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Preparation of Some Homologous TEMPO Nitroxides and Oxoammonium Salts; Notes on the NMR Spectroscopy of Nitroxide Free Radicals; The Observed Radical Nature of Oxoammonium Salt Solutions Containing Trace Amounts of Corresponding Nitroxides In An Equilibrium Relationship

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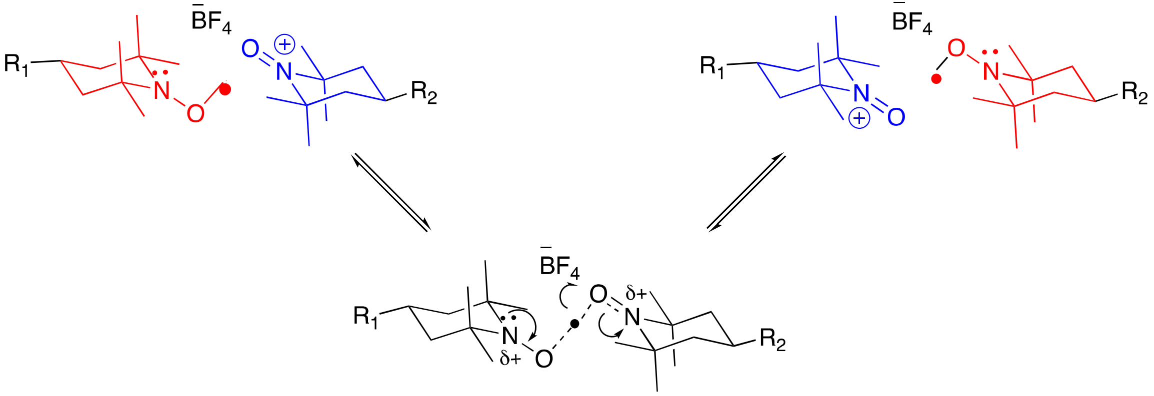
* Supporting Information



Abstract: Three new homologous TEMPO oxoammonium salts and three homologous nitroxide radicals have been prepared and characterized. The oxidation properties of the salts have been explored. The direct ^{13}C NMR and EPR spectra of the nitroxide free radicals and the oxoammonium salts, along with TEMPO and its oxoammonium salt, have been successfully measured with little peak broadening of the NMR signals.

In the spectra of **all ten** compounds (nitroxides and corresponding oxoammonium salts), the carbons in the 2,2,6,6-tetramethylpiperidine core do not appear, implying paramagnetic properties. This unpredicted overall paramagnetism in the oxoammonium salt solutions is explained by a redox equilibrium as shown between oxoammonium salts and trace amounts of corresponding nitroxide. This equilibrium is confirmed by electron interchange reactions between nitroxides with an N-acetyl substituent and oxoammonium salts with longer acyl side chains.

■ Introduction

Previously, we have reported on the use of the substituted TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), nitroxide **1b**, and its oxoammonium salt, **2b**, for the oxidation of alcohols to aldehydes or ketones.[1,2] The nitroxide radicals are intermediates in the synthesis of oxoammonium salts but, in conjunction with a secondary oxidant, have also been extensively studied in catalytic systems.[3,4]

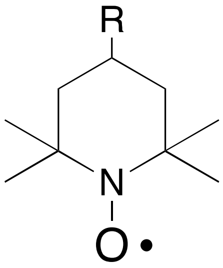
In this paper, we would like to report on three new TEMPO oxoammonium salts; to present evidence that ^{13}C NMR spectroscopy is **more useful** than ^{1}H spectroscopy in nitroxide chemistry; to show that carbons located **far enough** from radical centers can be "seen" in NMR spectroscopy and are useful for compound characterization; and, finally, to show that solutions of oxoammonium salts such as the nitroxide series (**2a**-**2**e) of compounds appear to have radical character, due to traces of nitroxide impurity. In addition, we show that a redox equilibrium exists between nitroxides and oxoammonium salts having **different acyl** side chain structures. The study of these trace nitroxide impurities have been a window into the equilibrium behavior between nitroxide radicals and oxoammonium salts.

The "S" figures and tables refer to the Supporting Information entries.

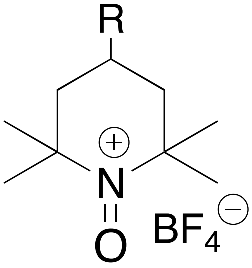
■RESULTS AND DISCUSSION

■ NITROXIDES

We have prepared and characterized three homologous nitroxide radicals; 4-propanamido-TEMPO (**1c**), 4-butanamido-TEMPO (**1d**), and 4-pentanamido-TEMPO (**1e**). They were prepared by well known reactions[1,2] and were compared with TEMPO itself and TEMPO nitroxides. Nitroxides **1c** and **1d** have been previously prepared and studied for their EPR properties.[5,6,7]



1a R = H, TEMPO
1b, R = $NHCOCH_3$
1c, R = $NHCOCH_2CH_3$
1d, R = $NHCO(CH_2)_2CH_3$
1e, R = $NHCO(CH_2)_3CH_3$



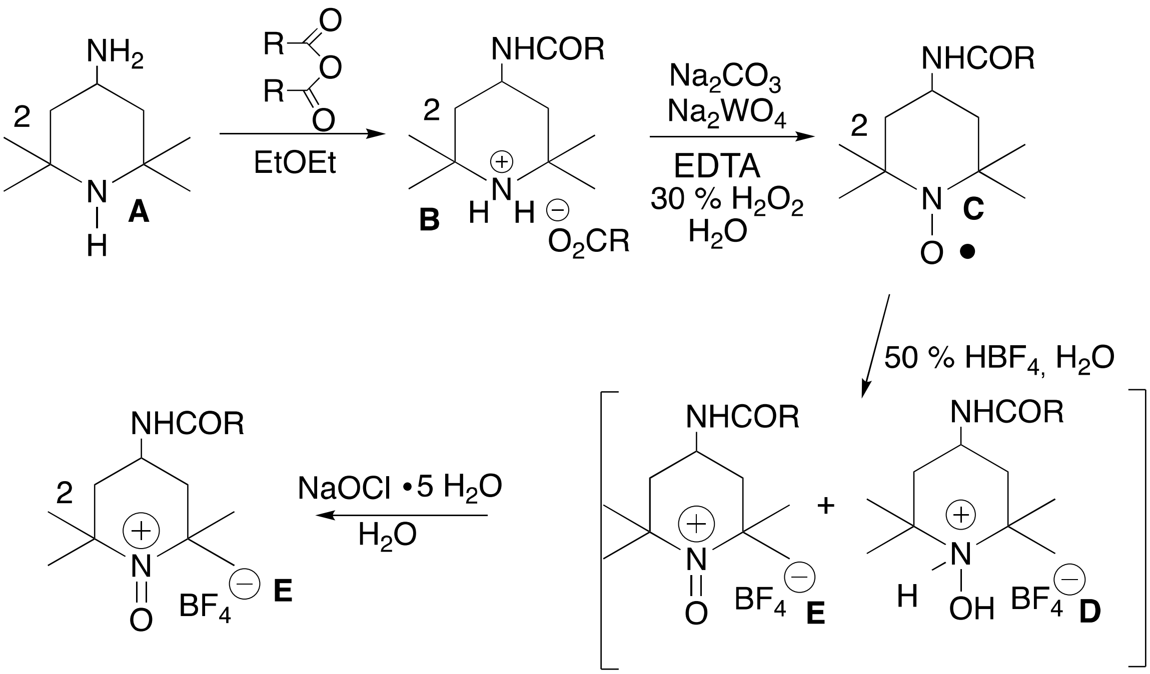
2a, R = H
2b, R = $NHCOCH_3$
2c, R = $NHCOCH_2CH_3$
2d, R = $NHCO(CH_2)_2CH_3$
2e, R = $NHCO(CH_2)_3CH_3$

For the purpose of clarity, a system of nomenclature based on TEMPO will be used. Thus, compound **1b** will be named 4-acetamido-TEMPO, and **2b** will be named 4-acetamido-TEMPO$^+$ BF_4^-. Other prefixes will be 4-propanamido-, 4-butanamido- and 4-pentanamido-.

■ Oxoammonium Salts

The new oxoammonium tetrafluoroborate salts, 4-propanamido-TEMPO$^+$ BF_4^- (**2c**), 4-butanamido-TEMPO$^+$ BF_4^- (**2d**), and 4-pentanamido-TEMPO$^+$ BF_4^- (**2e**) were prepared by known reactions [2] (slightly modified) and characterized. The generalized synthetic method is shown in Scheme 1.

Scheme 1. The general synthetic path to TEMPO nitroxides and oxoammonium salts.



Two major changes from the published procedure[2] were incorporated in this paper. First, the nitroxides **1b** and **1c** form crystalline solids (C) on formation, but the longer chain **1d** and **1e** nitroxides melt lower, and are also contaminated with the sodium acylate salts during their isolation. They sometimes precipitate and sometimes separate as a heavy insoluble oil on the bottom of the beaker or flask. They must be separated and the salt crystallized separately. The second modification is the use of a solid form of bleach in the oxidation of D and E to E. This solid, pure NaOCl pentahydrate (45 % NaOCl),[8] was recently made available from TCI. This reduces the water used.

The relative reaction rates for the oxidation of 3-phenyl-1-propanol to 3-phenylpropanal with the four oxoammonium salts were measured in DCM and are shown in Figure 1 with silica gel as a catalyst.[2] The silica gel not only serves as a catalyst; but also aids in product isolation. Comparable rate studies for the reactions in the absence of silica gel are given in Figure S1. It is of interest that the two small salts (**2b** and **2c**) oxidize at about the same rate and that the two longer chain molecules (**2d** and **2e**) are also similar to one another and react faster. The faster oxidation reactions are likely to be due to the increased solubility of the salts in DCM. The solubilities of the oxoammonium salts in DCM and water are given in the Table S1.

