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Oxidation of *N,N*-benzylalkylamines to nitrones by Mo(VI) and W(VI) polyperoxo complexes

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Abstract

Oxidation of *N,N*-benzylalkylamines in chloroform by Mo(VI) and W(VI) polyperoxo complexes (PPC) of general formula $Q_3^+\{PO_4[MO(O_2)_2]_4\}^{3-}$ (Q^+ = onium ion) yield the corresponding nitrones as oxidized products quantitatively. Only in the case of *N,N*-benzylmethylamine the formation of nitrone is accompanied by 25% of benzaldoxime. Oxidation of *N,N*-benzyltertbutylamine and *N,N*-benzylisopropylamine follows second order kinetics. This finding does not disqualify the hypothesis that the reaction might occur by a rate determining nucleophilic attack of the amine onto the peroxide oxygens leading, through a Bartlett-type transition state, to the probable formation of the corresponding hydroxylamine, which then is converted to nitrone in a faster step. Under this respect PPC behavior seems related to that of the corresponding anionic monuclear oxidants $Q^+[MO(O_2)_2L]^-$ (L = anionic ligand). On the other hand PPC toward *N,N*-benzylmethylamine behave similar to neutral mononuclear oxidants, $MO(O_2)_2L$, since in both cases the formation of an oxidant–substrate association complex appears a probable event along the reaction coordinate. However, whereas for the neutral mononuclear oxidants this oxidant–substrate adduct seems to react further toward external amine molecules through a Bartlett-type transition state, for PPC such an adduct seems to evolve to products through unimolecular events akin enzymatic processes.

Keywords: Polyperoxo complexes; *N,N*-benzylalkylamines; Oxidation; Nitrones; Reaction mechanism; Anionic oxidants

1. Introduction

Polyoxoperoxo complexes (PPC) of general formula $Q_3^+\{PO_4[MO(O_2)_2]_4\}^{3-}$ (Q^+ = onium ion, M = Mo(VI) and W(VI)) have been shown to be versatile oxidant agents [1]. Their oxidative ability has been tested toward many organic substrates such as alkenes, alkynes, alcohols, diols, sulphoxides and amines [2–10]. All these reactions proceed smoothly providing fairly high yields of the oxidation products.

It is worth noting, however, that mononuclear Mo(VI) and W(VI) peroxo complexes, $MO(O_2)_2L$ (L = ligand), appear to be less versatile. For example $MoO(O_2)_2HMPA$, a neutral oxidant which epoxidizes simple alkenes, is unreactive toward alcohols, whereas $[MoO(O_2)_2PICO]^-Bu_4N^+$ (PICO = picolinate *N*-oxido anion), an anionic oxidant (so called because, like PPC, it is the anionic part of the molecule to bear the transferable oxygen) oxi-

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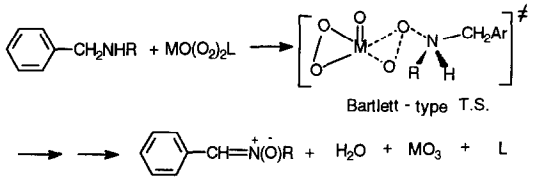
dizes primary and secondary alcohols to the corresponding carbonyl compounds but it does not react with olefins [9,11]. This superior versatility of PPC in the oxidation of olefins and alcohols seems due mainly

(i) to the presence of a negative charge on the anionic oxidants, which has been suggested to allow the necessary formation of an alcohol–oxidant association complex [11]. Such a complex, then, evolves to products by a radical process occurring within the coordination sphere of the metal center;

(ii) to the formation of PPC ion pairs, which facilitates the negative charge dispersion and thus allows the nucleophilic attack of substrates such as thioethers or alkenes to the peroxide oxygens [1].

In this paper we present a kinetic investigation aiming at establishing the reactive behaviors of some Mo(VI) and W(VI) PPC toward benzylalkylamines in comparison with those of mononuclear peroxometal complexes.

