Transition metal salts catalysis in the aerobic oxidation of organic compounds
Thermochemical and kinetic aspects and new synthetic developments in the presence of *N*-hydroxy-derivative catalysts

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Dedicated to Professor Renato Ugo on the occasion of his 65th birthday.

Abstract

The catalytic system formed by Mn(II) and Co(II) or Cu(II) nitrates has shown to be particularly effective for the oxidation of ketones and aldehydes by molecular oxygen under mild conditions. The process has a general character, but it is particularly selective for the oxidation of alkyl–aryl ketones to aromatic carboxylic acids, alkyl-cyclopropyl ketones to cyclopropane carboxylic acids and cycloalkanones to dicarboxylic acids. Mn salt plays a key role in this catalysis, which catalyses the enolisation of the carbonyl compound and initiates a free-radical redox chain with oxygen by an electron-transfer process. Co and Cu salts alone are inert, but they exalt the catalytic activity of the Mn salt, being more effective in the decomposition of the hydroperoxides.

The same metal salt complexes, associated with TEMPO revealed particularly effective for the aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones under mild conditions (with air or oxygen at room temperature and atmospheric pressure); the mechanism of the catalysis is discussed.

Thermochemical and kinetic investigations by EPR spectroscopy, concerning *N*-hydroxy compounds, have allowed to evaluate the Bond Dissociation Enthalpies (BDE) of several O–H bonds and the absolute rate constants for the formation of the phthalimide-*N*-oxyl (PINO) radical from *N*-hydroxyphthalimide (NHPI) and for the hydrogen abstraction from several C–H bonds by the PINO radical. The thermochemical and kinetic results have allowed us to explain the opposite catalytic behaviour of the two nitroxyl radicals, TEMPO and PINO, the former being an inhibitor of free radical processes, the latter a promoter of free-radical chain, and to develop new selective processes concerning the aerobic oxidation of alcohols, amines, amides, silanes and the substitution of heteroaromatic bases.
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Keywords: Transition metal salt catalysis; Oxidation of organic compounds; TEMPO; *N*-hydroxyphthalimide; Oxygen

1. Introduction

The catalysis by transition metal salts plays a fundamental role in the autoxidation of organic compounds

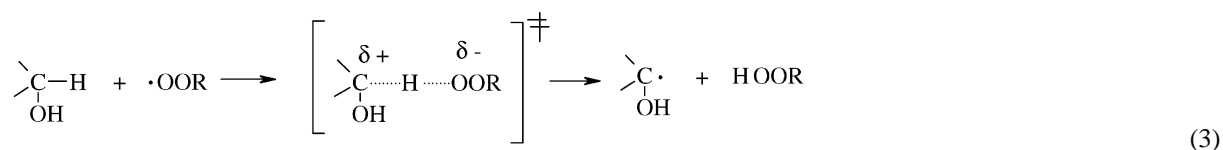* Corresponding author. Fax: +39-02-23993080.
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involving processes of great industrial interest. Free-radical redox chains, such as those described by Eqs. (1) and (2), are considered important in this catalysis [1].

$$ROOH + Co(II) \rightarrow RO^\bullet + OH^- + Co(III) \qquad (1)$$

$$ROOH + Co(III) \rightarrow ROO^\bullet + H^+ + Co(II) \qquad (2)$$
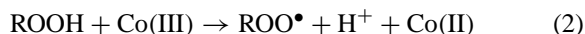
Recently we have reported [2–6] that the combination of Mn(II) nitrate with Co(II) or Cu(II) nitrates is a particularly effective catalytic system for the selective aerobic oxidation of carbonyl compounds under mild conditions. This catalysis appears to be of particular interest for the oxidation of alkyl–aryl ketones to aromatic carboxylic acids [2–4], of alkyl-cyclopropyl ketones to cyclopropane carboxylic acid [4] and of cycloalkanones to dicarboxylic acids [5,6] (adipic acid was obtained from cyclohexanone with high selectivity at atmospheric pressure of oxygen and room temperature).

The secondary alcohols corresponding to the ketones are substantially inert under these conditions; this behaviour could appear contradictory, considering that the alcohols are much more reactive than the ketones in uncatalysed autoxidation, mainly due to polar effects in hydrogen abstraction by peroxyl radicals (Eq. (3))

dation of primary and secondary alcohols to aldehydes and ketones with a variety of oxidants, in order to carry out the aerobic oxidation of the mixture of cyclohexanone and cyclohexanol to adipic acid. TEMPO, however, is a stabilised and persistent [7] radical, which reacts quickly with a variety of other radicals (Eq. (4)) inhibiting free-radical chain processes.

$$(4)$$

Thus, the combination of Mn(II) and Co(II) or Cu(II) nitrates with TEMPO revealed to be particularly effective for the aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones, while the further oxidation of the carbonyl compounds, which easily occurs under the same conditions in the absence of TEMPO, is completely inhibited. This behaviour is related to the fact that the oxidation of alcohols, catalysed by TEMPO, is an ionic process [8], while the oxidation of the carbonyl compounds, catalysed by Mn(II) and Co(II) or Cu(II) nitrates is a free-radical redox chain. However, the aerobic oxidation of primary and secondary alcohols

$$(3)$$

The mechanism of the catalysis by Mn(II) and Co(II) or Cu(II) nitrates, however, well explains the much higher reactivity for the aerobic oxidation of cyclohexanone compared to cyclohexanol and in general of ketones compared to the corresponding secondary alcohols, as it will be discussed later on.

Now the industrial production of adipic acid, one of the most important intermediates for nylon, is based on the autoxidation of cyclohexane to a mixture of cyclohexanone and cyclohexanol at low conversion in order to have high selectivity, followed by the nitric acid oxidation of the ketone and alcohol mixture.

We have considered the possibility to combine the metal salt with nitroxyl radical catalysis, such as TEMPO, which was well-known to catalyse the oxi-

to aldehydes and ketones, catalysed by these metal salts, revealed to be one of the most convenient among the numerous reactions developed for this purpose, particularly for practical applications, due to the simple and mild conditions, the general character and the high selectivity [9].

Recently an interesting aerobic oxidation of organic compounds, catalysed by N-hydroxyimides, such as N-hydroxyphthalimide (NHPI), and transition metal salts, was developed particularly by the Ishii group [10]. A key step of this catalysis appears to be the hydrogen abstraction from C–H bonds by the phthalimide-N-oxyl (PINO) radical, generated "in situ" from NHPI (Eq. (5)).

$$ \text{(5)} $$
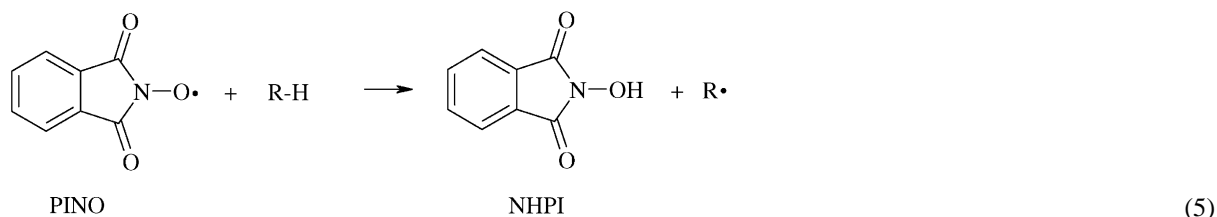
Even though TEMPO and PINO are formally quite similar (both are *N*-oxyl radicals), the catalytic behaviour is opposite: PINO induces free-radical chain processes, while TEMPO inhibits these processes. Since the enthalpic effect is the factor determining such opposite trend, we undertook a thermochemical investigation, concerning the bond dissociation enthalpy (BDE) of the O–H bond in *N*-hydroxy derivatives and a kinetic evaluation for the formation of the PINO radical and the hydrogen abstraction reactions. The thermochemical and kinetic results well explain the opposite catalytic behaviour of the PINO and TEMPO radicals in the aerobic oxidation of organic compounds allowing, on this basis, the development of new synthetic processes for the selective oxidation of alcohols, amines, amides, silanes and for the homolytic substitution of heteroaromatic bases by nucleophilic carbon-centred radicals.

2. Aerobic oxidation of ketones, catalysed by Mn(II) and Co(II) or Cu(II) nitrates

2.1. Oxidation of alkyl–aryl ketones to aromatic carboxylic acids

The conversion of alkyl–aryl ketones to carboxylic acids appears to be particularly interesting for general purposes and for the industrial applications, due to the ready availability of ketones by electrophilic aromatic acylation with a variety of acylating reagents (acyl chlorides, anhydrides, carboxylic acids) and catalysts (AlCl$_3$, FeCl$_3$, homogeneous and heterogeneouos protic acids, zeolites) [11], or by autoxidation of alkylaromatics with primary alkyl groups. A variety of reagents have been utilised for the conversion of alkyl–aryl ketones to aromatic carboxylic acids: sodium bromite [12], *t*-BuOOH-Re$_2$O$_7$ [13], sodium nitrite-pyridinium poly(hydrogen fluoride) [14],

tetrabutyl ammonium periodate [15], KOH [16], C$_6$F$_5$I(OCOCF$_3$)$_2$ [17], disodium nitrosylpentacyanoferrate [18], NaOCl [19].

The aerobic oxidation of alkyl–aryl ketones to aromatic carboxylic acids, in which the alkyl group is methyl, a primary or a secondary group (ketones with tertiary alkyl groups are completely inert), catalysed by Mn(II) and Co(II) or Cu(II) nitrates, revealed to be particularly effective and selective under mild conditions [2–4].

The origin of our interest for this catalytic oxidation was related to the investigation for improving the industrial process for the production of vanillin by aerobic oxidation of lignin [20]. 4-Acetyl-veratrole was a by-product of this oxidation; it was utilised for the industrial production of veratric acid by NaOCl oxidation [19] (Eq. (6)).

$$ \text{(6)} $$
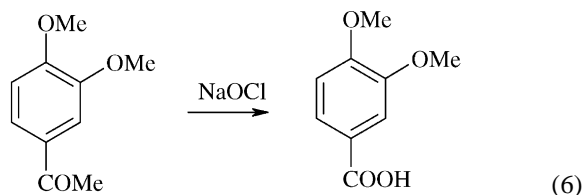
The selectivity of Eq. (6) was not particularly high [19] due to the formation of nuclear chlorinated aromatic by-products. The investigation of a variety of transition metal salts for the aerobic oxidation of 4-acetyl-veratrole to veratric acid has allowed us to develop an efficient and selective catalytic system, based on the combination of Mn(NO$_3$)$_2$ with Co(NO$_3$)$_2$ or Cu(NO$_3$)$_2$ under mild conditions (70–100 °C) and atmospheric pressure of O$_2$ [2–4]. The catalytic system has shown a quite general character not only for the oxidation of alkyl–aryl ketones (Table 1), but also for all kinds of ketones with, at least, one C–H bond in α-position to the carbonyl group; it is much more convenient than all the other processes of oxidation before mentioned.

Table 1
Aerobic oxidation of alkyl–aryl ketones, Ar-CO-R to carboxylic acids Ar-COOH, catalysed by metal nitrates[a]
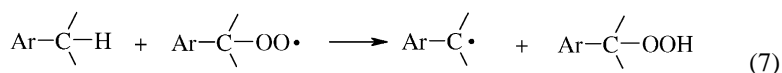
Ar	R	Catalyst (nitrates)	Conversion(%)	Ar-COOH selectivity (%)
Ph	Me	Mn–Co	97	95
Ph	Me	Mn–Cu	96	96
Ph	Et	Mn–Cu	100	98
Ph	Et	Mn–Co	98	97
Ph	CHMe$_2$	Mn–Co	100	95
Ph	CMe$_3$	Mn–Co	–	–
4-Me-C$_6$H$_4$	Me	Mn–Cu	98	93
4-Me-C$_6$H$_4$	Me	Mn–Co	96	91
4-Et-C$_6$H$_4$	Et	Mn–Co	94	89
4-Me$_2$CH-C$_6$H$_4$	Me	Mn–Co	96	85
4-MeO-C$_6$H$_4$	Me	Mn–Cu	100	95
4-MeO-C$_6$H$_4$	Me	Mn–Co	100	96
2-MeO-C$_6$H$_4$	Me	Mn–Co	100	91
3,4-(MeO)$_2$-C$_6$H$_3$	Me	Mn–Cu	100	96
3,4-(MeO)$_2$-C$_6$H$_3$	Me	Mn–Co	100	98
4-Cl-C$_6$H$_3$	Me	Mn–Co	93	95
1-Naphth	Me	Mn–Co	100	97
1-Naphth	n-Bu	Mn–Cu	100	92
1-Naphth	CHMe$_2$	Mn–Co	100	97
2-MeO-6-Naphth	Et	Mn–Cu	100	94
C$_{10}$H$_6$-1,5	Me, Me	Mn–Co	93	1,5-C$_{10}$H$_6$(COOH)$_2$, 94
Ph-C$_6$H$_4$	Me	Mn–Co	100	95
Ph-C$_6$H$_4$	Et	Mn–Co	100	96
4-C$_6$H$_4$-C$_6$H$_4$-4′	Me, Me	Mn–Co	92	4-HOOC-C$_6$H$_4$-C$_6$H$_4$-COOH-4′, 90

[a] Ketone (10 mmol), Mn(NO$_3$)$_2$·6H$_2$O (0.2 mmol), Co(NO$_3$)$_2$·4H$_2$O (0.2 mmol) or Cu(NO$_3$)$_2$·3H$_2$O (0.2 mmol) in 20 ml of acetic acid with O$_2$ at atmospheric pressure at 100 °C for 6 h.

The mechanism of the oxidation must account for the following results:

(i) *t*-Butyl-aryl ketones are completely inert under conditions in which methyl, ethyl and isopropyl-aryl ketones are easily oxidised to aromatic carboxylic acids, which means that a C–H bond in α-position to the carbonyl group is necessary for the oxidation to occur.

$$Ar-\overset{/}{\underset{\backslash}{C}}-H \ + \ Ar-\overset{/}{\underset{\backslash}{C}}-OO\bullet \ \longrightarrow \ Ar-\overset{/}{\underset{\backslash}{C}}\bullet \ + \ Ar-\overset{/}{\underset{\backslash}{C}}-OOH \tag{7}$$

(ii) When alkyl and acyl groups are both present in the aromatic ring, such as in methyl, ethyl and isopropyl-acetophenone, only the acetyl group is oxidised in the presence of the couple Mn(II) and Co(II) nitrates, while only the oxidation of the alkyl group occurs in the presence of the Co(II) salt at higher temperature. The latter is the classical autoxidation process, in which the selectivity is determined by the hydrogen abstraction by the peroxyl radical (Eq. (7)); enthalpic and polar effects promote the hydrogen abstraction from the benzylic C–H bond.

