Multiplicity of Reaction Pathways in the Processes of Oxygen Transfer to Secondary Amines by Mo(VI) and W(VI) Peroxo Complexes[†]

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Received March 21, 1996[⊗]

Oxidation of *N*,*N*-benzylmethylamine, *N*,*N*-benzylisopropylamine, and *N*,*N*-benzyl-*tert*-butylamine by both anionic and neutral Mo(VI) and W(VI) oxodiperoxo complexes yields the corresponding nitrones quantitatively. The oxidation reactions employing anionic oxidants were performed in $CHCl_3$ and follow second-order kinetics, first order with respect to the amine and to the oxidant. The data were rationalized on the basis of a rate-determining nucleophilic attack of the amine onto the peroxide oxygen of the oxidant, with a transition state in which N−O bond formation and O−O bond cleavage occur in a concerted way (electrophilic oxygen transfer mechanism). This attack yields the corresponding hydroxylamine, which then is furtherly oxidized to nitrone in a fast step. On the other hand, in the case of neutral oxidants ^{1}H-NMR data as well as kinetic data indicate that amine coordinates the metal center replacing the original ligand HMPA and yields a new peroxo complex. For *N*,*N*-benzyl-*tert*-butylamine such a complex was isolated and characterized. These new peroxo complexes can themselves behave as electrophilic oxidants, transferring oxygen to external amine molecules through the same pathway followed by anionic oxidants, or can yield the reaction product by intramolecular oxidation of the coordinate amine. Measurements of added HMPA effects on oxidation rate would seem more consistent with the electrophilic oxygen transfer mechanism.

Introduction

Oxidation of amines is a reaction of relevant interest both for biological implications (e.g., the in vivo metabolism) and for synthetic applications aimed to introduce oxygen into nitrogen-containing compounds.[1] It has been reported that primary and secondary amines are efficiently oxidized by Mo(VI) and W(VI) peroxo complexes and particularly that benzylalkylamines are selectively and quantitatively transformed into nitrones.[2]

Despite the interest and the relevance of such reactions no kinetic study has been undertaken in order to collect some piece of information on the possible reaction pathways. This prompted us to mechanistically investigate oxidation reactions of model benzylalkylamines to nitrones by Mo(VI) and W(VI) peroxo complexes. Previous investigations indicated that organic substrates with reaction sites carrying lone pairs or π electrons, such as thioethers and alkenes, react as nucleophiles toward Mo(VI) and W(VI) peroxo complexes, through a clean bimolecular process, attacking the peroxide oxygen along the O−O bond (electrophilic oxygen transfer).[3] This mechanism is very similar to that suggested by Bartlett for the electrophilic oxidations by peracids or by acidic hydrogen peroxide.[4]

On the other hand, the peroxo complex bears a second electrophilic site, i.e., the metal center. Therefore, a nucleophilic substrate might attack the oxidant also or alternatively on the metal and enter the coordination sphere of the peroxo complex, thus behaving as a ligand and yielding a substrate−oxidant association complex. Such a complex might evolve into products through intramolecular events (which in some documented cases imply radical processes)[5] or it might behave as a new electrophilic oxidant transferring oxygen to a second external molecule of substrate.[6]

The data obtained in this investigation disclose some peculiar mechanistic aspects for the oxidation of secondary amines by Mo(VI) and W(VI) peroxo complexes. Such substrates undergo different reaction pathways depending on the nature of the amine and of the ligand.

Results and Discussion

Oxidation Reactions with PICO-M, PIC-M, and BENZ-Mo (M = Mo^{VI}, W^{VI}). As shown in Chart 1, these peroxo complexes are ammonium salts, whose anionic parts bear the transferable oxygen (for this reason they are called "anionic oxidants"). PIC and PICO are coordinatively saturated peroxometal complexes, containing

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[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1996.

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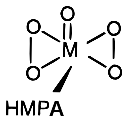
(5) Campestrini, S.; Di Furia, F. *Tetrahedron* **1994**, *50*, 5119−5131.

(6) Di Furia, F.; Modena, G. *Pure Appl. Chem.* **1982**, *54*, 1853−1866.

S0022-3263(96)00544-0 CCC: $12.00

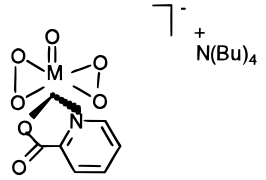
Chart 1



1

1a: M=Mo

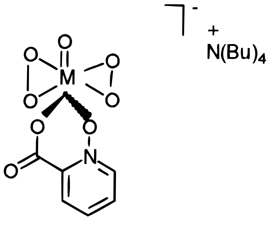
1b: M=W



2

2a: M= Mo=PIC-Mo

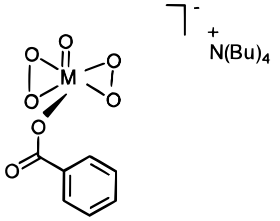
2b: M=W = PIC-W



3

3a:M=Mo=PICO-Mo

3b:M=W=PICO-W



4

4a: M=Mo=Benz

the bidentate picolinate and picolinate *N*-oxide ligands, respectively.[7] Therefore, coordination of a substrate to the metal would require the opening of a tooth of the bidentate ligand in order to make available a coordination site. On the other hand, BENZ-Mo contains the monodentate carboxylate ligand and has a free coordination site. However, X-ray data indicate that the apical position is not completely free and some hindrance to the entering of a ligand may occur, due to the short distance between the molybdenum atom and the carbonyl oxygen of the carboxylate group.[8]