Oxidation of benzylalkylamines by anionic mononuclear Mo(VI) and W(VI) peroxo complexes, $[MO(O_2)_2L]^-Bu_4N^+$ (L = picolinate or picolinate *N*-oxide or benzoate anion), involves a rate determining nucleophilic attack of the amine onto the peroxide oxygens with formation of the corresponding hydroxylamine through a Bartlett-type transition state, followed by a faster step in which hydroxylamine is oxidized to nitrone [12]:



On the other hand the oxidation process by neutral peroxo complexes, $MO(O_2)_2HMPA$, seems to occur through the replacement of the original ligand HMPA by the benzylalkylamine, which leads to the formation of the new species $MO(O_2)_2 \cdot R_2NH$ and $MO(O_2)_2 \cdot 2R_2NH$ [12]. Such species are themselves oxidant agents and therefore can oxidize external amine molecules through a pathway, which envisages a nucleophilic attack of the amine onto the peroxide oxygens:

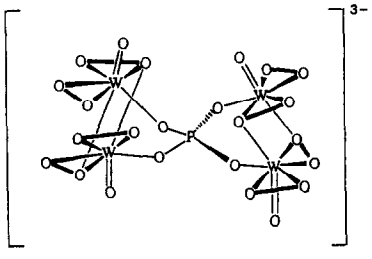
$$MO_5L + R_2NH \overset{K}{\rightleftharpoons} MO_5R_2NH + L$$

$$MO_5R_2NH + R_2NH \overset{K'}{\rightleftharpoons} MO_5 \cdot 2R_2NH$$

$$MO_3R_2NH + R_2NH \overset{k_2}{\rightarrow} P$$

$$MO_5 \cdot 2R_2NH + R_2NH \overset{k'_2}{\rightarrow} P.$$

This different reactive behavior between anionic and neutral oxidants seems related to the availability of a free coordination site on the metal center, because anionic mononuclear peroxo complexes are coordinatively saturated species, whereas neutral peroxo complexes have a free coordination site. PPC are anionic peroxo complexes but differently from the anionic mononuclear oxidants they have a free coordination site on each of four metal centers and therefore, from this viewpoint, they might behave as neutral mononuclear peroxo complexes:



The X-ray structure of the anion $\{PO_4[WO(O_2)_2]_4\}^{3-}$ (Ref. [3]).

2. Experimental

2.1. Materials

N,*N*-benzylmethylamine, *N*,*N*-benzylisopropylamine, *N*,*N*-benzyltertbutylamine and *N*,*N*-

dibenzylamine (Aldrich) were purified by distillation over calcium hydride.

N,N-dibenzylhydroxylamine was prepared refluxing 25 g (0.2 mol) of $C_6H_5CH_2Cl$ with 6.9 g (0.1 mol) of $NH_2OH \cdot HCl$ and 32 g (0.3 mol) of Na_2CO_3 in 400 mL of CH_3OH/H_2O (75:25) for 4 h according to the procedure reported by De La Mare and Coppinger [13]. Elemental analysis gave 78.71%, 6.46% and 7.08%, respectively, for C, N and H in good agreement with calculated values 78.77%, 6.56% and 7.09% (m.p. = 122–124°C from isooctane).

Chloroform (Aldrich, ACS) was washed by H_2SO_4, dried on $CaCl_2$ and then distilled before use over P_4O_{10}, whereas HMPA (hexamethylphosphoric triamide), a J.T. Baker product, was used as received.

Triscetylpyridinium tetrakis(diperoxomolybdo) phosphate (PCMP) [14], triscetylpyridinium tetrakis(diperoxotungsto) phosphate (PCWP) [15], tristetrahexylammonium tetrakis(diperoxomolybdo) phosphate (TEAM) [9] and tristetrahexylammonium tetrakis(diperoxotungsto) phosphate (TEAW) [3] were prepared following the previously reported original procedures.

2.2. Kinetics

All reactions were carried out under a nitrogen atmosphere. In a typical run, a solution of 5 mL of $CHCl_3$ containing 0.038 mmol of oxidant was added to a 5 mL $CHCl_3$ solution containing 1–20 mmol of amine in a glass reactor maintained at the appropriate temperature. Aliquots of the reaction mixture were withdrawn at various time intervals and the disappearance of the oxidant was followed by iodometric titration. Blank experiments indicated that the decomposition of the oxidant is a negligible process in the time scale of the oxidation reactions. The reactions followed pseudo first order kinetics for 2 half-lives; pseudo first order rate constants, obtained as slopes from conventional plots of $\ln[O]_{act}$ versus time, were evaluated by using a linear least-square computer program (Plot it 3.0).

The study of the stoichiometry of the oxidation reaction concerning $C_6H_5CH_2NHC(CH_3)_3$ was performed by ^{1}H-NMR monitoring the resonances of nitrone CH=N which occur at 7.54 ppm and employing $(C_6H_5)_3CH$ as internal standard.