(iii) The manganese salt is necessary for the oxidation to occur; Co(II) and Cu(II) alone are inactive, but they exalt the catalytic activity of the Mn(II) salt;

the nitrates proved to be particularly effective among the different salts (Table 2).

(iv) The overall stechiometry of the oxidation is given by Eq. (8).

$$Ar\text{-}CO\text{-}\overset{/}{\underset{\backslash}{C}}H + O_2 \longrightarrow Ar\text{-}COOH + O=C\overset{/}{\underset{\backslash}{}} \tag{8}$$
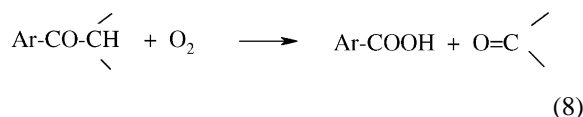
All these results suggest a free-radical redox chain mechanism, in which the manganese salt has two functions: it catalyses the enolisation of the ketone and determines the electron-transfer oxidation of the enol form leading to the α-ketohydroperoxide (Eqs. (9)–(11))
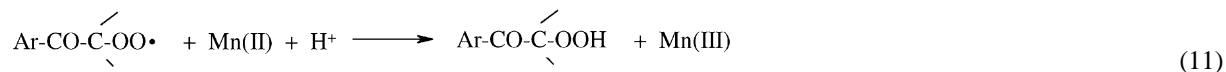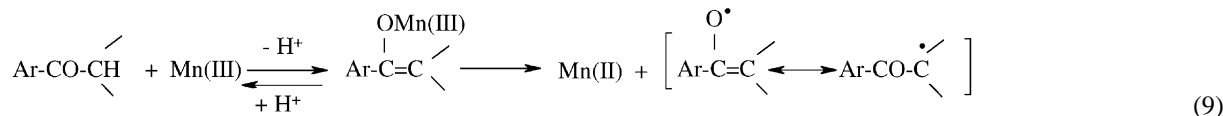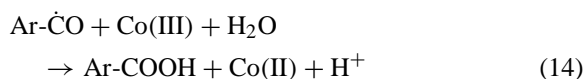
$$Ar\text{-}CO\text{-}\overset{/}{\underset{\backslash}{C}}H + Mn(III) \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} Ar\text{-}\overset{OMn(III)}{\underset{}{C}}=C\overset{/}{\underset{\backslash}{}} \longrightarrow Mn(II) + \left[Ar\text{-}\overset{O^\bullet}{\underset{}{C}}=C\overset{/}{\underset{\backslash}{}} \longleftrightarrow Ar\text{-}CO\text{-}\overset{\bullet/}{\underset{\backslash}{C}} \right] \tag{9}$$

$$Ar\text{-}CO\text{-}\overset{\bullet/}{\underset{\backslash}{C}} + O_2 \rightleftharpoons Ar\text{-}CO\text{-}\overset{/}{\underset{\backslash}{C}}\text{-}OO^\bullet \tag{10}$$

$$Ar\text{-}CO\text{-}\overset{/}{\underset{\backslash}{C}}\text{-}OO^\bullet + Mn(II) + H^+ \longrightarrow Ar\text{-}CO\text{-}\overset{/}{\underset{\backslash}{C}}\text{-}OOH + Mn(III) \tag{11}$$

Table 2
Effect of the metal salt in the aerobic oxidation of acetophenone to benzoic acid[a]

Catalyst	T (°C)	Conversion (%)	Selectivity (%)
$Mn(NO_3)_2$	90	56	96
$Cu(NO_3)_2$	90	–	–
$Co(NO_3)_2$	90	–	–
$Mn(NO_3)_2, Cu(NO_3)_2$	90	97	95
$Mn(NO_3)_2, Co(NO_3)_2$	90	95	96
$Mn(OAc)_2, Co(OAc)_2$	90	30	97
$Mn(OAc)_2, Cu(OAc)_2$	90	32	95
$MnSO_4$	90	–	–
$MnCl_2$	90	–	–
$Mn(NO_3)_2$	75	40	95
$Mn(NO_3)_2, Co(NO_3)_2$	75	72	98
$Mn(NO_3)_2, Co(NO_3)_2$	50	38	97
$Mn(OAc)_2, Co(OAc)_2$	50	–	–

[a] The procedure of Table 1 was utilised with the catalyst and the temperature reported in the table.

The oxidation of ketones by Mn(III) salt to form α-keto-alkyl radicals is well-known [21–23]. Moreover, the α-keto-peroxyl radicals have a higher oxidation potential compared to simple peroxyl radicals, making easier the oxidation of Mn(II) (Eq. (11)). The roles of the cobalt and copper salts are related to the decomposition of the α-keto-hydroperoxide by a further free-radical redox chain according to Eqs. (12)–(14).

$$Ar\text{-}CO\text{-}\overset{/}{\underset{\backslash}{C}}\text{-}OOH + Co(II) \longrightarrow Ar\text{-}CO\text{-}\overset{/}{\underset{\backslash}{C}}\text{-}O^\bullet + OH^- + Co(III) \tag{12}$$

$$Ar\text{-}CO\text{-}\overset{/}{\underset{\backslash}{C}}\text{-}O^\bullet \longrightarrow Ar\text{-}\overset{\bullet}{C}O + O=C\overset{/}{\underset{\backslash}{}} \tag{13}$$

$$Ar\text{-}\overset{\bullet}{C}O + Co(III) + H_2O$$
$$\rightarrow Ar\text{-}COOH + Co(II) + H^+ \tag{14}$$

The manganese salt is less effective for the redox chain of Eqs. (12)–(14); moreover Co(III) salt can contribute to the oxidation of Mn(II) to Mn(III) (Eq. (15)) due to its higher oxidation potential.

$$Co(III) + Mn(II) \rightarrow Co(II) + Mn(III) \tag{15}$$
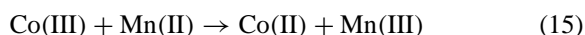
2.2. Oxidation of alkyl-cyclopropyl ketones to cyclopropane carboxylic acid

The catalytic system discussed in Section 2.1 has shown to be particularly selective for the oxidation of alkyl-cyclopropyl ketones to cyclopropane carboxylic acid [4] (Eq. (16)).
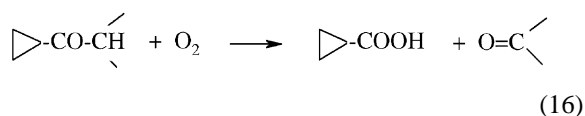
$$\triangleright\text{-}CO\text{-}\overset{/}{\underset{\backslash}{C}}H + O_2 \longrightarrow \triangleright\text{-}COOH + O=C\overset{/}{\underset{\backslash}{}} \tag{16}$$

Table 3
Aerobic oxidation of alkyl-cyclopropyl ketones, R-CO-C_3H_5, to cyclopropane carboxylic acid, C_3H_5-COOH[a]

R	Catalyst (nitrates)	Yields of C_3H_5-COOH (%)
Me	Mn–Cu	92
Me	Mn–Co	93
Et	Mn–Cu	94
Et	Mn–Co	91
n-Bu	Mn–Co	92
i-Pr	Mn–Cu	97
i-Pr	Mn–Co	96

[a] The procedure of Table 1 was utilised.

The high selectivity observed for the oxidation with a variety of alkyl groups (Table 3) is related to the bond dissociation enthalpies of the C–H bonds, which are higher in the cyclopropane ring than in the alkyl groups due to the ring strain. That is reflected in the enolisation equilibria (Eq. (17)), involving the α-C–H bond in the alkyl group and leading to the cyclopropane carboxylic acid.

$$(17)$$
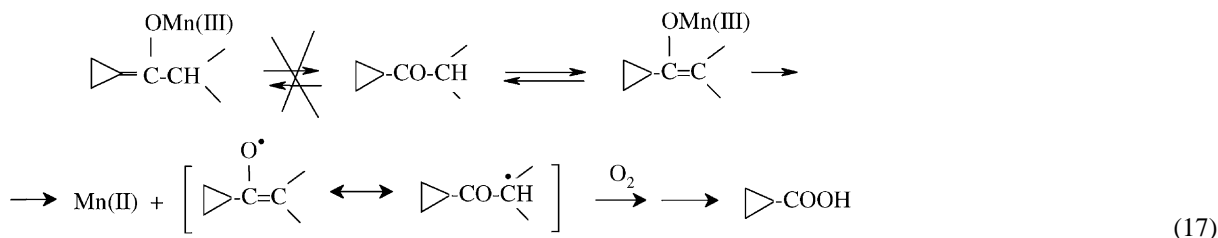
2.3. Oxidation of cycloalkanones to dicarboxylic acids

Aliphatic dicarboxylic acids are compounds of particular industrial interest. In particular, adipic, suberic, and 1,12-dodecandioic acids are valuable starting materials for the synthesis of polyamides and other polymeric materials. Several syntheses of dicarboxylic acids starting from cyclic ketones are known, some of them being performed on a commercial scale. The commonly used oxidant is nitric acid, which has several drawbacks, resulting mainly from its corrosivity and environmental problems, due to the formation of nitrogen oxides.

The aerobic oxidation of cycloalkanones, catalysed by the couples Mn(II)–Co(II) or Mn(II)–Cu(II) nitrates revealed to be particularly effective and selective for the synthesis of dicarboxylic acids under mild

conditions [5,6]. The oxidation takes place at ambient temperature and atmospheric pressure of oxygen and is characterised by an induction period, followed by an exothermic reaction in the case of cyclohexanone. The milder conditions, compared to the oxidation of alkyl–aryl ketones, are due to the easier enolisation of cyclohexanone. Also in this case, as for the oxidation of alkyl–aryl ketones, the manganese salt is necessary for the oxidation to occur; $Co(NO_3)_2$ alone is only slightly active, while $Cu(NO_3)_2$ is completely inactive, as shown by the results reported in Table 4, concerning the oxidation of cyclohexanone.

The results with different cycloalkanones are reported in Table 5. The Co(II) or Cu(II) nitrates, in this case, not only exalt the catalytic activity of the Mn(II) nitrates, but also significantly increase the selectivity of the oxidation. The main by-product of oxidation is the dicarboxylic acid with loss of a carbon atom (glutaric acid from cyclohexanone); its formation is explained by a competition between a redox free-radical (Eq. (18a)) and a minor acid-catalysed (18b) (the oxidation is carried out in acetic acid

Table 4
Aerobic oxidation of cyclohexanone to adipic acid; effect of the catalyst[a]

| Catalyst	T (°C)	Conversion (%)	Selectivity (%)
$Mn(NO_3)_2$, $Co(NO_3)_2$	20	69	92
$Mn(NO_3)_2$, $Cu(NO_3)_2$	20	72	93
$Mn(NO_3)_2$	20	34	81
$Co(NO_3)_2$	20	6	80
$Cu(NO_3)_2$	20	–	–
$Co(OAc)_2$	20	–	–
$Mn(OAc)_2$	20	9.1	83
$Mn(NO_3)_2$, $Cu(NO_3)_2$	40	92	90
$Mn(NO_3)_2$, $Co(NO_3)_2$	40	96	91
$Mn(OAc)_2$, $Cu(OAc)_2$	40	17	91
$Mn(OAc)_2$, $Co(OAc)_2$	40	19	90

[a] The procedure of Table 1 was utilised with the catalyst and the temperature reported in the table.

Table 5
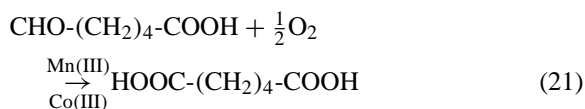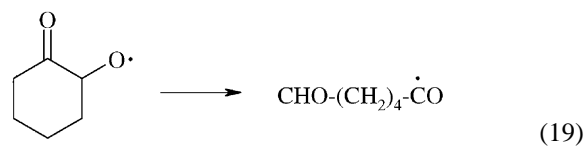Aerobic oxidation of cycloalkanones to dicarboxylic acids[a]

Ketone	Catalyst	Conversion (%)	Reaction products	Selectivity (%)
Cyclopentanone	$Mn(NO_3)_2$, $Co(NO_3)_2$	98	$HOOC-(CH_2)_3-COOH$	92
Cyclopentanone	$Mn(NO_3)_2$, $Cu(NO_3)_2$	96	$HOOC-(CH_2)_3-COOH$	93
Cycloheptanone	$Mn(NO_3)_2$, $Co(NO_3)_2$	99	$HOOC-(CH_2)_5-COOH$	93
Cycloheptanone	$Mn(NO_3)_2$, $Cu(NO_3)_2$	94	$HOOC-(CH_2)_5-COOH$	94
Cyclooctanone	$Mn(NO_3)_2$, $Co(NO_3)_2$	98	$HOOC-(CH_2)_6-COOH$	92
Cyclooctanone	$Mn(NO_3)_2$, $Cu(NO_3)_2$	95	$HOOC-(CH_2)_6-COOH$	92
Cyclododecanone	$Mn(NO_3)_2$, $Co(NO_3)_2$	99	$HOOC-(CH_2)_{10}-COOH$	92
Cyclododecanone	$Mn(NO_3)_2$, $Cu(NO_3)_2$	97	$HOOC-(CH_2)_{10}-COOH$	91

[a] The procedure of Table 1 was utilised at 60 °C.

solution) decomposition of the α-keto-hydroperoxide, formed also in this case by a mechanism similar to that shown by the Eqs. (9)–(11).

(18)
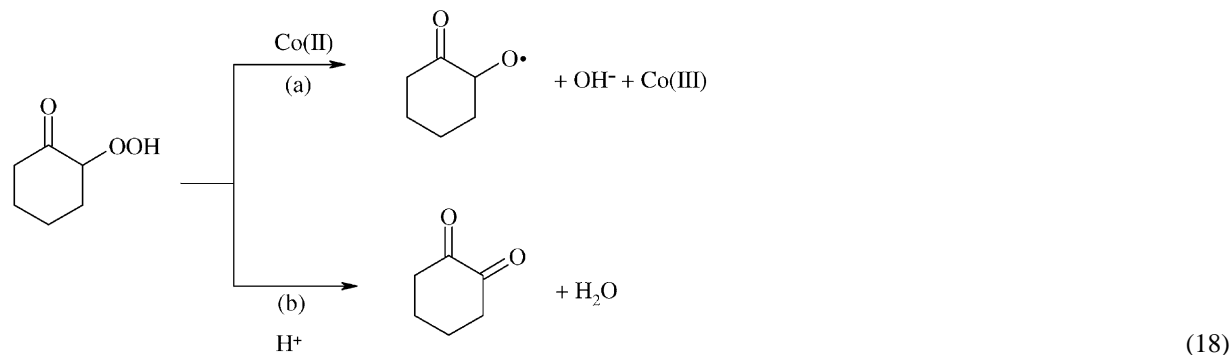
The α-diketone was, actually, isolated as by-product, when the oxidation catalysed by $Mn(NO_3)_2$ alone, was carried out with partial conversion. It was shown that the further oxidation of the α-diketone under the same conditions leads to glutaric acids. The formation of adipic acid is explained by β-fission of the α-keto-alkoxyl radical (Eq. (19)), formed according to Eq. (18a) and by further oxidation of the acyl radical intermediate (Eqs. (20) and (21)).