N,*N*-Benzylmethylamine (Me), *N*,*N*-benzylisopropylamine (Pr^i), and *N*,*N*-benzyltertbutylamine (Bu^t) are transformed quantitatively into nitrones by these peroxo complexes in $CHCl_3$ according to the following equation:

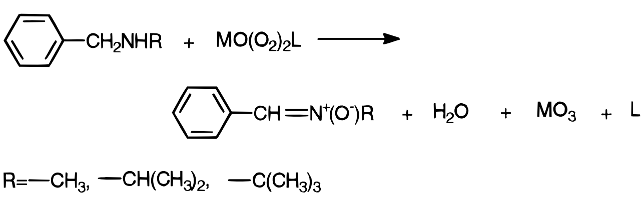
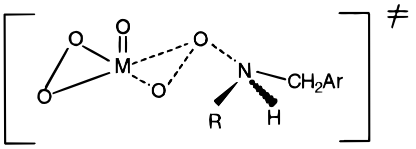


Table 1. Second-Order Rate Constants for the Stoichiometric Oxidation of *N*,*N*-Benzylalkylamines $C_6H_5CH_2NHR$ to Nitrones by Anionic Peroxo Complexes in $CHCl_3$

	$R =$		
oxidant	$-CH_3$ $10^4k_2{}^a$ (M^{-1} s^{-1})	$-CH(CH_3)_2$ $10^4k_2{}^a$ (M^{-1} s^{-1})	$-C(CH_3)_3$ $10^4k_2{}^b$ (M^{-1} s^{-1})
1. PICO-Mo	8.80	1.35	4.08
2. PIC-Mo	7.93	0.980	1.44
3. BENZ-Mo	10.9	1.19	3.46
4. PIC-W	22.4	15.9	20.2 ($2.75^{a)}$)
5. PICO-W			36.6

[a] $T = 10$ °C. [b] $T = 40$ °C.

The reactions follow second-order kinetics, first order with respect to each reactant. Pertinent results are displayed in Table 1. For the molybdenum series the data suggest that the coordination sphere of the metal does not play any appreciable role. In fact, the observed reactivity sequence PICO-Mo $\cong$ BENZ-Mo $\cong$ PIC-Mo is particularly telling in showing the scarce sensitivity of the reaction rate upon the identity of the coordination sphere of the oxidant, excluding therefore the possibility of an attack of the substrate to the metal center. This behavior is similar to that observed in the oxidation of strong nucleophiles such as thioethers to sulfoxides.[9] Consequently, the results can be rationalized on the basis of the external electrophilic oxygen transfer mechanism, which involves a rate-determining nucleophilic attack of the amine onto the peroxide oxygen of the oxidant, with a transition state in which N−O bond formation and O−O bond cleavage occur in a concerted way. This attack yields the corresponding hydroxylamine, which then in a faster way is further oxidized to nitrone.[10]



T.S.

The amine reactivity sequence Me > Pr^i > Bu^t might reflect the presence of steric effects during the nucleophilic attack, which favor the less hindered nucleophile, i.e., $C_6H_5CH_2NHCH_3$.

The same mechanism suggested for molybdenum derivatives still keeps for tungsten oxidants. The higher reaction rate displayed by these oxidants follows the observed general trend that W(VI)-peroxo complexes are nearly 10−30 times more reactive than Mo(VI)-peroxo complexes in reactions involving an external attack to the peroxide oxygens by a nucleophilic substrate.[11] This behavior probably can be ascribable to a Lewis acidity of tungsten peroxo complexes higher than that of molybdenum derivatives, which might be responsible of a higher electrophilicity of peroxide oxygens.[12]

In order to have further support for the mechanistic picture that envisages a simple bimolecular oxidation reaction and check whether a coordination process is or

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[7] Bortolini, O; Campestrini, S.; Di Furia, F.; Modena, G. *J. Org. Chem.* **1987**, *52*, 5467−5469.

[8] Campestrini, S.; Di Furia, F.; Rossi, P.; Torboli, A. *J. Mol. Catal.* **1993**, *83*, 95−105.

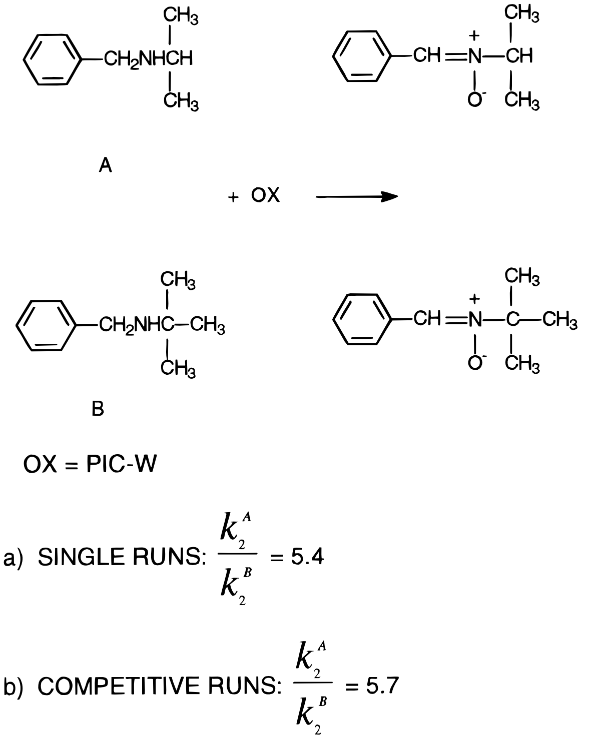
[9] Campestrini, S.; Conte, V.; Di Furia, F.; Modena, G. *J. Org. Chem.* **1988**, 53, 5721−5724.