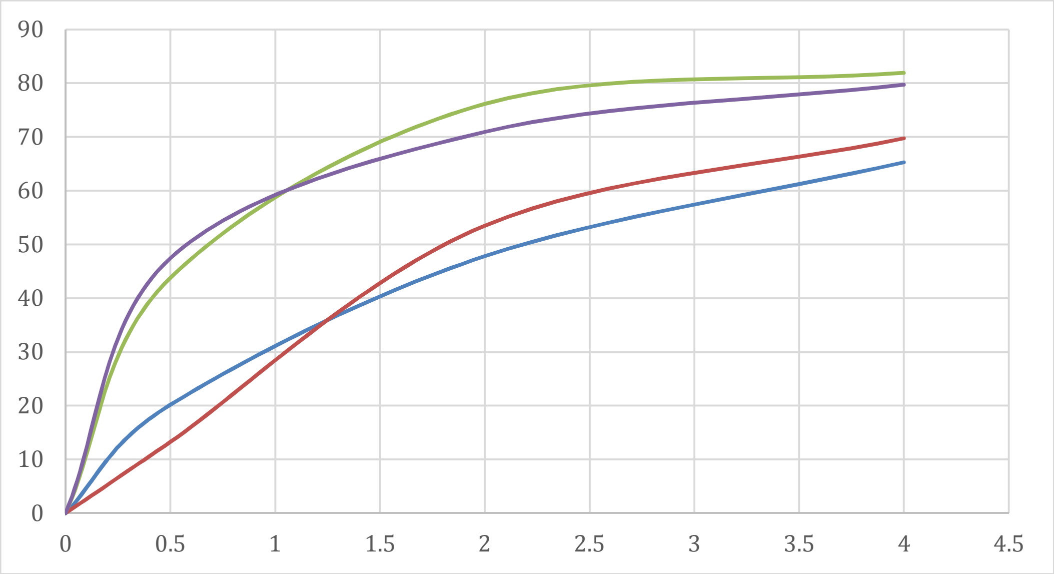


Figure 1. Relative oxidation rates of 3-phenyl-1-propanol by salts **2b** (blue), **2c** (maroon), **2d** (green), and **2e** (purple) in DCM with silica gel catalysis. The units are percent conversion vs. time in h.

In separate experiments, **2b-2e** were used to oxidize 1-octanol to octanal under the standard conditions (silica gel and a 20 % excess of oxidant).[2] Yields of octanal ranged from 97 % to 100 % as measured by ^{1}H NMR spectroscopy.

■ NMR SPECTROSCOPY OF FREE RADICALS

In our studies of oxoammonium oxidations, particularly in the presence of bases,[9,10] we have had occasion to measure NMR spectra of TEMPO nitroxide radicals in reaction mixtures. It has long been assumed that these materials, being paramagnetic, do not give useful NMR spectra. There are two reasons for this assumption. First, paramagnetic molecules such as nitroxide radicals cause the peaks in both ^{1}H and ^{13}C spectra to be displaced downfield and distorted,[11-15] The second is the absence of observable carbon and proton peaks in regions near the radical site.[16, 17, 18] In one text,[19] it is clearly stated that, “for organic radicals, the broadening obliterates the spectrum entirely”. However, this statement may or may not apply to nitroxide radicals. If this does apply to nitroxide radicals, the results in this paper prove the statement to be incorrect.

If atoms are sufficiently far from the paramagnetic or radical center, they do become visible in NMR spectra. However, these concepts, especially the latter, have not been much explored in recent years using modern instrumentation.

The influence of nitroxides on ^{1}H and ^{13}C spectra are of two types. The first is in the influence of the nitroxide in solvents alone, such as $CDCl_3$, and the second is the influence of nitroxides on non-radicals in solvents. There is also a very big difference in whether ^{1}H or ^{13}C is being measured. In Figures 2 and 3, the influence of 4-acetamido-TEMPO (**1b**) in $CDCl_3$ alone, and in the same solvent containing 3-phenyl-1-propanol, in ^{13}C spectroscopy is shown. The peaks appear as clean singlets, and the displacement is minimal. For comparison with proton spectra, see Figure S2. The ^{1}H spectra are severely displaced and, at higher concentrations, severely distorted.

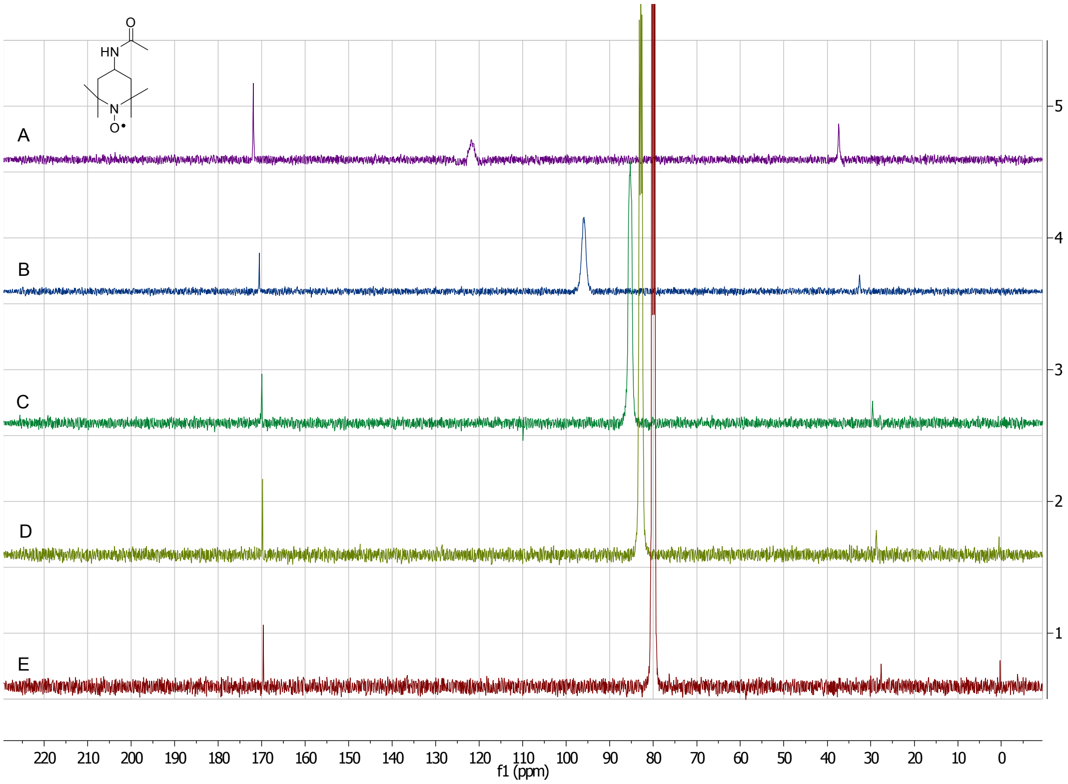


Figure 2. ^{13}C NMR spectra of 4-acetamido-TEMPO (**1b)** in $CDCl_3$ at various concentrations. A) 1 molal **1b**, B) 0.5 molal **1b**, C) 0.25 molal **1b**, D) 0.125 molal **1b,** E) 0.062 molal **1b**. The small peaks at about

27 and 170 ppm are those of the side-chain acetyl group in **1b**.

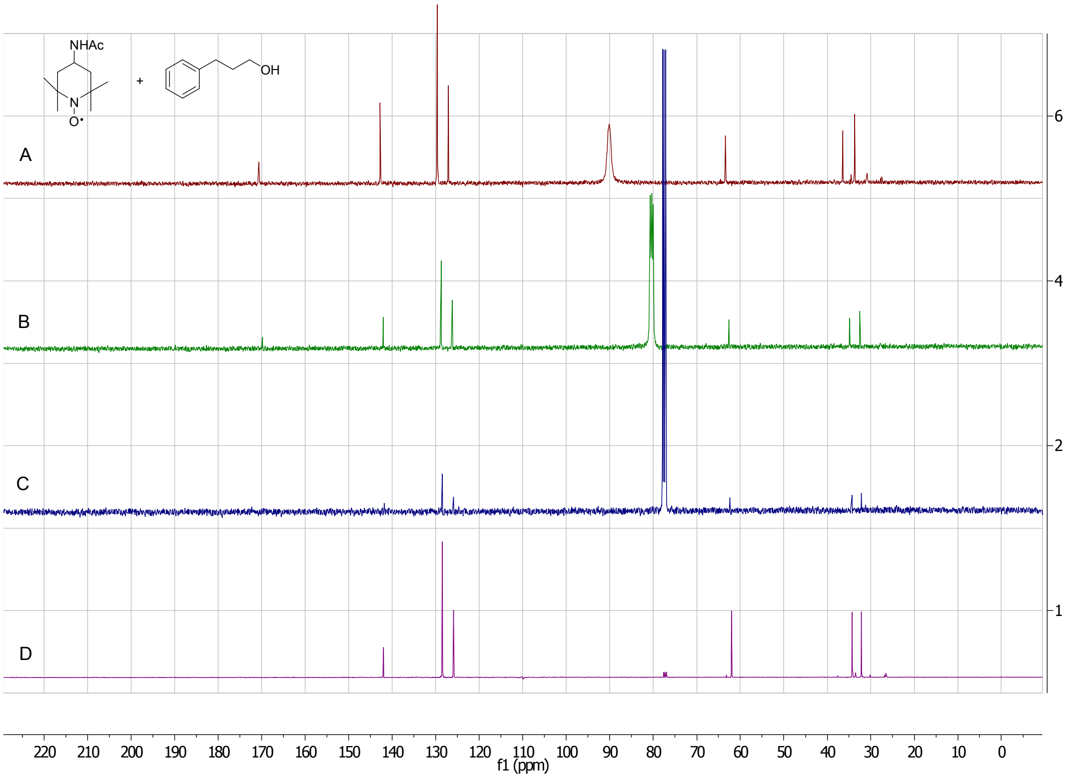


Figure 3. ^{13}C NMR spectra of 3-phenyl-1-propanol with A) 0.5 molal **1b**, B) 0.125 molal **1b**, C) 0.031 molal **1b**, D) no **1b** (in $CDCl_3$). The large peaks ranging from 90 ppm to 78 ppm are solvent peaks.