(19)

$$CHO-(CH_2)_4-\dot{C}O + Co(III) + H_2O$$
$$\rightarrow CHO-(CH_2)_4-COOH + H^+ \qquad (20)$$

$$CHO-(CH_2)_4-COOH + \tfrac{1}{2}O_2$$
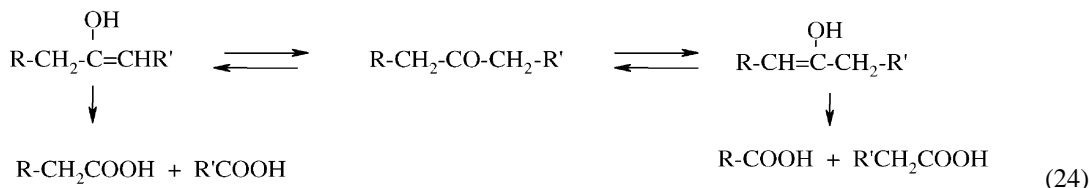$$\underset{Co(III)}{\overset{Mn(III)}{\rightarrow}} HOOC-(CH_2)_4-COOH \qquad (21)$$

The aliphatic aldehydes are, in fact, readily oxidised to the corresponding carboxylic acids under the same catalytic conditions.
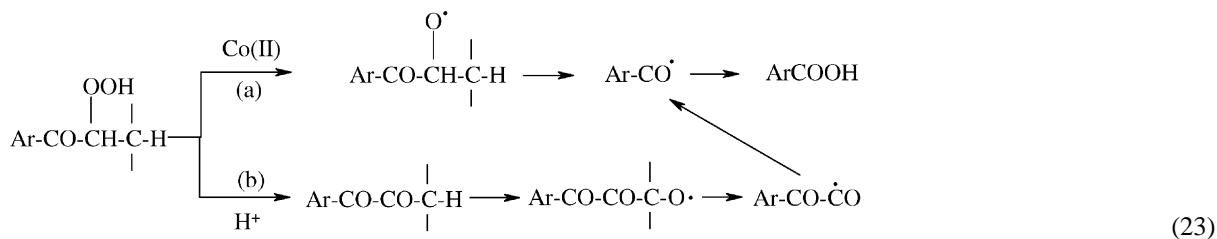
The formation of glutaric acid from the α-diketone follows a similar mechanism, with the difference that the α-keto-acyl radical is less stable and it easily loses CO (Eq. (22)).

(22)
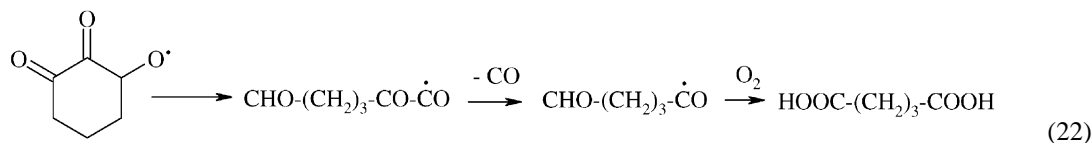
The higher selectivity for adipic acid observed in the presence of Co(II) or Cu(II) salts (Table 4) is alkyl groups leading to a mixture of carboxylic acids (Eq. (24)).

$$R\text{-}CH_2\text{-}\overset{\overset{\textstyle OH}{|}}{C}\text{=}CHR' \;\rightleftarrows\; R\text{-}CH_2\text{-}CO\text{-}CH_2\text{-}R' \;\rightleftarrows\; R\text{-}CH\text{=}\overset{\overset{\textstyle OH}{|}}{C}\text{-}CH_2\text{-}R'$$

$$R\text{-}CH_2COOH + R'COOH \qquad\qquad\qquad R\text{-}COOH + R'CH_2COOH \tag{24}$$

in relation to the higher effectiveness of these salts for the redox decomposition of the hydroperoxides (Eq. (18)), compared to the Mn salt. This last aspect is unimportant for what concerns the selectivity in the oxidation of alkyl–aryl and alkyl-cyclopropyl ketones; both the reactions corresponding to (18a) and (18b) lead to the aromatic and cyclopropane carboxylic acids as final reaction products according to (23a) and (23b) and the selectivity is always very high.

The results for the oxidation of a variety of ketones, which follows Eq. (24), are reported in Table 7. The small amount of octanoic acid from methyl-nonyl ketone, pentanoic acid from methyl-hexyl ketone and propanoic acid from di-*n*-butyl ketone are formed through the intermediates α-diketones according to reactions similar to (18b) and (22).

When a secondary alkyl group is linked to the carbonyl group, the ketone, formed as intermediate

$$\underset{\text{Ar-CO-CH-C-H}}{\overset{\overset{\textstyle OOH}{\textstyle |}}{}} \begin{array}{c} \xrightarrow[\text{(a)}]{\text{Co(II)}} \; \underset{\text{Ar-CO-CH-C-H}}{\overset{\overset{\textstyle O^{\bullet}}{\textstyle |}}{}} \longrightarrow \text{Ar-CO}^{\bullet} \longrightarrow \text{ArCOOH} \\ \\ \xrightarrow[\text{H}^+]{\text{(b)}} \; \text{Ar-CO-CO-C-H} \longrightarrow \text{Ar-CO-CO-C-O}^{\bullet} \longrightarrow \text{Ar-CO-}\overset{\bullet}{\text{C}}\text{O} \end{array} \tag{23}$$

2.4. Oxidation of acyclic aliphatic ketones

The catalytic oxidation of acyclic aliphatic ketones occurs easily leading to the fragmentation of the aliphatic chain and the formation of a variety

oxidation product, is successively oxidised; thus ethyl-cyclohexyl ketone gives adipic acid as main reaction product, through the intermediate cyclohexanone and cyclohexane carboxylic acid as minor product (Eq. (25)) (Table 7).

$$\tag{25}$$
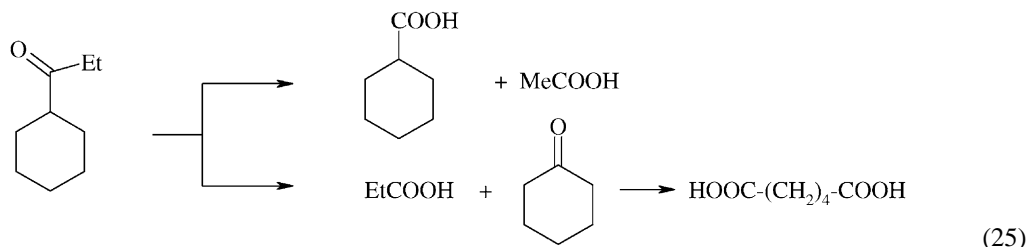
of carboxylic acids. When one of the alkyl group bonded to the carbonyl group is tertiary the oxidation is very selective: ketones of general structure *t*-Bu-CO-C(R'R'')-H, with R', R'' = H or alkyl group, lead to pivalic acid with high yields (Table 6). In the other cases the enolisation generally involves both

3. Aerobic oxidation of alcohols, catalysed by Mn(II) and Co(II) or Cu(II) nitrates in combination with TEMPO

As discussed in Section 2.3, cyclohexanone is selectively oxidised to adipic acid by oxygen under

Table 6
Aerobic oxidation of alkyl-t-butyl ketones, R-CO-But to pivalic acid, t-Bu-COOH[a]

R	Catalyst	Conversion (%)	Selectivity (%)
Me	Mn(NO$_3$)$_2$, Co(NO$_3$)$_2$	90	96
Me	Mn(NO$_3$)$_2$, Cu(NO$_3$)$_2$	92	94
Et	Mn(NO$_3$)$_2$, Co(NO$_3$)$_2$	94	93
Et	Mn(NO$_3$)$_2$, Cu(NO$_3$)$_2$	91	95
n-Bu	Mn(NO$_3$)$_2$, Co(NO$_3$)$_2$	95	96
i-Pr	Mn(NO$_3$)$_2$, Co(NO$_3$)$_2$	97	92
i-Pr	Mn(NO$_3$)$_2$, Cu(NO$_3$)$_2$	94	96

[a] The procedure of Table 1 was utilised at 70 °C.

mild catalytic conditions, while cyclohexanol is completely inert under the same conditions. The reaction mechanism previously described well explains this behaviour. On the other hand, the catalytic use of TEMPO for the selective oxidation of alcohols by a variety of oxidants is well-known [8]; a particularly convenient method, involving a two-phase system (CH$_2$Cl$_2$/H$_2$O), hypochlorite as oxidant and bromide ion as cocatalyst, was reported by Montanari and coworkers [24–26]; modifications of the "Montanari process" were recently [27] utilised for the production of fine chemicals. A variety of metal salt complexes was utilised in combination with TEMPO for the aerobic oxidation of alcohols [28–30]. Copper salts proved to be effective with benzylic and allylic alcohols, while they were less effective with primary and secondary aliphatic alcohols [28]. RuCl$_2$-P(Ph)$_3$ afforded an efficient catalyst at 100 °C and 10 bar of pressure [29]. A more complex catalyst, involving CuBr·Me$_2$S and perfluoro-alkylated bipyridine, was utilised at 90 °C in a biphasic solvent system (perfluorooctane-chlorobenzene) [30].

The combination of TEMPO with Mn(II) and Co(II) or Cu(II) nitrates revealed to be particularly efficient for the aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones under very mild conditions (with the most reactive alcohols the oxidation takes place with air at atmospheric pressure and room temperature) [9]. It appears to be the cheapest and the most effective process among the numerous oxidations developed for this purpose, particularly convenient for practical applications (Table 8).

The mechanism of the catalysis must explain the following results:

(i) In the absence of TEMPO no oxidation of the alcohols occurs, while the oxidation of the corresponding aldehydes and ketones to carboxylic acids readily takes place.
(ii) In the presence of TEMPO the oxidation of the alcohols leads to the corresponding aldehydes and ketones, which are not further oxidised under the same condition of (i).
(iii) The combination of Mn(II) either with Co(II) or Cu(II) nitrates increases the catalytic effectiveness, as the results of Table 9 show.
(iv) The catalytic system is effective in acidic medium; the oxidation takes place readily and selectively in acetic acid solution, but no substantial oxidation occurs in acetonitrile solution under the same conditions.

Since it is well established [8,24–26] that the actual oxidant of the alcohol is the oxo-ammonium salt (Eq. (26)), these results suggest that TEMPO has two functions in the catalytic cycle: it generates the
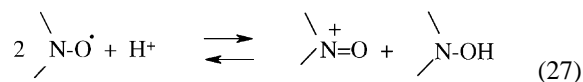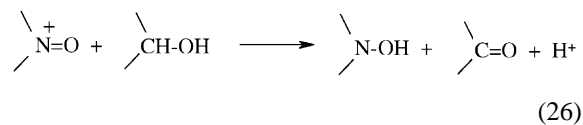
Table 7
Aerobic oxidation of dialkylketones to carboxylic acids[a]

Ketone	Catalyst	Reaction products
Di-n-butyl	Mn(NO$_3$)$_2$, Co(NO$_3$)$_2$	n-Pentanoic (46.6), n-butanoic (45.9) and n-propanoic (6.1) acids
Di-n-butyl	Mn(NO$_3$)$_2$, Cu(NO$_3$)$_2$	n-Pentanoic (46.1), n-butanoic (45.3) and n-propanoic (6.6) acids
Methyl-n-hexyl	Mn(NO$_3$)$_2$, Co(NO$_3$)$_2$	n-Hexanoic (71.2), n-heptanoic (22.3) and n-pentanoic (4.9) acids
Methyl-n-hexyl	Mn(NO$_3$)$_2$, Cu(NO$_3$)$_2$	n-Hexanoic (70.7), n-heptanoic (23.1) and n-pentanoic (5.5) acids
Methyl-n-nonyl	Mn(NO$_3$)$_2$, Co(NO$_3$)$_2$	n-Nonanoic (69.1), n-decanoic (24.2) and n-octanoic (5.3) acids
n-Butyl-n-heptyl	Mn(NO$_3$)$_2$, Co(NO$_3$)$_2$	n-Butanoic (22.3), n-pentanoic (21.7), n-heptanoic (23.2) and n-octanoic (21.9) acids
Ethyl-cyclohexyl	Mn(NO$_3$)$_2$, Co(NO$_3$)$_2$	Adipic (68.6), glutaric (4.2), cyclohexan-carboxylic (19.1) acids
Ethyl-cyclohexyl	Mn(NO$_3$)$_2$, Cu(NO$_3$)$_2$	Adipic (69.1), glutaric (4.3), cyclohexan-carboxylic (18.8) acids

[a] The procedure of Table 1 was utilised at 70 °C.

