Mechanisms of the Aerobic Oxidation of Alcohols to Aldehydes and Ketones, Catalysed under Mild Conditions by Persistent and Non-Persistent Nitroxyl Radicals and Transition Metal Salts − Polar, Enthalpic, and Captodative Effects

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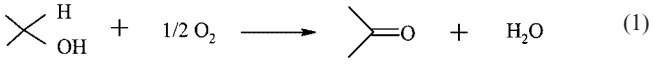
The oxidation of alcohols to aldehydes and ketones by air or oxygen under mild conditions (room temperature and atmospheric pressure), catalysed by persistent and non-persistent nitroxyl radicals in combination with transition metal salts, appears to be the most convenient of the numerous processes developed for these purposes. The thermochemistry, the kinetics, and the Hammett correlations have allowed us to establish, on a quantitative basis, the fundamental difference between the oxidation catalysed by persistent and non-persistent nitroxyl catalysts. In the latter case, an interesting significant captodative effect is displayed for the first time for the oxidation of substituted benzyl alcohols; the importance of enthalpic and polar effects is emphasised.

Introduction

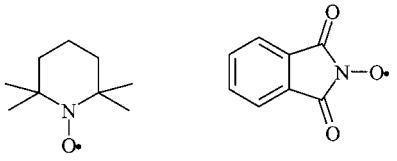
In recent preliminary reports, we have described new highly selective catalysts for the aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones based on persistent[1] and non-persistent[2] nitroxyl radicals in combination with transition metal salts [Equation (1)].



(1)

These processes appear to be particularly convenient, among the numerous processes developed for these purposes, not only with regard to general synthetic involvements, but also for industrial applications, because of the high selectivity, the possibility of recovering and recycling the catalysts, the simple and mild reaction conditions and the cheap oxidant (air or oxygen at room temperature and atmospheric pressure).

Two catalytic systems are particularly useful: the persistent tetramethylpiperidine-*N*-oxyl (TEMPO) radical (**1**) in combination with Mn^{II} and Co^{II} nitrates[1] and the non-persistent phthalimide-*N*-oxyl (PINO) radical (**2**), generated in situ from *N*-hydroxyphthalimide (NHPI), associated with a Co^{II} salt.[2]



1 (TEMPO) **2** (PINO)

TEMPO has been utilised widely as a catalyst for the oxidations of alcohols with a variety of oxidants.[3]

The aerobic oxidation, catalysed by TEMPO in combination with other transition metal salt complexes, has also been utilised: TEMPO/$CuCl_2$ catalyses the aerobic oxidation of benzyl alcohols to aromatic aldehydes, but it is ineffective with less-reactive aliphatic and alicyclic alcohols;[4] TEMPO/[$RuCl_2(PPh_3)_3$] affords an efficient catalyst at 100 °C and 10 bar of pressure;[5] a system of TEMPO/CuBr·Me_2S, perfluorinated bipyridine and biphasic perfluoroctane/chlorobenzene has been utilised at 90 °C;[6] TEMPO/PhenS/$Pd(OAc)_2$ at 100 °C and 30 bar is an effective system for the oxidation of a variety of alcohols.[7]

Our catalytic system, TEMPO in combination with small amounts of $Mn(NO_3)_2$ and $Co(NO_3)_2$, appears, to the best of our knowledge, to be the cheapest and most effective (the oxidation of alcohols occurs with high selectivity and complete conversion with air at room temperature and at-

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mospheric pressure).[1] In a recent review, Sheldon et al.[5a] reported that our aerobic oxidation procedure of alcohols is catalysed by copper salts, which cause the reoxidation of TEMPO to the oxoammonium cation; this statement is erroneous because the most-active metal salt in our process is $Mn(NO_3)_2$,[1] whose catalytic activity is exalted in combination with $Co(NO_3)_2$; only in a few cases has $Mn(NO_3)_2$ been associated with $Cu(NO_3)_2$, which, by itself, is much less active than the Mn^{II} salt. Moreover, the metal salt does not reoxidise TEMPO to the oxoammonium cation, but instead the oxidation of *N*-hydroxypiperidine to TEMPO, while the oxoammonium cation is formed by disproportination of TEMPO catalysed by the acidic medium.[1]

The aerobic oxidation of primary alcohols to carboxylic acid catalysed by NHPI has been reported by the Ishii group,[8] who did not realise, however, the different behaviour of benzylic and aliphatic alcohols during this catalysis. We have shown[2] that the oxidation of primary benzylic alcohols, catalysed by NHPI, leads to aromatic aldehydes in high selectivity and only after the complete conversion of the benzylic alcohols does the further oxidation of the aromatic aldehydes to carboxylic acids occur; in contrast, the oxidation of primary aliphatic alcohols leads to carboxylic acids without significant formation of aldehydes, even at low conversion.

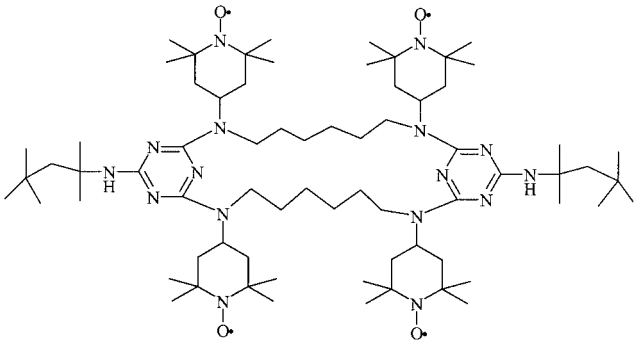
These selectivities clearly indicate that, with PINO catalysis, the primary benzyl alcohols are much more reactive than the corresponding aromatic aldehydes, while for non-benzylic alcohols the corresponding aldehydes are, in contrast, much more reactive than the starting alcohols. With TEMPO catalysis, the alcohols are much more reactive in all cases than the corresponding aldehydes.

For practical applications in the synthesis of aldehydes, the catalysis by TEMPO has the advantage of a general character with respect to the oxidation of benzylic and non-benzylic alcohols and higher stability relative to the PINO radical, which undergoes a much faster decomposition by a unimolecular process.[9] The aerobic oxidation by PINO radical catalysis is limited to the synthesis of aromatic aldehydes, but it has the advantage that the radical is generated in situ from the cheap NHPI, which is readily prepared from phthalic anhydride and hydroxylamine; moreover NHPI can be more easily recovered and recycled, relative to TEMPO, because of its low solubility in several solvents.

