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On the Reaction of Chloroform with Base in the Presence of Spin-traps.

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Abstract: In the presence of spin traps, and in aerated solutions, the reaction of chloroform with base generates carbon-centred radical artifacts.

It is well-known that chloroform reacts with base,[1] via dichlorocarbene[2a] (from an S_N1cB reaction of hydroxyl anion, OH^-, on chloroform[3a]) and its rapid reaction with water, to give carbon monoxide:[4] slow hydrolysis of the latter gives formate. The formation of dichlorocarbene is the basis of the Reimar-Tiemann reaction.[1] Yields from this reaction are at best moderate, and tarry by-products are not uncommon.[1]

Also, investigations on the aerial oxidation of a redox-active porphyrin[5] in basified solutions, show that a porphyrin radical was produced with a shorter half-life in chloroform than other chlorinated solvents (e.g., DCM and 1,1,1-trichloroethane).[6]

These observations suggested the possible intermediacy of oxygen-centred radicals (conceivably produced via reaction of dichlorocarbene[2b] or trichlorocarbanion[3b] with oxygen) during reaction of chloroform with base, and the use of spin-traps to identify them. As an extensive literature exists on the generation and spin-trapping of oxygen-centred radicals from carbon tetrachloride,7 we decided to investigate whether spin-trapping could be used to probe radical production during the reaction of base and chloroform. We found that radicals are produced, but these are artefacts generated by aerial oxidation of diamagnetic carbon-centred adducts with the spin-traps. This paper reports our findings.

EXPERIMENTAL

The spin-traps (Aldrich) used were 2-methyl-2-nitroso-propane (MNP), phenyl-t-butyl nitrone (PBN), and 5,5-dimethyl-1-pyrro-line-N-oxide (DMPO). MNP and DMPO were purified by literature methods·[8] PBN was used as supplied. Chloroform (as supplied) was aerated prior to use.

The spin-trap (50 mg, PBN, MNP as the dimer, or 0.1 ml of an aqueous 1M solution of DMPO) was added to the chloroform (2ml). For MNP, light was excluded, the solution gradually turning blue as MNP monomer formed.

Aliquots of solutions (or DMPO suspension) were transferred to an esr flat-cell and placed in the cavity (at 20°C) of a Bruker ER 200D (microwave frequency, 9.75 - 9.77 GHz) or a Varian E-3 (microwave frequency, 9.36 - 9.38 GHz) esr spectrometers. All solutions were esr-silent. Addition of methanolic tetra-n-butylammonium hydroxide (tnBAH; 1M, 0.1 ml) to the chloroform and spin-trap solutions, and transfer of a fresh aliquot of each solution to the spectrometer gave esr spectra. Hyperfine splitting constants (hfsc's) were measured.

RESULTS AND DISCUSSION

When air was excluded from the reaction solutions (by N_2 bubbling for 1 hour), no esr spectra were obtained on mixing. This indicates that spin-adduct formation is artifactual and oxygen-dependent.

RADICALS WITH MNP

Addition of base to the blue chloroform MNP solution, gave a radical with a triplet spectrum (Figure 1a: a_N = 0.838 mT; g = 2.013). Over an hour, or on addition of more tnBAH (0.1 ml), the triplet disappeared, to be replaced by another with a larger nitrogen hfsc (Figure 1b: a_N = 1.31 mT; g = 2.010). The spectrum of di-t-butyl nitroxide[9a] was run under similar conditions, as a comparison (Figure 1c: a_N = 1.53 mT; g = 1.974).

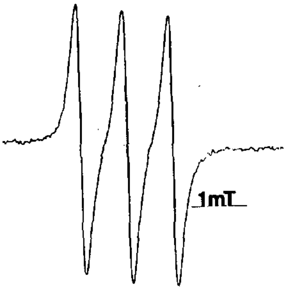

Figure 1a: First spin-adduct with MNP.