On the other hand, in the case of $C_6H_5CH_2NHCH(CH_3)_2$ we monitored the resonances of CH of the isopropyl group in the nitrone (4.42 ppm); for $C_6H_5CH_2NHCH_3$ (100% of conversion), the nitrone (75%) was determined by monitoring the resonances of CH_3 protons (3.80 ppm) whereas the corresponding oxime (25%) was determined by HPLC, employing a Hypersil column (0.5 μm, 250 × 4.6 mm), flow rate 1.0 ml/min, detector set at λ = 275 nm, standard = biphenyl, mobile phase, (A) hexane, (B) chloroform, gradient, 0–10 min 100% A, 10–15 min 30% B, 15–20 min 30% B, 20–25 min 100% A.

2.3. Instrumentation

HPLC analyses were performed on a Varian 5000 instrument equipped with a UV–VIS detector (Jasco UV Dec-100) and LCI-100 Perkin-Elmer integrator.

^{1}H-NMR spectra were obtained on a Bruker AC 200 Mhz spectrometer. C, H, N analyzer Fisons mod EA 1108 was used for elemental analyses.

3. Results and discussion

Kinetic studies were carried out in $CHCl_3$ under pseudo first order conditions employing an excess of amine on the oxidant, the following stoichiometry having been established (Eq. (1)):

$$4C_6H_5CH_2NHR + Q_3^+\{PO_4[MO(O_2)_2]_4\}^{3-} \xrightarrow{CHCl_3} 4C_6H_5CH{=}\overset{+}{N}(\overset{-}{O})R + Q_3PO_4 + 4MO_3 + 4H_2O \quad (1)$$

R = Me, Pr^i, Bu^t; M = Mo(VI), W(VI); Q^+ = cetylpyridinium, tetrahexylammonium ion.

Kinetic data concerning the oxidation process of $C_6H_5CH_2NHC(CH_3)_3$ are reported in Table 1.

The data indicate that the process, regardless of the identity of the oxidant, follows a second order rate law, first order with respect to each reactant. Thus, these results do not disqualify the hypothesis that the reaction occurs through a simple bimolecular process, which presumably involves a rate determining external nucleophilic attack of the amine on the peroxide oxygens, leading to the formation of hydroxylamine through a Bartlett-type transition state. Therefore, the reaction pathway would be similar to that observed for anionic mononuclear peroxo complexes.

This rationalization seems also supported by the kinetic measurements performed in HMPA as a solvent, which show only small rate depressions with respect to $CHCl_3$ (see Table 1). HMPA is a ligand which does have a good affinity for the metal center of mononuclear peroxo complexes [16]. We checked that HMPA is a good ligand also for the metal centers of polyperoxo complexes. In fact ^{1}H-NMR spectra of a $CDCl_3$ solution containing TEAM and HMPA show the presence of a doublet at 2.67 and 2.62 ppm, which corresponds to the proton signals of free HMPA in $CDCl_3$, and of a second doublet at 2.96 and 3.01 ppm, which can be attributed to the proton signals of HMPA bound to the metal center.

Therefore, it seems conceivable that in HMPA oxidant species are also present containing the HMPA ligand bound to the metal center, e.g. $\{[MO(O_2)_2]_3O_3P{-}O{-}MO(O_2)_2 \cdot HMPA\}^{3-}$, which are less reactive electrophilic oxidants than $\{PO_4[MO(O_2)_2]_4\}^{3-}$. Thus, within the framework of the electrophilic oxygen transfer mechanism, a small rate depression is expected and indeed observed on changing the solvent from $CHCl_3$ into HMPA.

Table 1
Oxidation of $C_6H_5CH_2NHBu^t$ in $CHCl_3$ at 10°C

Oxidant [a] (M)	$[ArCH_2NHBu^t]$ (M)	$k_{obs} \cdot 10^4$ (s^{-1})	$k_{obs}/[ArCH_2NHBu^t] \cdot 10^4$ ($M^{-1}\,s^{-1}$)	$k_2 \cdot 10^4$ ($M^{-1}\,s^{-1}$)
PCMP	0.209	2.68	12.8	
	0.503	4.76	9.50	9.42 (2.13) [c]
	0.810	6.74	8.32	
	1.01	7.16	7.08	
TEAM	0.304	0.430	1.41	
	0.300 [b]	0.366 [b]	1.22 [b]	
	0.503	0.559	1.11	1.17 (0.15) [c]
	0.503 [b]	0.440 [b]	0.875 [b]	
	1.00	1.09	1.09	
	1.50	1.50	1.00	
	2.00	2.51	1.26	
PCWP	0.104	1.39	13.4	
	0.214	2.11	9.86	11.0 (1.41) [c]
	0.307	3.30	10.7	
	0.447	4.51	10.1	
TEAW	0.197	2.47	12.6	
	0.414	5.27	12.7	12.3 (0.84) [c]
	0.927	10.6	11.4	
	1.34	15.2	11.4	
	2.11	28.6	13.6	

[a] In all experiments 0.0039 M.
[b] In HMPA as a solvent.
[c] Standard deviation.