Table 8
Aerobic oxidation of alcohol to aldehydes and ketones catalysed by TEMPO and Mn(II)–Co(II)or Cu(II) nitrates[a]

Alcohol	Catalyst	Oxidant	Reaction time (h)	T (°C)	Reaction products (%)
Benzyl alcohol	Mn(II)–Co(II)	O_2	6	20	Benzaldeyde (98)
Benzyl alcohol	Mn(II)–Co(II)	Air	8	20	Benzaldeyde (97)
Benzyl alcohol	Mn(II)–Cu(II)	O_2	8	20	Benzaldeyde (99)
2-OMe-benzyl alcohol	Mn(II)–Co(II)	O_2	4	20	2-OMe-benzaldeyde (98)
2-OMe-benzyl alcohol	Mn(II)–Co(II)	Air	8	20	2-OMe-benzaldeyde (97)
2-OMe-benzyl alcohol	Mn(II)–Cu(II)	O_2	6	20	2-OMe-benzaldeyde (96)
2-NO_2-benzyl alcohol	Mn(II)–Cu(II)	O_2	6	20	2-NO_2-benzaldeyde (99)
2-NO_2-benzyl alcohol	Mn(II)–Co(II)	O_2	6	20	2-NO_2-benzaldeyde (96)
1-Phenylethanol	Mn(II)–Cu(II)	O_2	6	20	Acetophenone (99)
1-Phenylethanol	Mn(II)–Cu(II)	Air	8	20	Acetophenone (98)
Cinnamyl alcohol	Mn(II)–Co(II)	O_2	3	40	Cinnamaldehyde (99)
1-Heptanol	Mn(II)–Co(II)	O_2	6	40	1-Heptanal (97)
2-Heptanol	Mn(II)–Cu(II)	O_2	4	40	2-Heptanone (96)
1-Nonanol	Mn(II)–Co(II)	O_2	6	40	1-Nonanal (98)
2-Nonanol	Mn(II)–Co(II)	O_2	5	40	2-Nonanone (100)
Cyclohexanol	Mn(II)–Cu(II)	O_2	9	20	Cyclohexanone (96)
Cyclohexanol	Mn(II)–Co(II)	O_2	9	20	Cyclohexanone (98)
2-Adamantanol	Mn(II)–Co(II)	O_2	6	20	2-Adamantanone (97)

[a] Alcohol (12.5 mmol), TEMPO (1.5 mmol), Mn(NO$_3$)$_2$·6H$_2$O (0.25 mmol), Co(NO$_3$)$_2$·4H$_2$O (0.25 mmol) or Cu(NO$_3$)$_2$·3H$_2$O (0.25 mmol) in 12.5 ml of acetic acid with O_2 or air at atmospheric pressure.

oxo-ammonium salt by disproportionation, catalysed by the acidic medium [31] (Eq. (27)), and it inhibits the further oxidation of aldehydes and ketones, which occurs by a free-radical process under the same condition (Eqs. (9)–(14), (18)–(21)) in the absence of TEMPO; this last, being a persistent radical, acts as inhibitor of free radical chains (Eq. (4)).

$$\underset{/}{\overset{\backslash}{N}}{=}O\ +\ \underset{/}{\overset{\backslash}{C}}H{-}OH\ \longrightarrow\ \underset{/}{\overset{\backslash}{N}}{-}OH\ +\ \underset{/}{\overset{\backslash}{C}}{=}O\ +\ H^+ \tag{26}$$

$$2\ \underset{/}{\overset{\backslash}{N}}{-}O^\bullet\ +\ H^+\ \rightleftharpoons\ \underset{/}{\overset{\backslash}{N}}{=}O\ +\ \underset{/}{\overset{\backslash}{N}}{-}OH \tag{27}$$

The function of O_2 and the metal salt catalysis is to regenerate TEMPO from the *N*-hydroxy derivative (Eq. (28)).

$$\underset{/}{\overset{\backslash}{N}}{-}OH\ \xrightarrow[\text{Mn(II), Co (II)}]{O_2}\ \underset{/}{\overset{\backslash}{N}}{-}O^\bullet \tag{28}$$
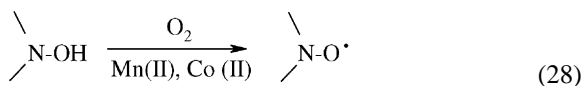
Table 9
Effect of the metal salt catalyst in the aerobic oxidation of cyclohexanol catalysed by TEMPO at 20 °C[a]

Catalyst	Reaction time (h)	Conversion (%)
–	8	Traces
Co(NO$_3$)$_2$	2	14
Co(NO$_3$)$_2$	4	16
Co(NO$_3$)$_2$	8	21
Cu(NO$_3$)$_2$	2	16
Cu(NO$_3$)$_2$	4	18
Cu(NO$_3$)$_2$	8	28
Mn(NO$_3$)$_2$	2	19
Mn(NO$_3$)$_2$	4	26
Mn(NO$_3$)$_2$	8	45
Mn(NO$_3$)$_2$, Co(NO$_3$)$_2$	2	29
Mn(NO$_3$)$_2$, Co(NO$_3$)$_2$	4	42
Mn(NO$_3$)$_2$, Co(NO$_3$)$_2$	8	100
Mn(NO$_3$)$_2$, Cu(NO$_3$)$_2$	2	30
Mn(NO$_3$)$_2$, Cu(NO$_3$)$_2$	4	47
Mn(NO$_3$)$_2$, Cu(NO$_3$)$_2$	9	100

[a] The procedure of Table 1 was utilised.

The very mild conditions of the overall oxidation are related to Eq. (28); in non-acidic medium, where disproportionation (Eq. (27)) does not occur, more drastic oxidation conditions or more effective oxidants are required in order to oxidise TEMPO to the oxo-ammonium salt (Eq. (29)).
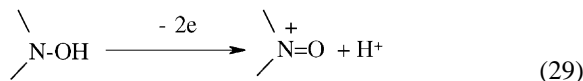
$$\diagdown \!\!\!\! \underset{\diagup}{N}\text{-OH} \quad \xrightarrow{\;-2e\;} \quad \diagdown \!\!\!\! \underset{\diagup}{N}\!\!\!=\!\!O \;+\; H^+ \qquad (29)$$

4. Aerobic oxidation of organic compounds, catalysed by N-hydroxyimides and transition metal salts

Recently the aerobic oxidation under mild conditions of organic compounds, catalysed by N-hydroxyimides and transition metal salts, has been particularly developed by Ishii and coworkers [10]. All the evidences would indicate that, when NHPI was utilised as catalyst, the hydrogen abstraction from the C–H bonds by the PINO radical (Eq. (5)), generated in situ, plays a key role in free-radical chains.

1a

2a

3a

4a

5a; R_1 = Me, R_2 = Ph

6a; R_1 = CMe$_3$, R_2 = 3,5(NO$_2$)$_2$C$_6$H$_3$

A remarkable aspect of this catalysis concerns the fact that two N-oxyl radicals, TEMPO and PINO, have completely opposite behaviour; the former inhibits free-radical chains, as previously discussed, while the latter promotes them. The fact is noticeable considering that the BDE value of the O–H bond for TEMPO–H (69.6 kcal/mol) [7] is relatively low, while

the BDE values O–H bonds for N-hydroxy-amides were not known. A BDE value for the O–H bond in NHPI of the same order of magnitude as for TEMPO–H could not justify on enthalpic basis a reaction such as Eq. (5) (the hydrogen abstraction would be endothermic for more than 20 kcal/mol, as the BDE value of several C–H bonds involved in the oxidations are higher than 90 kcal/mol).

Thermochemical and kinetic investigations have allowed to determine the BDE value of O–H bonds in N-hydroxyamides and imides and the absolute rate constants for the hydrogen abstraction from C–H bonds by the PINO radical. The results have been used for giving a quantitative basis to the catalysis by the N-hydroxyimides and for developing new selective synthetic processes of oxidation.

4.1. Thermochemistry of N-hydroxy derivatives

A thermochemical study on NHPI and other N-hydroxy derivatives (1a–6a) was undertaken in order to investigate the effect of alkyl, aryl and carbonyl substituents on the O–H bond strength.

The EPR radical equilibration technique [32–36] has been used in order to measure BDE values of the O–H bonds in N-hydroxy derivatives. The method consists in measuring the equilibrium constant for the hydrogen atom transfer reaction between a N-hydroxy derivative, an appropriate reference compound, AH, whose BDE value is known, and the corresponding radicals

Table 10
EPR spectral parameters of nitroxides 1b–6b and PINO and BDE values of the O–H bond in the parent hydroxylamines 1a–6a and NHPI

Radical	Solvent[a]	a_N (Gauss)	Other (Gauss)	g-Factor	BDE (kcal/mol)
1b	Benzene	9.28	3.09 (1H), 2.89 (1H), 1.03 (2H)	2.0058	70.6 ± 0.3
2b	Benzene	10.80	2.71 (2H), 1.03 (2H)	2.0058	71.4 ± 0.3
3b	Benzene	10.88	1.03 (2H)	2.0056	69.7 ± 0.4
4b	Benzene	5.82	0.79 (1H), 0.67 (1H)	2.0062	78.5 ± 0.5
5b	Benzene:*t*-BuOH (10:1)	7.20	8.05 (3H)	2.0065	79.2 ± 0.5
6b	Benzene:*t*-BuOH (10:1.5)	7.25	–	2.0068	80.2 ± 0.5
PINO	*t*-BuOH	4.36	0.45 (2H)	2.0073	88.1 ± 0.6

(Eq. (30)).

$$R_2N\text{-}OH + A^\bullet \underset{}{\overset{K_e}{\rightleftarrows}} R_2N\text{-}O^\bullet + AH \qquad (30)$$
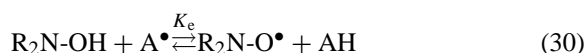
The persistent nitroxyl radicals 1b–3b were generated from 1a to 3a by hydrogen exchange with TEMPO (Eq. (31)) and the less persistent ones (PINO and 4b–6b) by photolysis of di-*t*-butyl peroxide in the presence of NHPI and 4a–6a (Eqs. (32) and (33)).

$$TEMPO^\bullet + R_2N\text{-}OH \rightleftarrows TEMPO\text{-}H + R_2N\text{-}O^\bullet \quad (31)$$

$$t\text{-BuO-OBut} \overset{\lambda\nu}{\to} 2t\text{-BuO}^\bullet \qquad (32)$$

$$R_2N\text{-}OH + t\text{-BuO}^\bullet \to R_2N\text{-}O^\bullet + t\text{-BuOH} \qquad (33)$$
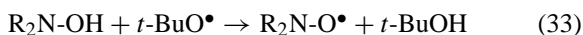
The measured hyperfine splitting constants and the g-factors are reported in Table 10. They are strongly dependent on the nature of the substituent linked to the nitroxide group, a_N decreasing and the g-factor increasing along the series dialkylnitroxides, monoacylnitroxides, diacylnitroxides.

This behaviour is known [37] and it is explained on the basis of the resonance structures I and II (Eq. (34)).

$$
\begin{array}{ccc}
\overset{\displaystyle |}{X\text{-}N\text{-}O}\cdot & \longleftrightarrow & \overset{\displaystyle |}{X\text{-}N\text{-}O}^- \\
& & \overset{.+}{} \\
I & & II
\end{array} \qquad (34)
$$
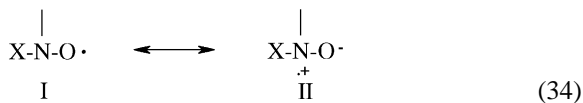
The structure I does not contribute to the nitrogen splitting constant, whose value is determined by structure II. In dialkyl-nitroxides structures I and II contribute to the mesomeric system approximately to the same extent [37], while in acyl nitroxides structure I will be favoured by the presence of the electron-withdrawing carbonyl group (X), which makes less stable structure II. This will result in a reduction of spin density on oxygen and of the g-value

because of the larger spin–orbit coupling of oxygen with respect to nitrogen or carbon.

After characterising spectroscopically the nitroxide radicals PINO and 1b–6b, equilibration experiments were carried out to measure the BDE value of the O–H bond. In the case of 1a–3a, which give rise to the persistent radicals 1b–3b, TEMPO was used as a reference compound (Eq. (31)) and from the EPR spectra resulting from superimposition of lines from both TEMPO and one of the nitroxides 1b–3b the relative amounts of the two radicals were obtained either by numerical integration or by computer simulation, while the concentrations of the corresponding N-hydroxy derivatives were calculated by the differences as shown in Eq. (35), where $[TEMPO]_0$ and $[R_2NOH]_0$ are the initial concentrations of the two species.

$$K_e = \frac{[R_2NO^\bullet]([TEMPO]_0 - [TEMPO])}{[TEMPO]([R_2NOH]_0 - [R_2NO^\bullet])} \qquad (35)$$

The equilibrium constant K_e was used to calculate the free energy of the hydrogen atom transfer from 1a to 3a to TEMPO (Eq. (31)), which was considered equal to the enthalpy of reaction, by assuming that the entropic contribution is negligible [32–36]. The BDE values of 1a–3a were then calculated by means of Eq. (36) by using the known BDE value (69.6 kcal/mol) of TEMPO–H.
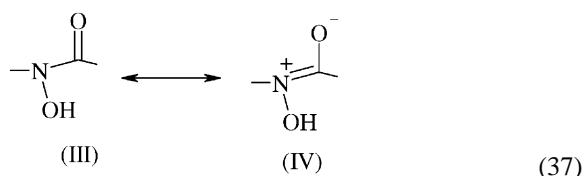
$$BDE(R_2NO\text{-}H) = BDE(TEMPO\text{-}H) - RT \ln K_e \quad (36)$$

TEMPO was not a suitable reference compound to determine the BDE values of the O–H bond for the monoacyl hydroxylamines 4a–6a. Namely, when mixing solution of the hydroxylamines with TEMPO in a wide range of concentrations, no signals due to the

nitroxides 4b–6b were detected, clearly indicating that the O–H bond in these *N*-hydroxy derivatives are much stronger than in TEMPO–H or in 1a–3a. Reference compounds with stronger O–H bond had to be used in order to measure the BDE values of 4a–6a. By testing different phenols, 2,6-di-*t*-butyl-4-methylphenol (BHT) characterised by an O–H BDE of 81.0 kcal/mol [32–35], was found to be the most suitable one. The radicals were generated photolytically according to Eqs. (32) and (33) and the initial concentrations of BHT and R_2NOH were used in the calculation of K_e, since the experiments were performed on concentrated solution of the radical precursors, while the relative concentrations of the two radical species ($ArO^\bullet$ and $R_2NO^\bullet$) were determined by both simulation and numerical integration of the EPR spectra.

BHT, however, was not suitable to measure the BDE value of the O–H bond in NHPI and other phenols with larger O–H bond strength were used, in particular, 3,5-di-*t*-butyl-phenol, whose BDE value is 86.6 and 88.8 kca/mol, respectively in benzene and *t*-butanol (the BDE values for the O–H bond of phenols, when no substituent is present in the *ortho* position, are affected by hydrogen bond acceptor solvents [38,39]) and 4-cyanophenol[1] whose experimental BDE value has never been reported, but it can be straightforwardly estimated by the substituent additivity rule [40] as 88.8 and 91.2 kcal/mol, respectively in benzene and *t*-butanol. This last solvent was used for the EPR radical equilibration experiments with NHPI, which is sparingly soluble in benzene. The measured BDE values, reported in Table 10, clearly show that the carbonyl group adjacent to the nitrogen atom strongly increases the strength of the O–H bond in the hydroxylamines [41].

Now the BDE value is a measure of the energy difference between the nitroxide radical and the parent hydroxylamine and any factor inducing a stabilisation of the hydroxylamine and/or a destabilisation of the nitroxide increases the strength of the O–H bond. Three factors appear to be important: acylhydroxylamines, compared to alkylhydroxylamines, are stabilised by the resonance structure IV with charge separation (Eq. (37)).

---

[1] The measured spectroscopic parameters of 4-cyanophenoxyl radical are: $a_H(ortho) = 6.86\,G$, $a_H(meta) = 2.31\,G$, $a_N = 1.38\,G$, $g = 2.0054$.

(37)

Moreover both experimental and computational results suggest that the presence of a carbonyl group reduces the relative weight of the polar structure II of the nitroxide, implying a lower resonance stabilisation. The third factor is the likely formation of an intramolecular hydrogen bond (structure V), that is important in stabilising the starting compound, while it is, obviously, absent in the corresponding nitroxides and in alkylhydroxylamines.