[10] In order to check the intermediacy of hydroxylamine in the formation of nitrone, we investigated the oxidation of *N*,*N*-dibenzylamine and of the corresponding hydroxylamine, i.e., *N*,*N*-dibenzylhydroxylamine, by PIC-W in $CHCl_3$. Both substrates yield the same nitrone quantitatively, and the oxidation rate of *N*,*N*-dibenzylhydroxylamine is nearly 10 times larger than that of *N*,*N*-dibenzylamine. Thus, these findings seem to give support to the probable involvement of hydroxylamine as an intermediate in these oxidation processes.

[11] Arcoria, A.; Ballistreri, F. P.; Tomaselli, G. A.; Di Furia, F.; Modena, G. *J. Mol. Cat.* **1984**, *24*, 189−196.

[12] Cyclic voltammetry measurements, performed by Di Furia et al. (Bonchio, M.; Conte, V.; Di Furia, F.; Modena, G.; Moro, S.; Carofiglio, T.; Magno, F.; Pastore, P. *Inorg. Chem.* **1993**, *32*, 5797−5799), indicated for W peroxo complexes reduction peak potentials less negative than those observed for the corresponding Mo derivatives. Furthermore, the authors reported a good correlation between these reduction peak potentials and IR O−O bond frequencies. On the basis of these observations, it might be conceivable to assume that the LUMO of W peroxo complexes, involving the peroxide oxygens, is lower in energy than that of Mo peroxo complexes and, therefore, that W peroxo complexes have a Lewis acidity higher than that of Mo oxidants.

Scheme 1



is not occurring, we performed a competitive experiment with two different amines, i.e., Pr^i and Bu^t. These two amines were pitted together to react with PIC-W at 10 °C in $CHCl_3$. If the two substrates were competing to form an appreciable concentration of oxidant−amine complexes, the observed ratio of the two corresponding nitrones should be different from that calculated from the rate constants measured in separate experiments.[13] What comes out from the pertinent results (Scheme 1) indicates that the observed ratio is, within the experimental error, that one expected from the rate constant ratio and suggests the absence of prior coordination equilibria. Furthermore, the activation parameters measured for the oxidation of Pr^i with PIC-W, $\Delta H^{\ddagger}{}_{293}\mathrm{K} = 51$ kJ mol^{-1}, and $\Delta S^{\ddagger}{}_{293}\mathrm{K} = -110$ J K^{-1} mol^{-1}, are those expected for a simple bimolecular mechanistic scheme.

Oxidation Reactions with $MO(O_2)_2$HMPA (M = Mo^{VI}, W^{VI}). Preequilibria Involving Coordination of Amine to the Oxidant. The peroxo derivatives of the title, differently from the anionic oxidants of the previous section, are neutral peroxometal complexes with a free coordination site. Thus, there is a higher probability that with these oxidants the amine might attack the metal center entering the coordination sphere of the metal itself.

Indeed, we observed that on adding *N*,*N*-benzyl-*tert*-butylamine into a $CHCl_3$ solution of MoO_5HMPA a precipitate is readily formed. The precipitate was isolated and analyzed. Elemental analysis, ^{1}H-NMR, and iodometric titer indicated the formation of a new peroxo complex, $MoO_5C_6H_5CH_2NHBu^t$ (**5a**), which is obtained from MoO_5HMPA by substitution of the HMPA ligand with a molecule of amine. Since such a complex is soluble in CH_3CN we decided to employ it to oxidize Bu^t in such solvent. The reaction affords the corresponding nitrone quantitatively, and the pertinent kinetic data are shown in Table 2. It can be noted that the process obeys a second-order rate law, first order in each reactant. This observation seems consistent with an external nucleophilic attack of the amine onto the peroxide oxygen, as discussed in the previous section.

Table 2. Oxidation of $C_6H_5CH_2NHBu^t$ by $MoO_5C_6H_5CH_2NHBu^t$ and by MoO_5HMPA in CH_3CN at 40 °C

[amine] (M)	$10^4 \cdot k_1$ (s^{-1})	$10^3 \cdot k_1$/[amine] (M^{-1} s^{-1})		oxidant
0.124	1.76	1.42		$MoO_5C_6H_5CH_2NHBu^t$
0.224	2.99	1.33		
0.303	3.37	1.11	$k_2 = 1.23 \times 10^{-3}$	
0.406	4.81	1.18		
0.604	6.80	1.13		
0.123	1.74	1.41		MoO_5HMPA
0.300	3.41	1.14		
0.409	5.15	1.26		
0.508	6.30	1.24	$k_2 = 1.23 \times 10^{-3}$	
0.602	7.00	1.16		
1.00	11.8	1.18		

Table 3. Oxidation of $C_6H_5CH_2NHR$ (R = Me, Pr^i) by MoO_5HMPA in CH_3CN at 40 °C

R	[amine] (M)	$10^3 \cdot k_1$ (s^{-1})	$10^3 \cdot k_1$/[amine](M^{-1} s^{-1})
Me	0.089	2.52	28.3
	0.153	3.97	25.9
	0.400	4.66	11.7
	0.788	5.80	7.36
	1.01	5.80	5.74
	1.40	7.45	5.32
	1.60	6.70	4.19
	1.91	6.45	3.38
Pr^i	0.202	1.32	6.53
	0.802	3.95	4.93
	1.30	5.30	4.08
	2.01	6.90	3.43

Oxidation reactions of amines with the two neutral peroxo complexes $MoO(O_2)_2$HMPA and $WO(O_2)_2$HMPA, respectively, were also performed in CH_3CN.

