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Reaction products and mechanism of the regioselective oxidation of *N*-phenylmorpholine by ozone

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ABSTRACT

The regioselective oxidation of *N*-phenylmorpholine by ozone in dichloromethane or acetonitrile produced a lactam and a diformylderivative. These products derive from the selective attack of ozone at the heterocyclic ring in one of the two non-equivalent reactive carbons. The reaction mechanism has been investigated by DFT calculations, which show that the reaction occurs through the insertion of ozone at the carbon–hydrogen bond of a methylene group of the morpholine ring. The regioselectivity is due to the significantly lower energy barrier calculated for the attack of ozone α to nitrogen than α to oxygen. In addition, the energy barrier decreases with increasing the polarity of the solvent, explaining the higher conversions observed for the reaction carried out in acetonitrile than in dichloromethane.

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1. Introduction

The fundamental problem in the functionalization of saturated hydrocarbons is that their components, carbon and hydrogen, do not have electron pairs, and do not have an easily accessible orbital of proper energy. Thus, very reactive reagents and/or extreme reaction conditions are usually required. Moreover, reaction products are usually more reactive than the starting materials, and thus undesired side reactions may occur.¹ Ozone is a metal-free alternative to these methods, and the reactivity of this compound with organic molecules has been the focus of organic synthesis research for decades.^{2–4}

Ozone has been used by some of us for the oxidation of cycloalkanes to cycloalkanol and cycloalkanones,⁵ ethers to esters,⁶ amines to amides.^{7–9} These studies suggest that ozone is a suitable oxidant, but also that the process requires improvement of both conversion and selectivity. In particular, with this oxidant it is difficult to control the oxidation position within the carbon chain. In fact, to our knowledge, the only studies where ozone was used in regioselective synthesis are the oxidation of functionalized imide proposed by Poschenrieder et al.,¹⁰ and the stereoselective oxidation of (+)-aromadendrene proposed by van Lier et al. where ozone reacts with a more reactive tertiary carbon.¹¹ In this work we present a combination of experimental and quantum chemical studies for elucidating the reaction products and the mechanism of the regioselective oxidation with ozone of the aromatic amine *N*-phenylmorpholine **1**. This molecule has been selected as a suitable model for this study as non-equivalent CH_2 groups α to nitrogen and α to oxygen are present.

Ozonation of aliphatic tertiary amines has been extensively investigated in water as well as in organic solvents showing that the main product in most of the reaction conditions is the corresponding amineoxide.^{12–15} However, strong solvent and temperature effects were observed in the products distribution: high yields of amine-oxide were reported in solvents such as chloroform, methanol, and water, while only a small amount of amine-oxide is obtained in butyl-chloride and pentane. In the proposed mechanism the amine-oxide is formed through addition of O₃ to nitrogen of the amine to give the R₃N–O₃ adduct followed by elimination of singlet dioxygen (Eq. 1 in Scheme 1). The other reaction products occur from the oxidation of the amine side chains. In this case the mechanism should proceed through the dissociation of the N–O₃ adduct to give the amine radical cation R₃N⁺ and the ozonide radical O_3^- , or from an intramolecular hydrogen abstraction of the R₃N–O₃ adduct and the subsequent rearrangement of the intermediate (Eqs. 2 and 3 in Scheme 1). An alternative mechanism considered in Ref. 14 is the 1,3 dipolar insertion reaction at one C-H bond of the side chains to give the hydrotrioxide intermediate (Eq. 4 in Scheme 1). Indeed, the latter mechanism has been proposed to account for the reaction products upon ozonation of aromatic aldehydes and aliphatic ethers. This mechanism may proceed by a hydrogen





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$$R_3N + O_3 \longrightarrow R_3N - O - O - O^- \longrightarrow R_3N - O + O_2$$
 Eq. 1

$$R_{3}N + O_{3} \longrightarrow \begin{array}{c} O-O-O^{-} & O-O-OH \\ | \\ NR_{2}CH_{2}R' \\ + \end{array} \longrightarrow \begin{array}{c} O-O-OH \\ R_{2}N=CHR' \\ R_{2}N=CHR' \\ + \end{array} \longrightarrow \begin{array}{c} OH \\ R_{2}N-CHR' \\ R_{2}N-CHR' \\ + \end{array} + O_{2} \qquad Eq. 2$$

$$R_3N + O_3 \longrightarrow 0^{-O-O^-} \longrightarrow 0^{-O-OH} \longrightarrow 0^{-O-OH} \qquad \longrightarrow 0^{-O-OH} \qquad P_1 \longrightarrow 0^{-O-O-OH} \qquad P_2N \longrightarrow$$

Scheme 1.