V
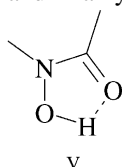
4.2. Kinetics of the oxidations catalysed by NHPI

The rate of hydrogen abstraction by PINO from a given substrate (RH) (Eq. (5)), and thus the rate of the catalysed oxidation by molecular oxygen, has been evaluated by using both EPR spectroscopy and a device for measuring the oxygen consumption in closed systems. The rate constants were determined following the decay of the EPR signals of PINO radical in the presence of increasing amount of substrate [41]. The decay of PINO follows good first-order kinetics both in the absence and in the presence of the oxidisable investigated substrates (toluene, ethylbenzene, cumene, benzyl alcohol, cyclohexane). In the former case this is likely due to a fragmentation of the carbonyl C–N bond, similar to what is previously reported [42] for another acylnitroxide. Thus, the decay traces were nicely described by Eq. (38), where k_d is the first-order rate constant for self-decay and k_H is the second-order rate constant for hydrogen abstraction from R-H.

$$\ln \frac{[\text{PINO}]_t}{[\text{PINO}]_0} = -(k_d + k_H[\text{RH}])_t \qquad (38)$$

The experimentally determined values of the pseudo-first-order rate constant $k_{EPR} = k_d + k_H[\text{RH}]$ are plotted in Fig. 1 as function of the substrate
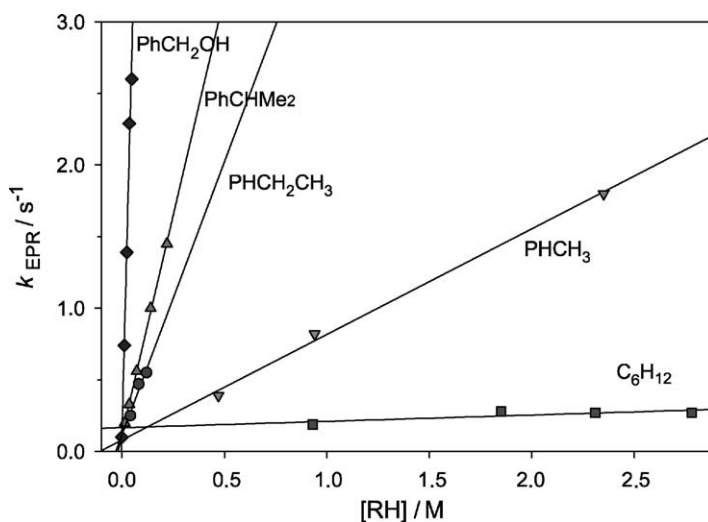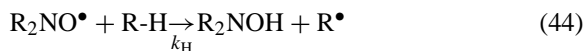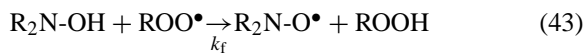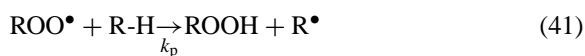
Fig. 1. Pseudo-first-order rate constants for the decay of PINO radicals in the presence of different amounts of hydrogen atom donors.

concentration, and the resulting k_H, obtained from the slopes of these plots, are shown in Table 11 together with the rate constants reported in the literatures [1,43] for the related hydrogen abstraction from RH by the peroxyl radicals $ROO^\bullet$ and t-$BuOO^\bullet$ [41].

In any case the reactivity of PINO with various substrates is larger than that of peroxyl radicals, the phenomena being particularly marked with the most reactive substrates (cumene, benzyl alcohol); that makes PINO an useful oxidation catalyst. Since the BDE values of the O–H bonds of NHPI and t-BuOO–H, are the same (88 kcal/mol), the higher reactivity of PINO compared to peroxyl radicals can be reasonably ascribed to a more marked polar effect, as it will discussed later on.

In order to better understand the factors determining the rates of NHPI catalysed oxidations of organic compounds, the thermally initiated autoxidation of

cumene, chosen as a model system, has been investigated by measuring the rate of oxygen uptake in the presence and in the absence of NHPI. The results have been rationalised on the basis of the reaction mechanism reported in Eqs. (39)–(44).

$$In \xrightarrow{R_i} R^\bullet \tag{39}$$

$$R^\bullet + O_2 \rightarrow ROO^\bullet \tag{40}$$

$$ROO^\bullet + R\text{-}H \underset{k_p}{\rightarrow} ROOH + R^\bullet \tag{41}$$

$$2ROO^\bullet \underset{2k_t}{\rightarrow} products \tag{42}$$

$$R_2N\text{-}OH + ROO^\bullet \underset{k_f}{\rightarrow} R_2N\text{-}O^\bullet + ROOH \tag{43}$$

$$R_2NO^\bullet + R\text{-}H \underset{k_H}{\rightarrow} R_2NOH + R^\bullet \tag{44}$$

From the solution of the simultaneous differential equations, describing the time evolution of the various species, under the assumption that the steady-state approximation holds for all the free radical species, Eq. (45) was obtained for the rate of oxygen consumption where the first term described the non-catalysed and the second one the catalysed oxidation.

$$-\frac{d[O_2]}{dt} = k_p[RH]\left(\frac{R_i}{2k_t}\right)^{1/2} + k_f[R_2NO\text{-}H]\left(\frac{R_i}{2k_t}\right)^{1/2} \tag{45}$$

Table 11

Absolute rate constants for the hydrogen abstraction reaction from RH by PINO at 25 °C $k_{H(PINO)}$ and by t-BuOO radical, $k_{H(t\text{-BuOO}^\bullet)}$

RH	$k_{H(PINO)}$	$k_{H(t\text{-BuOO}^\bullet)}$	$k_{H(PINO)}/k_{H(t\text{-BuOO}^\bullet)}$
$PhCH_3$	0.38	0.036	10.5
$PhCH_2CH_3$	2.24	0.20	11.2
$PhCHMe_2$	3.25	0.22	14.8
$PhCH_2OH$	28.3	0.13	218.0
Cyclohexane	0.047	0.0034	13.8

A series of measurements, carried out at different cumene concentrations, both in the absence and in the presence of NHPI, has shown that the plot obtained by subtracting the rate of non-catalysed to the rate of catalysed oxidation does not significantly depend on the cumene concentration. On the basis of Eq. (45), the slope of the plot reporting $-d[O_2]/dt$ versus [NHPI] has provided $k_f(R_i/2k_t)^{1/2}$ and from the known values of R_i and k_t a value of 7.2×10^3 M/s at $30\,^\circ$C was obtained in chlorobenzene for the rate constant k_f [41], which represent the key kinetic factor of the overall catalysed reaction.

Actually the aerobic oxidation, catalysed by NHPI, becomes particularly effective in combination with transition metal salts, such as Co(II) salts. The overall kinetics become more complex due to the superimposition of redox chains to the radical chains of Eqs. (39)–(44) with the involvement of alkoxyl radicals by the redox decomposition of the hydroperoxides (Eq. (1)). Alkoxyl radicals are much more reactive in hydrogen abstraction than the peroxyl radicals for obvious enthalpic reasons (the BDE values for RO–H and ROO–H are 104

$$R_2N\text{-OH} + RO^\bullet \xrightarrow{k} R_2N\text{-O}^\bullet + ROH,$$

$$k > 10^9 \, \text{M}^{-1}\,\text{s}^{-1} \quad (46)$$
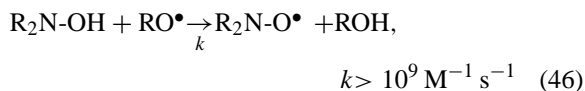
4.3. Oxidation of benzyl alcohols to aromatic aldehydes

Recently the aerobic oxidation of primary alcohols to the corresponding carboxylic acids, catalysed by NHPI combined with Co(II) salts under mild conditions, has been reported [44]. The hydrogen abstraction by the PINO radicals from the C–H bond of the -CH$_2$OH and -CHO groups was suggested to be responsible for the selectivity.

On the other hand, also recently, we have reported the oxidation of alcohols, ethers and amides by H$_2$O$_2$, catalysed by bromine; in particular, primary benzylic alcohols give selectively the aromatic aldehydes, while non-benzylic alcohols give the carboxylic acids even at low conversions [45–47]. The selectivity in the H$_2$O$_2$ oxidation is determined by the hydrogen abstraction by the electrophilic bromine atom (Eq. (47)).

$$(47)$$
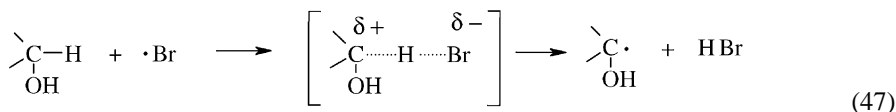
and 88 kcal/mol, respectively). The alkoxyl radicals abstract a hydrogen atom from C–H bonds with rate constants 10^6–10^7 larger than the peroxyl radicals; if the hydrogen abstraction from the O–H bond of NHPI by the alkoxyl radicals (Eq. (46)) occurs with a similar rate extent, compared to the peroxyl radicals, it should be characterised by a diffusion-controlled rate.

Now the BDE values of H–Br and O–H bond in NHPI are substantially identical (ca. 88 kcal/mol) so that the enthalpic effect should be quite similar in hydrogen abstraction by Br$^\bullet$ (Eq. (47)) and by PINO (Eq. (48)); moreover also PINO is an electrophilic radical and the hydrogen abstraction from the alcohols should be significantly affected by the polar effect (Eq. (48)).

$$(48)$$
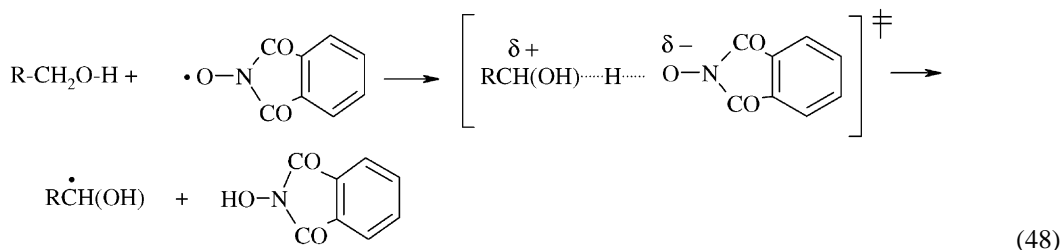
Nitroxyl radicals are in general electrophilic radicals, but the electrophilic character is considerably enhanced by the carbonyl group linked to the PINO nitrogen (Eq. (49))

$$(49)$$
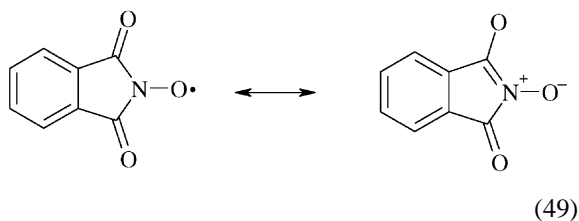
The effect is similar to that observed with acylperoxyl radicals, $R\text{-}C(=O)OO^\bullet$, compared to alkylperoxyl radicals, $ROO^\bullet$, and with acyloxyl radical, $R\text{-}C(=O)O^\bullet$, compared to alkoxyl radicals; $R\text{-}C(=O)O^\bullet$ and $R\text{-}C(=O)O^\bullet$ are more electrophilic than $ROO^\bullet$ and $RO^\bullet$ radicals [48]. The phenomena would be more marked with PINO than with acylperoxyl and acyloxyl radicals because nitrogen can settle a positive charge, as in Eq. (49), better than carbon.

The results obtained in the oxidation of primary alcohols, catalysed by bromine, suggested that a non-benzylic primary alcohols gives carboxylic acids, even at low conversion.

This synthesis of aromatic aldehydes from benzyl alcohols, together with the aerobic oxidation catalysed by TEMPO and Mn(II)–Co(II) or Cu(II) nitrates, previously discussed, appears to be the cheapest and the most effective among the numerous processes developed for this purpose (the oxidation takes place in both cases with air or oxygen at atmospheric pressure and room temperature with high selectivity), suitable for industrial applications.

The advantage of using TEMPO for the synthesis of aldehydes is related to the general character for the oxidation of benzylic and non-benzylic alcohols while the use of NHPI is limited to benzylic for the mechanistic aspects discussed below, but NHPI (obtained from phthalic anhydride and NH_2OH) is cheaper than TEMPO and moreover it can be more easily recovered and recycled due to its low solubility in several solvents.

More recently, however, we have developed in collaboration with Ciba Speciality Chemicals, a TEMPO analogous catalyst of more complex structure A for the aerobic oxidation of alcohols.

A
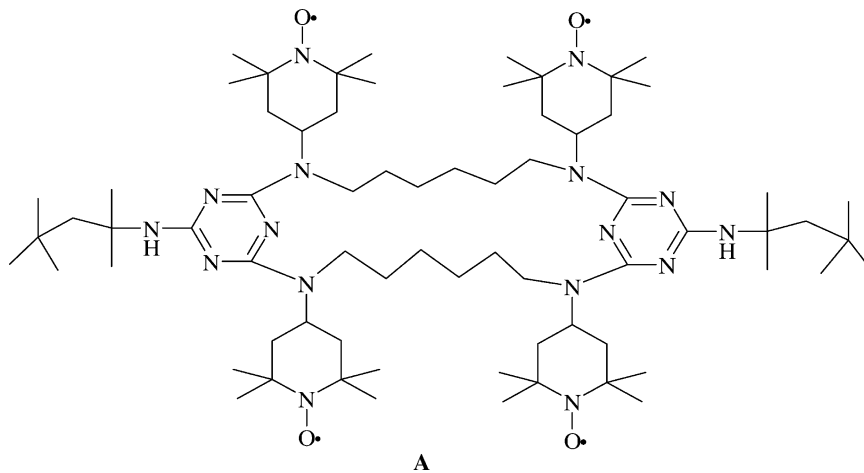
similar selectivity should be expected in the hydrogen abstraction by PINO on the ground of polar and enthalpic effects.

Actually the aerobic oxidation of primary benzyl alcohols, catalysed by NHPI and Co(II) salts under mild conditions leads to aromatic aldehydes with high selectivity, without appreciable formation of carboxylic acids [49] (Table 12), while the oxidation of

This catalyst in combination with Mn(II) and Co(II) nitrates is highly effective for the oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones by oxygen under very mild conditions (room temperature and atmospheric pressure), but the presence of amino group presents the great advantage of an easy recover and recycle of the catalyst as ammonium salt, considering that the catalysis

is effective only in acidic medium, as previously discussed.