Under these conditions nitrones are again the oxidation products. The pertinent kinetic data are displayed in Tables 2−5.

For the reaction of MoO_5HMPA with Bu^t (Table 2) we observed a linear dependence of the pseudo-first-order rate constant k_{obs} on the amine concentration (a second-order overall reaction), which indicates that a simple bimolecular process is occurring. Furthermore, the observed k_2 value is equal, within the experimental error, to that observed employing **5a** as an oxidant. Therefore, these findings strongly suggest that the oxidation of Bu^t in these two cases is carried on by the same species, i.e., $MoO_5C_6H_5NHBu^t$. This implies that when the starting oxidant used is MoO_5HMPA a faster prior step is occurring, in which a molecule of amine coordinates the metal center replacing the original ligand HMPA and transforming readily and quantitatively MoO_5HMPA into the new peroxo complex **5a**, which then is attacked externally by a second amine molecule onto the peroxide oxygen to lead to the formation of products (Scheme 2).

Scheme 2

$$\mathrm{MoO_5L + R_2NH \overset{K}{\rightleftharpoons} MoO_5R_2NH + L} \tag{1}$$

$$\mathrm{MoO_5R_2NH + R_2NH \xrightarrow{k_2} P} \tag{2}$$

This scheme yields a rate law, $v_1 = k_2[\mathrm{MoO_5L}]_0[\mathrm{R_2NH}]_0$

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[13] Webb, J. L. In *Enzymes and Metabolic Inhibitors*; Academic Press: New York, 1963; pp 52−68.

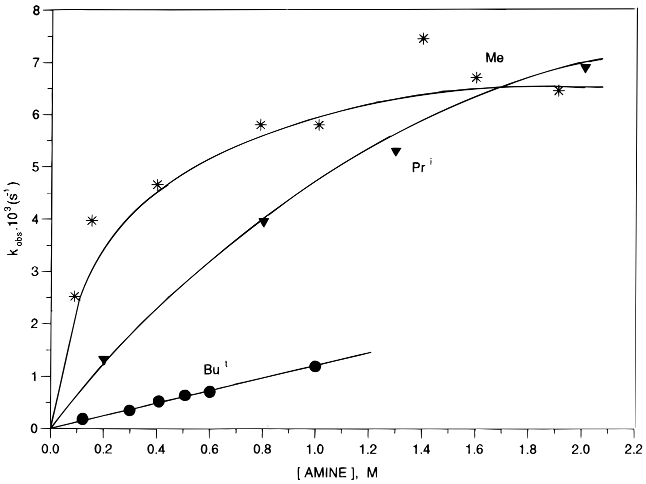

Figure 1. Oxidation of $C_6H_5CH_2NHR$ (R = Me, Pr^i, Bu^t) by MoO_5HMPA in CH_3CN at 40 °C.

(if $K[R_2NH] \gg [L]$), in agreement with the observed rate law and with all the experimental findings.

^{1}H-NMR Measurements. On the other hand, the data concerning the oxidation of Me and Pr^i (Table 3) and the relative plots, reporting the observed pseudo-first-order rate constants k_{obs} versus the concentration of amine, show a nonlinear dependence of the oxidation rate on the amine concentration (Figure 1), at variance with the behavior of Bu^t. In order to get information on possible coordination processes of amines with the oxidants, which might be responsible of these observed kinetics, we performed ^{1}H-NMR spectra of CD_3CN solutions containing a 1:1 ratio amine/oxidant. The spectra were recorded at −20 °C, because at such a temperature the oxidation process does not occur during the recording time interval (no signals due to the formation of nitrones are observed). Under these experimental conditions an 0.058 M solution of MO_5HMPA (M = Mo, W) in CD_3CN exhibits a doublet centered at 2.78 ppm due to the CH_3 resonance of the ligand (L_{bound}). Upon addition of 0.058 M of amine a decrease in the signals at 2.78 ppm and the appearance of a new doublet centered at 2.55 ppm is observed. By comparison with the ^{1}H-NMR spectrum of HMPA in the same solvent, the signals centered at 2.55 ppm are attributed to the CH_3 resonance of the free ligand (L_{free}). Furthermore, an increase in the amount of the added amine causes an increase in the signals at 2.55 ppm (L_{free}) at the expense of those at 2.78 ppm (L_{bound}). Meanwhile, the benzylic protons of amine, which lie at 3.68 ppm, are moved downfield (4.15 ppm). ^{1}H-NMR experiments suggest that a coordination process involving the amine is occurring. Unfortunately, we were not able to get any precipitate from the solution (even in $CHCl_3$, addition of $C_6H_5CH_2NHCH_3$ or $C_6H_5CH_2NHPr^i$ to a solution of MoO_5HMPA does not yield any precipitate). On the other hand, due to these coordination equilibria and compatibly to ^{1}H-NMR observations, different species might be formed as shown in the following equations:

$$\text{(i) } MO_5L\ (ox_1) + R_2NH \rightleftharpoons MO_5{\cdot}R_2NH\ (ox_2) + L$$

$$\text{(ii) } MO_5L\ (ox_1) + R_2NH \rightleftharpoons MO_5L{\cdot}R_2NH\ (ox_3)$$

$$\text{(iii) } MO_5L{\cdot}R_2NH\ (ox_3) + R_2NH \rightleftharpoons MO_5{\cdot}2R_2NH\ (ox_4) + L$$

The species ox_2 in tha case of *N*,*N*-benzyl-*tert*-butylamine corresponds to the peroxo complex $MoO_5C_6H_5CH_2NHBu^t$, isolated as reported in the previous section.