Peak diffusion is also present in the ^{13}C spectra, but it is harder to see due to carbon-proton decoupling. Actually, the peak displacements may be similar also, since, in the ^{13}C spectra, the spectral window is about 200 ppm, whereas in ^{1}H spectra, it is only 10-15 ppm. For practical purposes, it is wise to use minimum concentrations of sample and more scans to get more accurate spectra, especially for ^{1}H spectra. Arbitrarily, we suggest 0.1 molal.

While the radical center and its surrounding atoms are normally obscured and cannot be seen In either ^{1}H [20] or ^{13}C spectra,[16] there is a region removed from the radical center in which peaks ***can be "seen".*** Although there are few reports of ^{13}C spectra of nitroxides, some exist,[20,11,17,21-23] but the obscured atoms are seldom discussed.

Normally, nitroxides are reduced to hydroxy amines with phenyl hydrazine or some other reducing system before NMR measurement.[18, 24] These spectra of reduced samples clearly show all of the protons and carbons, but are not strictly the spectra of the radicals.

The ^{13}C spectra of the radical, 4-acetamido-TEMPO (**1b)** and the corresponding oxoammonium salt, 4-acetamido-TEMPO$^+$ BF_4^- (**2b),** are shown in Figure 4. One can clearly see the carbonyl chain attached to the nitrogen at C-4 of TEMPO at about 170 ppm (carbonyl) and about 23 ppm (acetyl methyl) in both spectra. However, none of the carbons or hydrogen atoms in the 2,2,6,6-tetramethylpiperidine ring or in the radical center appear **in either spectrum.** Ignoring **2b** for the moment, the spectrum of **1b** clearly shows that large molecules containing a radical center should give interpretable and interesting carbon spectra of the regions far enough from the radical center. As shown in Figure 5, none of the NMR carbon or proton spectra in this paper show peaks for the piperidine ring system, the doxyl ring system, the 2,5-dihydropyrrole ring system, or for any of the carbons or hydrogens attached to them, (except when the spectra of oxoammonium salts are measured in strong acid, see below and Table 1).

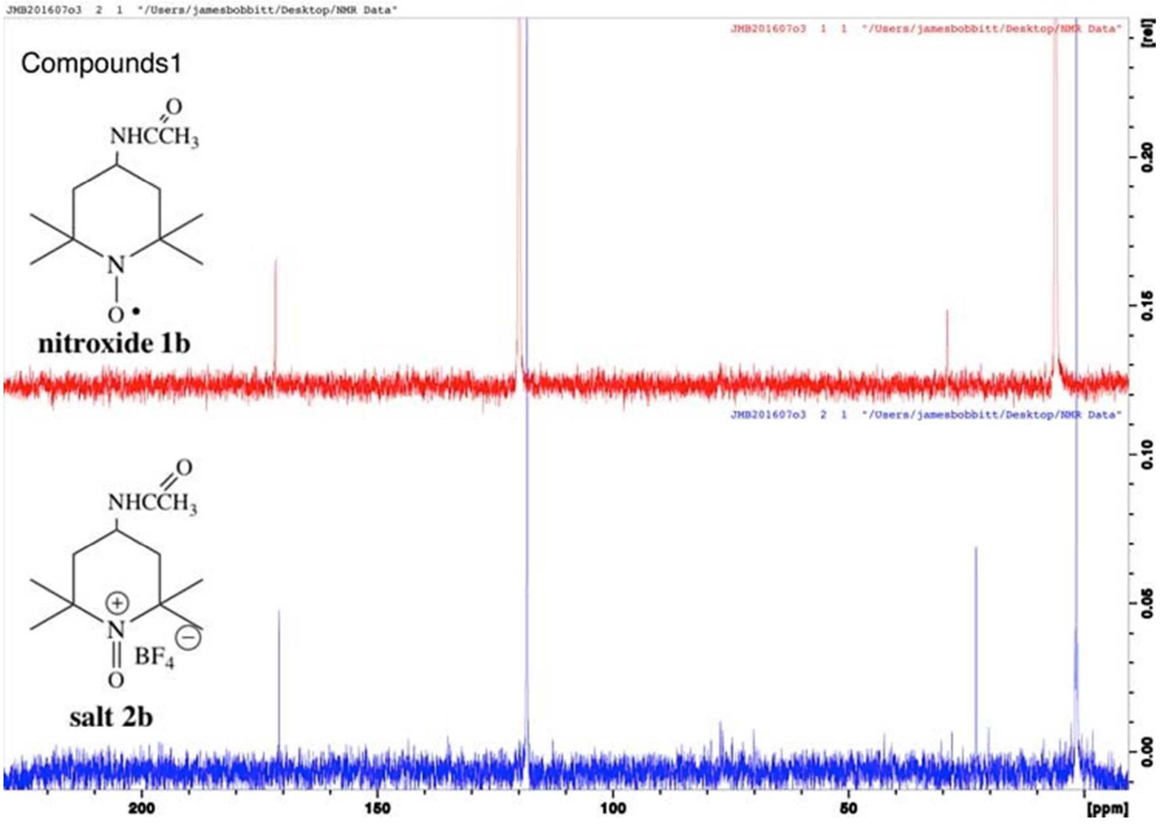
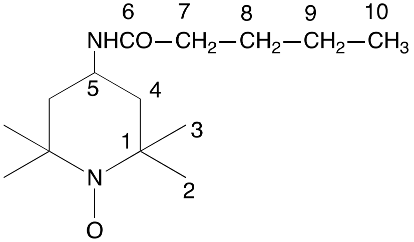


Figure 4. Comparison of ^{13}C NMR spectra of nitroxide (**1b**) and its oxoammonium salt (**2b**). Comparable spectra of the other nitroxide-

oxoammonium salt pairs (**1a**-**1e**, and **2a**-**2b**) are given in the Figures S3.

As suggested by a referee, all of the NMR data for these compounds are summarized in Table 1 for ^{13}C and Table 2 for ^{1}H. The spectra measured in TFA are more meaningful in that they show **all** of the peaks for the oxoammonium salts, since any contaminating nitroxide content is suppressed by the Golulbev disproportionation reaction (Figure 9). The spectra of the nitroxides **1a**-**1e** cannot be measured in TFA since the Golubev reaction would provide two compounds, an oxoammonium salt and a hydroxylamine tetrafluoroborate (compound compounds D and E in Scheme 1).

Table 1. ^{13}C Chemical Shifts of **1a-e** and **2a-e**

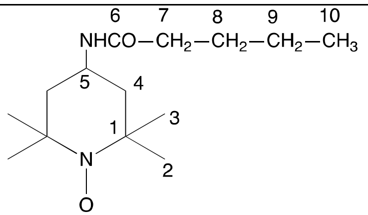


Carbon	**1a**	**2a**	**1b**	**2b**	**1c**	**2c**	**1d**	**2d**	**1e**	**2e**
1	-	105.3^{a}	-	103.9^{a}	-	103.9^{a}	-	103.9^{a}	-	103.9^{a}
2	-	29.0^{a}	-	31.3^{a}	-	31.3^{a}	-	31.4^{a}	-	31.4^{a}
3	-	29.0^{a}	-	27.6^{a}	-	27.7^{a}	-	27.6^{a}	-	27.7^{a}
4	-	40.7^{a}	-	43.0^{a}	-	43.1^{a}	-	43.2^{a}	-	43.2^{a}
5	-	15.8^{a}	-	41.8^{a}	-	41.7^{a}	-	41.7^{a}	-	41.7^{a}

6	-	-	170.1^{b}	177.8^{a} (178.6^{c})	173.4^{b}	181.6^{a} (180.2^{c})	172.5^{b}	180.7^{a} (179.4^{c})	173.0^{b}	181.0^{a} (174.4^{c})
7	-	-	26.6^{b}	20.0^{a} (26.6^{c})	33.7^{b}	28.4^{a} (32.1^{c})	40.3^{b}	36.8^{a} (40.5^{c})	42.4^{b}	34.9^{a} (36.3^{c})
8	-	-	-	-	10.6^{b}	8.5^{a} (12.1^{c})	21.5^{b}	19.4^{a} (21.5^{c})	31.5^{b}	28.0^{a} (28.8^{c})
9	-	-	-	-	-	-	15.9^{b}	11.9^{a} (15.2^{c})	25.7^{b}	21.9^{a} (21.5^{c})
10	-	-	-	-	-	-	-		17.4^{b}	11.9^{a} (13.5^{c})

[a]Chemical shift values in trifluoroacetic acid (TFA). [b]Chemical shift values in $CDCl_3$. [c]Chemical shift values in D_2O. Spectra are given in the Supporting Information.

Table 2. ^{1}H Chemical shifts of **1a-e** and **2a-e**

										
Proton	**1a**^{a}	**2a**^{b}	**1b**^{a}	**2b**^{b}	**1c**^{a}	**2c**^{b}	**1d**^{a}	**2d**^{b}	**1e**^{a}	**2e**^{b}
1	-	-	-	-	-	-	-	-	-	-
2	-	2.21 (s)	-	2.47 (s)	-	2.47 (s)	-	2.48 (s)	-	2.47 (s)
3	-	2.21 (s)	-	2.08 (s)	-	2.08 (s)	-	2.08 (s)	-	2.08 (s)
4	-	3.08 (m)	-	3.34 (d, *J* = 8.1 Hz)	-	3.35 (m)	-	3.35 (m)	-	3.35 (m)
5	-	2.99 (m)	-	5.90 (sext., *J* = 8.1 Hz)	-	5.92 (m)	-	5.95 (m)	-	5.94 (m)
6	-	-	-	-	-	-	-	-	-	-
7	-	-	2.31 (s)	2.85 (s)	2.50 (bs)	3.09 (q, *J* = 7.8 Hz)	2.46 (bs)	3.04 (t, *J* = 7.6 Hz)	2.56 (bs)	3.07 (t, *J* =8.8 Hz)

8	-	-	-	-	1.50 (s)	1.75 (t, *J* = 7.6 Hz)	2.04 (bs)	2.23 (sext., *J* = 7.6 Hz)	2.07 (bs)	2.15 (pent., *J* = 7.7 Hz)
9	-	-	-	-	-	-	1.29 (bs)	1.47 (t, *J* = 7.4 Hz)	1.76 (bs)	1.86 (sext., *J* = 7.3 Hz)
10	-	-	-	-	-	-	-	-	1.31 (bs)	1.38 (t, *J* = 7.3 Hz)
NH	-	-	-	8.68 (d, *J* = 6.7 Hz)	-	8.53 (d, *J* = 7.1 Hz)	-	8.61 (d, *J* = 7.2 Hz)	-	8.63 (d, *J* = 6.8 Hz)

[a]Chemical shift values in $CDCl_3$. [b]Chemical shift values in TFA with an external $CDCl_3$ standard.

