Nitrosation by Alkyl Nitrites. Part 7.[1] Comparison with Thionitrites: Reactions with Phenols

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Both isopentyl nitrite (IPN) and *S*-nitroso-*N*-acetylpenicillamine (SNAP) react with phenol in the pH range 2–9 to give overwhelmingly 4-nitrosophenol. For IPN the reaction is first order in both IPN and phenol and the measured rate constant is much reduced by the addition of isopentyl alcohol, suggesting that reaction occurs by prior hydrolysis of IPN to nitrous acid. When allowance is made for the nitrous acid ionisation we find no acid catalysis in the pH range 3.62–5.25 but acid catalysis at higher acidities. The corrected rate constant also increases with pH at pH values greater than 6. There is no bromide ion catalysis at pH 4 but a substantial kinetic primary hydrogen isotope effect (using [$^2H_6$]phenol) of 4.0 at pH 2.55 which decreases towards 1 as the pH is increased. All of these results are consistent with rapid and reversible hydrolysis of IPN, and phenol nitrosation results from the nitrous acid produced. All of the experimental features parallel those found in the nitrous acid nitrosation of phenol. The kinetic pattern for the reaction of SNAP with phenol is quite different, showing autocatalytic features. We have obtained an EPR spectrum from the photolysis of SNAP, characteristic of RS$^{\bullet}$, and for the phenoxy radical derived from the reaction mixture of SNAP with 2,6-di-*tert*-butyl-4-methylphenol at pH 7. We propose a radical mechanism for the reaction of SNAP with phenol involving hydrogen-atom abstraction by the RS$^{\bullet}$ radical and subsequent reaction of the phenoxy radical with nitric oxide formed by homolysis of SNAP.

In neutral or mildly basic solution, alkyl nitrites can act as nitrosating agents by a mechanism whereby the NO group is directly transferred to a suitable substrate. Reactions with amines have been well studied[2] and are believed to involve a four-centred cyclic transition state in which N–N bond formation is concurrent with O–H bond formation and O–N and H–N bond breaking. Reactions have also been described involving NO transfer to ^-OR[3] and RSH[1,4] (where reaction probably occurs *via* the thiolate anion). In general, alkyl nitrites are not particularly reactive, and reaction is only observed for transfers to quite nucleophilic centres. Their reactivity (towards amines and thiolate anions), however, is greatly increased by the presence of β-electron withdrawing groups,[1,5,6] such as OH and the halogens, so much so that, for example, the reaction of β-trichloroethyl nitrite with the thiolate ion derived from cysteine is too fast to measure even by stopped-flow spectrophotometry. The rate constants for reaction with a number of amines correlate quite well with the basicity of the amines.[7] In acid solution, however, rapid and reversible hydrolysis of alkyl nitrites is a competing process and many reactions then occur *via* the nitrous acid released,[8] although in non-aqueous solvents such as ethanol[9] a direct reaction occurs in acid solution which probably involves the protonated form of the alkyl nitrite, particularly for very reactive substrates such as thiourea and thioglycolic acid.

Thionitrites (or *S*-nitrosothiols) RSNO are much less well-known than are the corresponding alkyl nitrites, due in part to their lower stability in general, although there are a few examples of relatively stable thionitrites.[10] There are also in the literature a few examples of nitrosation reactions brought about by thionitrites,[11,12] but these often refer to reactions in organic solvents and under rather forcing conditions, and no mechanistic study has been undertaken. In principle it is to be expected that RSNO would be a better electrophilic nitrosating species than the corresponding RONO since RS^- is the better leaving group. However, the hydrolysis of a thionitrite has been studied under acid conditions[13] and has been found to be (*a*) much slower than that of alkyl nitrites and (*b*) effectively irreversible, again contrasting with the alkyl nitrite situation. These results have been interpreted in terms of the relative basicities of O and S sites (O > S) for the hydrolysis reactions where acid catalysis occurs, and the relative nucleophilicities of O and S sites (S > O) for the reverse reactions *i.e.* nitrosation.

In this work we set out intially to compare the relative reactivities of RONO and RSNO quantitatively. However, during the course of the work we discovered interesting features regarding their reactions with phenols, which we now report.

