AM1-SM2 Calculations Model the Redox Potential of Nitroxyl Radicals Such as TEMPO

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Nitroxyl radicals can be oxidized to *N*-oxo ammonium salts that are themselves useful oxidants for primary and secondary alcohols. Several computational methods were investigated in order to predict the redox potential of nitroxyl radicals and to better understand the behavior of different nitroxides as catalysts for alcohol oxidation. The difference in calculated heats of formation for *N*-oxo ammonium ions and nitroxyl radicals using AM1 did not lead to a useful correlation with experimental redox potential as measured by cyclic voltammetry. However, when both the *N*-oxo ammonium ion and the nitroxyl radical were evaluated using the Cramer−Truhlar solvation model (SM2), a linear correlation was observed between the difference in heats of formation and the experimental redox values. This correlation may be used to correctly predict the redox potential of new nitroxyl radicals.

Nitroxyl radical-catalyzed oxidations of alcohols play an increasingly important role in organic synthesis.[1] Desirable characteristics of these oxidations include the use of 1 mol % or less of the catalyst, stoichiometric use of the bulk oxidant, and high selectivity for primary alcohols. Several groups have investigated the use of nitroxyl radicals for enantioselective oxidation of alcohols.[2,3] In our own work, 3,5-dihydro-3,3,5,5-tetramethyl-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine-*N*-oxyl (**16**) was found to be an effective oxidation catalyst, but its practicality is limited by the modest selectivity factor (ca. 5−7).[4] We prepared several new nitroxyl radicals based on Lai's strategy,[5] but the majority of these compounds were ineffective as oxidation catalysts. To better understand the structural features necessary for efficient catalysis, the redox behavior of a series of new nitroxyl radicals has been investigated in parallel with computational studies, and the results are described below.

The most efficient large-scale alcohol oxidation using TEMPO was developed by Anelli and uses bleach as the bulk oxidant.[6] A number of other bulk oxidants have been developed that show better functional group compatibility,[7] but the bleach procedure remains the most practical from the standpoint of cost and waste disposal.
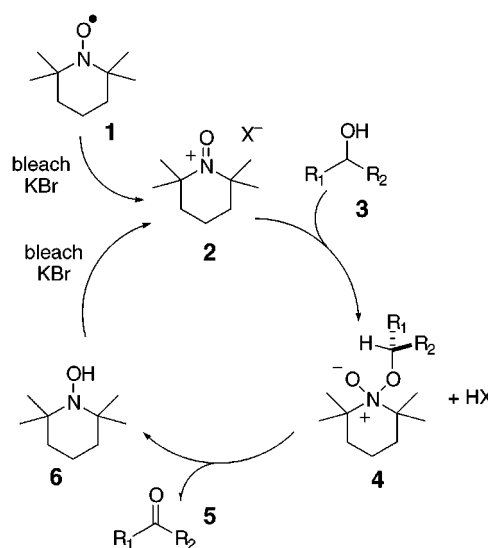

Figure 1. Catalytic cycle for the oxidation of an alcohol using TEMPO (**1**) and bleach.

A catalytic cycle for TEMPO-mediated oxidation using bleach is shown in Figure 1.[1b] TEMPO (**1**) is oxidized to the *N*-oxo ammonium ion **2** by the action of bleach and KBr. Addition of the alcohol to **2**, followed by an oxa-Cope fragmentation produces a carbonyl compound and the hydroxylamine **6**. Reoxidation of the hydroxylamine to the *N*-oxo ammonium ion **2** completes the catalytic cycle. A cyclic elimination of the intermediate **4** is consistent with Semmelhack's mechanistic investigation;[8] however, both Golubev and de Nooy have pointed out that the reaction is pH dependent,[1,9] and so a change in

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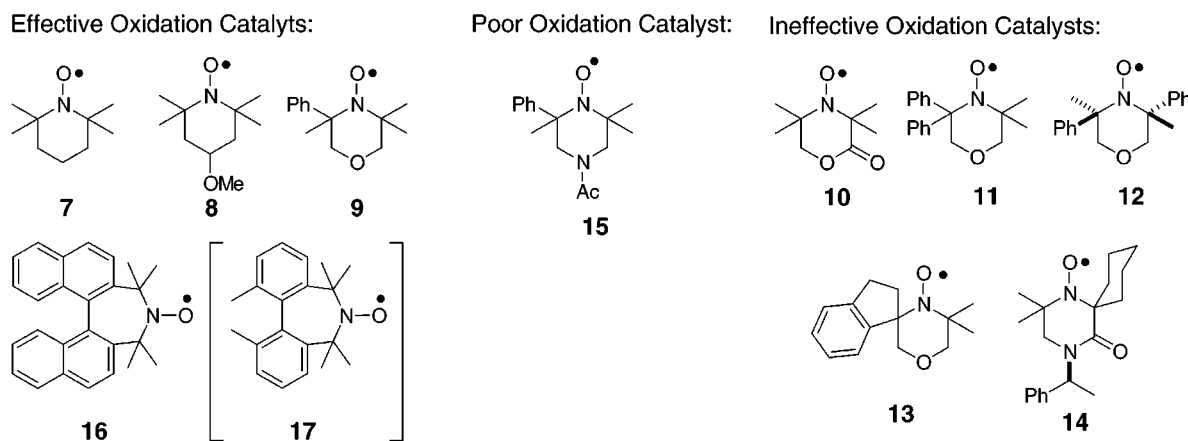
Figure 2. The structures of several nitroxyl radicals and their usefulness as oxidation catalysts under the Anelli conditions using NaOCl solutions (bleach) as the stoichiometric oxidant. Compound **17** has not been prepared (see text).