The ^{1}H NMR spectra of the four oxoammonium salts in D_2O are given in the Figure S5, and the spectra in TFA are given in Figures S6 and S7. In these spectra, the protons in the side chains are clearly seen with appropriate coupling constants, but, again with no peaks for the protons in the piperidine system.

The obscurity of the piperidine carbons and protons is illustrated in Figure 5 containing compounds **1a** to **1e** and other miscellaneous nitroxides. The peak locations are distorted from the influence of the radicals, but the number of peaks is valid. The red atoms in the Figure are “seen” in the NMR spectra, both ^{1}H and ^{13}C.

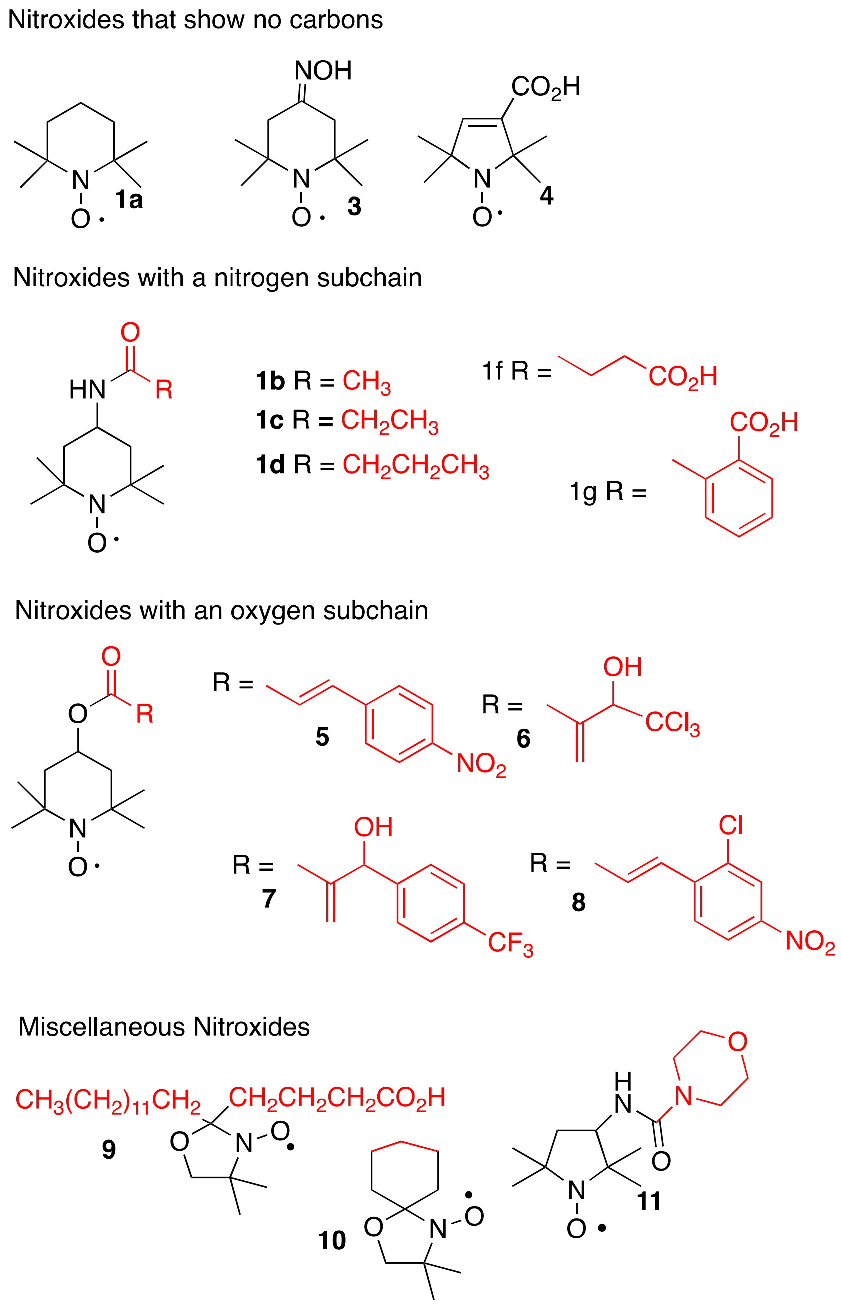


Figure 5. Nitroxides: The highlighted atoms can all be “seen” in NMR spectra. All other carbons in the nitroxides or salts are obscured and cannot be “seen”. The actual ^{13}C spectra are given in the Figures S4.

Pertinent references are: **1a** and **9**, Sigma-Aldrich Chemical Co., **3**,[25] **4**,**[26]** **1b** to **1e** and **11** (this paper), **5**,**[27]** **6-8**,[24] **10**.[28, 29]

It is clear that the oxygen radical obscures the carbons and protons close to it, through magnetic interactions. It is much less clear exactly how far this magnetic interaction reaches, and whether the influence is, in fact, a space or is passed through bonds. From measurements of models and the crystal structure of 4-acetamido-TEMPO (**1b**),[30] it appears that the distance between the oxygen radical and the last "lost" carbon (C-4) is about 4 angstroms (center to center), which would be about the same for all of the TEMPO nitroxides. For compound **10** in which only the C-4 in the cyclohexane is "seen", there are two conformations for the cyclohexane ring, one has a distance (between the oxygen radical and carbon 3) of 3.6 angstroms and the other conformation has a distance of 4.03 angstroms. When other measurements of oxygen radicals become available, it may be possible to more carefully describe the magnetic interactions around the oxygen radical.

■ THE RADICAL NATURE OF OXOAMMONIUIM SALT SOLUTIONS (The Case of the "Wandering Electron")

Although we had expected to see that the 2,2,6,6-tetramethylpiperidine ring system would not show up in the spectra of the radical, 4-acetamido-TEMPO (**1b**) in Figure 4, we were surprised to see that the spectrum of its corresponding oxoammonium salt, 4-acetamido-TEMPO$^+$ BF_4^- (**2b**) also did not show any peaks for the tetramethylpiperidine system, indicating that the oxoammonium salt solutions exhibit a paramagnetic character of some type. In fact, the stacked spectra of (**1b**), and its corresponding spectrum of (**2b**) are almost identical (Figure 4) as are those in the Figure S3 for the other members of the series (**1a** and **2a**, **1c** and **2c**, **1d** and **2d**, and **1e** and **2e**). This phenomenon was observed in H_2O, D_2O, DCM, ACN and with a commercial (TCI) sample of **2b**.

There seem to be very few recorded ^{13}C NMR spectra of oxoammonium salts in neutral or basic solutions,[22,23,31] In one example,[32] oxoammonium salt **1b** was examined in trichloroacetic acid as solvent; both oxoammonium salt and hydroxylamine (see Figure 9) were present. These were examined, and spectra were described for both compounds. In the second example, TEMPO nitroxides were oxidized with nitrosonium tetrafluoroborate in an NMR tube, and the spectra were measured in ACN.[33] The spectra of **1b** was also measured in trichloroacetic acid.[34] In all three cases, no paramagnetic evidence was noted. A TEMPO containing peptide has been reported.[35] Thirty-two carbon peaks are recorded in the ^{13}C NMR spectrum, while the actual carbon count in the formula is 37. In another case with heterocyclic compounds,[21] the discrepancy is five-six carbons. In neither case is the discrepancy discussed. The difference may well be in the absence of the TEMPO ring atoms.

In an attempt to find a source of our observed radical character, the oxoammonium salt **2b** was recrystallized five successive times from water and **2d** was recrystallized three successive times: the NMR spectra were still paramagnetic. In addition, the salt was boiled two days in DCM (in which the nitroxide is very soluble), filtered and dried. Again, the NMR spectrum was unchanged. Recrystallization from ACN, an aprotic solvent also produced no difference.

The EPR spectra of 4-acetamido-TEMPO (**1b**) and its oxoammonium salt **2b** were measured, and are shown as overlays in Figure 6. Both compounds show a signal, but in the oxoammonium salt, the radical signal is much smaller. When the areas of the peaks were integrated, the oxoammonium salt was found to contain about 1% of the nitroxide radical impurity. The EPR spectra of the other oxoammonium salts are given in the Figure S9. They contain 2% of the comparable nitroxides.

