyl, benzyl, RCO–H, etc.). Recently we have evaluated[7]

the BDE value of the O–H bond in NHPI (88.1 kcal/mol); this value suggests to us that peracids and dioxiranes could give induced homolysis of NHPI (Eqs. 3 and 4) under mild conditions generating the phthalimido-*N*-oxyl (PINO) radical which plays a key role in the aerobic oxidations catalyzed by NHPI.[7,8]



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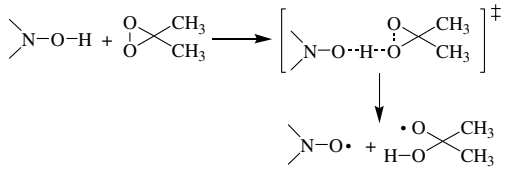
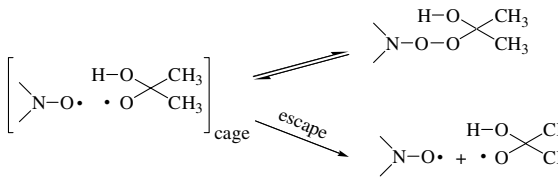


(4)

The hypothetical coupling of the radical pairs generated in Eqs. 3 and 4 is very likely reversible, so that the PINO radical and the acyloxyl (Eq. 5) or the alkoxyl (Eq. 6) radicals can escape from the solvent cage giving the typical free-radical reactions.

(5)



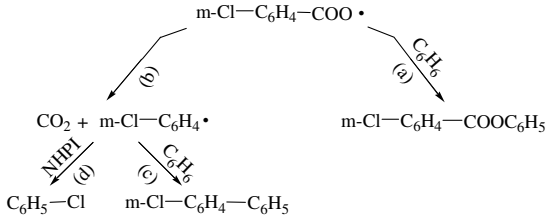
(6)

Spectroscopic and chemical evidences, actually, support this assumption. The EPR spectrum of the PINO radical[7,9] was readily observed simply by adding at rt NHPI to a solution of *m*-chloroperbenzoic acid in acetonitrile ($a(2H) = 0.46$ G; $a(N) = 4.77$ G) or dimethyldioxirane in acetone ($a(2H) = 0.44$ G; $a(N) = 4.70$ G), as it is shown in Figure 1.

HPLC and GC analysis of the products arising from *m*-chloroperbenzoic acid and NHPI in acetonitrile at rt reveal the presence of *m*-chlorobenzoic acid as main reaction product (~90%) and chlorobenzene (~10%) as by-product. Moreover the same reaction in benzene solution at rt always leads to *m*-chlorobenzoic acid as the main reaction product, whereas phenyl *m*-chlorobenzoate and *m*-chlorobiphenyl are the by-products.

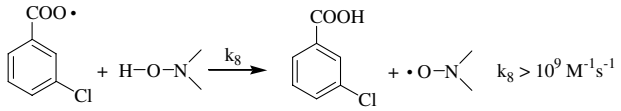
Figure 1. EPR spectrum of PINO obtained by mixing NHPI (0.01 M) with *m*-CPBA (0.01 M) in CH_3CN at room temperature.

The only possible explanation for these last by-products and for chlorobenzene is the formation of the acyloxyl radical (Eq. 3), which reacts according to Eq. 7a–d.



(7)

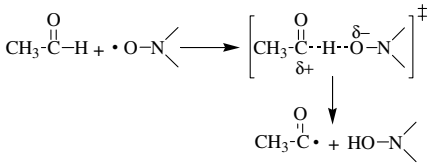
m-Chlorobenzoic acid is the main reaction product because it is formed by hydrogen abstraction from NHPI by the acyloxyl radical (Eq. 8).



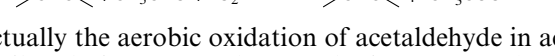
(8)

We expect Eq. 8 to be a very fast reaction on the basis of the known rate constants for the hydrogen abstraction by the peroxyl radical (7.2×10^3 M^{-1} s^{-1})[7] and alkoxyl radical (10^9 M^{-1} s^{-1});[10] Eq. 8 is more exothermic respectively of 22 and 6 kcal/mol than the corresponding hydrogen abstractions by the peroxyl and alkoxyl radicals.

Our recent results[7,8] have shown that the hydrogen abstractions from C–H bonds by the PINO radical are considerably faster than the corresponding hydrogen abstractions by peroxyl radicals, in spite of the same enthalpy variation; a more marked polar effect in the reaction by the PINO radical is, in our opinion,[11] a factor which contributes to this behavior. These results, combined with the induced homolysis of NHPI by peracids (Eq. 3) have suggested to us the possibility to utilize the aerobic oxidation of aldehydes, catalyzed by NHPI, for the epoxidations of alkenes by peracids generated 'in situ' under mild conditions (Eq. 10).



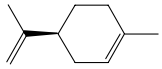
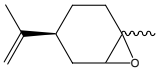
(9)



(10)

Actually the aerobic oxidation of acetaldehyde in acetonitrile solution at rt and atmospheric pressure of oxygen in the presence of alkenes and catalytic amount of NHPI leads to the corresponding epoxides. No oxidation occurs under the same conditions in the absence of NHPI, clearly indicating that Eq. 9 plays a key role in the aerobic epoxidation. However the selectivity observed with several alkenes is quite different from that well-known[12] with peracetic acid (Table 1).