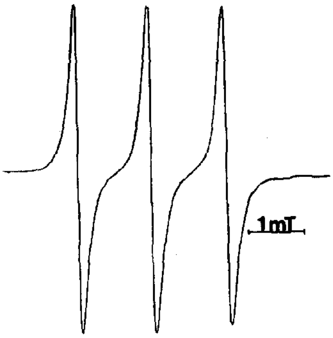

Figure 1b: Second spin-adduct with MNP.

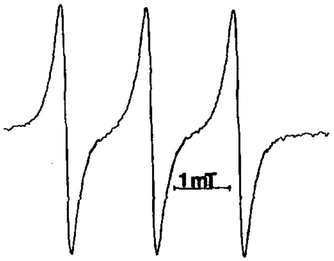

Figure 1c: Di-t-butyl nitroxide in chloroform and base.

RADICALS WITH PNB

Addition of methanolic tnBAH to the solution of PBN in chloroform immediately led to the formation of a radical species. This afforded an esr spectrum consisting of a triplet of doublets (Figure 2a: a_N = 1.35 mT; a_H = 0.174 mT; g = 2.009). Over an hour, or on addition of extra methanolic tnBAH solution (0.1 ml) to the esr cell, a new esr spectrum appeared also consisting of a triplet of doublets (Figure 2b: a_N = 1.45 mT; a_H = 0.23 mT; g = 2.009).

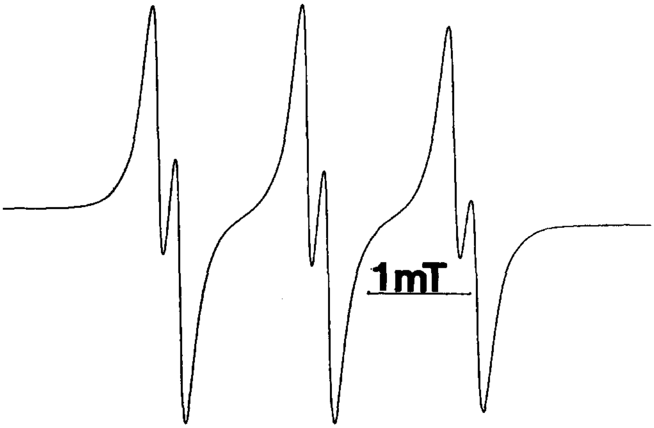

Figure 2a: First spin-adduct with PBN

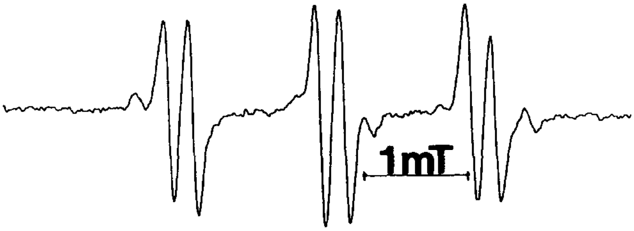

Figure 2b: Second spin-adduct with PBN

RADICALS WITH DMPO

Thorough mixing of a suspension of aqueous DMPO in chloroform, followed by addition of methanolic tnBAH immediately led to the formation of a mixture of radical species. A complex esr spectrum was obtained, the main components of which could be analysed in terms of <u>two</u> overlapping doublets of triplets (Figure 3a: $a_{N(1)}$ = 1. 41 mT; $a_{H(1)}$ = 1.97 mT; g = 2.012: $a_{N(2)}$ = 1.37 mT; $a_{H(2)}$ = 1.61 mT; g = 2.013). After an hour, the first of these doublet of triplets had decayed (Figure 3b).

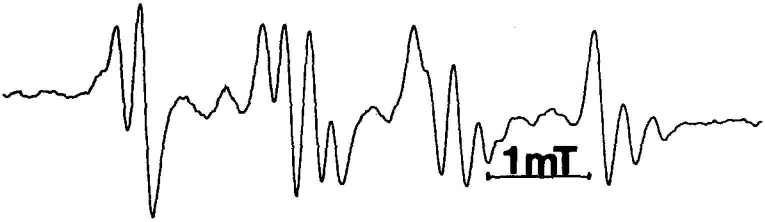

Figure 3a: First spin-adduct with DMPO.