abstraction followed by the formation of the radical pair R···OOOH, which then recombine to form ROOOH,¹⁶ or by a hydride abstraction with the formation of the ion pair R⁺ –OOOH that again recombine to form ROOOH,¹⁷ as also reviewed for the reactions of acetals with ozone.^{18–22} However, experimental results seem to exclude this mechanism for aliphatic tertiary amines.¹⁴

Ozonation of tertiary aromatic amines has been less studied than the corresponding reaction with aliphatic amines.^{23,24} In particular, it was demonstrated that amine-oxide, which is the major product for aliphatic amines, is not formed in the ozonation of aromatic amines. Meth-Cohn and Kerr also showed that the absence of the amine-oxide is not due to further reactions of this species with ozone.²⁴ On this basis they proposed a mechanism in which O₃ adds to the nitrogen atom to give the N–O₃ adduct, followed by an intermolecular hydrogen abstraction and a decomposition of the corresponding adduct to give radical and/or cationic intermediates, which further recombine to give the final products (Eq. 5 in Scheme 1). In the section 'Results and discussion' we first report on the product distribution obtained from the ozonation of *N*-phenyl-morpholine at several temperatures and in different solvents, then we discuss the reaction mechanism on the basis of the results obtained from the theoretical investigation. In particular, it will be shown that a low energy pathway can account for the product distribution.

0,

Eq. 5

2. Results and discussion

2.1. Experimental results

N-Phenylmorpholine **1** was reacted in dichloromethane or acetonitrile with excess ozone at different temperatures and at different reaction times in order to study the effect of the reaction conditions over the distribution of the products. Table 1 summarizes the obtained results.

Table 1

Conversions and isolated yields of the products 2 _N and 3 in the reaction of N-phenylmorpholine 1 with ozone (DCM=dichloromethane; ACN=acetonitril

Entry	<i>T</i> (°C)	<i>t</i> (h)	Solvent	Ozone	Conversion ^a (%)	Lactam 2_Nb %	Diformylderivative 3^b (%)	Other (%)
1	25	1.5	DCM	Excess	80	20	6	
2	0	1.5	DCM	Excess	84	24	7	5 :tr
3	-20	0.5	DCM	Excess	100	23	4	4:tr; 5:tr
4	25	24	DCM	10:1	38	4	3	6:tr
5	25	24	DCM	5:1	6	1	3	6:tr
6	25	0.5	ACN	Excess	99	24	17	
7	0	0.5	ACN	Excess	100	34	14	
8	-20	0.5	ACN	Excess	98	27	6	
9	25	24	ACN	10:1	100	46	8	
10	0	1	ACN	1:1	30	16	3	

^a Conversion is calculated on the basis of the unreacted *N*-phenylmorpholine recovered.

^b Isolated yield after silica gel chromatography (see the Experimental part).

In dichloromethane at 25 °C, after 1.5 h, 80% of the starting material was converted into products. Two reaction products could be separated by silica gel chromatography and were identified as the lactam $\mathbf{2}_{N}$ and the diformylderivative **3** (Scheme 2) by comparison of their IR, MS, ¹H NMR, and ¹³C NMR spectra with those of authentic samples.^{25,26}



Scheme 2. Reaction products from the ozonation of N-phenylmorpholine 1.

The reaction was repeated in dichloromethane at 0 °C for 1 h and at -20 °C for 0.5 h. The conversion was higher compared to the reaction carried out at room temperature and products **2** and **3** were again isolated.

In all these experiments recovery of material after silica gel chromatography was poor: approximately one half of the starting material was converted into highly polar products produced by the decomposition of the parent compound.

Moreover, traces of other reaction products were observed in the GC–MS chromatograms of the crude reaction mixture. On the basis of the detected mass spectra and tentative structural elucidation they were recognized as the dehydroderivative $4 (m/z=161 (M^+), 132, 104, 77)$ and stereoisomers of the dimeric structure $5 (m/z=322 (M^+))$.

Oxidation of *N*-phenylmorpholine **1** in acetonitrile as solvent, with excess of ozone at 25, 0 and -20 °C for 0.5 h, gave a complete conversion, and again lactam **2**_N and diformylderivative **3** were isolated. Also in these cases, poor recovery was observed (less than 50%).

Since shorter reaction times did not give higher mass balance, experiments were performed using a controlled amount of ozone in the attempt to minimize the further oxidation of primary reaction products.

Using a 10:1 excess of ozone and a 24 h reaction time at room temperature, in dichloromethane a better recovery was obtained: 38% of the starting material and minute amounts of compounds 2_N and **3** were present. Also isomers deriving from the chlorination of the starting material **6** were detected in the GC–MS of the crude reaction mixture. By replacing dichloromethane with acetonitrile and using the same conditions, complete conversion was instead observed. Compounds 2_N and **3** were present in 31 and 15% yields, respectively.