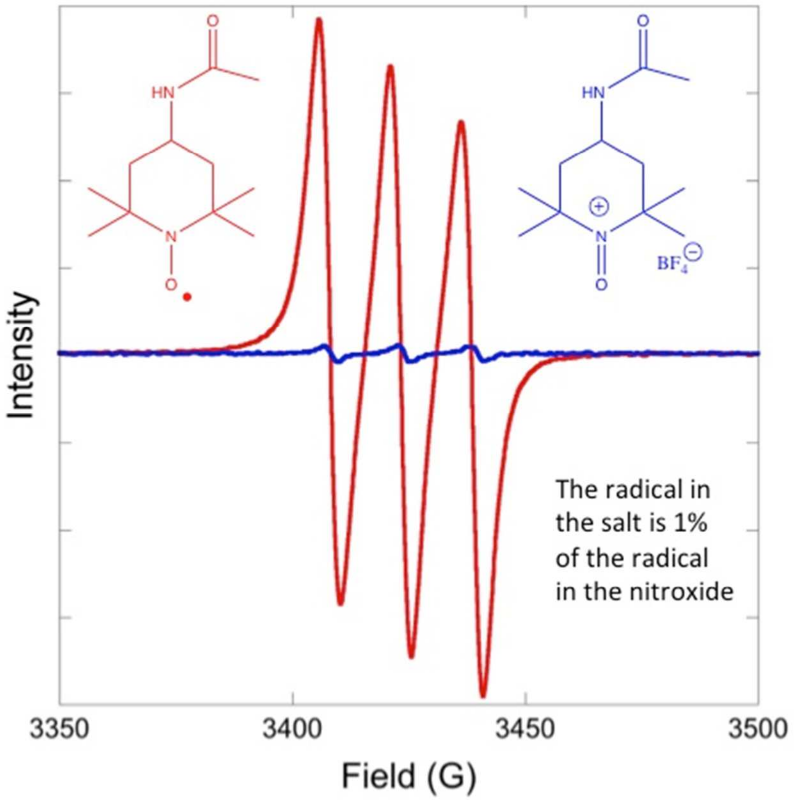
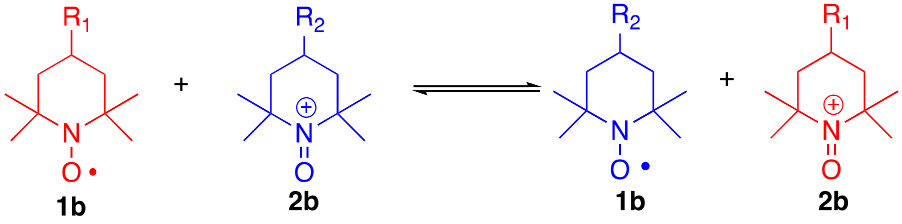


Figure 6. The X-band EPR spectra of 0.1 m solutions of acetamido-TEMPO (**1b**) (red) and 4-acetamido-TEMPO$^+$ BF$_4^-$ (**2b)** (blue) in ACN. The oxoammonium salt appears to contain about 1% of nitroxide.

Thus, it was concluded that each of the oxoammonium salts was contaminated by a small amount of corresponding nitroxide. The problem then became to explain why the small nitroxide contaminant converted the entire sample to a paramagnetic solution. We suggest a redox equilibrium between the nitroxide and the oxoammonium salt (Figure 7).

Simple 2-D Equilibrium Equation



3-D Mechanistic Equilibrium Equation

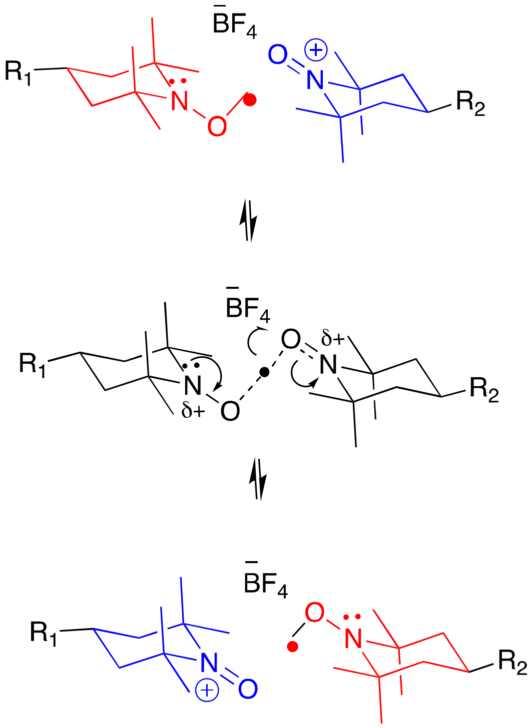


Figure 7. Suggested redox equilibria explaining the paramagnetic character of oxoammonium salt solutions contaminated by paramagnetic nitroxide (in a simple 2-D example and a more detailed 3-D picture).

In the equilibrium, the radical electron is shifted to an oxoammonium salt at the same time as the anion BF_4^- is shifted to the nitroxide. Thus, “the wandering electron”. This reaction should be much faster than the NMR spectrum can be measured, and one should see the average peak location in the spectrum.

After this work was completed, we became aware of two papers proposing similar electron migrations. In the first paper,[36] an electron transfer reaction was proposed between an oxoammonium salt and phenothiazine and between a TEMPO oxoammonium salt and TEMPO with an equilibrium reaction identical with the one shown in Figure 7. The reactions were studied using EPR spectroscopy and, in the case of phenothiazine, line broadening in proton NMR. The reaction was called a “single electron transfer reaction”. In the second paper,[37] the TEMPO oxoammonium salt and TEMPO equilibrium was suggested and called an “electron self-exchange” reaction. The reaction was studied by EPR and IR spectroscopy. In neither case was ^{13}C spectroscopy studied. We prefer to call such reactions “redox equilibrium reactions”, This theory can be supported by several experiments.

In the first experiment, if one looks carefully at Figure 4, there is a difference between the side-chain peaks of the two substances. The methyl peak appears at 26.6 ppm for the nitroxide **1b** and at 22.4 ppm for the salt **2b.** The carbonyl carbon appears at 170.3 ppm for **1b** and at 170.6 ppm for **2b.** If this equilibrium concept is correct, the average peak locations for five concentrations at 0%, 25%, 50%, 75%, and 100% of nitroxide in oxoammonium salt in $CDCl_3$ should be directly proportional to the concentrations. When the peak positions were plotted against concentrations, the curves were essentially straight lines, shown in the Figure 8 by straight lines.

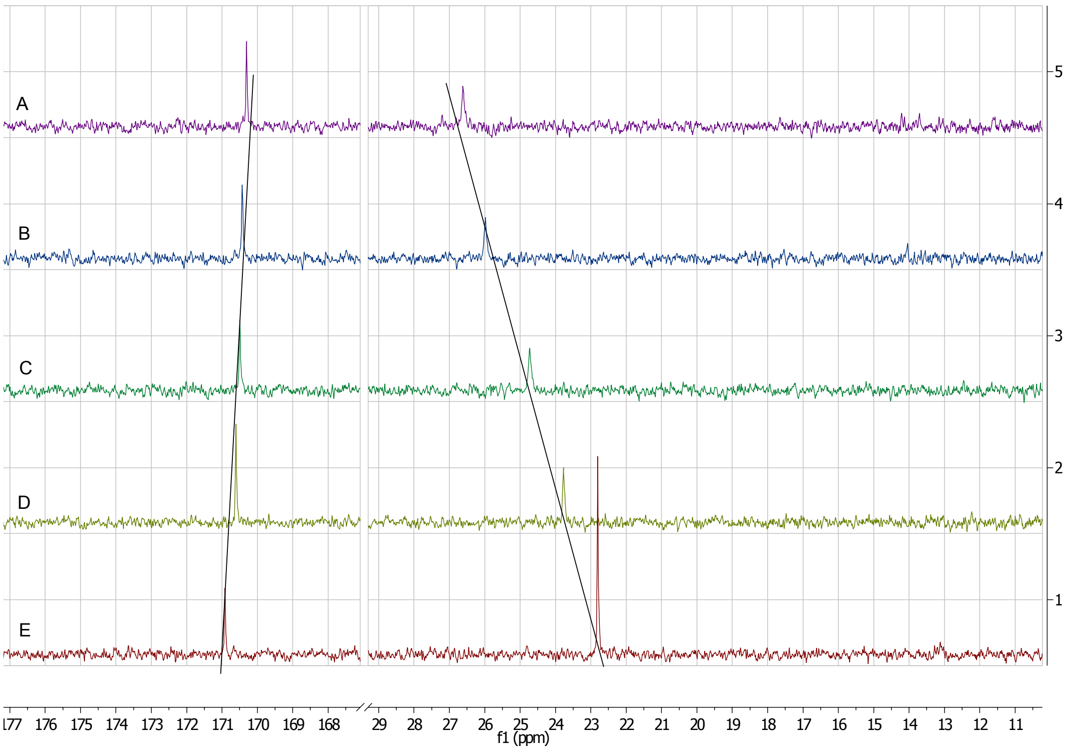
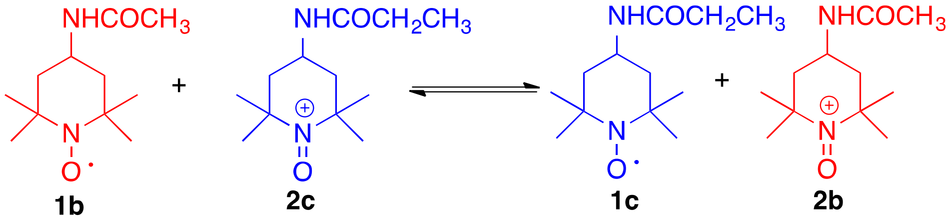


Figure 8. Spectra at different concentrations ranging from pure oxoammonium salt (**2b**) in red at the bottom to pure nitroxide (**1b**) at the top in purple. Intermediate concentrations are at 25% intervals. The straight lines connect the average peak locations.

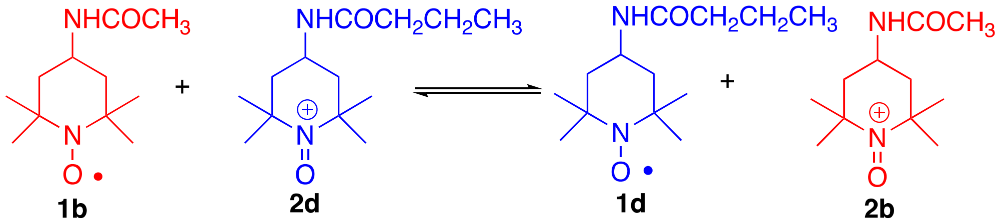
In the second experiment, we found that it is possible to equilibrate nitroxides and oxoammonium salts between compounds with

different side chains, as in Table 3. In some cases, measurements were acquired in duplicate and the range is given in the Table.