Results and Discussion

(a) *Reaction of Isopentyl Nitrite (IPN).*—We chose to examine the reactions of IPN as a typical alkyl nitrite which was easy to handle experimentally. The reaction with phenol was examined in water at 25° over the pH range 2.55–9.54. Throughout, the product was almost entirely (>90%) 4-nitrosophenol as analysed by TLC and ^1H NMR spectroscopy. There was evidence of the presence of a small amount of the 2-nitroso isomer. This is the same product distribution reported in the literature[14] for the nitrous acid reaction with phenol. The kinetics were studied with $[PhOH]_0 \gg [IPN]_0$ noting the increasing absorbance at 380 nm due to the product formation. Good first-order behaviour was found consistently and the reaction was also strictly first order in PhOH as indicated in Fig. 1 for results at pH 4.3 and 7.2, thus establishing rate eqn. (1). Values of k as a function of pH are shown in Table 1. There

$$\text{Rate} = k[\text{IPN}][\text{PhOH}] \quad (1)$$

was no bromide ion catalysis at pH 3.0 (see Table 2), and the kinetic hydrogen isotope effect was measured at three pH values for the reactions of [$^2H_6$]phenol. The findings are shown in Table 3. At pH 2.55 there is a substantial primary kinetic isotope effect of 4.0 which decreases towards 1 as the pH is increased. Further, the value of the measured rate constant is very much reduced by the addition of a large excess of isopentyl alcohol.

All of these results are consistent with a mechanism involving rapid reversible hydrolysis of IPN followed by conventional

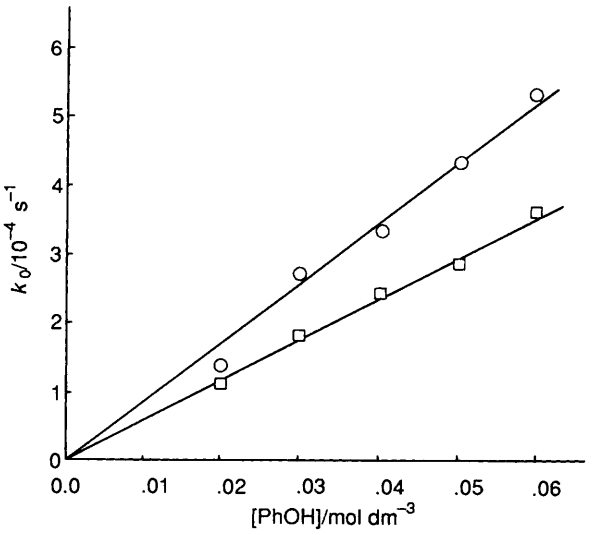


Fig. 1 Plot of the measured first order rate constant (k_0) *vs.* [PhOH] for the reaction of IPN with phenol at pH 4.3 (○) and 7.2 (□)

Table 1 Values of k [eqn. (1)] and k'[a] as a function of pH for the reaction of IPN (1×10^{-3} mol dm^{-3}) with phenol (0.02 – 0.06 mol dm^{-3})

pH	k/dm^3 mol^{-1} s^{-1}	k'/dm^3 mol^{-1} s^{-1} [a]
2.55	0.285	0.357
3.02	0.143	0.249
3.62	0.037	0.146
3.98	0.016	0.124
4.30	8.9×10^{-3}	0.135
5.25	1.02×10^{-3}	0.130
6.47	1.46×10^{-4}	0.306
7.00	1.06×10^{-4}	0.752
7.20	1.00×10^{-4}	1.13
8.54	0.84×10^{-4}	21
9.09	0.77×10^{-4}	67
9.54	0.64×10^{-4}	158

[a] $k' = k(K_N + [H^+])/[H^+]$.

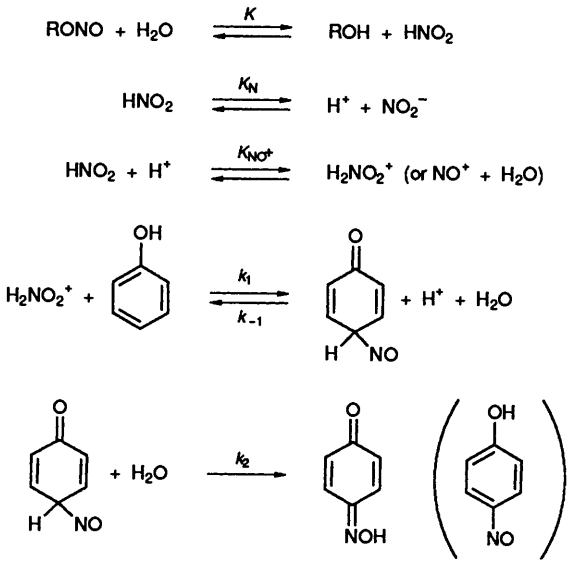
Table 2 Effect of Br^- on the rate constant for reaction of IPN with phenol at pH 3.0