More recently, to eliminate the disadvantages (high cost and difficulties in recovering and recycling the catalyst) in using TEMPO catalysis, we[10] developed, in collaboration with CIBA Speciality Chemicals, a new TEMPO-analogous catalyst, characterised by a macrocyclic polypiperidine-*N*-oxyl radical structure **3**, that is even more active than TEMPO for the aerobic oxidation of benzylic and non-benzylic alcohols to the corresponding aldehydes and ketones, but above all the presence of amino groups presents the great advantages of easy recovery and recycling of the catalyst as its ammonium salt, considering that the catalysis is effective only in acidic medium as we discuss below.

Several groups have addressed the problem of recycling the rather expensive nitroxyl radicals utilised in catalytic oxidations by anchoring TEMPO to solid supports, such as silica[11] and the mesoporous silica, MCM-41,[12] entrapping TEMPO in a sol-gel,[13] or utilising the nitroxyl derivative of a commercially available antioxidant, CHIMASSORB® 944, which is an oligomeric, sterically hindered amine (MW ca. 3000).[14] In all these cases, however, the catalysts are active when using NaOCl as the oxidant, but they appear much less active for aerobic oxidations, particularly with aliphatic alcohols.

Thus, the radical **3** appears to be, as far as we know, the most useful nitroxyl radical for the aerobic oxidation of benzylic and aliphatic primary and secondary alcohols to the corresponding aldehydes and ketones under very mild conditions, as well as for the ease of recycling of the catalyst.



3

We have suggested in preliminary reports[1,2] that the different selectivities of the two *N*-oxyl radicals, TEMPO and PINO, as catalysts for the oxidation of alcohols, should be related to the thermochemical aspects concerning the O−H bonds of the corresponding hydroxylamines, TEMPO-H and PINO-H(NHPI), and to polar effects. To understand the factors that affect these different selectivities, we have determined the Bond Dissociation Enthalpies (BDE) of the O−H bonds in the hydroxylamine derivatives, the effects of substituents in the oxidation of alcohols catalysed by the nitroxyl radicals TEMPO and **3**, and the absolute rate constants for the hydrogen atom abstraction from benzylic C−H bonds of substituted benzyl alcohols by the PINO radical, pointing out in this paper, on a quantitative basis, the relative importance of the enthalpic and polar effects and displaying, for the first time, an interesting kinetic captodative effect in a free radical autoxidation.

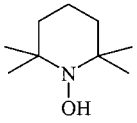
Results and Discussion

Catalysis by TEMPO and CIBA CBX

A remarkable aspect of the catalysis by the persistent nitroxyl radical TEMPO or **3** and non-persistent PINO radicals is the fact, reported in our preliminary reports,[1,2] that in the aerobic oxidation of primary alcohols the two different kinds of catalyst, even though they are formally quite similar (*N*-oxyl radicals), give different results.

The uncatalysed oxidation of organic compounds by molecular oxygen under mild conditions is generally characterised by free radical chain processes (autoxidation).

A thermochemical investigation of the values of the BDE of the O−H bonds in hydroxylamine derivatives (TEMPO-H, **4**, *N*-benzoylmethyl hydroxylamine, **5**, and NHPI, **6**) allowed us to obtain useful quantitative information concerning the mechanism of the aerobic oxidation of alcohols catalysed by hydroxylamines.



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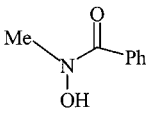

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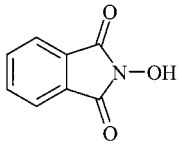

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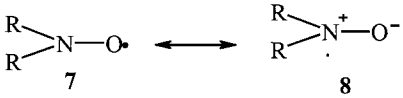
We used the EPR radical equilibration technique[15] to measure the values of BDE of the O−H bonds; Table 1 presents the results.[9]

Table 1. Values of the BDE for the O−H bonds in the hydroxylamines **4**, **5**, and **6**

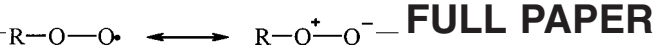
Hydroxylamine	BDE (kcal/mol)
4	69.6
5	79.2
6	88.1

These data indicate that the carbonyl groups directly bonded to the nitrogen atom (*N*-acylhydroxylamines) strongly increase the values of the BDE of the O−H bonds relative to alkylhydroxylamines.

Qualitatively, the phenomenon is similar to that observed for the values of BDE of the O−H bonds in alcohols (RO−H, 104 kcal/mol) and hydroperoxides (ROO−H, 88 kcal/mol) relative to carboxylic acids (RCOO−H, 110 kcal/mol) and peracids [R(CO)OO−H, 93 kcal/mol). Even in these cases, an acyl group increases the strength of the O−H bonds and this effect can be ascribed to the energy difference between the oxygen-centred radicals and the corresponding hydroxyl derivatives. The effect is much more marked for acyl hydroxylamines, because of the fact that in dialkyl nitroxides the structures **7** and **8** contribute to the resonance to approximately the same extent[16] [Equation (2)]; such a stabilisation is not possible for alkoxyl, R−O·, radicals and it has a lower contribution for peroxyl, ROO·, radicals [Equation (3)]. The presence of carbonyl groups reduces the importance of the mesomeric structures **8** and **10**, because of its electron-accepting character, but the effect is larger for structure **8**.

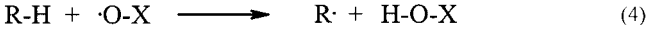


7 **8** (2)



9 **10** (3)

The results listed in Table 1 clearly indicate that the quite general reaction of hydrogen atom abstraction from a C−H bond by an oxygen-centered radical [Equation (4)] is largely endothermic with TEMPO [Equation (5)] ($\Delta H \approx 12-25$ kcal/mol), while it is slightly exothermic ($\Delta H \approx -6$ to -3 kcal/mol) for benzyl alcohols and endothermic ($\Delta H \approx 7-8$kcal/mol) for aliphatic alcohols in the reactions with PINO [Equation (6)].