In summary, the collected data show that:

- A major conversion is always observed in acetonitrile compared to dichloromethane. In fact, in the reactions with excess ozone the conversion of *N*-phenylmorpholine 1 in acetonitrile is complete at all of the temperatures investigated. In dichloromethane the conversion is complete only at −20 °C, while partial conversion is observed at 0 and 25 °C. Moreover, with a 10:1 excess of ozone the starting material is completely converted in acetonitrile, not in dichloromethane. This may be explained by a solvent polarity effect on the reaction mechanism (vide infra).
- 2. In dichloromethane the conversion seems to be higher at lower temperatures than at higher temperatures.
- 3. Mass balance is generally poor, probably due to the further oxidation of the primary reaction products. The higher recovery was obtained in the reactions performed in acetonitrile with a 10:1 excess of ozone, but the yields in compounds 2_N and 3 were very similar to those of the reactions performed with excess ozone. This suggests that further oxidation of the primary reaction products is faster than the oxidation of the starting material.
- 4. Notwithstanding the poor recovery, all the reactions showed a very interesting regioselectivity and further developments are underway in our laboratory in order to develop a valuable synthetic procedure. In particular, the main isolated reaction products, *N*-phenylmorpholinone 2_N and the diformylderivative of the *N*-phenylmorpholine **3**, both derive from the regioselective attack of ozone at the heterocyclic ring, involving at some step of the reaction pathway the activation of the methylene group α to nitrogen. No traces of products deriving from the attack α to oxygen were isolated. Moreover, the diformylderivative could be one of the degradation products deriving from further oxidation of the intermediate alcohol 7_N (see Scheme 2) that seems to be preferred.

These results are in line with those obtained earlier.²⁴ In fact, the formation of lactam 2_N from *N*-phenylmorpholine **1** corresponds to the formation of an *N*-methylformanilide derivative from *N*,*N*-dimethylaniline and its 4-substituted derivatives. However, in the case of *N*,*N*-dimethylaniline the path, which leads to the dehydrointermediate **4**, and consequently to the diformylderivative **3**, is not possible since the substituent at nitrogen is a one-carbon unit.

2.2. Theoretical investigation of the reaction mechanism

The mechanism and the regiochemistry of the reaction have been investigated by quantum mechanics calculations through the identification of the relevant stationary points (minima and saddle points) along the reaction coordinate of the pathways A and B reported in Scheme 3. The concurrent ozonation of the aromatic ring by the mechanism shown in Scheme 4 has been studied, as well. Indeed, decomposition of the aromatic ring may account for the partial recovery of the reaction products. The calculations were performed in vacuum, as well as in acetonitrile and dichloromethane to evaluate the solvent effect on the reaction mechanism.

In the following, for the sake of clarity, the subscripts N and O will be added to labels of chemical species, to indicate regioisomers differing by substituents or reacting centers α to nitrogen and oxygen, respectively.

The first step in the proposed mechanism could be the formation of intermediates A_N and A_0 , or B_N and B_0 , through pathways A, or B, respectively (Scheme 3).

Pathway A, as proposed for the oxidation of *N*,*N*-dimethylaniline in Ref. 24, occurs with the addition of O₃ to nitrogen leading to **Int**_A [reaction (1a)], followed by an intramolecular hydrogen transfer from a methylene group α to nitrogen or α to oxygen to the terminal oxygen atom to give the intermediate **A**_N or **A**_O, respectively



Scheme 3. The regiochemistry of the ozonation of *N*-phenylmorpholine. **A**₀, **B**₀, **Rad**₀ and **Cat**₀, not reported in the scheme, are derived from **A**_N, **B**_N, **Rad**_N and **Cat**_N, respectively, by placing the reacting center or the functional group *α* to the oxygen atom.

[reaction (2a)]. Finally, elimination of O₂ and OH⁻/OH• from A_N or A₀, and the subsequent recombination of OH⁻/OH with the radical/ cationic substrate leads to the *N*-phenylmorpholinone 2_N or 2₀ [reaction (3a)]. Alternatively, the adduct Int_A may dissociate into the ozonide radical O₃⁻ and the *N*-phenylmorpholyl radical cation 1⁺ [reaction (4a)]. The ozonide may further react with 1⁺ by abstracting a hydrogen atom or a proton from a methylene group of the morpholine ring to form HO₃• and Rad_N or Rad₀ (proton abstraction), or HO₃⁻ and Cat_N or Cat₀ (hydrogen abstraction) [reaction (5a)]. This pathway then proceeds with the recombination of the two species to form the hydrotrioxide B_N or B₀ of the pathway B

discussed below. **Int**_A may also loose singlet dioxygen producing the amine-oxide **12** [reaction (6a)]. The last reaction, which is the major route for aliphatic amines, should not occur for tertiary aromatic amines, as the amine-oxide has never been isolated from the ozonation of this class of compounds.²⁴