$[Br^-]$/mol dm^{-3}	k/dm^3 mol^{-1} s^{-1}
0.03	0.14
0.05	0.16
0.07	0.14
0.10	0.14
0.20	0.15

Table 3 Kinetic hydrogen isotope effect for the reactions of phenol and [$^2H_6$]phenol with IPN

pH	k_H/dm^3 mol^{-1} s^{-1}	k_D/dm^3 mol^{-1} s^{-1}	k_H/k_D
2.55	0.285	0.0713	4.0
4.30	8.9×10^{-3}	2.7×10^{-3}	3.3
7.20	1.00×10^{-4}	6.7×10^{-5}	1.5

electrophilic aromatic substitution in the phenol brought about by a species derived from the nitrous acid released (*i.e.* $H_2NO_2^+$ or NO^+) as outlined in Scheme 1. A similar scheme can be written for the reaction involving XNO (*e.g.* BrNO) as the electrophilic species in the presence of X^-. Reactions of a number of other species (*e.g.* sulphamic acid, hydrazoic acid



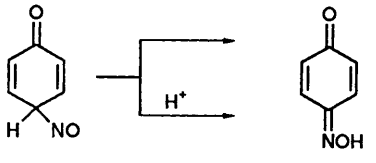
Scheme 1

and cysteine) using alkyl nitrites in aqueous acid solution have been interpreted in this way.[8] Both the hydrolysis of alkyl nitrites[15,16] and the nitrous acid nitrosation of phenol have been studied mechanistically separately[17,18] and both processes are reasonably well understood.

When the pH of the reaction mixture is $<ca.$ 2.5 it is necessary to allow for the ionisation of nitrous acid to nitrite anion (pK_a 3.15). This means that the rate constant values k [eqn. (1)] must be multiplied by $(K_N + [H^+])/[H^+]$, where K_N is the acid dissociation constant of nitrous acid (7.1×10^{-4} mol dm^{-3}). These 'corrected' values of k are given as k' in Table 1. Clearly in the pH range 3.02–5.25 k' is essentially constant, whereas at higher acidities acid catalysis occurs. This is very close to the situation encountered by Challis and Lawson.[18] The predicted form of k' from Scheme 1 is given in eqn. (2).

$$k' = \frac{k_1 K_{NO^+} k_2 [H^+] K}{(k_{-1}[H^+] + k_2)(K + [ROH])} \quad (2)$$

Normally $K \gg [ROH]$, so k' is effectively constant in any one experiment. When the limiting condition $k_{-1}[H^+] \gg k_2$ applies then no acid catalysis occurs. The results for the pH range 3–6 are consistent with this interpretation. The acid catalysis at lower pH is thought[18] to arise by the advent of a parallel pathway for the decomposition of the dienone intermediate [eqn. (3)] which is acid catalysed. At higher pH values the



(3)

possibility arises of reaction *via* the phenolate ion (pK_a 10.0). It is to be expected that this species would be more reactive than phenol itself. A more quantititative analysis bears this out indicating that the phenolate ion is more reactive by a factor of $ca.$ 5×10^3.

The decreasing value of the kinetic isotope effect with increasing pH is also consistent with eqn. (2), predicting a maximum effect when $k_{-1}[H^+] \gg k_2$ and a value of k_H/k_D of 1 when the other limit $k_2 \gg k_{-1}[H^+]$ applies. Again, these results parallel those found for the reactions of nitrous acid with phenol[18] and 2-naphthol,[19] and result from a change in the rate limiting step from the formation of the dienone intermediate to proton loss from the dienone intermediate.