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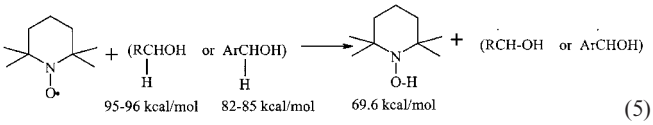
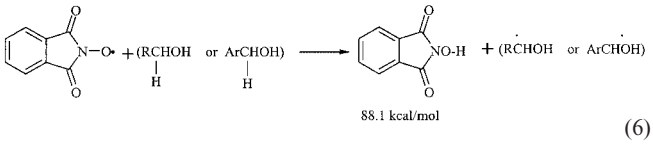
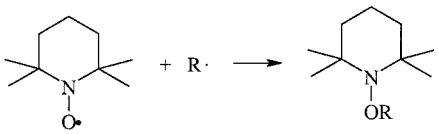


95-96 kcal/mol 82-85 kcal/mol 69.6 kcal/mol (5)



88.1 kcal/mol (6)

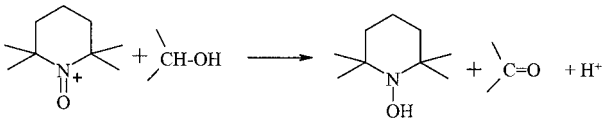
The hydrogen atom abstraction by TEMPO [Equation (5)] is too endothermic, especially for non-benzylic alcohols, to occur under mild conditions. The non-radical character of the aerobic oxidation of the alcohols catalysed by TEMPO and $Mn(NO_3)_2$/$Co(NO_3)_2$ is, in any case, clearly demonstrated by the fact that under the same conditions, but in the absence of TEMPO, the aldehydes and ketones are readily oxidised to carboxylic acids by free-radical chains, while the corresponding alcohols are quite inert.[17,18] Thus, TEMPO has two basic functions during the catalysis: it catalyses the oxidation of the alcohols, but it also inhibits further aerobic oxidation of aldehydes and ketones, which occurs readily under the same conditions in the absence of TEMPO,[17,18] that determines its very high selectivity. The inhibition of the aerobic oxidation of aldehydes and ketones is related to the fact that TEMPO is a persistent radical that reacts rapidly with a variety of different radicals [Equation (7)] and breaks free-radical chains.



(7)

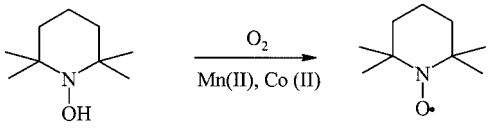
In addition, the catalysed oxidation of alcohols by O_2 and TEMPO in combination with $Mn(NO_3)_2$ and $Co(NO_3)_2$ must be, therefore, related to the reaction of the oxoammonium salt, generated from TEMPO, and the alcohols [Equation (8)], as suggested by a variety of different

oxidants,[3] in contrast to the other aerobic oxidations catalysed by TEMPO associated with Ru or Pd complexes for which the suggested[5] role of the nitroxyl radical involves the oxidation of the metal complex to a higher oxidation state, which is the actual oxidant of the alcohol.



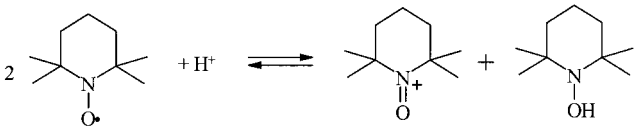
(8)

The function of O_2 in combination with $Mn(NO_3)_2$ and $Co(NO_3)_2$ is to regenerate TEMPO from the *N*-hydroxypiperidine [Equation (9)].



(9)

The catalysis is effective only in an acidic medium (the oxidation takes place in acetic acid solution, but not in acetonitrile under the same conditions, that allows the use of the catalyst **3** as its ammonium salt with *p*-toluenesulfonic acid), which indicates that the oxoammonium salt is generated by the disproportionation equilibrium of TEMPO [Equation (10)].



(10)

This equilibrium [Equation (10)] is affected by the acidity of the reaction medium, but even when it is unfavourable the fast reaction between the oxoammonium salt and the alcohol [Equation (8)] shifts the equilibrium to the right.

The mechanism of Equation (8) is still not completely clear and we have investigated the effects that the substituents on the aromatic ring have on the aerobic oxidation of benzyl alcohols using competitive kinetics. The results with TEMPO and **3** in acetic acid and in the presence of *p*-toluenesulfonic acid are reported in Table 2 and the Hammett correlations from these results are presented in Figures 1, 2, and 3.

Table 2. Relative rates, for the aerobic oxidation of substituted benzyl alcohols catalysed by TEMPO, **3**, and **3**/*p*-toluenesulfonic acid (PTS) in conjunction with Mn^{II}/Co^{II}

X	TEMPO k_X/k_H	**3** k_X/k_H	**3** + PTS k_X/k_H
p-OMe	2.88	2.47	3.74
m-OMe	0.93	1.02	0.74
p-Me	2.23	–	–
m-Me	1.10	1.04	1.02
p-Cl	0.30	1.05	0.94
m-Cl	0.24	0.78	0.64
p-CN	0.13	0.81	0.43
m-CN	0.13	0.43	0.42
p-NO_2	0.14	0.49	0.54
m-NO_2	0.12	–	–

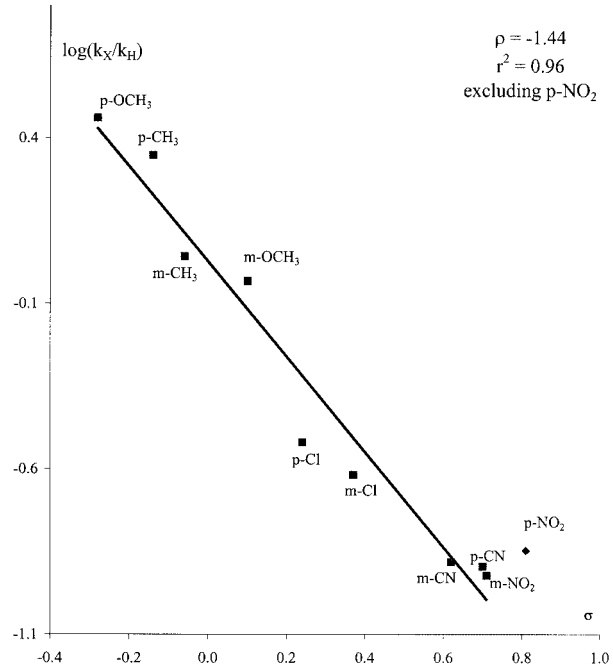


Figure 1. Substituent effects in the aerobic oxidation of substituted benzyl alcohols under TEMPO catalysis

