SHORT PAPER

Comparative evaluation of oxidising and nucleophilic properties of some α-nucleophiles[†]

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Six α-nucleophiles were evaluated at pH = 8 in an aqueous methanolic solution for their oxidising power towards tetrahydrothiophene, and the nucleophilic properties towards paraoxon. MMPP and *m*-CPBA are the most versatile reagents and can act as nucleophiles as well as oxidising agents.

Keywords: α-nucleophile, oxidising agent, nucleophile, kinetic

Many α-nucleophiles are particular reagents which can react either as nucleophiles or as oxidizing agents.[1] The balance between these two behaviours is caused by the nature of the α-nucleophile itself and also by the nature of the substrate. For removal of decontamination by chemical warfare nerve agents and particularly organophosphorus toxics, knowledge of this nucleophile oxidising agent balance is absolutely essential to achieve their complete destruction:[2] Indeed, VX agent **1**, an irreversible inhibitor of acetyl cholinesterase enzyme (AchE), has three reaction centres (phosphorus, nitrogen and sulfur atoms) towards the α-nucleophiles.[3] Accordingly, its detoxification is still a question of interest due to its possibilities of degradation by nucleophilic displacement and/or oxidation.[4] Therefore, a major effort must be made to achieve its inactivation: the simple hydrolysis in aqueous alkaline media gives no satisfactory decontamination, due to the formation of a stable and still toxic hydrolysis product resulting from the EtO–P bond cleavage. Hydrolysis using oxidising α-nucleophiles can lead intermediately to the oxidation of the sulfur atom allowing consequently an easier nucleophilic substitution on the phosphorus atom and the cleavage of the P–S bond.

$$Me \overset{\overset{\displaystyle O}{\|}}{\underset{EtO}{>}}P-SCH_2CH_2N(i\text{-}Pr)_2$$

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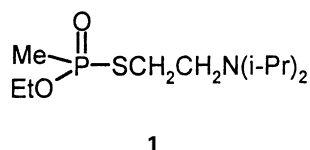
In this work, we evaluated the nucleophilic oxidising properties of six different α-nucleophiles: magnesium monoperoxyphthalate (MMPP), *meta*-chloroperbenzoic acid (*m*-CPBA), potassium monopersulfate (curox, which is a mixture of 2 $KHSO_5$, $KHSO_4$, K_2SO_4), hydrogen peroxide (H_2O_2), hydrogen peroxide with boric acid (H_2O_2/H_3BO_3) at pH 8 in an aqueous methanolic solution. This pH was chosen because it minimises the corrosion risk when a depollution solution is used on metallic furniture or implements.

Results and discussion

Oxidation of tetrahydrothiophene: Sulfides are generally good substrates for the investigation of oxidation reactions. Indeed, oxidation of divalent sulfur compounds like tetrahydrothiophene takes place via the initial formation of sulfoxide **3** which may react subsequently to give sulfone **4**.[5] A kinetic investigation of two oxidations was performed in an aqueous methanolic solution (50/50). Pseudo-first order rate conditions were maintained by keeping 10 equivalents excess of oxidising reagents and following the evolution of the reaction by GC. These oxidation experiments show that the reagents can be classified in three categories (Table 1).
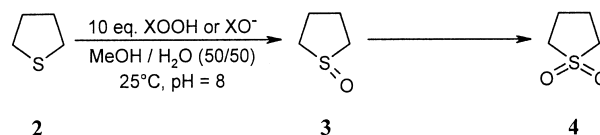
Scheme 1

Table 1

Reagent	reaction time/h	% **3**	k_{SO}/h^{-1}	% **4**	k_{SO_2}/h^{-1}
MMPP	8	6	(a)	94	1.17
m-CPBA	8	20	(a)	80	1.68
Curox	1.5	0	(a)	100	2.72
H_2O_2	2	100	1.84	0	–
Perborate	5	100	0.734	0	–
ClO$^-$	0.083	0	a	85	a

^{a}The reaction is too fast to determine rate constant.