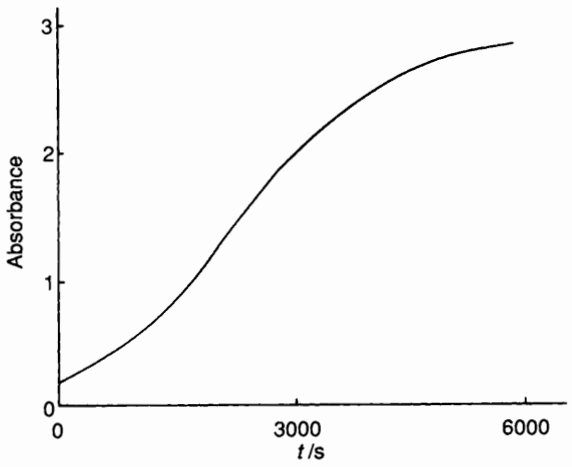


Fig. 2 Absorbance (at 380 nm) *vs.* time plot for the reaction of SNAP with phenol at pH 7

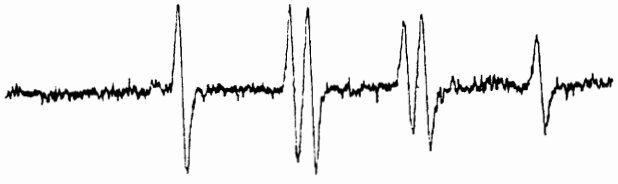


Fig. 3 EPR spectrum obtained on irradiation of SNAP in aqueous solution at pH 7 (1 G ≡ 2 mm)

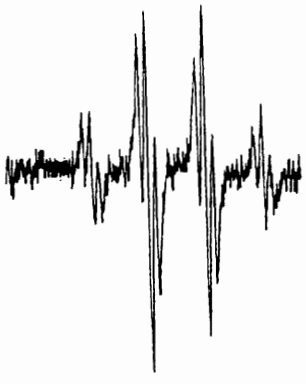


Fig. 4 EPR spectrum obtained from the reaction mixture containing SNAP and 2,6-di-*tert*-butyl-4-methylphenol at pH 7

In the presence of bromide ion, where reaction now occurs by BrNO attack, the corresponding expression for k' is given in eqn. (4). Now, when $k_{-1}[Br^-][H^+] \gg k_2$, k' is independent

$$k' = \frac{k_1[Br^-]K_{BrNO}[H^+]k_2K}{[k_{-1}[Br^-][H^+] + k_2)(K + [ROH])} \quad (4)$$

of $[Br^-]$ as we find at pH 3.0. We have not investigated bromide ion catalysis at other acidities, but in the nitrosation of phenol and 2-naphthol by nitrous acid both limiting cases have been identified experimentally.[18–20]

The value of K for the hydrolysis of IPN has not been measured, but it expected to be close to 0.83 mol dm^{-3}, which is the value measured directly for the structurally similar ethyl nitrite.[21] Thus, in any one experiment $K \gg [ROH]$ and k' should be constant throughout the experiment, as we find. However, the addition of 1 mol dm^{-3} ROH produces a significant reduction as expected.

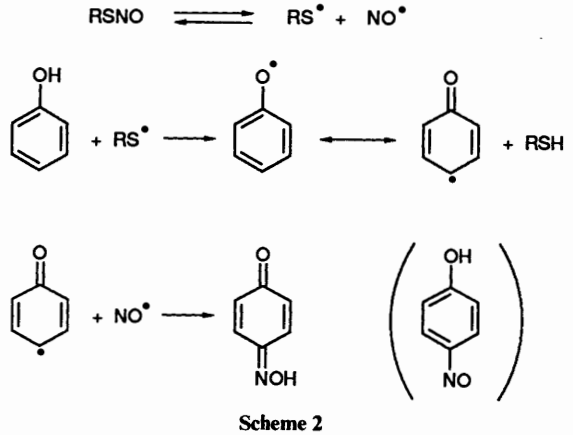
The reaction of 2,4,6-trimethylphenol with IPN was studied in a preliminary way, and showed the same general characteristics as did the phenol reaction, notably showing the absence of acid catalysis in the pH range 2.3–4.3. Experiments with ascorbic acid also were first order in IPN but zero order in ascorbic acid for reactions at pH 4. Catalysis by both Br^- and H^+ was noted. Here again the results are interpreted in terms of a prior hydrolysis of IPN but in this instance the reaction of the nitrosating species with ascorbic acid (or the anion) is so rapid as to ensure that the hydrolysis of IPN is the rate-limiting step. Similar behaviour has previously been noted[8] for reaction of other alkyl nitrites with very reactive substrates such as thiourea.