In the pathway B the first step is a hydride or hydrogen transfer from a methylene carbon atom to the terminal oxygen atom of O_3 . The hydride abstraction from a methylene group α to nitrogen or α to oxygen of the morpholine ring leads to the formation of the *N*-phenylmorpholyl cation **Cat**_N or **Cat**_O, respectively, and the hydrotrioxide anion (HO₃⁻) [reaction (1b₂)]. Alternatively, the hydrogen transfer leads



Scheme 4. Mechanisms for the ozonation of the aromatic ring,

to the formation of the *N*-phenylmorpholyl radicals **Rad_N** or **Rad_O** and the hydrotrioxide radical HO₃• [reaction (1b₁)]. The recombination of the terminal oxygen atom of HO₃⁻ or HO₃• with the methylene carbon atom then gives the hydrotrioxide **B**_N or **B**_O [reaction (2b₁ or 2b₂)]. The process may also occur through a concerted mechanism where hydrogen transfer and C–O bond formation occurs simultaneously.

The key hydrotrioxide intermediates B_N and B_0 may further evolve following the pathways:

- Dissociation to a carbonyl compound (2_N or 2₀) and hydrogen peroxide [reaction (3b)].
- (2) Dismutation to an alcohol (7_N or 7₀) and dioxygen [reaction (4b)]. Singlet dioxygen is reported to be formed in this step.²⁷
- (3) Rearrangement to an aldehyde hydroperoxide ($\mathbf{8}_{N}$ or $\mathbf{8}_{O}$) with further oxidation to carboxylic acids [reaction (5b)].

Previous studies on cycloalkanes⁵ and ethers⁶ reported that decomposition of the intermediate hydrotrioxide to form carbonyl compounds predominates over their fragmentation to the corresponding alcohols or to open chain compounds.

Concerning the regiochemistry of the reaction, fragmentation of hydrotrioxide B_N gives the lactam 2_N [reaction (3b)], which, in fact is the major product observed experimentally. The alternative formation of the isomeric hydrotrioxide B_0 seems not to occur because the lactone 2_0 has never been found.

Scheme 5 shows the decomposition of the intermediate alcohols 7_N and 7_0 . Dehydration of alcohol 7_N should give the dehydroderivative **4**, which was found in trace amounts because of its fast oxidation to the diformylderivative **3**. Alternatively, the dehydration of 7_N to the immonium ion **9** is the origin of the dimeric material **5**, in accord with the dimerization of *N*-phenylpyrrolidine upon ozonation.²⁴ Again, alcohol **7**₀ seems not to be formed, since the final formylderivative **11** was never found.



Scheme 5. The fate of the intermediate alcohols.

The computational investigation of the reaction mechanism, summarized by the energy profile shown in Fig. 1, explains the regioselectivity and the product distribution observed experimentally. Energies and relevant energy differences for the species considered in this work are reported in Supplementary data.

The full electron transfer from **1** to O_3 to give the pair of separate radical ions **1**⁺ and O_3^- [reaction (7a)] is a process in which the products are less stable than **1** and O_3 by about 112, 11, and 2 kcal mol⁻¹ in vacuum, CH₂Cl₂ and CH₃CN, respectively. It is worth noting that in a strongly polar solvent such as water the pair of radical ions **1**⁺ and O_3^- are likely to be significantly more stable than separate reactants, due to the large solvation energy of ionic species. This is consistent with the large yield of OH• formed from the ozonation of aniline in aqueous solution, for which the precursor is O_3^- .²⁸ These results also suggest that the reaction could occur with different mechanisms depending on the polarity of the solvent.

Notably, any attempt to find an energy minimum for Int_A in pathway A leads to the dissociation of O_{3} ,²⁹ or to the evolution of singlet O_2 with the formation of the amine-oxide **12** [reaction (6a)], depending on the initial geometry for the optimization. Therefore, the key intermediate Int_A , with an oxygen atom of O₃ covalently bounded to nitrogen, in pathway A is not likely to be formed. In addition, A_N and A_0 are not stable species as the geometry optimization of these compounds leads to the dissociation of the O₃H group. These results clearly indicate that the mechanism proposed in Ref. 24, corresponding to pathway A in Scheme 3 does not occur for *N*-phenylmorpholine. In this respect, we note that the formation of a positive nitrogen in the rate-determining step, as for Int_A. should imply a much higher reactivity of 4-methoxy-N.N-dimethylaniline over *N*.*N*-dimethylaniline due to an electronic effect. This effect was not observed in Ref. 24 suggesting that also for N,Ndimethylaniline and its 4-substituted derivatives the reaction may occur with a different mechanism than that illustrated in path A.