First, hypochlorite anions are the strongest oxidising species and can be considered as the most efficient in our set. Although, only sulfone **4** can be detected after 5 minutes with this reagent, the reaction is not quantitative due to the short half life of the hypochlorite reagent at pH = 8 ($t_{1/2} = 5$ min). Secondly, curox, MMPP and *m*-CPBA are less efficient: they generally give in the first step, quantitatively sulfoxide **3** in less than 5 minutes. Sulfoxide to sulfone oxidation occurs more slowly and pseudo-first order rate constants show that curox is respectively better than *m*-CPBA and MMPP. The incomplete reaction of *m*-CPBA is consistent with its degradation in basic media and a half-life for the reagent of 12 minutes

at pH = 8. Finally, hydrogen peroxide and perborate are not strong enough to oxidise sulfoxide **3** into sulfone **4**. However, they are stable enough in our conditions to lead quantitatively to sulfoxide **2**.

As a consequence, the effectiveness of the α-nucleophiles as oxidising agents can be classified as follow:

ClO⁻ > curox > *m*-CPBA > MMPP > H₂O₂ > perborate.

Reactions with paraoxon: Nucleophilicity of the reagents is determined by nucleophilic substitution reactions on paraoxon **5**.[6] This reaction proceeds by attack of the nucleophilic species on the phosphorus atom leading to the stabilised *p*-nitrophenoxide anion as leaving group and the formation of a phosphorus – nucleophile bond. The kinetics of the reaction are followed through the formation of the *p*-nitrophenoxide anion **7** measured by UV spectrophotometry over a 100 hours period (Scheme 2). The observed rate constants are summarised in Table 2. Although the conditions are sometimes different (using micellar catalysis, concentration and pH), literature results are also given.

The susceptibility of **5** to nucleophilic displacement is pH dependent since the intrinsic reactivity of protonated or unprotonated forms of α-nucleophiles are quite different and their proportions depend on the HO⁻ concentration. Further, the possibility of peroxygenated anion formation increases considerably the nucleophilicity of α-nucleophiles. In a first experiment, hydrolysis of **5** in a carbonate/hydrogenocarbonate buffer by hydroxide displacement was studied to determine the rate of solvolysis. Indeed, reactions with α-nucleophiles in aqueous media are formally the superposition of the solvolysis reaction and nucleophilic displacement by peroxygenated anion.

Due to the acidity of the peroxygenated carboxylic function, only MMPP and *m*-CPBA are predominantly in their anionic form at pH = 8. Consequently, they can react as nucleophiles and the observed rates are the highest of all reagents. Curox is a weak nucleophile due to the low concentration of the anionic form at this pH. Hypochlorite anion does not give nucleophilic substitution and exhibits the lowest rate of all the reagents. Indeed, it is generally considered as a very weak nucleophile. Moreover, as previously mentioned, hypochlorite ions are quickly destroyed at pH = 8. Hydrogen peroxide and perborate have a low nucleophilic character, because at pH = 8, hydrogen peroxide is not acidic enough to form hydroperoxide anion. Moreover, in diluted aqueous solution, perborate decomposes to give boric acid and hydrogen peroxide.

Then, we have the following order of practical nucleophilicity:

MMPP > *m*-CPBA > H₂O₂ > curox > perborate > ClO⁻.
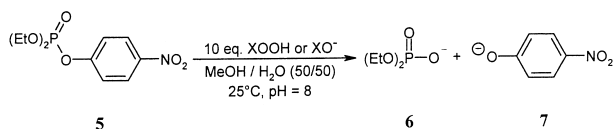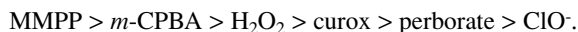
Scheme 2

In conclusion, peroxygenated carboxylic reagents (MMPP, *m*-CPBA) are the most efficient reagents for both oxidation and nucleophilic substitution reactions at pH = 8. However hypochlorite anion shows that it can react exclusively as an oxidising agent. Under non nucleophilic conditions (pH = 8), hydrogen peroxide and perborate can oxidise a sulfur atom to sulfoxide and cannot complete the reaction to produce sulfone.