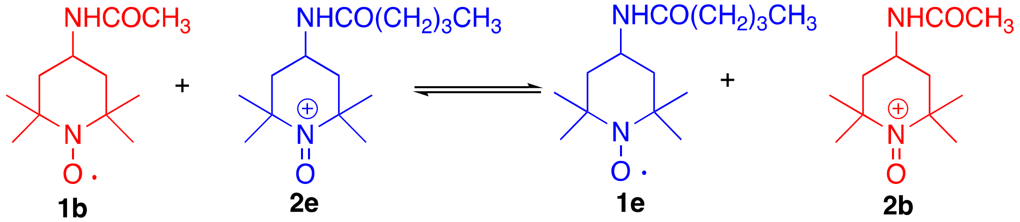
Table 3. Crossed equilibria between 4-acetamido-TEMPO (**1b**) and 4-propanamido-TEMPO$^+$ BF_4^- (**2c**) (forward and backward). In addition, crossed equilibria data between **1b** and **2d**, and **1b** and **2e** are shown.



	1b^b	**2c**^{c}	**1c**^{b}	**2b**^{c}
Forward	31-39%	35-36%	61-69%	64-65%
Reverse	33%	30%	67%	70%



1b^b	**2d**^{c}	**1d**^{b}	**2b**^{c}
10-19%	21-22%	78-81%	78-79%



1b^b	**2e**^{c}	**1e**^{b}	**2b**^{c}
8-11%	12-13%	85-89%	87-88%

Equimolar amounts of nitroxide and salt were dissolved in D_2O, and an equilibrium was reached after about two hours. The nitroxides were extracted with DCM and analyzed by GC-MS. The aqueous layer was examined by ^{13}C NMR and compared with the proton NMR spectra of the oxoammonium salts in Supporting Information. The percentage figures under the structures are the concentrations of the four components of the equilibrated mixture. In cases where two measurements were made, the range is given. The concentrations of the two nitroxides (**1b** and **1c**) add up to about 100 % as do the two oxoammonium salts (**2c** and **2b**). The equilibration was measured in a forward direction and in a reverse direction; the results were close to the same. The GC scans and NMR spectra for **1b** and **2c** are given in Figure S10. The analyses show an equilibrium behavior.

These analyses results were not very precise, but there was sufficient evidence in the GC scans and ^{1}H NMR spectra to guarantee the structures of the products. There is a problem in that the oxoammonium salts are not totally stable in water as shown in the Figure S11 and the literature.[38]

It is not clear just why the equilibrium points vary with the chain lengths of the N-acyl groups. When the side chains are the same between nitroxide and oxoammonium salts shown in Figure 8, the equilibrium peak at equal concentrations is in the middle. This distinction with different chain lengths is consistent; longer N-acyl chain lengths move the equilibrium toward longer N-acyl radicals and more of the salts with shorter chains. This could mean that the longer chain salts are better oxidizing agents, or it could simply be a matter of solubility or stability.

In the third experiment, the equilibrium is supported by spectra in strong acids as discussed above. In such acids, nitroxides can be **completely** removed using the Golubev disproportion relationship (Figure 9).[34,39,40] In base, the reaction is reversed and one sees the nitroxide.

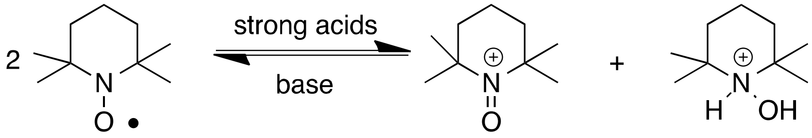


Figure 9**.** The Golubev disproportion reaction.

In the titration in Figure 10, the red line is the 4-acetamido-TEMPO$^+$ BF_4^- (**2b)** nitroxide solution in neutral or slightly basic solution. If the solution is made acidic with TFA, the nitroxide is removed, and the true spectrum of the oxoammonium salt is formed as the green line in

Figure 10 (along with the peaks associated with the acid). This method was used to measure the real spectrum of nitroxides (using **1b**).[32,41] If the solution is then made basic with $NaHCO_3$, the original spectrum is restored in the blue line (along with TFA lines). The ^{13}C spectra of oxoammonium salts **2a** to **2e** in TFA are given in Table 1 and in Figure S7.

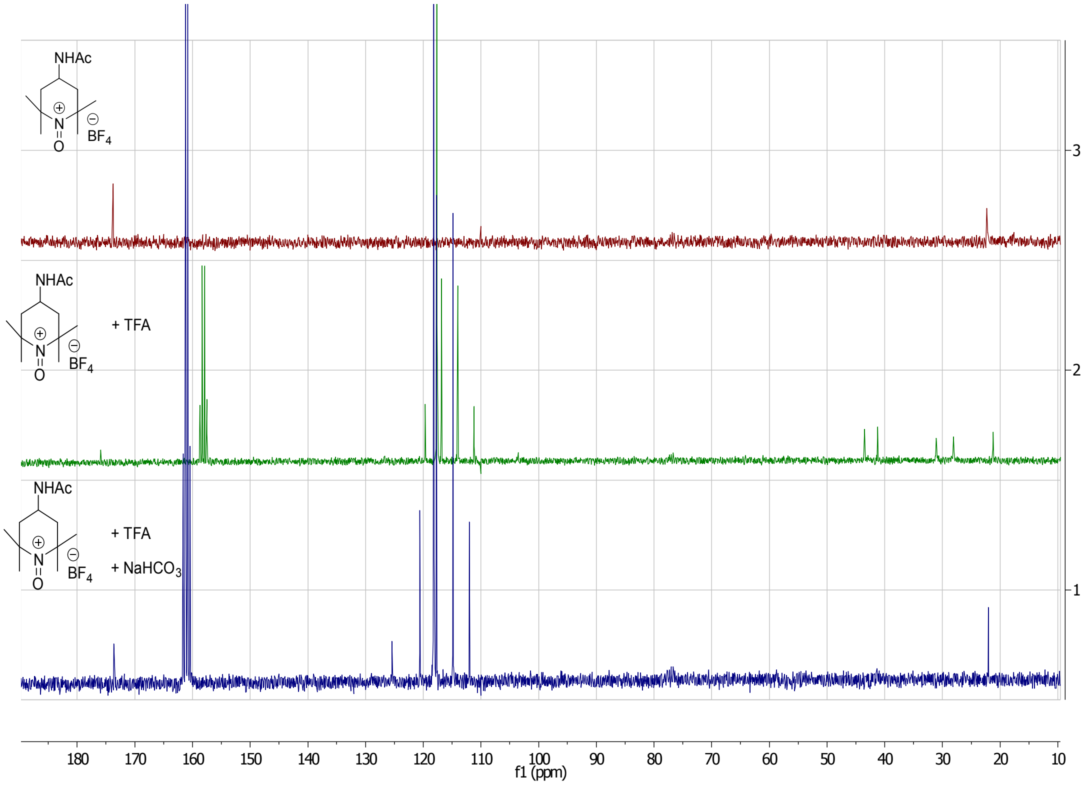


Figure 10. Titration spectra.

In the fourth experiment, the ^{13}C NMR spectra of the oxoammonium salts (**2b** to **2e**) were measured in the solid state (Figure S8).[25] The normal spectra of the salts showed all of the carbons in place. Thus, the equilibrium is destroyed in the absence of solvents and must be true.

Finally, the equilibrium might be more logical remembering the strong positive nature of oxygen in oxoammonium salts.[4] This should favor electron transfer from the radical to the salt.

From the data presented above, we concluded that the apparent paramagnetism in the oxoammonium salts **(2a-2e)** is caused by a small amount of contaminating nitroxide, varying from 1-2 % as shown from EPR measurements.

The source of this nitroxide is probably the oxidation of hydroxide ion (in water) by the oxoammonium salt.[38] In order to show this, we prepared a standard solution of 0.8% naphthalene in DCM. 4-Acetamido-TEMPO$^+$ BF_4^- (**2b**) was dissolved in H_2O (pH about 6) and stirred with the DCM solution. After one day, the liquids were separated, and the DCM solution was analyzed by GC. 4-Acetamido-TEMPO (**1b**) was found equal to 20 % of the naphthalene peak or about 0.14 % of nitroxide. A fresh sample of the DCM solution was added and stirred for another day. Again, about 20 % of **1b** was found in the DCM or about 0.14 % nitroxide. This was continued for one more day with similar results. In a separate experiment, an aqueous solution of **2b** was boiled for about three minutes (corresponding to an aqueous recrystallization) with the standard DCM solution. The extracted nitroxide corresponded to 35 % of the naphthalene peak or about 0.28%. These scans are shown in Figure S11.

The actual amounts of nitroxide formed are probably quite small, but very little is needed to establish the paramagnetic nature of oxoammonium solutions.

The Golubev group measured the proton NMR spectra of several oxoammonium salts derived from TEMPO and its derivatives and reported a plain diamagnetic spectrum.[39,42] However, when we prepared the oxoammonium salt, **2a**, from commercial TEMPO by the Golubev procedure,[4,43] we obtained a salt that appeared to be paramagnetic by ^{13}C NMR, like the other oxoammonium salts, (see item 4a in Figure S3).

■COMPUTATIONAL INSIGHT

To support the suggested equilibrium in Table 3 we carried out a series of quantum chemistry calculations with Density Functional

Theory (DFT). All DFT calculations utilized Gaussian 09.[44] Guided by the knowledge that all experimental observations were independent of the solvent (including low dielectric constant solvents), we performed all calculations in vacuum. The TEMPO nitroxides and oxoammonium salts were geometrically optimized using the Berny algorithm. All calculations used the hybrid density functional Becke, 3-parameter, Lee-Yang-Parr (B3LYP) and the 6-31G** basis set.