The results discussed above suggest that the amine-oxide **12** [reaction (6a)] may form directly from the reagents. However, the system composed by the amine-oxide **12** and singlet dioxygen is less stable than the separate reactants by about 7, 3 and 2 kcal mol⁻¹, in vacuum, dichloromethane, and acetonitrile. Notably, in the case of the tertiary aliphatic amine (CH₃)₃N, the system composed by the corresponding amine-oxide and singlet dioxygen is more stable than the separate reactants (CH₃)₃N and O₃ by 4 and 7 kcal mol⁻¹ in dichloromethane and acetonitrile, respectively, while it remains less stable by about 3 kcal mol⁻¹ in vacuum (data not shown). The different stability between the amine-oxide produced from the aliphatic tertiary amine (CH₃)₃N and the aromatic tertiary amine *N*-phenylmorpholine would explain why the amine-oxide is the main product in the ozonation of an aliphatic amine, while it is not observed in the ozonation of an aromatic amine.

In the pathway B, the reaction, starting from the reagents, can proceed along two different paths depending on the secondary carbon atom attacked by ozone, namely either α to nitrogen or α to oxygen.

In both cases the formation of the hydrotrioxide intermediates \mathbf{B}_N and \mathbf{B}_O proceeds through a hydrogen abstraction mechanism followed by recombination of the ionic or radical pairs (see below). In spite of the many attempts made, we were not able to find a transition state for the concerted mechanism.

The transition state for the hydrogen abstraction α to nitrogen **TS**_N is shown in Fig. 2. In vacuum, the corresponding activation energy (*E*_a), calculated with respect to the separate reactants, is equal to 7.6 kcal mol⁻¹. The hydrogen abstraction α to oxygen leads to the transition state **TS**₀ (see Fig. 2), which is 13.4 kcal mol⁻¹ higher in energy than the separate reactants; a value about 6 kcal mol⁻¹ higher than that calculated for **TS**_N.

It should be noted that in both cases the transition state involves the abstraction of an axial hydrogen. Any attempts to find a transition state for the abstraction of an equatorial hydrogen leads to





Fig. 1. (a) Energy profile along the reaction coordinate for the reaction of **1** with ozone calculated in vacuum. (b) Energy profile along the reaction coordinate for the first step of the reaction of **1** with ozone calculated in vacuum (______), dichloromethane (______), and acetonitrile (______). Solid and dashed lines indicate the pathway with H-abstraction *α* to nitrogen and oxygen, respectively.

a rearrangement of the heterocycle and a convergence of the geometry optimization to TS_N or TS_O .

The activation energies for both TS_N and TS_O became significantly smaller when the reaction is carried out in dichloromethane or acetonitrile solutions. The reduction of the activation energies is also a function of the polarity of the solvent. In fact, the activation energy for TS_N , calculated with respect to the separate reactants, decreases from 7.6 kcal mol⁻¹ in vacuum to 2.6 kcal mol⁻¹ in dichloromethane, to a value as small as equal to 1.6 kcal mol⁻¹ in acetonitrile. In the case of TS_O the reduction is parallel of that calculated for TS_N ; E_a decreases from 13.2 kcal mol⁻¹ in vacuum to 9.7 kcal mol⁻¹ in dichloromethane, and to 8.9 kcal mol⁻¹ in acetonitrile.

The effect of the aromatic nitrogen on the H-abstraction α to this atom is remarkable, as the E_a calculated for **TS**_N is significantly

smaller than that calculated for the H-abstraction of an aliphatic carbon atom. For example, the activation energy calculated in vacuum for the for the H-abstraction of cyclohexane is about 26 kcal mol⁻¹ (data not shown) a value 18 kcal mol⁻¹ higher than that calculated for **TS**_N.

The reaction, from **TS**_N and **TS**₀, can evolve through a homolytic bond dissociation to form a radical pair, or through a heterolytic bond dissociation to form an ionic pair. The homolytic H-abstraction α to nitrogen and oxygen leads to O₃H• and the radical species **Rad**_N and **Rad**₀, respectively [reaction (1b₁)]. In vacuum the system composed by the **Rad**_N–O₃H• radical pair is slightly lower in energy than the separate reactants (ΔE =–0.9 kcal mol⁻¹). The stability of the radical pair slightly increases in the two solvents considered; ΔE =–3.0 and –2.0 kcal mol⁻¹ in dichloromethane and acetonitrile, respectively (see Fig. 1b).



Fig. 2. Geometries of the transition states TS_{N} and TS_{O} calculated using the B3LYP/cc-pVTZ scheme.