reaction conditions may change the mechanism.[10] The *N*-oxo ammonium ion and the hydroxylamine disproportionate to the nitroxyl radical under the reaction conditions, and thus oxidation of the nitroxyl radical to the *N*-oxo ammonium salt can account for the oxidation of the hydroxylamine. The focus of this paper is on the redox chemistry of nitroxyl radicals.

Cyclic voltammetry is a widely used method for examining the redox properties of organic compounds, as it can provide both thermodynamic and kinetic data on unusual oxidation states of such compounds.[11] It has been used extensively to characterize nitroxyl radicals.[12] In this report, we use voltammetry to measure the oxidation potentials of the chiral nitroxyl compounds to be used in the catalytic asymmetric oxidation of alcohols. In conjuction with calculations, these potentials can serve as a predictor of reactivity under the Anelli conditions. Voltammetry also gives information on the stability of *N*-oxo ammonium salts, and we use digital simulation of the voltammetric data to estimate their lifetimes under the catalytic conditions.

Experimental Results

The structures of the nitroxyl radicals under discussion are listed in Figure 2 and are grouped according to their usefulness as catalysts in alcohol oxidations. We used the Anelli conditions[6] as the standard test: a solution of 2-octanol or *sec*-phenethyl alcohol in CH_2Cl_2 at 0 °C was treated with 1−5 mol % of the nitroxide and a modest excess of pH 8.6 bleach solution for 30 min. Nitroxyl radicals **7**, **8**, **9**, and **16** led to high conversion of the alcohol to the corresponding ketone. Nitroxyl radical **17** has not been prepared, vide infra. Compound **15** gave ca. 40% conversion to 2-octanone under these conditions. The remaining nitroxides led to <10% oxidation, consistent with the variable background reaction observed in the absence of any nitroxide catalyst.[13,14] The reactions with the successful catalysts showed pronounced color changes upon addition of bleach, indicating the intermediacy of

the colored *N*-oxo ammonium ions. Reactions using nitroxides **10**−**14** did not exhibit significant color changes. The nitroxyl radicals vary dramatically in their ability to act as oxidation catalysts. In our effort to understand these results, we evaluated each of the nitroxyl radicals by cyclic voltametry.

Cyclic voltammetry of these compounds yield two important pieces of information, namely the oxidation potential of the nitroxides and the stability of their oxidized products, the *N*-oxo ammonium salts. We find a direct correlation between the measured oxidation potential ($E° = [(E_{pa} + E_{pc})/2]$) of the nitroxide and the catalyst efficacy: the four compounds with the lowest redox potentials are the effective catalysts under Anelli's conditions. Compounds **7**−**9** and **16** all have oxidation potentials between 638 and 807 mV, whereas the ineffective catalysts have oxidation potentials above 852 mV.

The failure of these latter compounds to act as catalysts can be attributed to the insufficient oxidizing power of the bulk oxidant, hypochlorite. A number of other oxidants have been used in catalytic oxidations with nitroxyl radicals.[1,7] m-CPBA, for instance, was ineffective as a bulk oxidant with nitroxyl radicals **11**−**15**.[15] Several new bulk oxidants, such as ceric ammonium nitrate, oxone, and ozone, were investigated with TEMPO, but they were either ineffective or led to nonselective background oxidation with *sec*-phenethyl alcohol. Oxidation potentials are important criteria in the design of new nitroxyl radicals as alcohol oxidation catalysts.

The voltammetric data also demonstrate that the catalytically active *N*-oxo ammonium salts of the compounds in Table 1 have half-lives of greater than minutes under these conditions. The current ratio of the oxidation and reduction peaks, i_{pa}/i_{pc}, is near unity, indicating that the *N*-oxo ammonium species is stable during the length of the voltammetric scan. An exception is nitroxyl **15**, which is a modestly effective alcohol oxidation catalyst. It has a redox potential of 871 mV, near the threshold

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(13) Compounds **13** and **14** lead to partial oxidation of *sec*-phenethyl alcohol, but the reaction was not reproducible and these nitroxides were not effective catalysts for 2-octanol. However, **13** did catalyze the oxidation of 1-octanol, suggesting that the inability of **13** to catalyze the oxidation of aliphatic secondary alcohols may be due in part to the degree of steric hindrance around the nitroxide function.