Table 2
Oxidation of $C_6H_5CH_2NHCH(CH_3)_2$ in $CHCl_3$ at 0°C

Oxidant [a] (M)	$[ArCH_2NHPr^i]$ (M)	$k_{obs} \cdot 10^4$ (s^{-1})	$k_{obs}/[ArCH_2NH\ Pr^i] \cdot 10^4$ ($M^{-1}\ s^{-1}$)	$k_2 \cdot 10^4$ ($M^{-1}\ s^{-1}$)
PCMP	0.203	1.69	8.30	
	0.511	5.10	9.98	8.12 (0.97) [b]
	1.01	8.55	8.50	
	1.50	10.9	7.20	
	1.80	12.9	7.17	
	2.01	15.2	7.58	
TEAM	0.205	0.373	1.82	
	0.505	0.960	1.90	2.16 (0.31) [b]
	1.00	2.37	2.36	
	1.51	3.89	2.57	
PCWP	0.179	0.360	2.01	
	0.200	0.490	2.45	2.35 (0.31) [b]
	0.513	1.03	2.01	
	0.704	2.01	2.85	
	1.01	2.42	2.41	
TEAW	0.210	0.640	3.05	
	0.304	0.800	2.63	3.17 (0.33) [b]
	0.811	2.93	3.61	
	1.10	3.50	3.18	
	2.02	6.86	3.39	

[a] In all experiments 0.0038 M.
[b] Standard deviation.

Analogous mechanistic rationalization can be suggested for the oxidation of *N,N*-benzylisopropylamine by PPC. Also in this case, in fact, the pertinent kinetic data reported in Table 2 indicate a second order oxidation process.

As far as the identity of the oxidant is taken in consideration, we observe for both *N,N*-benzyltertbutylamine and *N,N*-benzylisopropylamine that there is an effect of countercation on the reaction rate. In particular within the series of Mo(VI) oxidants, cetylpyridinium cation (PCMP) is more reactive than tetrahexylammonium cation (TEAM). The situation appears less conclusive for W(VI) derivatives, since in such a case both oxidants PCWP and TEAW display more or less the same reactivity. We do not have an explanation for this behavior even if probably the formation of ion pairs might be also relevant in determining the different reactivity of these oxidants [1].

In conclusion the reactive behavior of PPC toward *N,N*-benzyltertbutylamine and *N,N*-benzylisopropylamine is analogous to that displayed by Mo(VI) and W(VI) anionic mononuclear oxidants, i.e. both classes of oxidants react through a bimolecular process, which involves a nucleophilic attack of the substrate on the peroxide oxygens. Probably the lack of a free site of coordination in the mononuclear oxidants or steric congestion around the coordination site in the case of PPC drive the attack of the two amines having the more sterically crowded nitrogen centers externally onto the peroxide oxygens [1].

[1] Also, *N,N*-dibenzylamine is oxidized to nitrone by TEAM at 0°C in $CHCl_3$ through a second order process, $k_2 = 6.12 \times 10^{-4}$ $M^{-1}\ s^{-1}$. Furthermore, under the same conditions the corresponding *N,N*-dibenzylhydroxylamine is oxidized to nitrone instantaneously. Thus, this observation seems to support the possibility that hydroxylamine may represent the first intermediate generated by the external nucleophilic attack of the amine on the peroxide oxygen, intermediate which then is converted to nitrone in a much faster following step.