Polar and enthalpic effects well explain the observed selectivity. The Co(II) salt appears to have a two-fold function: it can generate the PINO radical (Eqs. (50) and (51)), which initiates a free-radical chain leading to the hydroperoxide (Eqs. (52)–(54))
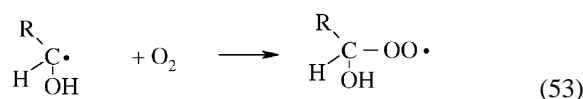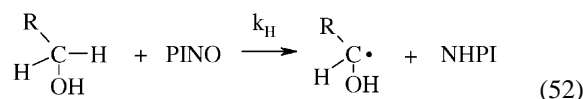
$$Co(II) + O_2 \rightarrow Co(III)OO^{\bullet} \tag{50}$$

$$NHPI + Co(III)OO^{\bullet} \rightarrow PINO + Co(III)OOH \tag{51}$$

$$\tag{52}$$

$$\tag{53}$$

$$\tag{54}$$
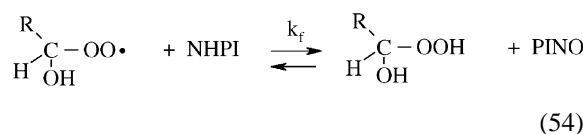
Table 12
Aerobic oxidation of benzylic alcohols, X-C$_6$H$_4$-CH$_2$OH, to aromatic aldehydes, catalysed by NHPI and Co(OAc)$_2$ at 20 °C at atmospheric pressure[a]

X	Oxidant	Reaction time (h)	Conversion (%)	Selectivity (%)
H	O$_2$	2	100	92
H	Air	3	86	91
p-OMe	O$_2$	1	75	94
p-OMe	Air	2	87	95
p-Me	O$_2$	2	100	95
p-Me	Air	3	91	93
p-Cl	O$_2$	3	100	95
m-Cl	O$_2$	3	92	97
m-CN	O$_2$	4	100	98
p-NO$_2$	O$_2$	3	100	98
m-NO$_2$	O$_2$	4	88	91

[a] Alcohol (6 mmol), NHPI (0.6 mmol) and Co(OAc)$_2$·4H$_2$O (0.06 mmol) in 12 ml of MeCN with O$_2$ or air.

Eq. (54) to the right with superimposition of a redox chain (Eqs. (55) and (56)), leading to the aldehyde, to the radical chain of Eqs. (52)–(54).

$$\tag{55}$$

$$\tag{56}$$
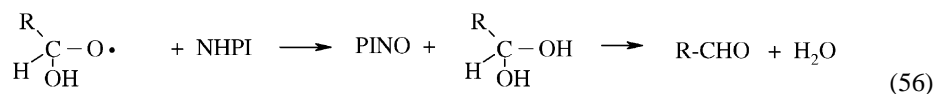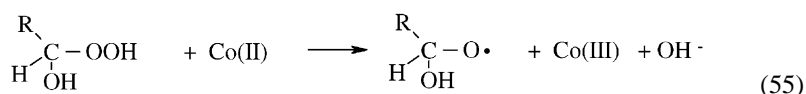
The mild reaction conditions are related to the hydrogen abstraction from the C–H bond of the benzyl alcohol which is much faster by the PINO radical (k_H of Eq. (52) = 28.3 M^{-1}s^{-1}) than by t-BuOO$^{\bullet}$ radical (0.13 M^{-1}s^{-1}) (Table 11). Since the BDE values of the O–H bonds in the t-BuOO–H and NHPI are identical (88 kcal/mol), the much faster hydrogen abstraction by the PINO radical must be ascribed to a particularly marked polar effect (Eqs. (48) and (49)). For the same reason Eq. (54) is an almost thermoneutral reaction and it must be considered an equilibrium process (k_f = 7.2 × 10^3 M^{-1}s^{-1}). The other function of the Co(II) salt concerns the redox decomposition of the hydroperoxide, shifting the equilibrium of

The Co(III) salt can be reduced to Co(II) either by NHPI (Eq. (57)) or the hydroperoxide (Eq. (58))

$$NHPI + Co(III) \rightarrow PINO + Co(II) + H^+ \tag{57}$$

$$ROOH + Co(III) \rightarrow ROO^{\bullet} + Co(II) + H^+ \tag{58}$$
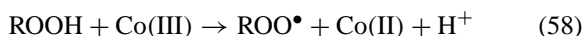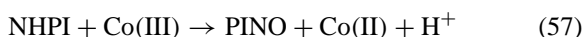
The enthalpic effect is similar for the hydrogen abstraction from benzylic alcohols (Eq. (52)) and aromatic aldehydes (Eq. (59)) by PINO (the BDE value is about 87 kcal/mol for both ArCHOH–H and ArCO–H) and it is the polar effect (Eq. (48)) which plays the key role making the alcohols (Eq. (52)) much more reactive than the aldehyde (Eq. (59)) so that it is possible that the complete conversion of the benzylic alcohols
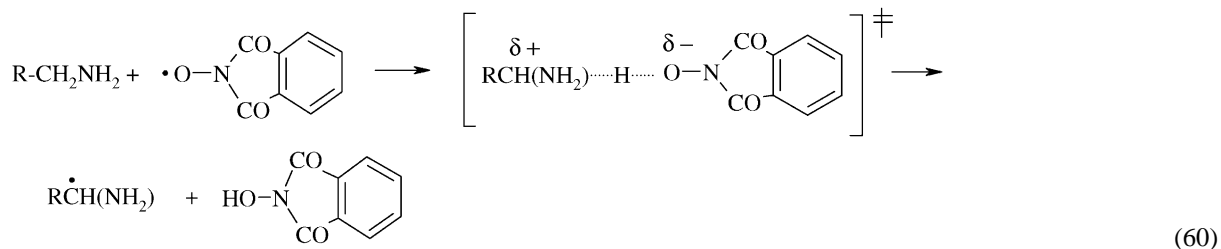
to the aromatic aldehydes without appreciable formation of carboxylic acids.

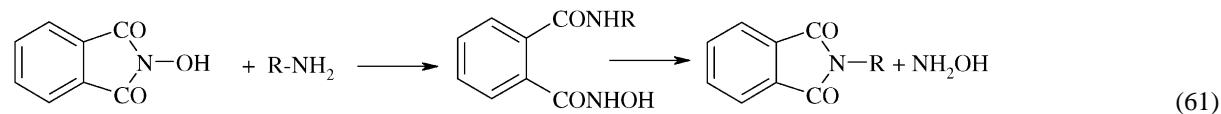$$RCHO + PINO \rightarrow R\text{-}\dot{C}O + NHPI \qquad (59)$$
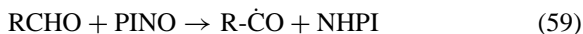
With non-benzylic alcohols the enthalpic effect is dominant (the BDE value of the RCHOH–H bond is 8–10 kcal/mol higher than that of the RCO–H bond) and it makes the aldehydes much more reactive than the alcohols leading selectively to the carboxylic acids even at low conversions. The importance of the polar effect is supported by the effect of the substituents in the aromatic ring [49].

4.4. Oxidation of t-benzylamines to aromatic aldeydes

The amino group is a more effective electron-releasing substituent than the hydroxy group and thus it would be expected to have a higher reactivity and stronger polar effect (Eq. (60)) for the hydrogen abstraction by PINO from benzylamines, making easier the aerobic oxidation, catalysed by NHPI, compared to the corresponding alcohols.

(Table 13) (Eq. (62)), the main by-product being the amide (Eq. (63))

$$ArCH_2NMe_2 + \tfrac{1}{2}O_2 \underset{Co(II)}{\overset{NHSI}{\rightarrow}} ArCHO + Me_2NH \qquad (62)$$

$$ArCH_2NMe_2 + \tfrac{1}{2}O_2 \rightarrow ArCONMe_2 + H_2O \qquad (63)$$

N-hydroxysuccinimide (NHSI) appears to give better results than NHPI (Table 13). The latter is a more effective catalyst, but it has two main drawbacks compared to NHSI: it catalyses faster the initial oxidation of the benzylamine but it is deactivated before the completion of the oxidation, particularly with less reactive benzylamine, such as the nitrosubstituted ones. With NHSI the oxidation is slower, but it goes to completion without deactivation of the catalyst, which is due to the formation of Me_2NH (Eq. (62)); according to Eq. (61) competitive experiments between NHPI and NHSI with Me_2NH have shown [50] that the former reacts faster than the latter. Moreover, the faster oxidation by NHPI catalysis makes the reaction somewhat less selective compared to the slower NHSI catalysis, increasing the amount of the amides according to Eq. (63).

$$(60)$$

However, primary and secondary benzylamines are completely inert towards the oxidation by O_2 and NHPI catalysis under the same conditions in which primary and secondary alcohols are easily oxidised. This behaviour is related to the reaction of amines with NHPI according to Eq. (61), which deactivates the catalyst.

The mechanism of the oxidation is substantially identical to that discussed for benzylic alcohols: free-radical and redox chains lead to the α-hydroxyamines, which hydrolyses to the aromatic aldehydes (Eq. (64)).
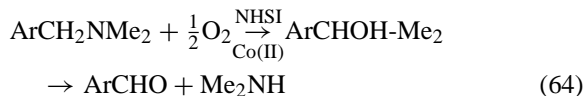

$$(61)$$

Tertiary benzylamines cannot react with NHPI according to Eq. (61) and the oxidation to the corresponding aromatic aldehydes readily occurs [50]

$$ArCH_2NMe_2 + \tfrac{1}{2}O_2 \underset{Co(II)}{\overset{NHSI}{\rightarrow}} ArCHOH\text{-}Me_2$$
$$\rightarrow ArCHO + Me_2NH \qquad (64)$$

Table 13
Aerobic oxidation of benzyldimethylamines $X-C_6H_4-CH_2-N(CH_3)_2$ to the aldehydes $X-C_6H_4-CHO$ catalysed by NHSI and NHPI[a]

X	Catalyst	T (°C)	Reaction time (h)	Conversion (%)	Selectivity (%)
H	NHSI	35	2	42	91
H	NHSI	50	2.5	100	88
H	NHPI	35	2	75	81
H	NHPI	50	9	90	70
p-OMe	NHPI	40	3	96	84
p-Cl	NHSI	50	7	100	86
p-Cl	NHPI	50	7	90	86
m-Cl	NHSI	35	7	100	78
m-Cl	NHPI	35	7	90	68
p-NO₂	NHSI	50	9	90	80
p-NO₂	NHPI	50	9	86	60
p-CN	NHSI	50	4	100	86
p-CN	NHPI	50	4	86	68

[a] Benzylamine (7 mmol), NHSI or NHPI (0.7 mmol) and Co(OAc)₂·4H₂O (0.07 mmol) in 15 ml of MeCN with O₂ at atmospheric pressure.

The faster oxidation by NHPI catalysis determines the further oxidation of the α-hydroxyamines before the hydrolysis (Eq. (64)) increasing the amount of the amide (Eq. (65)).

$$ArCHOH-NMe_2 + \tfrac{1}{2}O_2 \underset{Co(II)}{\overset{NHSI}{\rightarrow}} ArCONMe_2 + H_2O$$

(65)
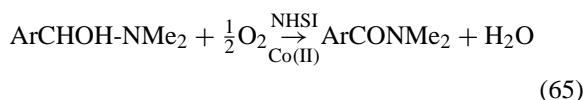
The importance of the polar effect in the oxidation of benzylamines is emphasised by competitive experiments between benzylamines and benzyl alcohols; only the former are oxidised. Since the enthalpic effect is substantially similar for the hydrogen abstraction from benzylamines and benzyl alcohols, the higher reactivity of the amines must be ascribed to a larger contribution of polar forms to the transition state (Eq. (60)).

If the benzyl group is secondary the oxidation selectively leads to the ketone (Eq. (66)).

$$ArCHR-NMe_2 + \tfrac{1}{2}O_2 \rightarrow ArCOR + Me_2NH \quad (66)$$
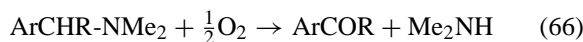
4.5. Oxidation of N-alkylamides

The aerobic oxidation of primary and secondary alkyl amines, catalysed by NHPI, is inhibited by the degradation of the catalyst (Eq. (61)). To avoid this deactivation the possibility to protect the amino group by

acylation was considered. The acetamido group has, obviously, a lower electron releasing character than the amino group, but the enthalpic and polar effects should be still marked enough for the selective aerobic oxidation of N-alkylamides, catalysed by NHPI and Co(II) salts.

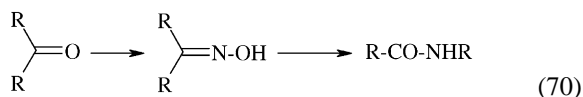Actually, the aerobic oxidation of N-alkylamides occurs under mild conditions leading to carbonyl products (imides, carboxylic acids, ketones, aldehydes) [51]. The reaction products depend on the structure of the alkyl group and the reaction conditions.

Classical organic reactions allow the transformation of carbonyl derivatives into amines: thus carboxylic acids can be converted to amines through well-known reactions, such as the Hofmann [52,53] (Eq. (67)) and the Curtius [54,55] (Eq. (68)) rearrangements.

$$RCOOH \rightarrow RCONH_2 \rightarrow RNH_2 \quad (67)$$

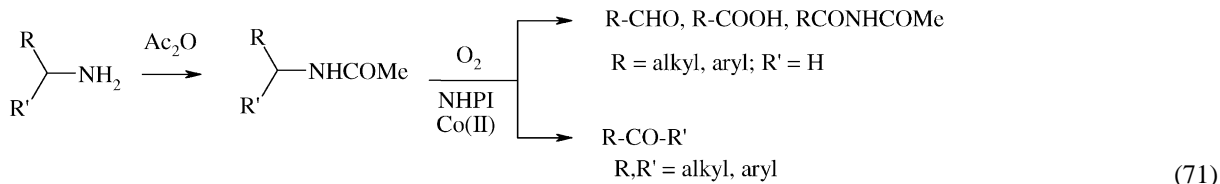$$RCOOH \rightarrow RCON_3 \rightarrow RNH_2 \quad (68)$$
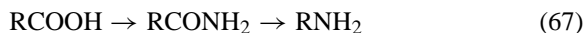
Moreover, carbonyl derivatives can be transformed into amino derivatives by reductive ammonolysis [56] (Eq. (69)) or Beckmann rearrangement [57,58] of the oximes (Eq. (70)).

$$\begin{array}{c} R \\ {>}{=}O + NH_3 + H_2 \longrightarrow {>}-NH_2 + H_2O \\ R \end{array}$$
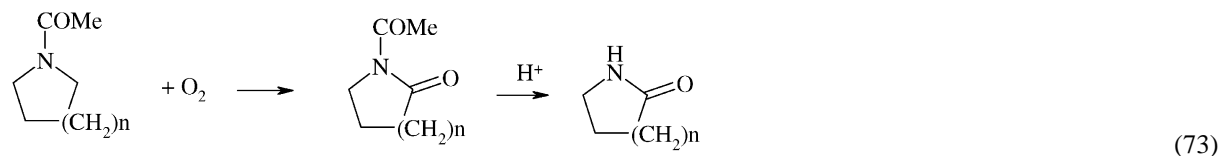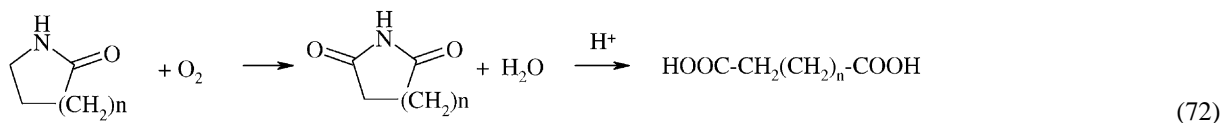
(69)

$$(70)$$
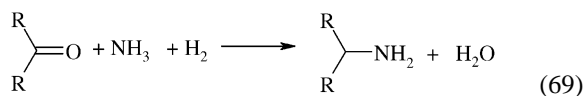
The aerobic oxidation of *N*-alkylamides allows the reverse transformation of amines to carbonyl compounds through the intermediate amides (Eq. (71)).
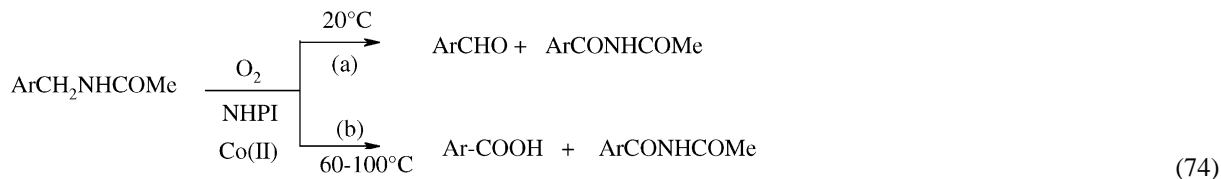

R-CHO, R-COOH, RCONHCOMe

R = alkyl, aryl; R' = H

R-CO-R'

R,R' = alkyl, aryl

$$(71)$$

N-benzylamide is more reactive than the corresponding aromatic aldehydes and the polar effect again determines the oxidation selectivity (the enthalpic effect is quite similar for hydrogen abstraction from *N*-benzylamide and aromatic aldehyde).