Table 1. Epoxidation of olefins by aerobic oxidation of acetaldehyde, catalyzed by NHPI[a]

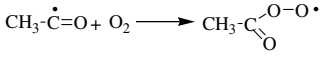
Olefin	Catalyst (%)	Reaction time (h)	Yield of epoxide (%)
1-Hexene	NHPI (10)	24	61
1-Hexene	NHPI (10)	48	70
1-Octene	NHPI (10)	24	80
1-Decene	NHPI (10)	24	81
1-Decene	NHPI (10)	48	94
1-Decene	—	24	—
1-Dodecene	NHPI (10)	23	81
Methyl oleate	NHPI (10)	24	—
cis-2-Hexene	NHPI (10)	24	—
Cyclooctene	NHPI (10)	27	96
Cyclooctene	—	24	—
	NHPI (10)	14	
R(+)-limonene			*cis* (67), *trans* (33)
2-Methyl-2-butene	NHPI (10)	24	—

[a] General procedure: a solution of 5 mmol of olefins, 15 mmol of acetaldehyde and 0.5 mmol of NHPI in 10 mL of acetonitrile was stirred at rt in atmospheric pressure of O_2 for the time reported in the table; the known epoxides were isolated by flash chromatography and characterized by NMR and MS spectra (identical with authentical samples).

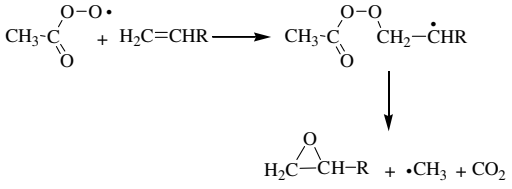
Thus α-olefins and cyclic olefins give good yields of epoxides, whereas internal acyclic olefins are unreactive under the same conditions; the internal acyclic olefins are, on the contrary, more reactive than α-olefins[12] with peracetic acid and also the stereochemistry for the epoxidation of limonene is different: in the aerobic epoxidation, 67% of the cis isomer and 33% of the trans isomer are formed, whereas 41% of the cis isomer and 59% of the trans isomer are the reaction products with peracid; moreover 2-methyl-2-butene is 300 times more reactive than propene with peracetic acid, whereas it is unreactive towards the aerobic epoxidation.

This selectivity clearly suggests that the epoxidation by aerobic cooxidation of aldehyde/olefin previously reported[13] occurs by a different mechanism since internal olefins are readily epoxidated.

Peracetic acid, therefore, does not appear to be responsible for the aerobic epoxidation of the alkenes, catalyzed by NHPI. Our interpretation involves the reaction of the acyl radical with O_2 (Eq. 11) followed by the addition of the acylperoxyl radical to the olefin and decomposition of the radical adduct (Eq. 12).

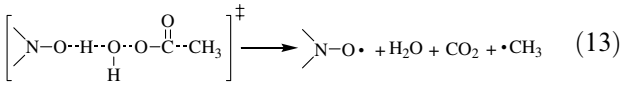


(11)



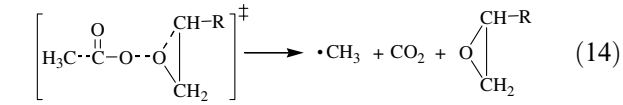
(12)

Acetaldehyde revealed to be much more effective than benzaldehyde for the epoxidation of alkenes; a possible explanation is that the CH_3–C bond could be involved in the transition state of the induced homolysis of NHPI by the CH_3COOOH (Eq. 13) contributing to lower the activation energy.



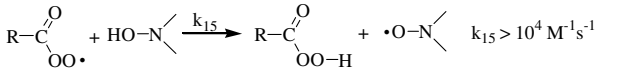
(13)

An analogous transition state should not occur with perbenzoic acid, as shown by Eq. 7a, due to the stronger Ph–C bond (that is reflected in the quite different rates of decarboxylation of $PhCOO^{\cdot}$ and $CH_3COO^{\cdot}$, respectively, $\sim 10^6$ and $\sim 10^9\ s^{-1}$). A transition state (Eq. 14) analogous to Eq. 13 could be involved for Eq. 12.



(14)

The fact that the internal acyclic olefins are unreactive towards the aerobic epoxidation could suggest that peracetic acid is not formed according to Eq. 15.



(15)

We have not evaluated the rate constant k_{15}, but we expect a value higher than $10^4\ M^{-1}\ s^{-1}$ because we have determined a value of $7.2 \times 10^3\ M^{-1}\ s^{-1}$ for the hydrogen abstraction from NHPI by *t*-BuOO$^{\cdot}$ radical and Eq. 15 is about 5 kcal/mol more exothermic (the BDE values of the O–H bonds are, respectively, 88 and 93 kcal/mol for *t*-BuOO–H and RCOOO–H). The high rate constant of k_{15} suggests that peracetic acid is actually formed according to Eq. 15 in competition to the addition of the olefin[12] (Eq. 12), but its reaction with NHPI (Eqs. 3 and 13) is faster than the epoxidation of alkenes.

The aerobic cooxidation of acetaldehyde and benzyl derivatives catalyzed by NHPI has also been reported,[14] but the authors did not realize that peracids give the induced homolysis of NHPI generating the PINO radical (Eq. 3), which plays the key role in the aerobic oxidation.

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