Previous results for the oxidation by the oxoammonium salt have shown that the hydrogen isotopic effect is higher under acidic conditions ($k_H/k_D \approx 3.1$)[20] than under alkaline ($k_H/k_D \approx 1.8$)[21] conditions. These results suggested[21] that under acidic conditions the rate-determining step should be the α-proton abstraction from the adduct **11** [Equation (11)], which justifies the higher kinetic isotopic effect, while under alkaline conditions the equilibrium formation of the complex **12** [Equation (12)] might occur at a rate similar to that of the proton transfer, and both contribute to the rate-determining step. The effect of the substituents on the oxidation of substituted benzyl alcohols would be opposite, when considering that the α-proton abstraction is favoured by electron-withdrawing groups and the forma-

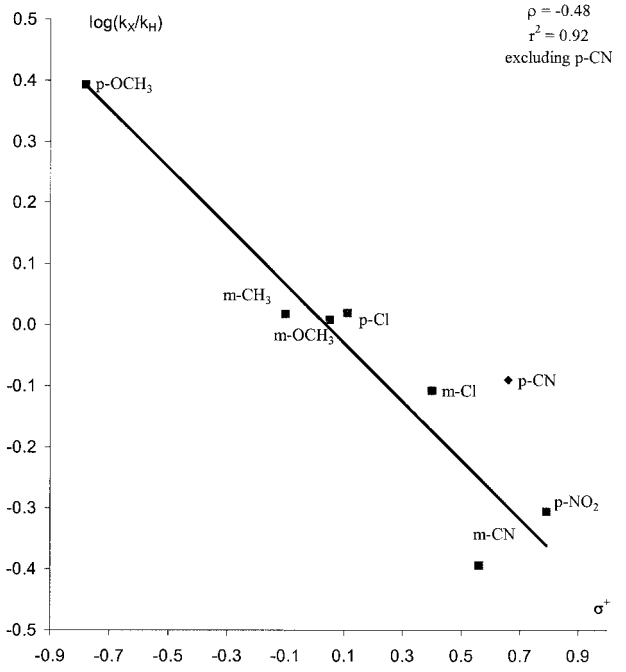


Figure 2. Substituent effects in the aerobic oxidation of substituted benzyl alcohols using **3** as catalyst

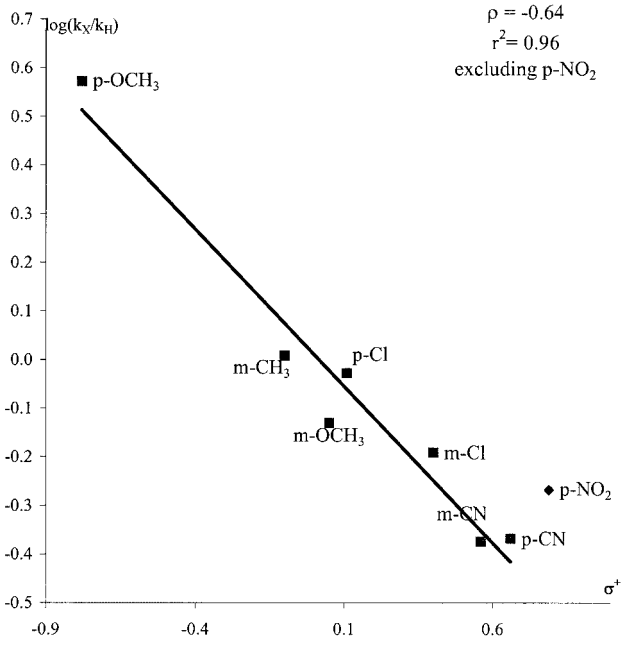
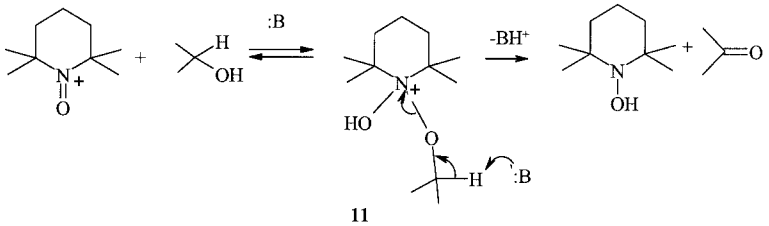


Figure 3. Substituent effects in the aerobic oxidation of substituted benzyl alcohols using **3** as a catalyst in the presence of *p*-toluenesulfonic acid

tion of the complexes **11** and **12** is favoured by electron-donating substituents.

The Hammett correlations (Figures 1−3) from the results presented in Table 2, however, indicate that also under acid conditions the rate of formation of the adduct **11** prevails over the deprotonation, with electron-donating groups activating and electron-withdrawing substituents deactivating the oxidation according to the nucleophilic character of the benzyl alcohols. The opposite behaviour is expected if the deprotonation is the rate-determining step. The polar effect of the substituents, however, is not high (the ρ parameters are relatively small); we explain this behaviour by suggesting that under acidic conditions the formation of the adduct **11**, which is favoured by electron-releasing substituents in the benzyl alcohols, occurs almost simultaneously with the α-proton abstraction favoured, in contrast, by electron-withdrawing substituents; both steps contribute with opposite polar effects to the rate determining step, which balances the overall polar effect, but the nucleophilic character of the substituted benzyl alcohols, which affects the addition rate to the oxoammonium salt, always prevails. This interpretation also explains the somewhat less satisfactory Hammett correlations presented in Figures 1−3 for the strongly electron-withdrawing substitu-



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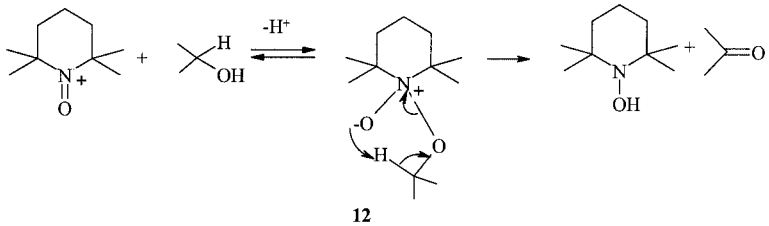


(12)

ents (p-NO_2 and p-CN), which further increase the rate of the α-proton abstraction in Equation (11) and contribute more to balance the less-marked nucleophilic character of p-nitro- and p-cyano-benzyl alcohols.

The same interpretation explains, in our opinion, the higher polar effect (larger value of ρ) observed with TEMPO relative to the radical **3**, which has a similar nitroxide group structure; the protonation of the amino groups in **3** increases the electrophilic character of the oxoammonium salt and the rate of addition of the benzyl alcohol, which increases the contribution of proton abstraction in Equation (11) to the rate-determining step.

Our catalytic system of aerobic oxidation is active only in an acidic medium because of the fundamental role of the disproportionation equilibrium of Equation (10), so that the effect of the substituents cannot be evaluated under alkaline conditions.