Figure 3b: Second spin-adduct with DMPO.

The combination of spin-trap with paramagnetic species deposits unpaired electron density on or near the nitrogen atom of the spin-trap.[10] The interaction of the magnetic moment of the unpaired electron with that of the nitrogen nucleus (S = 1) creates the fundamental 1:1:1 triplet esr spectrum.

Identification of a particular trapped species is facilitated by the value of the nitrogen hfsc and further hyperfine interactions with the nuclei of its atoms if they possess nuclear magnetic moments, e.g., H, F, P, Cl, etc. These interactions are more signifant the closer the spin-trap's nitrogen atom is to the site where trapping occurs. Thus, in MNP (and other nitroso spin-traps), trapping occurs at the nitrogen so that further hyperfine interactions are diagnostic for particular species. However, the resulting combination can be unstable.

In the nitrone spin-trap, PNB, trapping occurs at a carbon next to the nitrogen atom, leading to a more stable spin-adduct. However, further hyperfine interactions are weaker and more difficult to assign to a particular species. DMPO overcomes this difficulty, being more sensitive to the trapped radical, but spin-adducts are relatively short-lived. DMPO is good at detecting carbon-centred radicals which generally have hydrogen hyperfine splitting constants (hfsc's) that are approximately 50% larger then the nitrogen hfsc's.[11]

As a method for determining the independent existence of radicals in a reaction, spin-trapping can prove misleading. For example, reaction of a diamagnetic intermediate with a nitroso or nitrone spin-trap gives compounds highly labile to aerial oxidation·[9] producing spin-adducts. This results in esr spectra that are artifacts of the use of spin-traps. Removal of oxygen from reaction solutions usually indicates whether the spin-trapped radical is real or an artifact of aerial oxidation.

Initially, the reaction of base with chloroform produces diamagnetic trichlorocarbanion, CCl_3^-.[3] Reaction with MNP, followed by aerial oxidation would produce the MNP-$CCl_3\cdot$ spin-adduct. This species (as a genuine spin-trapped radical intermediate) has been observed before, during the pulse radiolysis of carbon tetrachloride in the presence of MNP,[7] and gives a complex esr spectrum due to hyperfine interactions with the three equivalent chlorine atoms. Clearly, the triplet spectra with MNP observed here cannot be assigned to the spin-adduct MNP-$CCl_3\cdot$.

Also, reaction of CCl_3^- with oxygen to generate a peroxy-radical, and its spin-trapping by MNP, is ruled out as such a spin-adduct would be expected to have a_N = 2.7 mT.[7]

The nitrogen hfsc's observed here are indicative of carbon-centred spin-adducts. We assign the first triplet esr spectrum observed with MNP, from the nitrogen hfsc (a_N = 0.838 mT) and its previous observation,[9b] to the artifactually-produced spin-trapped methoxycarbonyl radical, MNP-$CO_2CH_3\cdot$. A possible mechanism for its production would be reaction of CCl_3^- with MNP, followed by base-induced methanolysis of the adduct. Aerial oxidation produces the artifactual spin-trapped radical.

The second triplet esr spectrum observed with MNP was more difficult to assign. The nitrogen hfsc of this spin-adduct (a_N = 1.31 mT) compared to di-t-butyl nitroxide (a_N = 1.53 mT) under similar conditions, rules out the latter. We propose two possible origins for this second spectrum.

Over an hour, or on addition of more base, it is conceivable that the MNP-$CO_2CH_3\cdot$ spin-adduct undergoes base hydrolysis to give the carboxylate spin-adduct, MNP-$CO_2^{-}\cdot$. This has the attraction of a less electron-withdrawing carbonyl carbon. More spin density would now be localised on the nitrogen, giving the observed larger nitrogen hfsc over the methoxycarbonyl spin-adduct. We could find no confirmation for this assignment in the literature, which brings us to the second possibility.