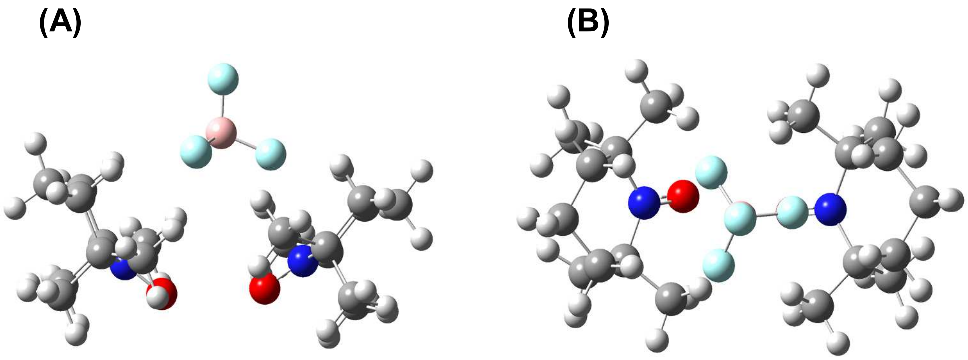


Figure 11. Side **(A)** and top **(B)** views of the lowest energy conformation dimer made up of the oxoammonium salt and the TEMPO nitroxide.

Starting from an X-ray structure of the oxoammonium salt,[30] a search of possible conformations of the oxoammonium salt-nitroxide complex was performed. Figure 11 shows a side and a top view of the lowest energy conformation found (see Supporting Information for

Cartesian coordinates). At this configuration, we computed the spin density population at each atom in the dimer. The population analysis showed an equal distribution of spin density between the two species, with approximately half of the spin distributed on each N=O group (see Supporting Information for a table of spin populations). This analysis explains why the ^{13}C NMR in Figure 4 does not show any line spectra for the cyclic carbon species of the oxoammonium salt in complex with nitroxide. This also supports the quantum tunneling effect that lead to the possible equilibrium structure shown in Figure 7. There still is an open question: why does a 1% contamination of the nitroxide radical drastically change the ^{13}C NMR spectra for the oxoammonium salt?

To answer this question, we calculated the dissociation energy between the radical (fragment 1) and the oxoammonium salt (fragment 2) in the dimer in Figure 11. A (very) low dissociation energy barrier would support the hypothesis that the nitroxide radical, even in a small percentage, is able to quickly dissociate and form complexes with neighboring oxoammonium salts molecules. The binding energy was found by performing independent calculations on the dimer, fragment 1, and fragment 2. The dissociation energy was then calculated as:

$E_{binding =}$ $-(E_{dimer} - (E_{fragment1} + E_{fragment2}))$

We calculated this quantity by properly adding basis set superposition error (BSSE) corrections via the counterpoise method. The calculated dissociation energy was 3.2 kcal/mol. This is indeed a very small energy. This small energy supports the fact that the radical, even in a 1% presence in the sample, can freely and quickly interact with the other oxoammonium salts in the sample in an average way, explaining why such a small amount of contamination gives an incomplete carbon spectra for the oxoammonium salt in Figure 4**.**

■CONCLUSIONS

We conclude that both ^{1}H and ^{13}C NMR spectroscopy can be applied to nitroxide molecules, but that ^{13}C NMR is more useful due to less carbon displacement and peak diffusion.

Second, we confirm early reports that the atoms placed near the radical site are obscured, but **that atoms far enough from the site can be clearly seen**.

Third, we find that most samples of oxoammonium salts used as oxidizing agents contain trace amounts of nitroxide which make NMR samples in solution **appear** to be paramagnetic. We propose that this latter fact is caused by the fast electron transfer between nitroxide and oxoammonium salt that cannot be visualized by the slower NMR spectroscopy. Finally, we propose a redox equilibrium between nitroxides and oxoammonium salts with **different** acyl functional groups which can explain the fast electron transfer.

■EXPERIMENTAL SECTION

The preparations of the nitroxides and oxoammonium salts were carried out using the procedures previously published for **1b** and **2b**[2,45] with some variations for the **d** and **e** series compounds.

All of the nitroxides (**1b-1e**) could be recrystallized from about 1.5 parts of EtOAc. The oxammoniuim salts were recrystallized from about 1.5 parts of H_2O in the following way, since they react slowly with it. The mixture of salt and water was warmed on a hot plate with a magnetic stirrer until it just dissolved. It was then cooled quickly in ice water, vacuum filtered, and dried under vacuum at 40 °C.

Caution. These synthetic reactions should be carried out in large open beakers, in ice baths, since heating and foaming are present, especially in the oxidations with peroxide and bleach. The oxidations with hydrogen peroxide are catalytic and can foam over. A large beaker is advised.

Rate Studies, (Fig. 1 and item 1 in SI). The rate studies were made on solutions containing 0.10 mol of 3-phenyl-1-propanol and 0.12 mol of the various oxoammonium salts in 10 mL of DCM. In Figure 1, the solutions contained 0.2 g of silica gel. In the SI example, there was no silica gel.

2,2,6,6-Tetramethlylpiperidine-1-oxyl (TEMPO) (**1a**) is a commercial sample from Acros. ^{13}C NMR (100 MHz, $CDCl_3$), no peaks. ^{1}H NMR (400 MHz, $CDCl_3$), no peaks.

2,2,6,6-T*etramethylpiperidine-1-oxonium tetrafluoroborate* (**2a**) was prepared from **1b** by a known procedure[4] (page 171), ^{13}C NMR (100 MHz, $CDCl_3$), no peaks; (100 MHz, TFA) δ = 105.3, 40.7, 29.0, 15.8. ^{1}H NMR (400 MHz, $CDCl_3$), no peaks; (400 MHz, TFA) δ = 3.08 (m, 2H), 2.99 (m, 4H), 2.21 (s, 12H).

4-Acetamido-2,2,6,6-tetramethylpiperidine-1-oxyl (**1b**). This compound is also commercially available (many vendors). However, it was prepared by our own method.[2] Acetic anhydride (40.8 g, 0.4 mol), dissolved in 300 mL of dry ether was added dropwise to a stirred solution of 50.0 g of 4-amino-2,2,6,6-tetramethylpiperidine (0.32 mol) in 300 mL of dry ether in a large beaker cooled in an ice bath. After three hours, the mixture was separated by filtration, and the solid was dried to give a quantitative yield of 4-acetamido-2,2,6,6-tetramethylpiperidinium acetate, which was not characterized. The salt was dissolved in 600 mL of water in a large beaker cooled in an ice bath, and basified with 55 .0 g (0.52 mol) of $Na_2CO_{3.}$ Sodium tungstate (7 g, 0.02 mol) and EDTA (7 g, 0.02 mol) was added, and 200 mL of 30 % peroxide (1.7 mol of H_2O_2) was added over 3 h. The mixture was stirred overnight at room temperature, cooled again in ice and filtered to yield, after drying, 61.1 g (89.5 % yield) of **1b**, mp 145-147^{o} C, lit.[2] 146-147^{o}C**,** ^{13}C NMR (100 MHz, DCM, 0.1 m solution) δ = 170.3, 26.6 (carbonyl and acyl methyl carbons).

4-Acetamido-TEMPO^{+} BF_4^{-} *(***2b).**[2,46] This compound is also well known and commercially available (Aldrich and TCI). Aqueous 50 % tetrafluoroboric acid (52 g, 0.29 mol) was added over 10 min to 61.1 g (0.29 mol) of 4-acetamido-TEMPO (**1b**) in a large beaker in an ice bath. The mixture was stirred until no more orange nitroxide was apparent (about 3 h). Solid NaOCl pentahydrate[8] (26.2 g, 0.16 mol) was added over 5 min, and the mixture was stirred until no orange crystals remained (about 1 h) The mixture was filtered, and the solid precipitate was dried to give 72.2 g of **2b,** mp 195° d, lit. 195-196° d[2], (75 % overall yield). ^{13}C NMR (100 MHz, $CDCl_3$, 0.1 m solution). δ = 170.6, 22.9 (carbonyl and acyl methyl). The peak displacement downfield is about 4 ppm); (100 MHz, TFA, 0.1 m solution), δ = 177.8, 103.9, 43.0, 41.8, 31.3, 27.6, 20.0. ^{1}H NMR (D_2O, 400 MHz) δ = 4.53, s (acyl methyl, displacement unknown); (400 MHz, TFA) δ = 8.68 (d, *J* = 6.7 Hz, 1H), 5.90 (sext, *J* = 8.1 Hz, 1H), 3.34 (d, *J* = 8.1 Hz, 4H), 2.85 (s, 3H), 2.47 (s, 6H), 2.08 (s, 6H).

*4-Propanamido-TEMPO (**1c**)*[5,6] Compound **1c** was prepared in exactly the same way as **1b** using propionic anhydride instead of acetic anhydride. The yield of **1c** was 62.9 g (86 % yield), and the product melted at 102-103° C. The analytical sample was recrystallized from EtOAc, dried under vacuum, and melted at 105-106° C. Anal. Calcd. for $C_{12}H_{23}N_2O_2$: C, 63.40; H, 10.20; N, 12.32. Found: C, 63.50; H, 10.10; N, 12.19. ^{13}C NMR (100 MHz, $CDCl_3$, 0.1 m solution). δ = 173.4, 33.7, 10.6 (carbonyl and acyl ethyl).