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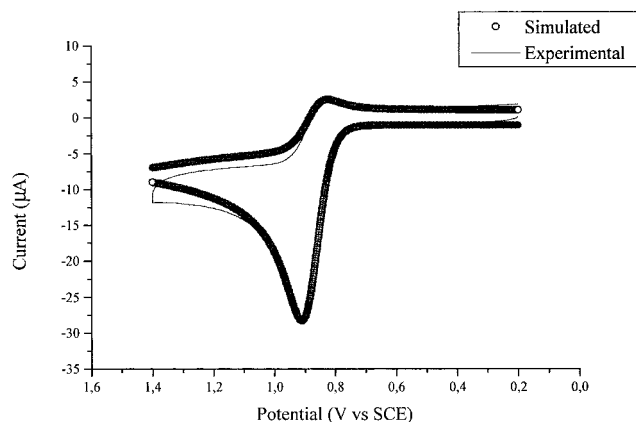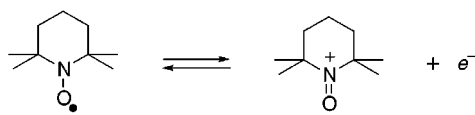
Figure 3. A cyclic voltammogram at 100 mV/s of compound **15** showing the chemical irreversibility of the oxidation. A digital simulation of the voltammetric data is included; see text for details and experimental conditions.

Table 1. Oxidation Potentials of Nitroxyl Radicals and AM1 Energies (kcal/mol) for the Nitroxyl Radical and *N*-Oxo Ammonium Cation

Compound	AM1 (rad)	AM1 (cat)	ΔE (cat-rad)	$E°$ from CV (mV)	ip_a/ip_c
7	−21.51	152.30	173.81	638	0.98
8	−59.53	115.77	175.30	692	0.94
9	−14.28	161.10	175.38	807	0.98
10	−79.60	110.28	189.88	1091	1.13
11	24.36	197.35	172.99	882	1.02
12	24.21	196.23	172.02	878	1.11
13	−13.02	162.25	175.27	852	1.09
14	−19.08	158.25	177.33	880	1.02
15	−2.88	172.15	175.03	871	3.11
16	103.24	274.65	171.41	656	0.99
17	55.86	223.22	167.36		

for an effective catalyst, but it is irreversibly oxidized, as seen in Figure 3, with a current ratio of greater than 3 at 100 mV/s. By digitally simulating the voltammogram using unimolecular decomposition as the source of the irreversibility, we obtain a half-life of 0.92 s for the corresponding *N*-oxo ammonium cation of **15**.

Computational Results

Nitroxyl radicals are normally stable only when no α-hydrogen atoms are present,[16] and this makes the preparation of these sterically hindered compounds challenging.[5] Most of the nitroxyl radicals in the literature are not useful oxidation catalysts because the *N*-oxo ammonium salts are not stable, or the redox potential is inappropriate. A method to predict the oxidation potential of a hypothetical nitroxyl radical would be a very useful tool for the design of new catalysts. In general, the oxidation potential of a nitroxyl radical is related to the
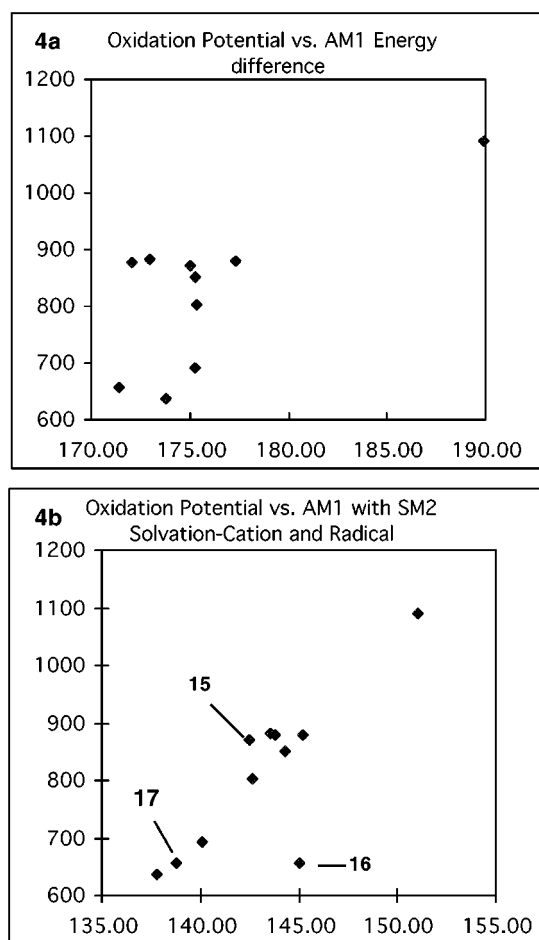