The oxidation of lactames or acetamides of cyclic amines does not lead to the cleavage of the ring, but to the formation of cyclic imides (Eq. (72)) or acetyl-lactames (Eq. (73)) (Table 14)

At higher temperature the carboxylic acid and the imide are the only reaction products (74b); the carboxylic acid prevails in MeCOOH solution, while the
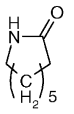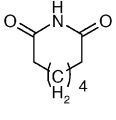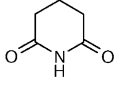

HOOC-CH$_2$(CH$_2$)$_n$-COOH

$$(72)$$

$$(73)$$

Thus, for example, caprolactame gives the cyclic imide in high yield and, by hydrolysis, it turns into adipic acid. Eq. (73) represents a simple procedure for the transformation of cyclic amines to lactames by acetylation, catalytic aerobic oxidation and hydrolysis.

The oxidation of *N*-benzylacetamides leads either to imides and minor amount of aromatic aldehydes at room temperature or to carboxylic acids and variable amounts of imides, depending on the reaction solvent, at higher temperatures (60–100 °C) (Eq. (74)) (Table 15).

imide is prevailing in MeCN solution. In any case the hydrolysis of the imides leads to the aromatic acids in high yields.
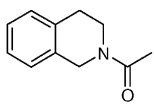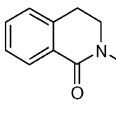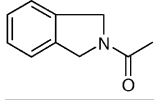
If the benzyl group is secondary the oxidation gives selectively the corresponding ketones (Eq. (75)).

$$\text{ArCHRNHCOMe} + \tfrac{1}{2}\text{O}_2 \rightarrow \text{ArC(HO)RNHCOMe}$$
$$\rightarrow \text{ArCOR} + \text{MeCONH}_2$$

$$(75)$$

20°C

(a)

ArCHO + ArCONHCOMe

ArCH$_2$NHCOMe

O$_2$

NHPI

Co(II)

(b)

60-100°C

Ar-COOH + ArCONHCOMe

$$(74)$$

No appreciable amount of carboxylic acid is formed under conditions of (74a), which means that the
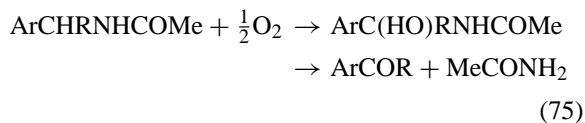
Two aspects of the oxidation of *N*-alkylacetamides are different from that of *N*-benzylacetamides

Table 14
Aerobic oxidation of lactams or acetamides of cyclic amines catalysed by NHPI[a]

Amide	T (°C)	Reaction time (h)	Conversion (%)	Selectivity (%)
	80	3	96	(98)
	80	5	87	(95)
	80	5	97	(93)
	80	4	45	(94)
	80	5	63	(96)
	20	1	100	(91)
	20	3	96	(94)

[a] Amide (5 mmol), NHPI (0.5 mmol), Co(OAc)$_2$·4H$_2$O (0.025 mmol) and m-chlorobenzoic acid (0.25 mmol) in 10 ml of MeCN with O$_2$ at atmospheric pressure.

Table 15
Aerobic oxidation of N-benzylacetamides, ArCH$_2$NHCOCH$_3$ catalysed by NHPI[a]

Ar	Solvent	T (°C)	Reaction time (h)	Conversion (%)	Selectivity (%)
Ph	CH$_3$CN	20	4	89	ArCHO (21), ArCO-NHCOCH$_3$ (77)
Ph	AcOH	100	2.5	75	ArCOOH (96), ArCO-NHCOCH$_3$ (3)
p-CH$_3$-C$_6$H$_4$-	CH$_3$CN	20	4	92	ArCHO (24), ArCO-NHCOCH$_3$ (73)
p-CH$_3$-C$_6$H$_4$-	AcOH	100	3	91	ArCOOH (93), ArCO-NHCOCH$_3$ (4)
m-CH$_3$-C$_6$H$_4$-	CH$_3$CN	20	4	88	ArCHO (22), ArCO-NHCOCH$_3$ (76)
m-CH$_3$-C$_6$H$_4$-	AcOH	100	3	93	ArCOOH (89), ArCO-NHCOCH$_3$ (8)
p-CH$_3$O-C$_6$H$_4$-	CH$_3$CN	20	2	97	ArCHO (16), ArCO-NHCOCH$_3$ (82)
p-CH$_3$O-C$_6$H$_4$-	AcOH	100	1	97	ArCHO (13), ArCOOH (82), ArCO-NHCOCH$_3$ (3)
p-Cl-C$_6$H$_4$-	CH$_3$CN	20	4	87	ArCHO (19), ArCO-NHCOCH$_3$ (78)
p-Cl-C$_6$H$_4$-	AcOH	100	2	92	ArCOOH (66), ArCO-NHCOCH$_3$ (32)

[a] The procedure of Table 14 was utilised.

Table 16
Aerobic oxidation of *N*-alkylacetamides, RNHCOCH$_3$, catalysed by NHPI[a]

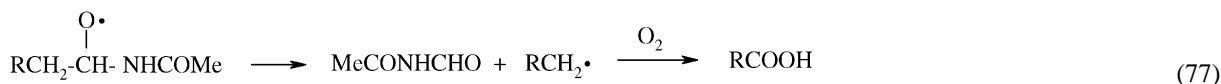| R	T (°C)	Conversion (%)	Selectivity (%)
n-Hexyl	20	70	*n*-C$_4$H$_9$-COOH (4), *n*-C$_5$H$_{11}$-COOH (15), *n*-C$_5$H$_{11}$-CONHCOCH$_3$ (67)
n-Hexyl	80	98	*n*-C$_4$H$_9$-COOH (14), *n*-C$_5$H$_{11}$-COOH (13), *n*-C$_5$H$_{11}$-CONHCOCH$_3$ (68)
n-Dodecyl	20	74	*n*-C$_{10}$H$_{21}$-COOH (2), *n*-C$_{11}$H$_{23}$-COOH (13), n-C$_{11}$H$_{23}$-CONHCOCH$_3$ (81)
n-Dodecyl	80	97	*n*-C$_{10}$H$_{21}$-COOH (6), *n*-C$_{11}$H$_{23}$-COOH (11), *n*-C$_{11}$H$_{23}$-CONHCOCH$_3$ (81)
Cyclohexyl	80	60	Cyclohexanone (98)

[a] The procedure of Table 14 was utilised.

(Table 16). No traces of aldehydes are formed at room temperature, even at low conversions, but the carboxylic acid and the imide are the reaction products when a primary alkyl group is involved. This behaviour is well-explained by the fact that with *N*-benzylamides the polar effect is dominant, while with *N*-alkylacetamides the enthalpic effect prevails, as already observed for the oxidation of benzylic and non-benzylic alcohols [49].

Also in this case the hydrolysis of the imide gives high yields of carboxylic acids, and the overall process represents a simple and cheap way to transform an alkylamine into a carboxylic acid (Eq. (76)).

$$RCH_2NH_2 \overset{Ac_2O}{\to} RCH_2NHCOMe$$
$$\overset{O_2}{\to} RCOOH + RCONHCOMe$$
$$\overset{H^+}{\to} RCOOH \qquad (76)$$
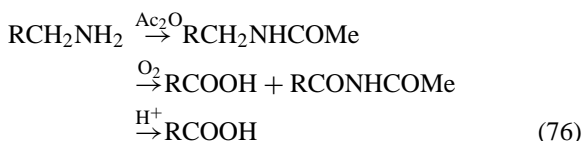
A second different aspect concerns the fact that, in addition to carboxylic acid corresponding to the alkyl group (R-CH$_2$-CH$_2$- → R-CH$_2$-COOH), also the carboxylic acid showing loss of a carbon atom is formed (R-CH$_2$-CH$_2$- → R-COOH) as by-product; this last is formed in small amount at room temperature, but it becomes more significant at higher temperature (Table 16). A plausible explanation for the formation of the by product is the β-fission of the alkoxyl radical intermediate (Eq. (77)) in competition with hydrogen abstraction from NHPI.

$$\overset{\overset{\displaystyle O\bullet}{|}}{RCH_2\text{-}CH\text{-}NHCOMe} \longrightarrow MeCONHCHO + RCH_2\bullet \overset{O_2}{\longrightarrow} RCOOH \qquad (77)$$

The β-fission is more favoured by an increase of temperature and by protic solvents with respect to the hydrogen abstraction [59].

4.6. Oxidation of silanes to silanols

Silanols are of considerable interest not only in organic synthesis [60] but also in industrial processes in which polymeric materials, such as polysiloxanes (silicones) [61] and sol–gel [62] are produced by condensation reactions of reactive silanols. A main approach for silanol synthesis is the oxidation of silanes by a variety of oxidants (peracids [63], KMnO$_4$ [64], Ag$_2$O [65], AgNO$_3$ [65], AgNO$_2$ [65], HgO [66], O$_3$ [67], dioxiranes [68]). Most of these methods give the corresponding siloxanes as undesired side products and utilise expensive oxidants which often involve environmental drawbacks. The aerobic oxidation of silanes, catalysed by NHPI and Co(II) salt under very mild conditions (ambient temperature and pressure) (Eq. (78)), revealed to be particularly effective for the selective synthesis of silanols, without appreciable formation of siloxanes [69]; it appears by far the most convenient process among the numerous methods of oxidation developed for this purpose (Eq. (78)) (Table 17).

$$R_3SiH + \tfrac{1}{2}O_2 \to R_3Si\text{-}OH \qquad (78)$$

The available thermochemical data on Si–H BDE values show that they are on average lower than C–H BDE values and that the factors dominating the thermochemistry of the C–H bonds are essentially unimportant in the silicon congeners [70]. For example, the BDE values for SiH$_3$–H, Me$_3$Si–H and
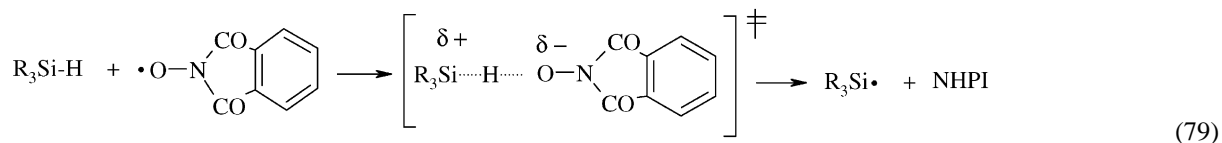
Table 17
Aerobic oxidation of silanes to silanols catalysed by NHPI[a]

Silane	T (°C)	Reaction time (h)	Conversion (%)	Selectivity (%)
Triethylsilane	20	3	100	87
Triphenylsilane	20	7	100	97
Cyclohexyl-dimethyl silane[a]	20	6	100	100
Methyl-diphenylsilane[b]	20	6	60	100
Methyl-diphenylsilane[a]	20	6	100	100
n-$C_{18}H_{37}$-SiMe2H[b]	50	7	48	82
Dimethyl-phenylsilane[a]	50	7	100	100

[a] Silane (3 mmol), NHPI (0.5 mmol), $Co(OAc)_2 \cdot 4H_2O$ (0.015 mmol) and m-chlorobenzoic acid (0.25 mmol) in 5 ml of MeCN with O_2 at atmospheric pressure.

$PhSiH_2$–H are 90.3, 90.3 and 88.2 kcal/mol, respectively, while the corresponding series of BDE values in hydrocarbon chemistry would span a range of 16 kcal/mol (BDE values for CH_3–H, Me_3C–H and $PhCH_2$–H are 104, 94 and 88 kcal/mol, respectively).

Thus, enthalpic and polar effects (Eq. (79)) suggest that the hydrogen abstraction from Si–H bonds by PINO should be, at least, as fast as from C–H bonds.

$$R_3Si\text{-}H + \cdot O{-}N\underset{CO}{\overset{CO}{\bigcirc}} \longrightarrow \left[\underset{R_3Si\cdots H\cdots}{\overset{\delta+}{}} \overset{\delta-}{O}{-}N\underset{CO}{\overset{CO}{\bigcirc}} \right]^{\ddagger} \longrightarrow R_3Si\cdot + NHPI$$
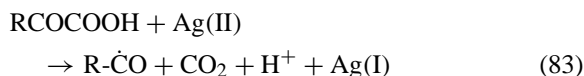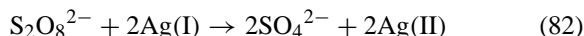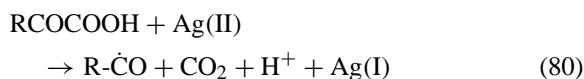
(79)

The hydrogen abstraction according to Eq. (79) is a thermoneutral or slightly endothermic process whose equilibrium is shifted to the right by the fast reaction of the silyl radical with oxygen. Free-radical and redox chains similar to Eqs. (52)–(56) lead to the formation of silanols.