Since the nucleophilicity of R_2NH is higher than that of HMPA the electrophilicity of the peroxide oxygens is expected to decrease on increasing the molecule number of amines in the coordination sphere of the metal, i.e., $MO_5L\ (ox_1) > MO_5R_2NH\ (ox_2) > MO_5L{\cdot}R_2NH\ (ox_3) > MO_5{\cdot}2R_2NH\ (ox_4)$. By ^{1}H-NMR we observed L_{free}/L_{bound} ratio values of 2.9, 7.5, and 175 for R = Me, Pr^i, and Bu^t, respectively, (amine/MoO_5L = 1).

The practically neglectable amount of L_{bound} observed in the case of Bu^t indicates the absence in solution of species bearing the ligand HMPA. Thus, ^{1}H-NMR observations also suggest a large value for K (eq 1), confirming the reaction mechanism reported in Scheme 2.

However, since under the pseudo-first-order conditions amine/oxidant ratios in the range 6−100 were adopted, we performed ^{1}H-NMR measurements employing an amine/oxidant ratio = 10. Under such conditions, in all cases we observed only the signals of L_{free}. Therefore, it seems reasonable to consider equilibrium 1 quantitatively shifted to the right side also for Me and Pr^i and so we are left with the possibility that the oxidant present in solution should be ox_2, regardless of amine or of metal identity. But, due to the large excess of amine, a second equilibrium, i.e., the equilibrium forming ox_4, should also be taken in consideration.

$$MO_5R_2NH + R_2NH \overset{K'}{\rightleftharpoons} MO_5{\cdot}2R_2NH \qquad (3)$$

In this case product formation also occurs through an additional route (eq 4), under the assumption that both MO_5R_2NH and $MO_5{\cdot}2R_2NH$ oxidize the amine electrophilically, the latter being less effective than the former.

$$MO_5{\cdot}2R_2NH + R_2NH \xrightarrow{k_2'} P \qquad (4)$$

A more complete reaction scheme, including eqs 2−4, should be considered, and the following rate law can be derived.

$$v_2 = \frac{k_2[R_2NH]_0[MO_5L]_0 + k'_2K'[R_2NH]_0{}^2[MO_5L]_0}{1 + K'[R_2NH]_0} \qquad (5)$$

In order to check the reliability of the kinetic model we processed the data concerning the oxidation process of $C_6H_5CH_2NHMe$ with MO_5HMPA (Table 3) by a computer iterative procedure. The outcome (Figure 2) indicates a fair agreement between the calculated (curve) and the observed (full triangles) values and allows us to obtain the following values $k_2 = (5.26 \pm 0.516) \times 10^{-2}$, $k'_2 = (5.68 \pm 1.27) \times 10^{-4}$ and $K' = 8.40 \pm 0.48$. The k_2 and k'_2 values, reckoned by eq 5, are in accord with the expectation that MoO_5R_2NH is an electrophilic oxidant more reactive than $MoO_5{\cdot}2R_2NH$.

Equation 5 becomes equal to v_1 for $K' \cong 0$. This is the case for Bu^t, probably because the size of the Bu^t group makes the entrance of a second molecule in the coordination sphere of Mo difficult, at least in the explored range of amine concentrations.

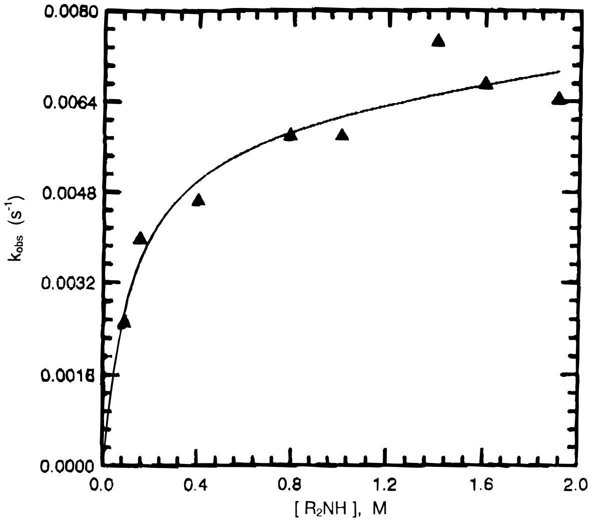

Figure 2. Oxidation rates of Me by MoO_5HMPA in CH_3CN. Calculated values (curve) and observed values (full triangles).

Table 4. Oxidation of $C_6H_5CH_2NHR$ (R = Me, Pr^i, Bu^t) by MoO_5HMPA in CH_3CN in the Presence of HMPA at 40 °C

[amine] (M)	[HMPT] (M)	$10^3 \cdot k_1$ (s^{-1})
Me		3.97
(0.153)	0.149	2.71
	0.793	0.725
	1.59	0.439
Pr^i		1.32
(0.202)	0.117	1.11
	0.325	0.595
	0.577	0.422
	1.49	0.450
Bu^t		0.246
(0.200)	0.500	0.271
	1.00	0.334
	2.00	0.408
	3.00	0.399

This reasoning seems supported by the data reported in Table 4, which show the effects of externally added HMPA on the oxidation rate of $C_6H_5CH_2NHR$ by MoO_5-HMPA. The addition of HMPA should give rise to the formation of the oxidant species $MO_5HMPA \cdot R_2NH$, through the equilibrium 6,

$$MO_5R_2NH + HMPA \overset{K''}{\rightleftharpoons} MO_5HMPA \cdot R_2NH \qquad (6)$$

which is less reactive than MO_5R_2NH, and therefore, a decrease in rate should be observed. This expectation is fulfilled for R = Me and Pr^i, which show a rate depression about 10 and 3 times, respectively, when HMPA ≅ 1.6 M is added, whereas for R = Bu^t essentially no rate decrease is observed on adding HMPA up to ≅ 3.0 M, indicating the difficulty of a second ligand to enter the coordination sphere of $MoO_5C_6H_5CH_2NHBu^t$.