The **Rad**₀–O₃H• radical pair is less stable in vacuum than in separate reactants by about 6 kcal mol⁻¹. The formation of the **Rad**₀–O₃H• radical pair is therefore disfavored with respect to the formation of the **Rad**_N–O₃H• pair by about 7 kcal mol⁻¹. The effect of the solvents on the stability of the **Rad**₀–O₃H• pair is parallel to that discussed for the **Rad**_N–O₃H• pair; in dichloromethane and acetonitrile the **Rad**₀–O₃H• pair is more stable than in vacuum, but always less stable than the separate reactants (ΔE =3.6 and 4.5 kcal mol⁻¹ in dichloromethane and acetonitrile, respectively).

The abstraction of the hydride ion from the methylene group α to nitrogen and oxygen produces the ionic pair composed by the carbocations **Cat**_N and **Cat**_O, respectively, and the hydrotrioxide anion O₃H⁻ [reaction (1b₂)]. The formation of the ionic pair is clearly disfavored in vacuum by more than 100 kcal mol⁻¹. As expected, the presence of a polar solvent strongly stabilizes the ionic pair. Indeed, the **Cat**_N–O₃H⁻ pair is more stable than the separate reactants by 5.7 and 15.5 kcal mol⁻¹ in dichloromethane and acetonitrile, respectively (see Fig. 1b). The effect of the solvents is similar for the **Cat**_O–O₃H⁻ pair, even though in the latter case the ionic pair remains less stable than the separate reactants by 15.3 and 4.8 kcal mol⁻¹ in dichloromethane and acetonitrile. Notably, these results also indicate that in the two solvents **Cat**_N is more stable than **Cat**_O by more than 20 kcal mol⁻¹.

After the formation of the ionic or radical pairs, the terminal oxygen of the O₃H⁻or O₃H[•] species can easily approach the unsaturated carbon atom forming a carbon–oxygen bond and giving the hydrotrioxides intermediates **B**_N and **B**₀. These intermediates have similar energies and are significantly more stable than the separate reactants (in vacuum ΔE =–51.0 kcal mol⁻¹ for **B**_N and –51.7 kcal mol⁻¹ for **B**₀). In addition, the stability of **B**_N and **B**₀ is not affected by the solvent.

The formation of the hydrotrioxide intermediates (**B**_N, **B**_O) is the crucial step in order to explain the regioselectivity of the reaction. The results illustrated above clearly show that the methylene group α to nitrogen is more reactive with ozone than the methylene group α to oxygen. This is due to the significantly smaller activation energy for the H-abstraction. In addition, the radical or ionic pair formed by the hydrogen abstraction α to nitrogen is more stable than that formed by H-abstraction α to oxygen. In fact, in dichloromethane and acetonitrile, the radical or ionic pair given by the attack of ozone α to nitrogen is always more stable than separate reactants, while the radical or ionic pair given by the attack of ozone α to oxygen is less stable than separate reactants. The smaller activation energy and the higher stability of the ionic or radical pair as intermediates in the reaction make significantly more favorable the functionalization α to nitrogen and the formation of the hydrotrioxide **B**_N.

In acetonitrile the ionic pair is more stable than the radical pair by about 13 kcal mol⁻¹ indicating that H-abstraction occurs through a ionic mechanism, as already observed for the ozonation of other substrates.^{19–22} In dichloromethane the radical and ionic pairs are almost isoenergetic, suggesting a competition between the ionic and radical mechanism.

A relevant result illustrated above is that the activation energy for the H-abstraction process decreases by raising the polarity of the solvent. This would explain the higher conversions observed experimentally in acetonitrile than in dichloromethane.

Hydrotrioxide B_N or B_O could evolve to give the final products following three different pathways [reactions (3b), (4b), (5b)] (Scheme 3). Calculations in vacuum were also performed for these pathways to dissect the mechanisms, which lead in the formation of the lactam 2_N , and the hemiaminal 7_N as precursor of the diformylderivative **3**.

Dismutation of hydrotrioxides (B_N and B_0) along the pathway (4b) gives hemiaminal 7_N or hemiacetal 7_0 and singlet O_2 . These intermediates are energetically less stable than B_N , and B_0 by about 6 and 4 kcal mol⁻¹, respectively. The activation energy of this reaction step is somewhat large; 46 and 45 kcal mol⁻¹ for **TS-Alc**_N and **TS-Alc**₀ (see Fig. 3) relative to the intermediates B_N and B_0 . However, it should be noted that the hemiaminal 7_N could still react



Fig. 3. Geometries of the transition states TS-Ket_N, TS-Ket_O, TS-Alc_N, and TS-Alc_O calculated using the B3LYP/cc-pVTZ scheme.

until a more stable product is formed, such as the dehydroderivative **4**, which then gives the diformylderivative **3**.