More recently,[22] TEMPO has been utilised as a catalyst for the aerobic oxidation of benzyl alcohols to aromatic aldehydes in combination with a much more expensive metal complex, the enzyme laccase (a family of "blue copper" oxidase proteins), with the results obtained being similar to those from our catalyst system, which, however, is more active. The effect of the substituents was quite peculiar in that all the substituents, either electron-withdrawing or electron-donating, activated the oxidation, as presented in the Table 3 where the results are compared with those obtained using our catalytic system.

Table 3. Relative rates for the aerobic oxidation of p-X-C_6H_4-CH_2OH catalysed by TEMPO and laccase or TEMPO and Mn^{II} and Co^{II} nitrates

X	TEMPO/laccase k_X/k_H	TEMPO/Mn^{II}/Co^{II}
OMe	2.5	2.80
Cl	1.8	0.30
NO_2	1.3	0.14
Me	1.2	2.23

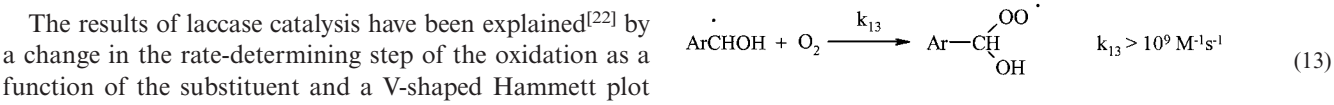
The results of laccase catalysis have been explained[22] by a change in the rate-determining step of the oxidation as a function of the substituent and a V-shaped Hammett plot has been obtained with the σ_I constants. Thus, the change of the rate-determining step from the nucleophilic O-attack to C-deprotonation should be a function not only of the medium's acidity,[19] as shown by the isotope effect, but also of the substituent.[22] The catalysis by TEMPO/laccase could be more complex, however, considering that the same system catalyses the aerobic oxidation of benzyl ethers to esters,[22] while our catalyst, which is more active in the oxidation of alcohols relative to the laccase system, is completely inert towards the oxidation of benzyl ethers.

The latter compounds, in contrast, are oxidised readily to esters by O_2 and NHPI catalysis in combination with a Co^{II} salt, which is a free-radical chain process as is discussed below.

Catalysis by *N*-Hydroxyphthalimide (NHPI)

The report by Ishii and co-workers[8] on the aerobic oxidation of primary alcohols to carboxylic acids under NHPI catalysis did not consider the different behaviour of benzylic and non-benzylic alcohols, as we demonstrated in a preliminary report.[2] The different selectivity is remarkable since a free-radical mechanism appears to be involved in this catalysis and aldehydes are generally more reactive than the corresponding alcohols in the uncatalysed free-radical autoxidation, simply because, for enthalpic and polar reasons,[23] the acylperoxyl radicals, RCOOO·, arising from aldehydes are more reactive than the α-hydroxyperoxyl radicals, RCH(OH)OO·, arising from alcohols. Next, we indicate that the thermochemistry, kinetics, and the substituent effects explain this behaviour well.

The value of the BDE of the O−H bond in NHPI (88.1 kcal/mol; Table 1) suggests that the hydrogen atom abstraction from benzyl alcohols by the PINO radical is slightly exothermic and Equation (6) must be considered an equilibrium, which, however, is shifted to the right by the fast reaction of the benzyl radical with O_2 [Equation (13)], followed by the hydrogen atom abstraction from NHPI [Equation (14)] and the generation of a catalytic cycle [Equations (6), (13), and (14)].



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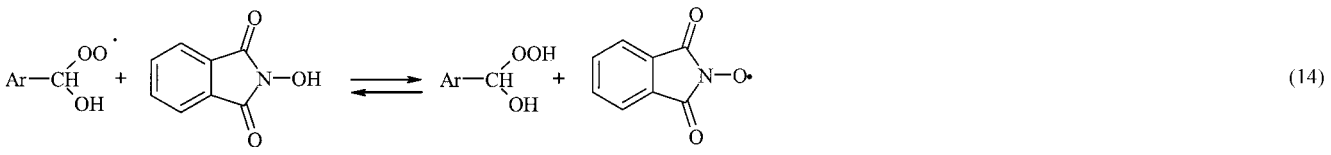

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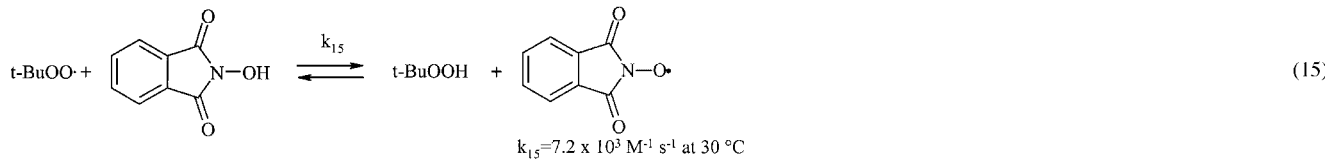
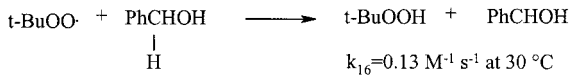


(15)

We have determined that the absolute rate constant for the hydrogen atom abstraction by the *tert*-butylperoxyl radical from the O−H bond of NHPI[9] [Equation (15)] supports Equation (14). In addition, Equations (14) and (15) can be considered equilibrium processes because the values of BDE of the O−H bonds in NHPI and ROO−H are almost identical (88 kcal/mol); the rate constant k_{15} [Equation (15)] is, however, much higher than that for the hydrogen atom abstraction by the peroxyl radical from benzyl alcohol [Equation (16)].



(16)

Thus, Equation (14) prevails highly over Equation (16), which justifies the catalytic cycle based on Equations (6), (13), and (14).

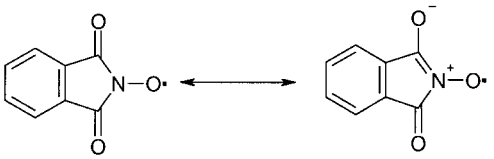
By EPR spectroscopy, we have verified the occurrence of hydrogen atom abstraction by the PINO radical from the C−H bonds of benzyl alcohol and other substrates, which strongly supports the radical character of these oxidations; moreover, we have evaluated the absolute rate constants of these hydrogen atom abstractions, which we compare with the corresponding hydrogen atom abstraction by the *tert*-butylperoxyl radical.[9,15]

In spite of the fact that the values of the BDE of the O−H bonds in NHPI and *t*BuOO−H are identical (88 kcal/mol), the PINO radical is considerably more reactive in the abstraction of the hydrogen atom from a C−H bond (Table 4) than is the peroxyl radical. This different reactivity cannot, therefore, be ascribed to the enthalpic effect, but instead to the polar effect in relation to a more-pronounced electrophilic character of the PINO radical relative to the peroxyl radical, and also by considering that the phenomenon is particularly marked for benzyl alcohol [Equation (17)].