4.7. Acylation of heteroaromatic bases by aerobic oxidation of aldehydes

The substitution of protonated heteroaromatic bases by nucleophilic carbon-centred radicals is one of the main general reactions of this class of aromatic compound for the large variety of successful radical sources, the high regio- and chemoselectivity and the simple experimental conditions [71]. It reproduces most of the Friedel–Crafts aromatic substitutions, but with opposite reactivity and selectivity, due to the high sensitivity to polar effects. Absolute rate constants in the range of 10^5–10^8 $M^{-1}s^{-1}$ at room tem-

perature makes the most reactive bases effective traps for nucleophilic carbon-centred radicals. Practically all the carbonyl σ-type radicals (acyl, carbamoyl and alkoxycarbonyl) and the alkyl π-type radicals without electron-withdrawing groups directly attached to the radical centre are suitable for these substitutions. In particular, two general sources of acyl radicals useful for the acylation of heteroaromatic bases have been developed: the use of t-BuOOH/Fe(II) redox system in the presence of aldehydes [72–74] (Eqs. (80) and (81)) and the oxidative decarboxylation of α-ketoacids by the $S_2O_8^{2-}$/Ag$^+$ redox system [75] (Eqs. (82) and (83)).

$$RCOCOOH + Ag(II)$$
$$\rightarrow R\text{-}\dot{C}O + CO_2 + H^+ + Ag(I) \quad (80)$$

$$t\text{-}BuO^\bullet + RCHO \rightarrow t\text{-}BuOH + R\dot{C}O \quad (81)$$

$$S_2O_8^{2-} + 2Ag(I) \rightarrow 2SO_4^{2-} + 2Ag(II) \quad (82)$$

$$RCOCOOH + Ag(II)$$
$$\rightarrow R\text{-}\dot{C}O + CO_2 + H^+ + Ag(I) \quad (83)$$

The aerobic oxidation of aldehydes, catalysed by NHPI and Co(II) salt, revealed to be effective for

Table 18
Acylation of heteroaromatic bases by aerobic oxidation of aldehydes, R-CHO, catalysed by NHPI[a]

| Heterocycle	R	Conversion (%)	Products selectivity(%)
Quinoline	Ph	50	2-Acyl (34), 4-acyl (41), 2,4-diacyl (22)
4-Methylquinoline	Ph	15	2-Acyl (98)
Quinoxaline	Ph	86	2-Acyl (85), 2,3-diacyl (14)
Quinoxaline[b]	t-Bu	100	2-Acyl (45), 2-t-Bu (52)
Quinoxaline	s-C_3H_7	51	2-Acyl (78), 2-i-Pr (16)
Quinoxaline	n-C_6H_{13}	91	2-Acyl (77), 2,3-diacyl (14)
Quinoxaline	Cyclohexyl	100	2-Acyl (43), 2,3-diacyl (32), 2-acyl-3-cyclohexyl (12)
Quinazoline	n-C_6H_{13}	100	3H-Quinazolin-4-one (96)
Quinazoline	Ph	100	3H-Quinazolin-4-one (98)
Pyrazine	n-C_6H_{13}	85	2-Acyl (96)
Pyrazine	Ph	82	2-Acyl (97)
Pyrimidine	n-C_6H_{13}	14	4-Acyl (98)

[a] Heterocycle (3 mmol), CF_3COOH (3 mmol), aldehyde (15 mmol), NHPI (0.3 mmol), Co(acac)$_2$ (0.005 mmol) and Co(OAc)$_2$·4H$_2$O (0.01 mmol) in 8 ml of PhCN with air at 70 °C for 12 h.
[b] 20 °C.

the acylation of protonated heteroaromatic bases (Eq. (84)) (Table 18) [76].

$$ \text{(84)} $$
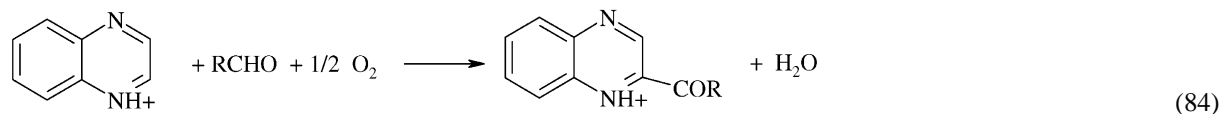
No acylation occurs under the same conditions in the absence of NHPI, which means that the acyl radical is generated by the hydrogen abstraction from the aldehyde by the PINO radical (Eq. (85)).

$$ RCHO + PINO \rightarrow R\dot{C}O + NHPI \qquad (85) $$
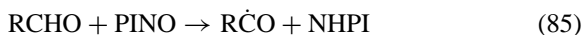
When R in Eq. (85) is a tertiary alkyl group, decarbonylation, which is a fast process [72–74], occurs in competition with the acylation and it increases with the temperature (Eq. (86)).

$$ t\text{-Bu}\dot{C}O \rightarrow t\text{-Bu}^\bullet + CO \qquad (86) $$

Decarbonylation takes place in smaller amount with secondary alkyl and it does not occur with primary alkyl groups and aromatic aldehydes.
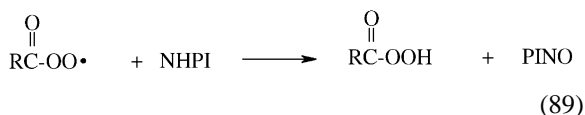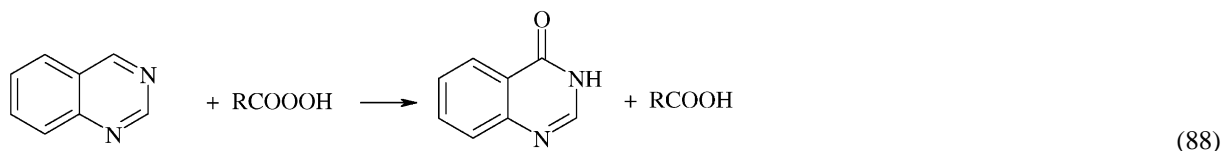
Carboxylic acids, R-COOH, arising from the oxidation of the aldehydes are by-products; the ratios between the products of the heterocyclic acylation and the carboxylic acids depend on the competition of Eq. (87); these ratios increase as the reactivity of the heteroaromatic base increases and the concentration of oxygen decreases.

$$ \text{(87)} $$
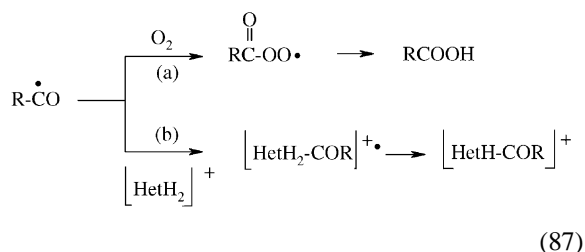
Thus with quinoxaline the ratio between 87a and 87b is lower with air than with oxygen; moreover more carboxylic acid is formed with quinoline than with the more reactive quinoxaline under the same conditions.
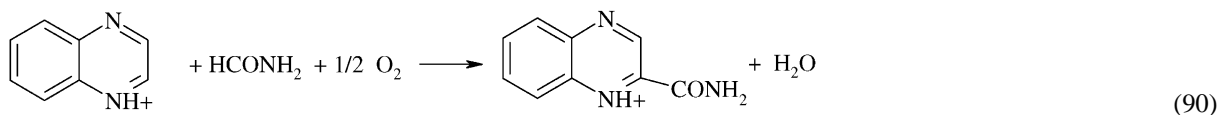
Quinazoline has an anomalous behaviour, compared to the other heteroaromatic bases; no acylation occurs under the same conditions, but 3-H-quinazolin-4-one is the only reaction product. The formation of this latter by oxidation of quinazoline with H$_2$O$_2$ in acetic acid is well-known [77]; its formation can be explained by an analogous oxidation with peracid

(Eq. (88)), formed by hydrogen abstraction by the acylperoxyl radical (Eq. (87a)) from NHPI (Eq. (89)) in a free-radical chain involving Eqs. (85), (87) and (89).

It was, then, considered the possibility to generate PINO radical by a different oxidant, in the absence of oxygen. Cerium ammonium nitrate (CAN) revealed to be particularly effective for this purpose (Eq. (91)).

$$+ \text{ RCOOOH} \longrightarrow \quad + \text{ RCOOH} \tag{88}$$

$$\text{NHPI} + \text{Ce(IV)} \rightarrow \text{PINO} + \text{H}^+ + \text{Ce(III)} \tag{91}$$

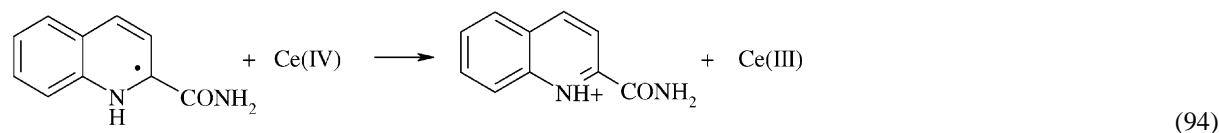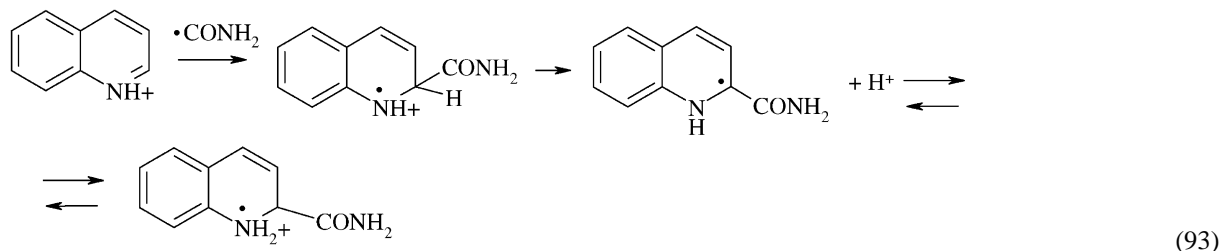$$\text{RC-OO}\bullet \ + \ \text{NHPI} \longrightarrow \text{RC-OOH} \ + \ \text{PINO} \tag{89}$$

4.8. Carbamoylation of heteroaromatic bases by aerobic and non-aerobic oxidation of formamide
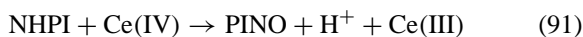
Attempts of aerobic oxidation of formamide, catalysed by NHPI and Co(II) salt, in order to obtain the carbamoylation of heteroaromatic bases similar to the acylation, above described, gave moderate results. The selectivity of carbamoylation of quinoxaline was high (Eq. (90)), but the conversion was low (19%).

When the oxidation of formamide by CAN, catalysed by NHPI, was carried out in the presence of protonated heteroaromatic bases and in the absence of oxygen the selective carbamoylation of the heterocyclic ring was observed [78] (Table 19). In the absence of NHPI no reaction occurs, clearly showing that PINO radical, generated according to Eq. (91), is responsible for the formation of the carbamoyl radical (Eq. (92)).

$$\text{H-CONH}_2 + \text{PINO} \rightarrow \ ^\bullet\text{CONH}_2 + \text{NHPI} \tag{92}$$

CAN has two-fold function: it generates the PINO radical (Eq. (91)) and determines the aromatisation

$$+ \text{ HCONH}_2 \ + \ 1/2 \ \text{O}_2 \longrightarrow \quad + \ \text{H}_2\text{O} \tag{90}$$

Conversions were even lower (<10%) with less reactive heteroaromatic bases (pyridine and quinoline derivatives), which means that the reaction of the carbamoyl radical was much faster with oxygen than with the heteroaromatic bases.

of the radical adduct between the carbamoyl radical and the heteroaromatic base (Eqs. (93) and (94)).

The same procedure applied to the oxidation of aldehydes, leads to the homolytic acylation of


$$\tag{93}$$

$$+ \text{ Ce(IV)} \longrightarrow \quad + \ \text{Ce(III)} \tag{94}$$

Table 19
Carbamoylation of heteroaromatic bases by oxidation of formamide with CAN catalysed by NHPI[a]

Heterocycle	Conversion (%)	Selectivity (%)
Quinoxaline[b]	100	100 (2)
Quinoline	78	95 (2); 5 (4)
4-Methylquinoline	66	100 (2)
2-Methylquinoline	18	100 (4)
Isoquinoline	78	100 (1)
4-Cyanopyridine	57	100 (2)
Pyrazine	62	100 (2)
Quinazoline	52	100 (2)

[a] Heterocycle (2.5 mmol), CAN (5 mmol), NHPI (2.5 mmol), CF_3COOH (5 mmol) in 10 ml of $HCONH_2$ at 70 °C for 6 h.
[b] H_2SO_4 (5 mmol) was used instead of CF_3COOH.

quinaxoline, but with less reactive heteroaromatic bases no acylation takes place because the faster oxidation of the acyl radical (Eq. (95)), compared to the carbamoyl radical, leads to the deactivation of NHPI (Eq. (96)).

$$R\text{-}C^\bullet O + Ce(IV) \rightarrow R\text{-}\overset{+}{C}O + Ce(III) \tag{95}$$

$$\tag{96}$$
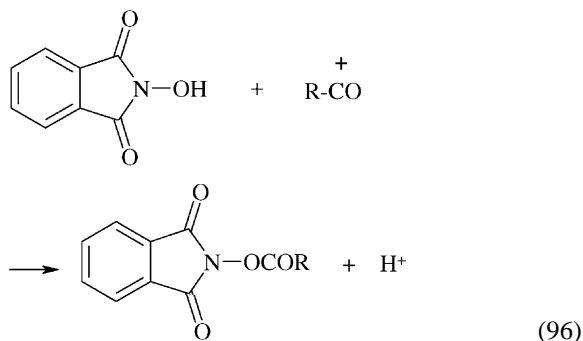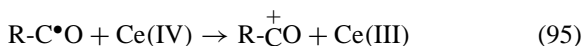
5. Conclusions

The catalytic system formed by $Mn(NO_3)_2$ associated with $Co(NO_3)_2$ or $Cu(NO_3)_2$ revealed to be particularly effective for the aerobic oxidation of ketones to carboxylic acids under mild conditions. The catalysis appears to be of particular interest for the industrial production of aromatic carboxylic acids by oxidation of alkylaromatic ketones and dicarboxylic acids, such as, adipic acid, from cycloalkanones.

A key step of these processes is the electron-transfer oxidation of the enol form of the ketone by the Mn(III) salt. The same catalytic system in association with TEMPO is particularly active and selective for the aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones at ambient temperature and pressure.

The investigation of the thermochemistry of the *N*-hydroxyderivatives and of the kinetics of the corresponding *N*-oxyl radicals has allowed for the first time to give a quantitative basis for understanding the catalytic behaviour of these radicals in the aerobic oxidation of organic compounds, well explaining the opposite behaviour of two *N*-oxyl radicals, TEMPO and PINO, the former inhibiting free-radical processes, the latter inducing free-radical chain. The rationalisation of this catalytic activity has allowed the development of a variety of new selective aerobic oxidations of organic compounds, suitable for industrial applications.

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