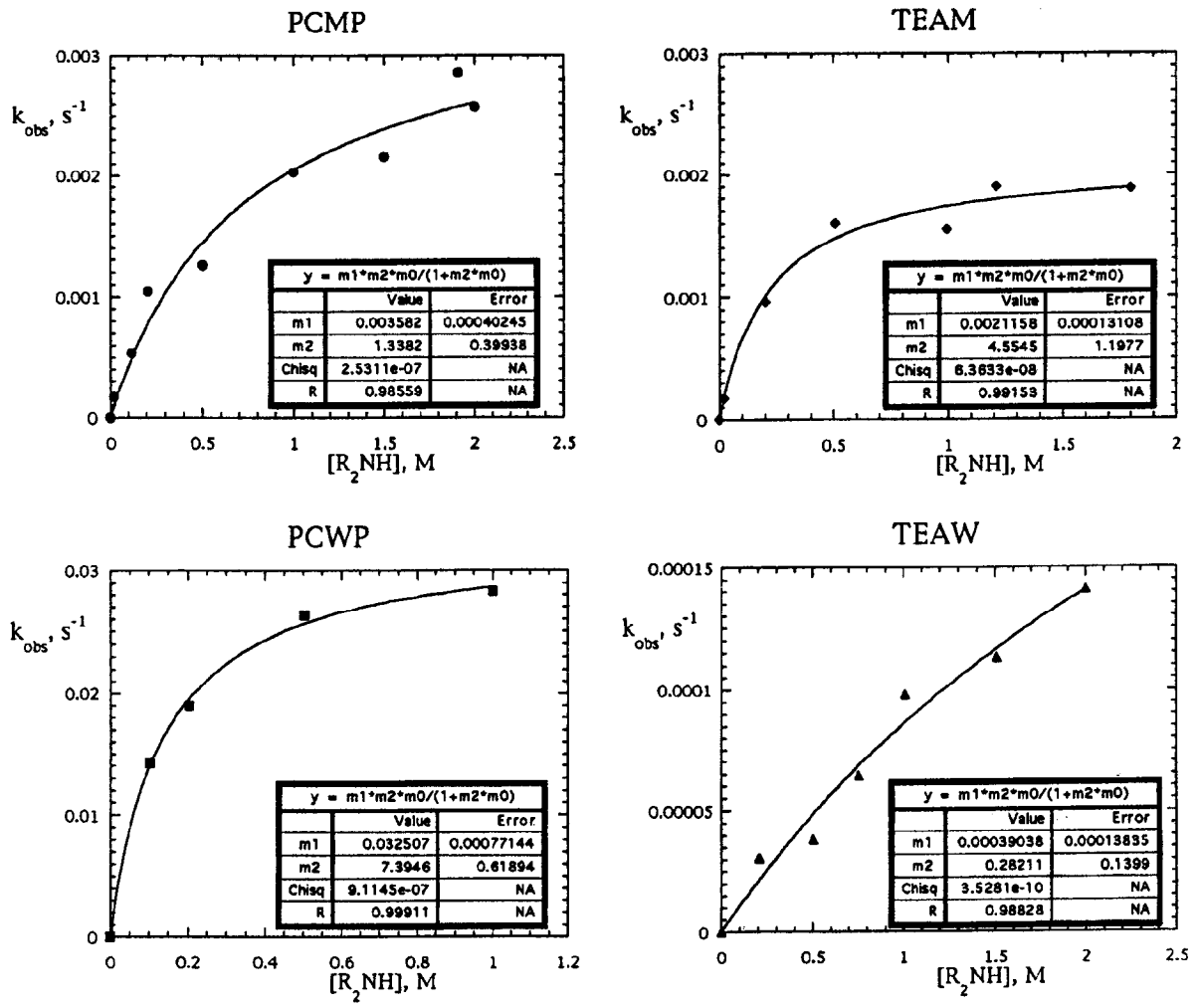


Fig. 1. Oxidation of *N,N*-benzylmethylamine with Mo(VI) and W(VI) PPC.

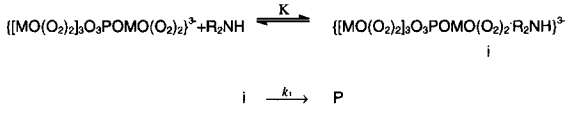
In contrast, the scenario is different when *N,N*-benzylmethylamine is employed as a substrate. In such a case, as the results reported in Table 3 show, the oxidation reaction appears more complex than a simple bimolecular process.

In fact, the pseudo first order rate constants k_{obs} increase on increasing the concentration of amine till a plateau is reached (Fig. 1). This Michaelis-Menten like behavior might be due to the occurrence of a prior step which involves the coordination of the amine on the metal center and subsequent oxidation within the coordination sphere of the complex (Scheme 1).