Table 4. Absolute rate constants at 25 °C for the hydrogen atom abstraction by PINO and *tert*-butylperoxyl radical[9]

RH	$k_{H\ (PINO)}$ $M^{-1}s^{-1}$	$k_{(tBuOO^{\bullet})}$ $M^{-1}s^{-1}$	$k_{H\ (PINO)}/k_{(tBuOO^{\bullet})}$
$PhCH_3$	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
cyclohexane	0.047	0.0034	13.8

Nitroxyl radicals are generally electrophilic in nature, but this polar character is considerably enhanced by the presence of the two carbonyl groups in PINO [Equation (18)].



(18)

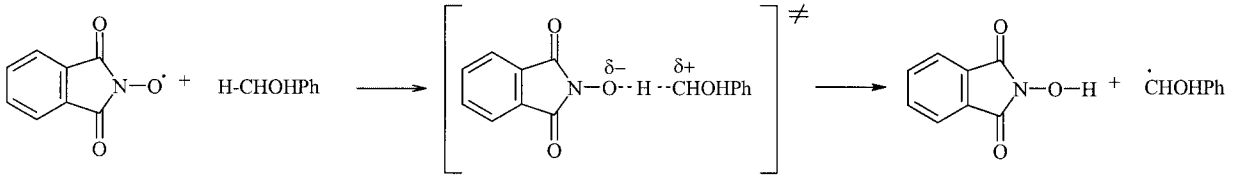
The effects are similar to those observed with acyl peroxyl, RC(=O)OO·, and acyloxyl, RC(=O)O·, radicals when compared to alkyl peroxyl, ROO·, and alkoxyl, RO·, radicals; the former are more electrophilic than the latter.[23] The phenomenon is more marked with PINO than with acylperoxyl and acyloxyl radicals because the nitrogen atom can stabilise a positive charge, as in Equation (18), better than carbon or oxygen atoms.

To evaluate the polar effect, we investigated the influence of the substituents on the aromatic ring toward the aerobic oxidation of benzyl alcohols catalysed by NHPI and determined the absolute rate constants by competitive kinetics. The results are reported in Table 5.

Table 5. Absolute rate constants for the hydrogen atom abstraction from *p*-X-C_6H_4-CHOH-H by PINO radical at 25 °C

X	k (M^{-1} s^{-1})	k_X/k_H
H	28.3	1.00
p-Me	65.9	2.33
m-Me	48.1	1.70
p-OMe	150.0	5.3
m-OMe	43.3	1.53
p-Cl	35.1	1.24
m-Cl	25.7	0.91
p-CN	30.6	1.08
m-CN	15.2	0.54
p-NO_2	27.5	0.97
m-NO_2	13.5	0.48

Figure 4 displays a Hammett correlation between the results presented in Table 5 and values of σ^+; a satisfactory correlation is observed with the exception of the data from the reactions of *p*-nitro- and *p*-cyanobenzyl alcohols, in which the strongly electron-withdrawing substituents have a negligible effect on the reactivity, while the *m*-nitro- and *m*-cyanobenzyl alcohols are significantly deactivated. We



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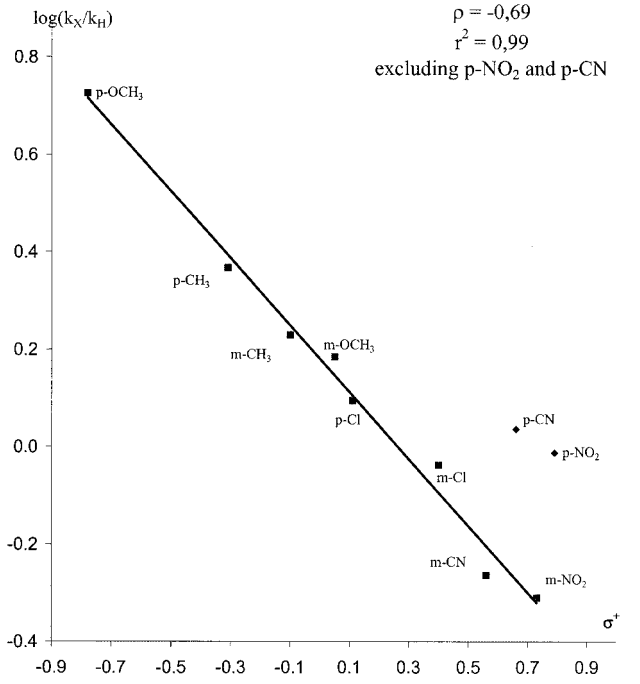
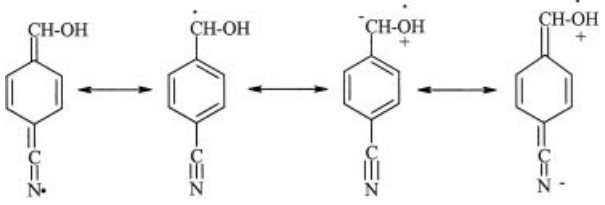


Figure 4. Substituent effects in the aerobic oxidation of substituted nder NHPI catalysis

explain this behaviour by a captodative effect, which, qualitatively,[24] suggests that pairs of substituents having opposite polarities act in synergy on the stabilisation of a radical according to the resonance structures of Equation (19).



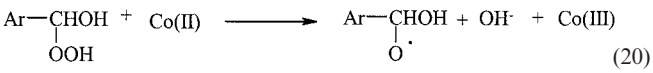
(19)

From a quantitative point of view, relationships have been observed between the α- and β-proton EPR spectroscopic hyperfine splitting constants and the radical stabilisation enthalpy (RSE) and with the BDE values of the corresponding C−H bond;[25] the overall effects exceed the sum of the individual substituent effects, which emphasises the synergetic captodative stabilisation.[25]

Although the phenylogy [Equation (19)] attenuates the substituent effect, relative to a captodative effect in which the two substituents are directly bonded to the radical centre, the results of Table 5 and Figure 4 indicate that the captodative effect is still relevant for the hydrogen atom abstraction from benzylic C−H bonds; that result is also supported by the proton hyperfine splitting constant of the *p*-cyanobenzyl methyl ether radical.[26] Thus, the captodative effect appears to determine the significant decrease of the values of the BDE of the benzylic C−H bonds in *p*-cyano- and *p*-nitrobenzyl alcohols; that phenomenon is reflected in a favourable enthalpic effect, which balances the unfavourable polar effect, resulting from the development of positive charge on the benzylic carbon atom in the transition state of the hydrogen atom abstraction [Equation (17)].