Reactivity data concerning the oxidation reactions with WO_5HMPA (Table 5) find a similar rationale, i.e., the reactivity curve profiles, obtained plotting k_{obs} values versus amine concentrations, depend on the simultaneous presence of the two electrophilic oxidizing species WO_5R_2NH and WO_52R_2NH, the latter less reactive than the former. Obviously, WO_52R_2NH concentration increases on increasing the initial concentration of the amine employed.

In the case of WO_5HMPA the behavior of Bu^t is similar to that of Me and Pr^i (Figure 3) but different from that observed for Bu^t itself with MoO_5HMPA. The difference might be due to the fact that for a second amine molecule to enter the coordination sphere of the metal center is easier with W than with Mo.

Table 5. Oxidation of $C_6H_5CH_2NHR$ (R = Me, Pr^i, Bu^t) by WO_5HMPA in CH_3CN at 40 °C

R	[amine] (M)	$10^3 \cdot k_1$ (s^{-1})	$10^3 \cdot k_1$/[amine] (M^{-1} s^{-1})
Me[a]	0.394	0.660	1.68
	0.795	1.26	1.58
	1.20	1.76	1.47
	1.60	1.67	1.02
	2.01	1.60	0.796
Pr^i	0.210	1.11	5.29
	0.799	1.92	2.40
	1.60	2.64	1.65
	2.12	3.34	1.58
Bu^t	0.0507	1.42	28.0
	0.200	2.27	11.4
	0.800	2.93	3.66
	1.30	2.73	2.11

[a] Values at 10 °C.

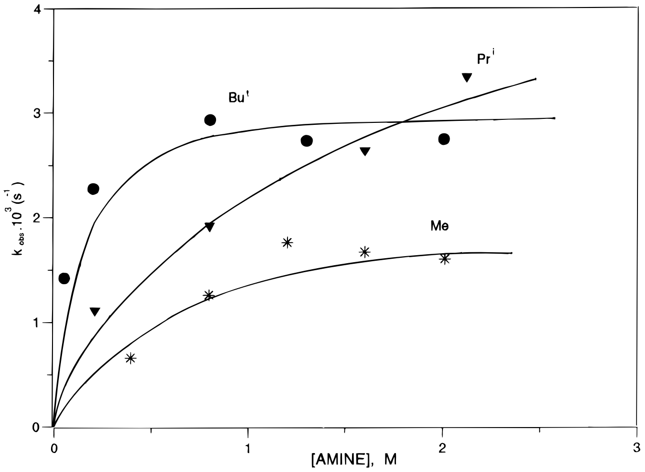

Figure 3. Oxidation of $C_6H_5CH_2NHR$ (R = Me, Pr^i, Bu^t) by WO_5HMPA in CH_3CN at 40 °C.

Michaelis-Menten Kinetic Model. A priori we cannot exclude the possibility that the formation of an amine–oxidant association complex is followed by the oxidation reaction of the coordinate amine within the coordination sphere of the metal, according to Scheme 3:

Scheme 3

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

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

$$MO_5R_2NH \xrightarrow{k_1} P \qquad (7)$$

$$MO_52R_2NH \xrightarrow{k_1'} P \qquad (8)$$

The kinetic expression related to Scheme 2 is

$$v_3 = \frac{k_1[MO_5L]_0 + k'_1K'[R_2NH]_0[MO_5L]_0}{1 + K'[R_2NH]_0} \qquad (9)$$

assuming a large value for K and thus $[MO_5L]_0 = [MO_5R_2NH]_0$.

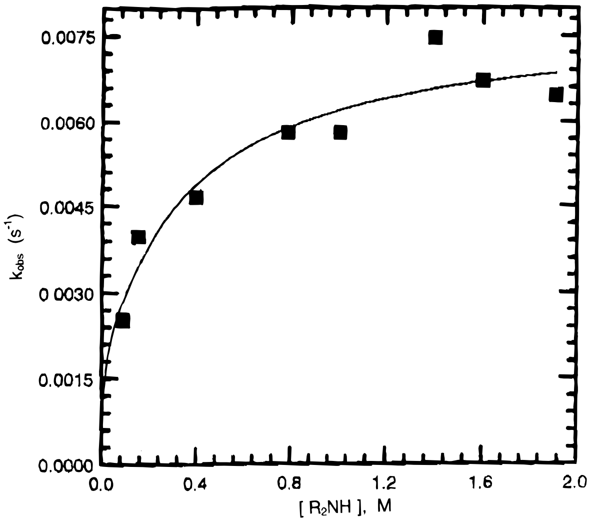

Figure 4. Oxidation rates of Me by MoO_5HMPA in CH_3CN. Calculated values (curve) and observed values (full squares).

We processed again by iterative procedure the data concerning the oxidation reaction of $C_6H_5CH_2NHCH_3$ with MO_5HMPA according to eq 9, and the outcome, obtained for $k_1 = (1.55 \pm 1.17) \times 10^{-3}$, $k'_1 = (7.82 \pm 1.1) \times 10^{-3}$, and $K' = 2.85 \pm 1.08$, indicates a fair agreement (Figure 4) also in this case between the experiments and the kinetic model of Scheme 3.