*4-Propanamido-2,2,6,6-tetramethylpiperidine-1-oxonium tetrafluoroborate **(2c)**.*[5,6] Compound **2c** was prepared in exactly the same way as **1c** using propionic anhydride instead of acetic anhydride. The product, **2c**, amounted to 62.2 g for an overall yield of 62.2 %, m. p. 175-176° C. It was recrystallized from 1.5 parts of H_2O and dried under vacuum to give an analytical sample, m. p. 180-181° C. Anal. Calcd. for $C_{12}H_{23}N_2O_2BF_4$: C, 45.88; H, 7.38; N, 8.92. Found. C, 46.03; H, 7.56; N, 8.71. ^{13}C NMR (100 MHz, $CDCl_3$, 0.1 m solution) δ = 180.2, 32.0, 12.1 (carbonyl and side chain carbons); (100 MHz, TFA, 0.1 m solution) δ = 181.6, 103.9, 43.1, 41.7, 31.3, 28.4, 27.7, 8.5. ^1H NMR (D_2O, 400 MHz) δ = 4.79 (q, *J* = 7.55 Hz), 3.63 (t, *J* = 7.41 Hz); (400 MHz, TFA) δ = 8.53 (d, *J* = 7.1 Hz, 1H), 5.92 (m, 1H), 3.35 (m, 4H), 3.09 (q, *J* = 7.8 Hz, 2H), 2.47 (s, 6H), 2.08 (s, 6H), 1.75 (t, *J* = 7.6 Hz, 3H).

*4-Butanamido-2,2,6,6-tetramethylpiperidine-1-oxyl (**1d**) and 4-butanamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate* (**2d**). These compounds were prepared by a variation of the methods used for **1b** and **2b**. Butyric anhydride (52.07 g, 0.3 mol) dissolved in 200 mL of dry EtOEt was added dropwise to 4-amino-2,2,6,6-tetramethylpiperidine (39.08 g, 0.25 mol) in 200 mL of EtOEt in a large beaker in an ice bath. The dense white 4-butanamido-2,2,6,6-tetramethylpiperidine butyrate was filtered and washed once with EtOEt. The solid was suspended in 600 ml of water and basified with Na_2CO_3 (35 g, 0.3 mole) at which point some free base precipitated. Na_2WO_4 (6 g, 0.02 mol) and EDTA (6 g, 0.02 mol) were added as catalysts, and H_2O_2 (30 %, 200 mL, about 6 moles) was added dropwise over about 6 hr. A dense white solid precipitated. This solid was a mixture of desired nitroxide and sodium butyrate. It was extracted carefully (to prevent emulsions) with three 100-mL portions of EtOAc. The EtOAc solution was filtered to remove the sodium butyrate, washed once with H_2O and evaporated in a large beaker at rt to near dryness to give 60.2 g of crude nitroxide **1d** as a thick semicrystalline syrup.

A portion of this syrup (**1d**,10 g, 0.041 mol) was crystallized from 15 mL of EtOAc to give 8.2 g of nitroxide **1d,** M. P. 86-87^{o} C. The analytical sample was recrystallized from 1.5 parts of EtOAc and had the same m. p. Anal. Calcd for $C_{13}H_{25}N_2O_2$: C, 64.70; H, 10.42; N, 11.60. Found: C, 64.48; H, 10.34; N, 11.44. ^{13}C NMR (100 MHz, DCM, 0.1 m solution). δ = 172.5, 40.3, 21.5, 15.1 (carbonyl and acyl propyl).

The remainder of this syrup was slurried with 100 mL of H_2O and treated with 50 % HBF_4 (40 g, 50 %, 0.22 mol) followed by NaOCl pentahydrate (20.5 g, 0.125 mole).[8] Water (100 mL) was added, and the mixture was stirred until no unreacted brown bleach remained, about 12 h. The yellow crystalline salt mixture was cooled in ice and filtered to give 58.23 g of **2d,** 69.8 % yield (counting the nitroxide **1d**), m. p. 145-146° C from starting 4-amino-2,2,6,6-tetramethylpiperidine. The analytical sample was recrystallized from 1.5 parts of H_2O and melted at 145-146° C (dec.) Anal. Calcd. for $C_{13}H_{25}N_2O_2BF_4$: C, 47.58; H, 7.68; N, 8.54. Found: C, 47.82; H, 7.79; N, 8.26. ^{13}C NMR (100 MHz, DCM, 0.1 m solution). δ = 179.4, 40.1, 21.5, 15.1 (carbonyl and acyl propyl); (100 MHz, TFA) δ = 180.7, 103.9, 43.2, 41.7, 36.8, 31.4, 27.6, 19.4, 11.9. ^1H NMR (D_2O, 400 MHz) δ = 4.76 (t, *J* = 6.51 Hz), 4.14 (q, *J* = 7.03 Hz), 3.63 (t, *J* =7.03); (400 MHz, TFA) δ = 8.61 (d, *J* = 7.2 Hz, 1H), 5.95 (m, 1H), 3.35 (m, 4H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.48 (s, 6H), 2.23 (sext, *J* = 7.6 Hz, 2H), 2.08 (s, 6H), 1.47 (t, *J* = 7.4 Hz, 3H).

*4-Pentanamido-2,2,6,6-tetramethylpiperidine-1-oxyl, **1e**, and 4-pentamido-2,2,6,6-tetramethylpiperidine-1-oxonium tetrafluoroborate, **(2e)**.* These compounds were prepared in the same manner as **1d** and **2d.** The analytical sample of **1e** was recrystallized from EtOAc and melted at 84-85 °C. Anal. Calcd. for $C_{14}H_{27}N_2O_2$: C, 65.85; H, 10.63; N, 10.97. Found: C, 65.59; H, 10.60; N, 10.84. ^{13}C NMR (100 MHz, DCM, 0.1 m solution). δ = 175.0, 42.4, 31.5, 25.7, 17.3 (carbonyl and acyl butyl).

The overall yield of oxoammonium salt **2e** from 50 g of 4-amino-2,2,6,6-tetramethylpiperidine was 51 g or 47 % (counting the nitroxide) , m. p. 130-132 °C. The analytical sample of **2e** was recrystallized from 1.5 parts of H_2O and melted at 132-133 °C. Anal. Calcd. for $C_{14}H_{27}N_2O_2$ BF_4: C, 49.14; H, 7.95; N, 8.19. Found: C, 49.14; H, 7.67; N, 8.11. ^{13}C NMR (100 MHz, DCM, 0.1 m solution): δ = 174.41, 36.31, 21.52, 28.85, 13.99 (carbonyl and acyl butyl); (100 MHz, TFA) δ = 181.0, 103.9, 43.2, 41.7, 34.9, 31.4, 28.0, 27.7, 21.9, 11.9. ^{1}H NMR (D_2O, 400 MHz) δ = 4.79 (t, *J* = 7.11 Hz), 4.10 (p, *J* = 7.28 Hz), 3.39 (h, *J* = 7.22), 0.94 (t, J = 7.62 Hz); (400 MHz, TFA) δ = 8.63 (d, *J* = 6.8 Hz, 1H), 5.94 (m, 1H), 3.35 (m, 4H), 3.07 (t, *J* = 8.8 Hz, 2H), 2.47 (s, 6H), 2.15 (pent, *J* = 7.7 Hz, 2H), 2.08 (s, 6H), 1.86 (sext, *J* = 7.3 Hz, 2H), 1.38 (t, *J* = 7.3 Hz, 3H).

Compound 11. A solution of trichloromethychloroformate (diphosgene), (0.1046 g, 0.53 mmol, 65 microL) in 1 mL of benzene was added, dropwise, to a solution of tribenzylamine (0.4397 g, 1.532 mmol) in 7 mL of benzene at 5° C. A solution of 3-amino-2,2,5,5-tetramethylpyrolidine-1-oxyl (0.1187 g, 0.7562 mmol) in 5 mL of benzene was added, also at 5° C. The mixture was allowed to rise to RT and stirred for 2 h, and the tribenzylamine hydrochloride was removed by filtration. The benzene was evaporated under reduced pressure to yield crude 3-isocyanato-2,2,5,5-tetramethylpyrolidine-1-oxyl (0.139 g), which was used in the next step. Morpholine (0.075 g, 0.8616 mmol, 75 microL) was added to the solution of crude nitroxide in 2.5 mL of anhydrous benzene. The solution was stirred at RT for 1 h and evaporated under reduced pressure. The residue (0.194 g) was purified by column chromatography (silica gel, benzene:methanol 9:1) to give yellow crystals of **11** (yield based on the 3-amino-2,2,5,5- tetramethylpyrolidine-1-oxyl used): 0.112 g, 54.9%, m.p. 157-162□C. ^{13}C NMR (100 MHz, ACN, 0.1 molal) δ = 43.1, 64.3. HR MS (EI) m/z: [M+] calcd for $C_{13}H_{24}N_3O_3$: 270.1818, found: 270.1821.

Oxidation Equilibriation Studies (Scheme 3). The two compounds to be equilibriated (0.5 mmol of each) were ground together, dissolved in 10 mL of D_2O and stirred for 2 hr. The mixture was extracted with

2 X 10 mL of DCM. The DCM layer was dried over Na_2SO_4 and analyzed by GC-MS. The aqueous layer was placed under vacuum to remove any DCM, diluted with an equal amount of D_2O and analyzed by ^1H NMR with 32 scans. The data from one example (**1b** and **2c**) are given in the Supporting Information.

*Oxidation of Hydroxide ion in Water by 4-Acetamido-TEMPO$^+$BF$_4^-$ (**2b**).*[38] A 0.8 % solution of naphthalene in DCM was prepared as a standard extracting reagent. A solution of 0.5 g of **2b** in 10 mL of H_2O was stirred with 10 mL of the DCM solution for 1 day, and separated. The DCM portion was dried over Na_2SO_4 and analyzed by GC-MS. The nitroxide peak was 20 % of the naphthalene peak corresponding to about 0.14 % of formed nitroxide. A fresh portion of DCM solutionwas added and again equilibrated for a day. Similar analysis of the DCM portion again showed the formation of 20 % of the standard corresponding to about 0.14 %. The same was true for a third day with similar results.

In a separate experiment the aqueous phase containing oxoammonium salt was boiled for about 3 minutes, cooled and extracted with the DCM solution. Formation of nitroxide amounted to

35 % of the standard naphthalene corresponding to 0.3 % nitroxide formed. This data is shown in S11.

■Associated Content

- Supporting Information. Associated data, spectra of compounds, and experimental procedures.

■AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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