The dissociation of hydrotrioxides (B_N and B_0) along the pathway (3b) leads to the formation of the lactam 2_N or the lactone 2_0 , and hydrogen peroxide. The final products are significantly more stable than the separate reactants (about 100 kcal mol⁻¹) and the barrier that should be overcome is about 38 kcal mol⁻¹ (TS-Ket_N, TS-Ket_O; see Fig. 3) relative to the intermediates B_N and B_0 . Although very large, the energy of the transition state is negative if compared to that of the separate reactants. The excess energy gained from the system to form intermediates B_N and B_0 may then be used to overcome this energy barrier.

In summary, the formation of the hemiaminal 7_N from hydrotrioxide B_N is an endothermic process, while the formation of the lactam 2_N is a strongly exothermic process with an activation energy smaller than that calculated for the formation of 7_N . However, as shown in Fig. 1 the excess of energy provided by the formation of B_N is enough to overcome the energy barriers for the formation of both the lactam 2_N and the hemiaminal 7_N . These results can account for the formation of the hemiaminal 7_N , observed experimentally, even though it is significantly less stable than the lactam 2_N , and with a higher energy barrier.

Ozonation of the aromatic ring may compete with the ozonation of the morpholine ring. The attack of ozone to the aromatic ring can lead to the formation of the Criegee ozonide **13**, or to the formation of the adduct 14 (see Scheme 4). These reactions have been extensively studied for benzene and other aromatic compounds.^{30–34} The Criegee ozonide **13** is more stable than the starting compounds 1 and O_3 by about -19, -21, and -22 kcal mol⁻¹ in vacuum, CH₂Cl₂, and CH₃CN, respectively. The activation energy of this reaction, calculated in vacuum with respect to the separate reactants, is equal to about 6 kcal mol^{-1} , a value in accord with that calculated, with a similar level of theory, for the ozonation of phenol in Ref. 44. The activation energy decreases up to 1.6 and 0.3 kcal mol⁻¹ in dichloromethane and acetonitrile, respectively. Notably, these values are similar to those calculated for the H-abstraction at the morpholine ring showing that the two mechanisms are kinetically competitive, and that the partial recovery of the reaction products can be explained by the decomposition of the aromatic ring.

The adduct **14** in vacuum is higher in energy than the separate reactant by about 9.5 kcal mol⁻¹. However, the solvent significantly affects the stability of the adduct as it becomes more stable than the separate reactants by about 5 and 8 kcal mol⁻¹ in dichloromethane and acetonitrile, respectively. In this case we were not able to locate the transition state, and we cannot compare the energetics of this reaction with the attack of O_3 at the morpholine ring.

3. Conclusions

This paper reports on the investigation of the reaction mechanism and primary products of the *N*-phenylmorpholine oxidation by ozone in different solvents, and at different temperatures. *N*-Phenylmorpholine was used in order to study the regiochemistry of the ozonation reaction with hetero-substituted carbons. The different secondary carbons are adjacent to nitrogen and oxygen heteroatoms, allowing to explore the regioselectivity in the oxidation by ozone of the carbon α to an aromatic amino nitrogen, and the carbon α to an ether oxygen.

In all of the conditions investigated two major reaction products have been characterized; the lactam 2_N and the diformylderivative **3**. The lactone 2_0 was not found, neither was the hemiacetal. The computational study of the reaction mechanism shows that the minimum energy pathway leads to the formation of the hydrotrioxide intermediate B_N through the H-abstraction from the CH₂ group α to nitrogen by O₃. The preferential attack of O₃ to the carbon atom α to nitrogen than α to oxygen is due to the smaller activation energy and to the larger stability of the ionic pair formed by the hydrogen abstraction. In addition, the activation energy calculated for the H-abstraction of *N*-phenylmorpholine is much lower than that calculated for an aliphatic hydrocarbon, explaining the faster reaction kinetic. The hydrotrioxide formed by the recombination of O_3H^{\bullet} with the substrate then evolve toward the formation of the lactam 2_N , which is a strongly exothermic process with an activation energy smaller than that calculated for the formation of the hemiacetal 7_N .

The computational investigation also shows that the mechanism suggested in Ref. 24, with the initial addition of ozone to the nitrogen atom cannot occur in *N*-phenylmorpholine since the reactive intermediate is not stable. In addition, for this aromatic amine, the amine-oxide is less stable than separate reactants, and therefore is not expected to be formed, in agreement with experimental results. Finally, ozonation of aromatic ring is expected to compete with ozonation of the morpholine ring since the energy barrier for the formation of Criegee ozonide is similar with respect to the energy barrier for the H-abstraction for the morpholine ring. Oxidation and subsequent fragmentation of the aromatic ring can account for the partial recovery of the reaction products.

4. Experimental and computational methods

4.1. General

Ozonations were performed with a corona-discharge-based ozone generator (Ozono Elettrica Internazionale s.r.l.) using a 30 L/h oxygen gas steam. The diffusion of the gas in the liquid phase was obtained through a Pasteur pipette 2 mm wide.