For $C_6H_5CH_2NHCH(CH_3)_2$ we obtained $k_1 = (1.61 \pm 1.76) \times 10^{-4}$, $k'_1 = (1.44 \pm 0.140) \times 10^{-2}$, and $K' = 0.441 \pm 0.083$.

Therefore, the kinetic treatment does not allow us to discriminate between the external electrophilic pathway and the Michaelis-Menten-type behavior.

HMPA Effects. On the other hand, it might be helpful in such systems to add a strong, nonoxidizable ligand, typically HMPA itself, and to study the effect on oxidation rate.

Within the framework of the mechanism that involves intramolecular oxidation of the coordinate substrate, we would expect that increasing amounts of added HMPA will continously inhibit the reaction rate until it will drop to zero, since the displacement of the coordinate amine by HMPA will give firstly $MO_5HMPA{\cdot}R_2NH$, which will be then converted into $MO_5(HMPA)_2$ on increasing the concentration of HMPA.

Alternatively, on the basis of the external electrophilic oxygen transfer mechanism, we would expect a continous slowdown of the reaction rate until a minimum value of the oxidation rate is reached, which corresponds to the oxidation rate performed by the species $MO_5(HMPA)_2$. This species, in fact, which is presumably the only oxidant present in solution at high concentration of HMPA, is still able to act as an electrophilic, even if poor, oxidant. The absence, under such conditions, of oxidant species bearing amine molecules in the coordination sphere of the metal, does not make operative the internal mechanism.

Therefore, a plot of k_{obs} vs 1/[HMPA] should display a straight line, whose intercept is zero in the case of the internal oxidation, whereas it is different from zero in the case of the electrophilic oxygen transfer mechanism.

The plot obtained from the data concerning the oxidation of $C_6H_5CH_2NHCH_3$ by MoO_5HMPT in CH_3CN (Figure 5), employing a low concentration of amine and adding increasing amounts of HMPA, shows an intercept value (1/[HMPA] → 0, [HMPA] → ∞), $k_{obs} = 4.98 \times 10^{-4}$ s^{-1}, which is significantly different from zero. Such a value is equal, within the experimental error, to that observed ($k_{obs} = 4.46 \times 10^{-4}$ s^{-1}) performing the same reaction in HMPA itself as a solvent.

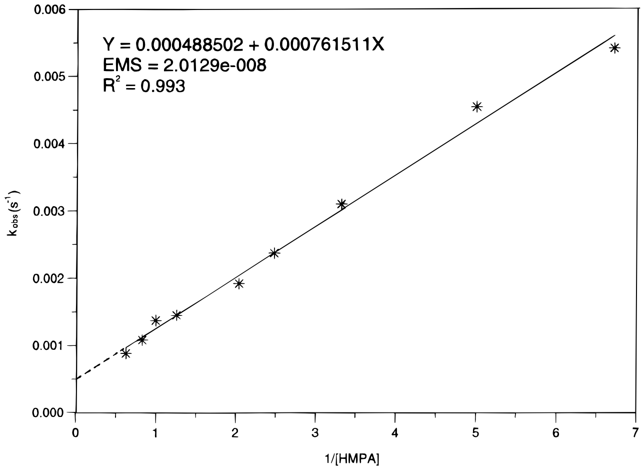

Figure 5. Effects of externally added HMPA on the oxidation rate of Me with MoO_5HMPA in CH_3CN at 40 °C. [Me] = 0.16M; [MoO_5HMPA] = 0.016M.

Therefore, such evidence seems consistent with an electrophilic behavior toward amines by these oxidants in analogy to that previously observed toward thioethers and alkenes.

Conclusions

Oxidation of *N*,*N*-benzylalkylamines by Mo(VI) and W(VI) peroxo complexes yield quantitatively nitrones through a reaction mechanism that depends on the ligand of the complex. When the ligand is strongly bound to the metal and it is not easy to make available a coordination site (anionic oxidants) the amine attacks externally the peroxide oxygen and, through a Bartlett-type transition state, yields the corresponding hydroxylamine, which is rapidly converted to nitrone. On the other hand, when the metal presents a coordination site free (neutral oxidants) the amine attacks the metal center and, under the experimental conditions adopted, removes the preexisting ligand HMPA and yields a new oxidant species, containing substrate molecules in the coordination sphere, which is itself able to act as an electrophilic oxidant toward the amine molecules.

Alternatively, the amine–oxidant association complex might evolve to products through an oxidation process that involves the coordinate substrate molecules (internal oxidation) and that presumably requires radical events.

However, a study of oxidation rate effects on adding increasing amounts of HMPA seems to be consistent with the external electrophilic oxygen transfer mechanism.

Experimental Section

Materials. Chloroform (Carlo Erba, RPE) and acetonitrile (Merck, LiChrosolv) were distilled before use over P_4O_{10} and over calcium hydride, respectively. *N*,*N*-Benzylmethylamine, *N*,*N*-benzylisopropylamine, and *N*,*N*-benzyl-*tert*-butylamine (Aldrich) were purified by distillation over calcium hydride. Tungsten(VI) and molybdenum(VI) oxodiperoxo complexes $MO(O_2)_2HMPA$,[14] molybdenum(VI) oxodiperoxopicolinate [MO-

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[14] Mimoun, H.; Seree De Roche, I.; Sajus, L. *Bull. Soc. Chim. Fr.* **1969**, 1481–1492.