For all the other substituents reported in Table 5, the effects on the values of the BDE of their benzylic C−H bonds is rather poor[27] and the polar effect largely prevails over the enthalpic effect, which leads to a good Hammett correlation.

The equilibrium of Equation (14) is shifted to the right by the redox decomposition of the hydroperoxide [Equation (20)]; a catalytic amount of *m*-chlorobenzoic acid avoids the precipitation of the cobalt salt; the presence of Co^{II} is necessary for the oxidation to occur.

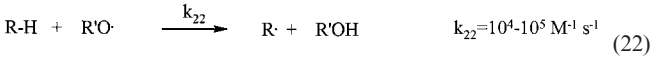


(20)

The alkoxyl radical reacts very fast with NHPI, which leads to the formation of the aldehyde and regeneration of the PINO radical [Equation (21)].

We have not evaluated the rate constant of Equation (21), but the alkoxyl radicals are much more reactive in hydrogen atom abstractions than are the peroxyl radicals for obvious enthalpic reasons (the values of the BDE for RO−H and ROO−H are 104 and 88 kcal/mol, respectively): the alkoxyl radicals abstract hydrogen atoms from C−H bonds [Equation (22)] with rate constants 10^5-10^7 times larger than do the peroxyl radicals [Equation (23)].

We have determined the absolute rate constant for the hydrogen atom abstraction from the O−H group of NHPI by the peroxyl radical (k_{15} = $7.2\cdot10^3$ $M^{-1}s^{-1}$) [Equation (15)]; if the rate of hydrogen atom abstraction by the alkoxyl radical occurs to the analogous extent of Equations (22) and (23), relative to the peroxyl radical, we should expect a diffusion-controlled rate for Equation (24).



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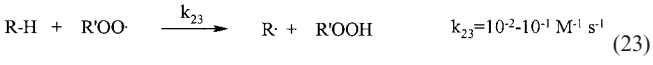

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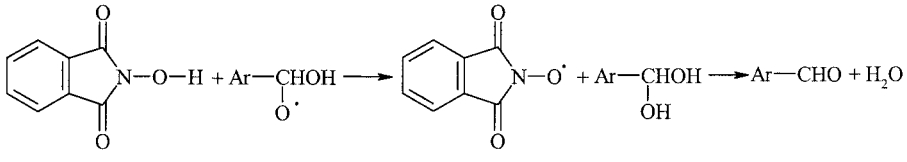

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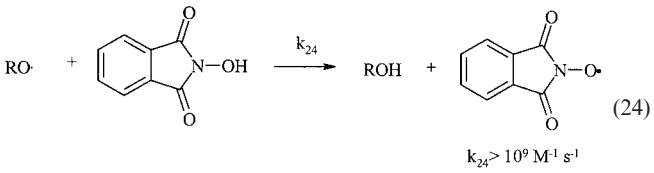
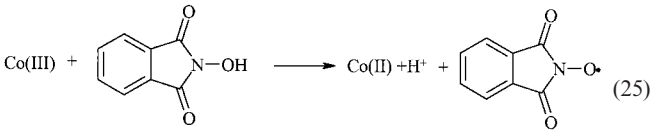


(24)

The Co^{III} salt can be reduced to Co^{II} either by NHPI [Equation (25)] or by the hydroperoxide [Equation (26)] to generate a redox chain.



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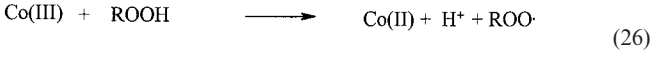
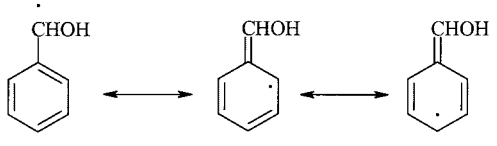


(26)

The results in Table 5 explain well the high selectivity observed in the oxidation of primary benzyl alcohols to aromatic aldehydes; these latter species can be oxidised further to carboxylic acids only after the complete oxidation of the starting benzyl alcohols, which clearly shows that the alcohols are much more reactive than are the corresponding aldehydes. The different reactivity must be ascribed to a more-marked polar effect in the hydrogen atom abstraction from the alcohols [Equation (17)] than that from the aldehydes, and also to a more-favourable enthalpic effect [Equation (6)].

With non-benzylic alcohols, in contrast, the enthalpic effect is dominant [the values of the BDE for RCH(OH)−H are 8−10 kcal/mol larger than those of RC(O)−H] and that phenomenon makes these aldehydes much more reactive than their corresponding alcohols, which are selectively oxidised to carboxylic acids, even at low conversions.

The different electronic configurations of the benzyl and benzoyl radicals explain the fact that the values of the BDE for both aromatic and aliphatic RC(O)−H bonds are effectively identical (ca. 87 kcal/mol). The values of the BDE of the benzylic ArCH(OH)−H bonds are lower than those of aliphatic RCH(OH)−H bonds because the benzyl radicals are π-type radicals and they are stabilised by resonance with the aromatic ring [Equation (27)] and, obviously, that is not possible with aliphatic ketyl radicals. the benzoyl radicals are σ-type radicals and they cannot be stabilised by a similar resonance effect [Equation (28)].