From this scheme one obtains:

$$k_{obs} = \frac{Kk_1[R_2NH]_0}{1 + K[R_2NH]_0}. \quad (2)$$

As Fig. 1 shows, Eq. (2) seems to give a reasonable match with the experimental observations for all the investigated oxidants. The



Scheme 1.

fitting provides the following values for k_1 and K, respectively

	$k_1 \cdot 10^3$ (s^{-1})	K (M^{-1})
PCMP	3.6	1.3
TEAM	2.2	4.5
PCWP	32.5	7.4
TEAW	0.39	0.28

PCWP is the most effective oxidant because of the higher association constant and a higher unimolecular decomposition rate, whereas TEAW is the least efficient oxygen donor. On the other hand, the proposed reaction Scheme 1 seems supported by some observations.

The oxidation process of *N,N*-benzylmetylamine by TEAM performed in HMPA shows a rate depression of nearly two orders of magnitude (Table 3), indicating that the presence of a ligand such as HMPA able to compete with amine for the coordination site has a large inhibition effect. The outcome is very different from the small depression observed previously with *N,N*-benzyltertbutylamine, which on the contrary reacts attacking the peroxide oxygens externally, but it is expected on the basis of the mechanism which involves intramolecular oxidation of the coordinate substrate. In fact the displacement of the coordinate amine by HMPA from (i) will reduce the reaction rate drastically. Coordination of all four metal centers by HMPA would cause the reaction rate to drop to zero.

A second observation is that the oxidation of *N,N*-benzylmethylamine, differently from that of other amines, always yields nearly 25% of $C_6H_5CH{=}N{-}OH$ together with the corresponding nitrone (75%). The formation of a demetila-

Table 3
Oxidation of $C_6H_5CH_2NHCH_3$ in $CHCl_3$ at 0°C

Oxidant [a] (M)	[$ArCH_2NHMe$] (M)	$k_{obs} \cdot 10^3$ (s^{-1})	k_{obs}/[$ArCH_2NHMe$] $\cdot 10^3$ ($M^{-1}\ s^{-1}$)
PCMP	0.119	0.534	4.49
	0.205	1.04	5.07
	0.504	1.25	2.48
	1.00	2.03	2.03
	1.50	2.16	1.35
	1.91	2.86	1.50
	2.00	2.57	1.29
TEAM	0.021	0.171	8.14
	0.010 [b]	0.0052 [b]	0.52 [b]
	0.200	0.962	4.80
	0.300 [b]	0.0017 [b]	0.0056 [b]
	0.506	1.60	3.16
	0.997	1.55	1.55
	1.21	1.90	1.57
	1.50	1.44	0.96
	1.80	1.88	1.04
PCWP	0.102	14.2	147
	0.204	19.0	93.1
	0.504	26.3	52.2
	1.00	28.3	28.3
	1.50	20.8	13.9
TEAW	0.207	0.0308	0.149
	0.503	0.0383	0.076
	1.01	0.0980	0.097
	1.51	0.113	0.075
	2.00	0.141	0.071

[a] In all experiments 0.0038 M.
[b] In HMPA as a solvent.

tion product such as the benzaldoxime would imply the involvement of radical precesses, which might be easier to occur within the coordination sphere of the metal after the formation of an oxidant–amine association complex.

The absence of formation of such oxidant–amine association complex in the case of *N,N*-benzyltertbutylamine and of *N,N*-benzylisopropylamine (probably for steric reasons) is responsible of their different behaviors with respect to that of *N,N*-benzylmethylamine. However, we cannot exclude that also with these two amines, as a leak of the ionic mechanism, some radical reactivity is present and does not cause very good reproducibility of the rate measurements (see Tables 1 and 2).

4. Conclusions

Oxidation of *N,N*-benzylalkylamines by PPC yields the corresponding nitrones quantitatively. Only in the case of *N,N*-benzylmethylamine the formation of nitrone is accompanied by nearly 25% of benzaldoxime.

From a mechanistic point of view PPC seem to behave toward *N,N*-benzyltertbutylamine and *N,N*-benzylisopropylamine as the related anionic mononuclear oxidants, i.e. the reaction occurs by a rate determining nucleophilic attack of the amine onto the peroxide oxygens which, through a Bartlett-type transition state, probably leads to the formation of the corresponding hydroxylamine, which then is converted to nitrone in a faster step.

On the other hand, PPC show a behavior toward *N,N*-benzylmetylamine similar to that of neutral mononuclear oxidants, since the formation of an oxidant–substrate association complex appears a probable event along the reaction coordinate. However, whereas for neutral mononuclear oxidants this oxidant–substrate adduct seems to react further toward external amine molecules through a Bartlett-type transition state, in the case of PPC such an adduct seems to evolve to products through unimolecular events akin enzymatic processes.

Acknowledgements

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