Reactions were monitored by thin-layer chromatography (TLC) on commercially available precoated plates (silica gel 60 F₂₅₄) and the spots of products were visualized under UV light (eluent mixture dichloromethane/acetate 8:2, **1** R_f =0.74, **2** R_f =0.86, **3** R_f 0.40). GC–MS analyses were performed with a Hewlett Packard 5890 instrument equipped with a 5971A Mass Selective Detector. A Supelco SPB-5 column (30 m, I.D. 0.25 mm, 0.25 µm film thickness) was used. Oven temp 50 °C for 5 min, then 10 °C min⁻¹ until 250 °C was reached. The temperature of 250 °C was kept for additional 5 min. Infrared (IR) spectra in solutions were recorded on a Nicolet Avatar 360 Fourier transform (FT)-IR spectrometer, using calcium fluoride cells previously purged with N₂. ¹H and ¹³C NMR were recorded on a Varian Mercury 400 instrument in CDCl₃. Chemical shifts are reported in parts per million (δ), relative to the internal standard of tetramethylsilane (TMS).

4.2. Representative experimental procedure for the oxidation of *N*-phenylmorpholine with excess of ozone

N-Phenylmorpholine **1** of 5 mmol was dissolved in 250 mL of solvent (dichloromethane or acetonitrile) and ozonized at the selected temperature. After the selected time of reaction, the suspension was filtered, evaporated under a nitrogen stream, and the residue was separated by flash chromatography over silica gel (R=100) eluting with the mixture dichloromethane/ethyl acetate 9:1.

4.3. Representative experimental procedure for the oxidations of *N*-phenylmorpholine with a limited amount of ozone

Ozone was bubbled for 15 min in 1 L of the appropriate solvent at the selected temperature. The content of ozone was measured by iodometric titration.³⁵ N-Phenylmorpholine **1** in the amount for the appropriate stoichiometry with ozone was then added to the solution. After 24 h reaction, the suspension was filtered, evaporated at reduced pressure, and the residue was separated by flash

chromatography over silica gel (R=100) eluting with the mixture dichloromethane/ethyl acetate 9:1.

4.3.1. *N-Phenylmorpholinone* (**2**). White powder: IR (CaF₂): 1655 cm⁻¹; MS: m/z=177 (M⁺), 148 (M⁺–CHO), 119 (M⁺–2CHO), 101 (M⁺–2CHO–CH₃); ¹H NMR (400 MHz, CDCl₃): δ 3.07 (t, *J*=5.1 Hz, 2H), 3.97 (t, *J*=5.1 Hz, 2H), 4.28 (s, 2H), 7.10–7.20 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 161.0, 129.0, 126.5, 124.0, 60.0, 43.5, 28.5.

4.3.2. Compound **3**. Yellow oil: IR (CaF₂): 1725, 1675 cm⁻¹; MS: m/z=193 (M⁺), 165 (M⁺–CO), 147 (M⁺–HCOOH), 134 (M⁺–CO–CHO); ¹H NMR (400 MHz, CDCl₃): δ 4.03 (t, J=5.1 Hz, 2H), 4.27 (t, J=5.1 Hz, 2H), 7.05–7.40 (m, 5H), 7.91 (s, 1H), 8.34 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 161.0, 160.0, 141.0, 130.0, 126.5, 124.7, 60.3, 44.1.

4.4. Computational methods

All calculations were performed in the framework of the Density Functional Theory (DFT)³⁶ by using the hybrid three parameters B3LYP exchange and correlation functional,^{37–40} and the valence triple- ζ basis set with polarization on all atoms cc-pVTZ.⁴¹ Stationary points of the energy hypersurface (minima and saddle points) were located by means of energy gradient techniques using the quantum mechanical Gaussian 03 suite.⁴² Geometry optimizations to minima and transition states were performed in vacuum as well as in the two solvents employed in the experiments (dichloromethane and acetonitrile). The effect of the solvents (dichloromethane: $\varepsilon = 8.93$: acetonitrile: ε =35.688) was evaluated according to the Polarizable Continuum Model (PCM) approach of Tomasi et al.^{43–46} as implemented in Gaussian 03. Due to the nature of the reaction investigated, individual spheres on hydrogen atoms, with UFF radius, were used in the definition of the polarizable cavity. Transition states were characterized by a full vibrational analysis. Due to the nature of the process, transition states for the hydrogen abstraction were calculated using the unrestricted formalism. However, wavefunctions always converged to the restricted solution, suggesting an ionic rather than a radical character of the TSs. The wavefunctions of the transition states were also tested for an internal and external stability⁴⁷ and in all cases the wavefunctions resulted to be stable.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.07.055.

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