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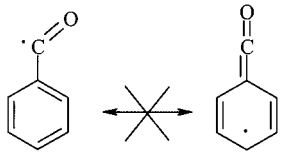

(28)

More recently,[28] NHPI also has been utilised as a catalyst for the aerobic oxidation of benzyl alcohols to aldehydes in combination with the enzyme laccase, with results similar to those obtained using our catalytic system, which, however, is always more active and much cheaper; the results suggest that both reactions have effectively the same mechanism. The function of laccase would be similar to that of the Co salt, i.e., in the regeneration of the PINO radical in a catalytic cycle according to reactions similar to those of Equations (14), (15), (18), (21), and (22). The effect, however, of the substituents and the Hammett correlation observed with laccase are rather different to those reported in this paper. No significant captodative effect was observed when using the NHPI/laccase catalyst, but a satisfactory Hammett correlation with respect to the σ^+ constants, having a value of ρ of −0.89, was reported, including the data for *p*-nitrobenzyl alcohol. Since both the values of the BDE and the rates of hydrogen atom abstraction of the benzylic C−H bonds are not generally affected by solvents (in contrast to the behaviour of phenolic O−H bonds for which both the values of the BDE and the rates of hydrogen atom abstraction are influenced by the solvents[29]), it is unlikely that the different solvents used with the NHPI/laccase and NHPI/$Co(OAc)_2$ catalyst systems can be the cause of the different results. It is likely that the mechanism of the oxidation is somewhat more complex in the reaction of the much more complex laccase/NHPI catalyst that it is for Co^{II}/NHPI.

Very recently, thermochemical data for the O−H bond in NHPI and kinetic data for the hydrogen atom abstraction from C−H bonds by the PINO radical have been reported.[30] The value of the BDE for the O−H bond in NHPI agrees very well with the results previously reported by us,[9] but the kinetic data are rather different and that phenomenon cannot be ascribed to a solvent effect, which is negligible for the hydrogen atom abstraction from C−H bonds.[27] In particular the higher rate constant reported by Espenson et al.[30] for the hydrogen atom abstraction from benzaldehyde relative to benzyl alcohol is in clean contrast with our result[2] that benzyl alcohol is quantitatively oxidised to benzaldehyde without formation of significant amounts of benzoic acid in the aerobic oxidation catalysed by NHPI. This result suggests that benzyl alcohol is much more reactive than benzaldehyde; moreover, all the results[2,8,17] indicate that the hydrogen atom abstraction from C−H bonds by PINO is the rate-determining step in these aerobic oxidations catalysed by NHPI. On the other hand, both polar and enthalpic effects suggest that benzyl alcohols must be more reactive than the corresponding aldehydes towards hydrogen atom abstraction by electrophilic radicals, and PINO is certainly an electrophilic radical on the basis of its structure and the results presented in Figure 4 and Table 5. The opposite behaviour demonstrated by aliphatic primary alcohols further supports the finding that the hydrogen atom abstraction by PINO is rate-determining; in this case, the enthalpic effect dominates and it makes the aldehydes much more reactive than the alcohols.

Experimental Section

Materials: The catalysts, with the exception of CIBA CBX (**3**), the benzyl alcohols and the aromatic aldehydes are commercially available and were used without further purification. The catalyst **3**, prepared according to a recent patent, was provided by CIBA Speciality Chemical Inc.[31]

General Procedures for Determining the Relative and Absolute Rate Constants of the Aerobic Oxidations of Substituted Benzyl Alcohols: Competitive kinetics were utilised to determine the relative rate constants of the aerobic oxidations of benzyl alcohols to aromatic aldehydes.

Since we have evaluated[9] by EPR the absolute rate constant for the hydrogen atom abstraction from benzyl alcohol by the PINO radical (28.3 $M^{-1}s^{-1}$ at 25 °C), which is the rate-determining step of the oxidation, the absolute rate constants for the substituted benzyl alcohols, reported in Table 5, have been obtained from their relative rates.

Competitive experiments were run between benzyl alcohol, $PhCH_2OH$, and substituted benzyl alcohols, $XC_6H_4CH_2OH$, and suitable reaction times were utilised to have low conversions of the benzyl alcohols to the aromatic aldehydes. The abundances of the latter compounds were determined by GC using internal standards and the response factors obtained from authentic samples. The relative rate constants were evaluated using Equation (29).

$$\frac{k_X}{k_H} = \frac{\log \dfrac{[XC_6H_4CH_2OH]_0 - [XC_6H_4CHO]}{[XC_6H_4CH_2OH]_0}}{\log \dfrac{[PhCH_2OH]_0 - [PhCHO]}{[PhCH_2OH]_0}} \qquad (29)$$

A) Aerobic Oxidation of Benzyl Alcohols Catalysed by TEMPO, $Mn(NO_3)_2$, and $Co(NO_3)_2$: A solution of benzyl alcohol (3 mmol), substituted benzyl alcohol (3 mmol), TEMPO (0.15 mmol), $Mn(NO_3)_2$ (0.06 mmol), and $Co(NO_3)_2$ (0.06 mmol) in acetic acid (10 mL) was stirred under an O_2 atmosphere for 1.5 h.

The yields of benzaldehyde and substituted benzaldehydes were determined by GC analysis using *p*-chlorobenzaldehyde and *m*-tolualdehyde as internal standards. The relative rates, evaluated by Equation (29), are reported in Table 2.

B) Aerobic Oxidation of Benzyl Alcohols Catalysed by 3, $Mn(NO_3)_2$, and $Co(NO_3)_2$: The procedure is identical to that described in A) with the only difference that the catalyst **3** (0.04 mmol) was used instead of TEMPO. The results are reported in Table 2.

C) Aerobic Oxidation of Benzyl Alcohols Catalysed by 3, $Mn(NO_3)_2$, $Co(NO_3)_2$, and *p*-Toluenesulfonic Acid: The procedure is identical to that described in B), except for the presence of *p*-toluenesulfonic acid (0.3 mmol). The results are reported in Table 2.

D) Aerobic Oxidation of Benzyl Alcohols Catalysed by NHPI and $Co(OAc)_2$: A solution of benzyl alcohol (3 mmol), substituted benzyl alcohol (3 mmol), NHPI (0.3 mmol), $Co(OAc)_2$ (0.015 mmol), and *m*-chlorobenzoic acid (0.15 mmol) was stirred in acetonitrile (5 mL) for 30 min. The quantitative analysis of the aldehydes was performed as in A) and the results are reported in Table 5.

E) Oxidation of Benzyl Alcohols Catalysed by 3 on a Preparative Scale: A solution of the alcohol (90 mmol), the nitroxyl radical catalyst **3** (2.2 mmol), *p*-toluenesulfonic acid (4.5 mmol), $Mn(NO_3)_2$ (1.8 mmol), and $Co(NO_3)_2$ (1.8 mmol) was stirred in acetic acid (100 mL) at room temperature for 3 h under air at atmospheric pressure. The acetic acid was evaporated and benzaldehyde was extracted with methyl *tert*-butyl ether (98% yield). The nitroxyl catalyst is insoluble and can be recovered as the ammonium salt of *p*-toluenesulfonic acid and recycled without loss of activity.

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