$(O_2)_2O_2CNC_5H_4]^-$ $[(C_4H_9)_4N^+]$ (PIC),[15] Mo(VI) oxodiperoxo picolinate *N*-oxide $[MoO(O_2)_2O_2C(O)NC_5H_4]^-$ $[(C_4H_9)N^+]$ (PICO),[15] and oxodiperoxo benzoate $[MoO(O_2)_2O_2CC_6H_5]^-$ $[(C_4H_9)_4N^+]$ (BENZ)[16] were prepared by the previously reported original procedures. (**Caution, explosion hazard!**)

Preparation of $MoO(O_2)_2C_6H_5CH_2NHBu^t$. To a 5 mL chloroform solution, containing 0.200 mmol of $C_6H_5CH_2NHBu^t$, was added at room temperature a 5 mL chloroform solution containing 0.203 mmol of $MoO(O_2)_2HMPA$. The precipitate readily formed was filtered, washed with $CHCl_3$, and dried. Elemental analysis (C, 38.99; H, 5.31; N, 4.07, respectively) is in agreement with the calculated values (C, 38.92; H, 5.05; N, 4.13) referred to the formula $MoO(O_2)_2C_6H_5CH_2NHBu^t$. An aliquot of the sample dissolved in CD_3CN gave the following ^1H-NMR spectrum: δ (CD_3CN) 7.44−7.60 (m, 5H, aromatic protons), 4.20 (s, 2H, benzylic protons), 1.47 (s, 9H, CH_3), iodometric titer of 0.0689 mmol of compound yielded 0.1322 mmol of active oxygen (96%), as expected for a diperoxo complex of general formula $MO(O_2)_2L$.

For comparison, $C_6H_5CH_2NHBu^t$ gave the following ^1H-NMR spectrum: δ (CD_3CN) 7.20−7.32 (m, 5H, aromatic protons), 3.72 (s, 2H, benzylic protons), 1.17 (s, 9H, CH_3). Thus, the downfield shift of benzylic protons (0.48 ppm) and CH_3 protons (0.30 ppm), respectively, is consistent with an amine molecule bound to the metal.

The same compound is obtained starting with 1.56 mmol of amine and 0.159 mmol of oxidant.

Kinetics. All kinetic runs were carried out under a nitrogen atmosphere. In a typical run, 5 mL of $CHCl_3$ (CH_3CN) containing 0.15 mmol of peroxo complex was added to a $CHCl_3$ (CH_3CN) solution (5 mL) containing 1−15 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, under pseudo-first-order conditions, employing a 10−100 times excess of substrate over the oxidant. 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 $[O]_{act}$ vs time, were evaluated by using a linear least-squares computer program (Plot it 3.0) and were reproducible within ±5%.

Kinetics were followed also by UV technique monitoring the formation of the nitrone; thus, in the case of $C_6H_5CH_2NHPr^i$ the formation of the nitrone was monitored at $\lambda = 297$ ($\epsilon = 2.03 \times 10^4$) and the pseudo-first-order rate constants were obtained from plots of ln ($[\text{product}]_\infty - [\text{product}]_t$) vs time (after correcting the o.d. values for a small and constant absorption due to the starting amine). Usually, the agreement between the two sets of rate constants, obtained by titration and by UV measurements, respectively, is within ±5% (rate data, obtained following the consumption of the oxidant by titration, must be divided by 2 to match the corresponding rate data obtained by UV since only half-oxidant is involved in the rate-determining formation of hydroxylamine).

Reaction products were isolated and characterized as reported previously.[2b]

For the study of the stoichiometry of the oxidation reactions an appropriate internal GC standard was added in the reaction mixture. Aliquots of the mixture were withdrawn at the desired time interval, and the amount of the products formed was determined by GLC, whereas in the same aliquot the content of the oxygen not reacted was determined by iodometric titration. Usually, conversion values are in the range 90−95%, whereas the yields in nitrone are 80−90% with respect to the oxidant reacted. For the reaction of $C_6H_5CH_2NHMe$ with MoO_5HMPA (conversion 98%), we obtained 82% of the corresponding nitrone and 12% of $C_6H_5CH{=}NOH$; in such a case the nitrone was determined by ^1H-NMR (internal standard $(C_6H_5)_3CH$) monitoring the CH_3 resonance of nitrone (3.80 ppm), whereas the oxime was determined by HPLC, employing a Hypersil silica column (0.5 μm, 250 × 4.6 mm), flow rate 1.0 mL/min, detector set at $\lambda = 275$ 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, 20−25 100% A.

Instrumentation. Gas chromatographic analyses of the reaction mixtures were carried out on a Perkin-Elmer 8420 gas chromatograph equipped with a flame ionization detector and program capability; a 25-m SE-30 capilllary column was used for product determinations.

HPLC analyses were performed on a Varian 5000 instrument equipped with a UV−vis detector (JASCO UV DEC-100) and a LCI-100 Perkin-Elmer integrator.

GC−MS analyses of reaction mixtures were performed on a Hewlett-Packard Model 5890 gas chromatograph (using an HP-1 dimethylpolysiloxane 25 capillary column) equipped with a Hewlett-Packard MS computerized system Model 5971A.

UV measurements were performed by a UV/vis Perkin-Elmer LAMBDA 2S spectrometer, using 1 cm thermostatic quartz cells.

^1H-NMR measurements were obtained on a Bruker AC 200 MHz spectrometer.

C, H, N, analyzer Fisons Model EA 1108 was used for elemental analyses.

Acknowledgment. Financial support from CNR and from MURST is gratefully acknowledged.

JO960544C

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(16) Campestrini, S. Ph.D. Thesis, Padova University, 1988.