(b) *Reaction of* S-*Nitroso*-N-*acetylpenicillamine* (*SNAP*).—The most stable (in its solid form) thionitrite known is that derived from *N*-acetylpenicillamine, and is very readily prepared by reaction with aqueous acidic nitrous acid,[12] as outlined in eqn. (5). We have used SNAP in this work because

$$HO_2CCH(NHAc)CMe_2SH \xrightarrow{HNO_2/H^+} HO_2CCH(NHAc)CMe_2SNO \quad (5)$$

of its relative stability. Reaction with phenol occurred readily in water at pH 7 to yield again 4-nitrosophenol as the major product. A small quantity of another product, probably the 2-nitroso isomer was noted, but was not positively identified. The kinetic behaviour of this reaction was, however, quite different from that encountered in the reaction of IPN. Reactions were followed in the same way, noting the increasing absorbance at 380 nm due to the product. The resulting absorbance time plots were, however, somewhat S-shaped as shown in Fig. 2 for a typical experiment at pH 7. A similar pattern was obtained at other pH values.

Hydrolysis of SNAP is not likely to be an important consideration at these pH values, in contrast with the behaviour of alkyl nitrites generally. In fact, the half-life of SNAP in its hydrolysis reaction to give the thiol and nitrous acid at 31 °C is 36 min in 0.94 mol dm^{-3} H_2SO_4. The extrapolated value for the rate constant to pH 7 is negligibly small. Thionitrites, however, are unstable towards disulphide formation, in a reaction believed to involve radicals[10] resulting from homolysis of the S–NO bond and dimerisation of the resulting RS$^\bullet$ radicals. In the presence of a radical scavenger such as 9,10-dihydroanthracene,[22] hydrogen atom abstraction occurs to give the thiol RSH. Such decompositions can be brought about thermally and photochemically. We have obtained an EPR spectrum (Fig. 3) consistent with a thiyl radical RS$^\bullet$ by irradiation of a dilute aqueous solution of SNAP at pH 7 using a 100 kW mercury lamp. Similarly, we have obtained an EPR spectrum (Fig. 4) characteristic of a phenoxy radical from the



Scheme 2

reaction mixture containing SNAP and 2,6-di-*tert*-butyl-4-methylphenol at pH 7. We used this highly hindered phenol rather than phenol itself since the phenoxy radical derived from the latter is rather short-lived and difficult to detect.

We suggest the mechanism outlined in Scheme 2 for the reaction of SNAP with phenol. The RS$^{\bullet}$ radicals formed from SNAP abstract the phenolic hydrogen atom forming the phenoxy radical, in which the spin density is known[23] to reside to a large degree at the 4-position. Capture then occurs by NO$^{\bullet}$ yielding the final product. The closely related 2,4,6-tri-*tert*-butylphenoxy radical produced by oxidation of the corresponding phenol is similarly captured by the $NO_2^{\bullet}$ radical to give the 4-nitro compound.[24]

Further support for this mechanism comes from the observation that no reaction occurs between SNAP and anisole (in which there is no phenolic hydrogen atom available) under the same conditions, whereas alkyl nitrites and nitrous acid[18] react with anisole with the same general characteristics as for the reaction with phenol. The disappearance of SNAP was much accelerated by the addition of the well-known radical trap 2-methyl-2-nitrosopropane, whereas the rate of the reaction of phenol with IPN is unaffected by the presence of this radical trap. As expected no radicals were detected by EPR spectroscopy during the reaction of IPN with 2,4,6-trimethylphenol.