Carbamates, $-NH.CO_2^-$, are known to be labile to decarboxylation.[12] The carboxylate spin-adduct might be expected to be similarly labile, especially in base, generating the $MNP^{-\cdot}$ radical anion. This has been previously observed[13] and reported nitrogen hyperfine splitting constants (1.12 - 1.22 mT) under different conditions (of solvent and neutrality), are near enough to the value we report for such an assignment to warrant serious consideration.

The two spectra observed using PBN as spin-trap support the above tentative assignments for the MNP spin-adducts. Thus, we assign the spectra to the artifactually-produced $PBN\text{-}CO_2CH_3\cdot$ and $PBN\text{-}CO_2^{-\cdot}$ spin-adducts on the basis of similar nitrogen and hydrogen hfsc's found in the literature.[14] The $PBN\text{-}CO_2^{-\cdot}$ spin-adduct would be expected to be stable to decarboxylation as the carboxylate moiety is attached to a carbon and not a nitrogen atom.

Assignment of the artifactual DMPO spin-adducts is more complicated. Acyloxy-spin-adducts (e.g., $O_2Bu^t\cdot$) have hydrogen hfsc's smaller than nitrogen hfsc's. The two doublet of triplets observed here have hydrogen hfsc's larger than their nitrogen hfsc's, so that assignment to an artifactual $DMPO\text{-}O_2CCH_3\cdot$ spin-adduct is not possible.[15] The second doublet of triplets (Figure 3b), however, is readily assignable to the $[DMPO\text{-}CO_2^-]\cdot$ spin adduct on the basis of literature nitrogen and hydrogen hfsc's,[16] obtained in more polar aqueous solution.[17]

The first doublet of triplets could be assigned to $DMPO\text{-}CO_2CH_3\cdot$, especially as it decays over an hour (leaving the second species, which decays over longer time). Such a decay could be rationalised in terms of base hydrolysis of the methyl ester to afford the carboxylate-spin-adduct. The $DMPO\text{-}CO_2CH_3\cdot$ spin-adduct has not previously been observed.

Another possiblity that fits recorded nitrogen and hydrogen hfsc's[18] and the known chemistry of DMPO, is that DMPO forms an unstable DMPO(3)-yl dimer in basic solutions.[19]

That CCl_3-spin-adducts are not observed probably reflects the fast reaction sequence that generates CCl_3^-, trapping, and attack by base and methanol to produce further spin-adducts. Esr spectroscopy combined with stopped-flow kinetics may allow observation of this spin-adduct.

The absence of oxygen-centred spin-adducts implies that oxygen-centred radicals do not participate in any of the steps involved in the reaction of chloroform with base. Confirmation of this view was obtained by performing a Reimar-Tiemann reaction on 2-naphthol[1,20] in the absence and presence of oxygen. The yields of the final formylated product, 2-hydroxy-1-naphthalenecarboxaldehyde, in each case were unchanged (52%), demonstrating that even if oxygen-centred radicals were formed, they are unimportant to the outcome of the Reimar-Tiemann reaction.

In conclusion, we have shown that the reaction of aerated chloroform with base in the presence of different spin-traps generates artifactual carbon-centred spin-adducts. We believe these arise from aerial oxidation and further base-induced reactions of a diamagnetic adduct formed between the spin-traps and the initially-formed trichlorocarbanion.

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15. DMPO-$O_2Bu^t\cdot$: a_N = 1.42 mT; a_H = 1.06 mT in aqueous solution (see Hall, R.D., Chamulitrat, W., Chignell, C.F., and Mason, R.P., J. Biol. Chem., (1989), 264, 7900.
16. DMPO-$CO_2^{-}\cdot$: a_N = 1.58 mT; a_H = 1.87 mT in aqueous solution (see refs. 14 and 17).
17. Nitrogen hfsc's larger in aqueous solution than in less polar organic solvents by about 0.2 mT (see Knauer, B.R., and Napier, J.J., J. Am. Chem. Soc., (1976), 98, 4395.

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