Table 2

Reagent	$10^3 \times k_{obs}$./h⁻¹ (UV)	$10^3 \times k_{obs}$./h⁻¹ (lit.) pH / eq. [O]
HCO₃⁻/CO₃²⁻	0.308	0.36[a] 8/–
MMPP[b]	8.59	1.33[c] 11.3/16
m-CPBA	1.88	–
Curox	0.368	–
H₂O₂	0.392	5760[d] 732[e] 9.93/10⁴ 10.07/3.5
Perborate	0.161	180[f] 10/125
ClO⁻	0.101	–

[a] [paraoxon] = 3.6×10^{-5} M, [Base] = 0.5 M, pH = 8 (carbonate buffer), *T* = 25°C. [6a]

[b] [paraoxon] = 2.8×10^{-2} M, [MMPP] = 0.28 M, pH = 8 (carbonate buffer), *T* = 25°C.

[c] [paraoxon] = 1.62×10^{-4} M, [MMPP] = 2.6×10^{-3} M, pH = 11.3 (carbonate buffer), *T* = 25°C.[7]

[d] [paraoxon] = 10^{-5} M, [H₂O₂] = 10^{-1} M, pH = 9.93 (NaOH buffer), *T* = 25°C.[8]

[e] [paraoxon] = 10^{-5} M, [H₂O₂] = $3.5 \ 10^{-5}$ M, pH = 10.07 (phosphate buffer), *T* = 37°C.[9]

[f] [paraoxon] = 2.0×10^{-5} M, [perborate] = 2.5×10^{-3} M, pH = 10 (borate buffer), *T* = 25°C.[6b]

Substitution reaction rates of paraoxon are strongly dependent on pH values. Consequently, reagents which are under the anionic form are the more efficient, such as MMPP and *m*-CPBA. These two reagents are polyvalent enough and they showed their prominent efficiency for the VX agent destruction under these conditions.[3]

Experimental

Oxidation study of tetrahydrothiophene: Solutions were prepared by adjusting concentration of tetrahydrothiophene to 10^{-3} M, and α-nucleophiles to 10^{-2} M in 200 ml water/methanol (50/50). The pH was adjusted to 8 by addition of 10^{-1} M solution of sodium hydrogeno carbonate for MMPP, *m*-CPBA, curox and H₂O₂, and by addition of sulfuric acid 0.2 M for perborate and hypochlorite. Ionic strength was adjusted to 0.1 with sodium, magnesium and potassium sulfates to have the same concentration of cations.

5 ml aliquots were mixed with 5 ml of triphenylphosphine solution (0.02M) in chloroform and extracted. 100 µl of DMSO are added to the organic phase as internal reference. The progress of the reaction was monitored by GC analysis using a Perkin–Elmer autosystem equipped with a 15 m × 0.32 mm capillary column AT 35. The injection port temperature was 230°C and detector 280°C. 1 µl aliquot samples were injected. Sulfide, sulfoxide and sulfone concentrations were determined by measuring the ratio of each species towards an internal standard (DMSO).

Reactions with paraoxon: Formation of *p*-nitrophenoxide ion was followed spectrophotometrically at λ = 402 nm using a Beckman DU-40 UV-VIS spectrophotometer equipped with a thermostatted cell. Temperature control was maintained at 25 ± 2°C. All kinetic experiments were carried out in a methanol/water solution (50/50) at pH = 8 with a 10^{-4} M concentration of paraoxon. Ionic strength was adjusted to 0.1 with sodium, magnesium and potassium sulfates to have the same concentration of cations. To determine the pseudo-first order rate constants, 10 equivalents excess of α-nucleophile were used.

The corresponding values of the rate constant k_{obs} are provided by the pseudo-first order kinetic plot of the absorbance as a function of time and extinction coefficients (see ref. 6b for details).

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