Experimental

A commercial sample of IPN was distilled prior to use. SNAP was prepared by the method of Field *et al.*[12] by the nitrosation of *N*-acetylpenicillamine using nitrous acid. All other materials (including [$^2H_6$]phenol) were commercial samples of high purity. All kinetic measurements were performed at 25 °C in aqueous solution, either in a conventional spectrophotometer, or, for the fast reactions, in a stopped-flow spectrophotometer. Experiments were carried out with $[phenol]_0 \gg [IPN]_0$ or $[SNAP]_0$ and were monitored at 380 nm noting the product formation. Ascorbic acid nitrosation was followed at 360 nm noting the disappearance of IPN. All of the IPN experiments gave a good first order fit with rate constants reproducible to ±5%. Buffer solutions were used to maintain constant pH values as follows: range 2.2–4.0, potassium hydrogen phthalate (0.1 mol dm^{-3}) and perchloric acid (0.1 mol dm^{-3}); range 4.1–5.9, potassium hydrogen phthalate (0.1 mol dm^{-3}) and sodium hydroxide (0.1 mol dm^{-3}); range 5.8–8.0, potassium dihydrogen phosphate (0.1 mol dm^{-3}) and sodium hydroxide (0.1 mol dm^{-3}); range 8.0–9.1, borax (0.025 mol dm^{-3}) and perchloric acid (0.1 mol dm^{-3}); range 9.2–10.8, borax (0.025 mol dm^{-3}) and sodium hydroxide (0.1 mol dm^{-3}); range 10.9–12.0, disodium hydrogen phosphate (0.05 mol dm^{-3}) and sodium hydroxide (0.1 mol dm^{-3}); and range 12.0–13.0, potassium chloride (0.2 mol dm^{-3}) and sodium hydroxide (0.2 mol dm^{-3}). Ionic strength effects were negligibly small.

EPR spectra were obtained at the Chemistry Department, York University, on a Bruker ESP300 X-band spectrometer with 100 kHz modulation using an aqueous sample cell.

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References

1 Part 6. H. M. S. Patel and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1990, 37.
2 S. Oae, N. Asai and K. Fujimori, *J. Chem. Soc., Perkin Trans. 2*, 1978, 1124.
3 A. D. Allen and G. R. Schonbaum, *Can. J. Chem.*, 1961, **39**, 947.
4 J. Mason, *J. Chem. Soc. A*, 1969, 1587; H. Lecher and W. Siefker, *Ber.*, 1926, **59**, 1314, 2594; G. Kresze and J. Winkler, *Chem. Ber.*, 1963, **96**, 1203.
5 B. C. Challis and D. E. G. Shuker, *J. Chem. Soc., Chem. Commun.*, 1979, 315.
6 J. Casado, A. Castro, F. Lorenzo and F. Meijide, *Monatsh. Chem.*, 1986, **117**, 335.
7 J. Casado, A. Castro, M. A. Lopez-Quintella and F. M. Lorenzo, *Bull. Soc. Chim. Fr.*, 1987, 401.
8 M. J. Crookes and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1339.
9 M. J. Crookes and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1989, 759.
10 S. Oae and K. Shinhama, *Org. Prep. Proced. Int.*, 1983, **15**, 165, and references therein.
11 S. Oae, D. Fukushima and Y. H. Kim, *J. Chem. Soc., Chem. Commun.*, 1977, 407.
12 L. Field, R. V. Dilts, R. Ramanthan, P. G. Lenhert and G. E. Carnahan, *J. Chem. Soc., Chem. Commun.*, 1978, 249.
13 S. S. Al-Kaabi, D. L. H. Williams, R. Bonnett and S. L. Ooi, *J. Chem. Soc., Perkin Trans. 2*, 1982, 227.
14 S. Veibel, *Ber.*, 1930, **63**, 1577.
15 A. D. Allen, *J. Chem. Soc.*, 1954, 1968.
16 S. E. Aldred, D. L. H. Williams and M. Garley, *J. Chem. Soc., Perkin Trans. 2*, 1982, 777.
17 K. M. Ibne-Rasa, *J. Am. Chem. Soc.*, 1962, **84**, 4962.
18 B. C. Challis and A. J. Lawson, *J. Chem. Soc. B*, 1971, 770.
19 B. C. Challis and R. J. Higgins, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1597.
20 A. Castro, E. Iglesias, J. R. Leis, M. Mosquera and M. E. Pena, *Bull. Soc. Chim. Fr.*, 1987, 83.
21 J. Casado, F. M. Lorenzo, M. Mosquera and M. F. R. Prieto, *Can. J. Chem.*, 1984, **62**, 136.
22 H. van Zwet and E. C. Kooyman, *Recl. Trav. Chim. Pays-Bas*, 1968, **87**, 45.
23 D. C. Nonhebel, J. M. Tedder and J. C. Walton, *Radicals*, Cambridge University Press, 1979, p. 26.
24 C. D. Cook and R. C. Woodworth, *J. Am. Chem. Soc.*, 1953, **75**, 6242

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