Figure 4. Plots of the calculated energy difference between the nitroxyl radical and the *N*-oxo ammonium cation (kcal/mol) vs the experimental oxidation potential (mV). The energy differences in the upper plot (**4a**) were calculated using AM1, while the energy differences in the lower plot (**4b**) were calculated using the Cramer−Truhlar solvation model SM2 at the AM1 minima.
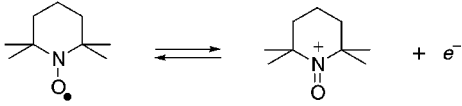
type and position of electron-withdrawing groups in the structure,[17] but this simple analysis is not easily generalized to structurally diverse nitroxyl radicals. A predictive model could save a great deal of effort on the synthesis of compounds unlikely to be useful catalysts. With this goal in mind, we considered various strategies for predicting the oxidation potential of nitroxyl radicals. Ab initio calculations might be useful, but some of the structures of interest (e.g., **16**) would have prohibitive computational costs. We decided to focus on semiempirical methods, which have been used to address related questions.[18]

AM1 calculations were investigated,[19] with the results shown in Table 1 and Figure 4. The reaction was treated as an adiabatic oxidation,[18c] and both the starting nitroxyl radical and the *N*-oxo ammonium structures were

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Table 2. Oxidation Potentials of Nitroxyl Radicals and AM1-SM2 Energies (kcal/mol) for the Nitroxyl Radical and *N*-Oxo Ammonium Cation

Compound	AM1-SM2 [rad(s)]	AM1-SM2 [cat(s)]	ΔE [(cat(s)-rad(s)]	E° from CV (mV)	E° from graph (mV)
7	−23.78	114.02	137.80	638	631
8	−62.62	77.44	140.06	692	710
9	−17.93	124.71	142.64	807	799
10	−84.60	66.41	151.01	1091	1091
11	20.87	164.39	143.52	882	830
12	19.22	163.06	143.84	878	841
13	−18.41	125.89	144.30	852	857
14	−23.44	121.78	145.22	880	889
15	−11.00	131.50	142.50	871[a]	795
16	99.54	244.55	145.01	656	882[b]
17	53.56	192.32	138.75		664

[a] Not reversible, see text. [b] Calculations show spin contamination, see text.

fully minimized using Spartan 5.0.3.[20] The calculated energies are listed in Table 1. The difference in energy, which one might expect to correlate with the oxidation potential of the nitroxyl radical, is plotted against the experimental CV data in Figure 4a. There is no obvious correlation between the calculated and experimental data. One problem with this simplistic analysis is the lack of solvation of the cation. Subsequent attempts to find a correlation involved solvation of the *N*-oxo ammonium cation, but was largely unsuccessful. Solvation of both the radical and the cation led to much better results, Table 2 and Figure 4b. The Cramer−Truhlar SM2 solvation model was applied to the AM1 minima using AM1-SM2.[21] Their solvation model was designed for water, but it is a good first approximation for solvation in general. The correlation was calculated using the first six nitroxyl radicals investigated (**7**−**10**, **13**, and **14**) and resulted in a very strong correlation with a coefficient $R = 0.996$.[22] This linear relationship may be used as a tool to predict the redox potentials of nitroxides without having to synthesize them.

The last column in Table 2 lists the predicted oxidation potential of compounds **7**−**16** based on the six-compound correlation.[22] The most serious deviations occur with compounds **15** and **16**. The *N*-oxo ammonium cation of **15** decomposes during the CV scan, which is expected to adversely affect the accuracy of the observed redox potential. The more interesting case is compound **16**, where the predicted oxidation potential is too high by 226 mV. The problem becomes apparent when the SOMO is examined in the AM1 calculation of nitroxyl radical **16**. The unpaired electron is delocalized into the aromatic system, rather than residing primarily in the N−O system. The AM1-SM2 structure of **16** has a spin

expectation value S^2 of 2.51, much higher than the theoretically predicted value of 0.75, indicating significant spin contamination. For comparison, nitroxyl radicals **7**−**15** have S^2 values of 0.75−0.92. When the spin states are contaminated in the AM1-SM2 calculation, the calculated oxidation reaction no longer corresponds to removal of an electron from the N−O odd-electron bond. To put the electron back where it belongs, spin contamination must be reduced. Nitroxyl radical **17** was selected as a model of **16**. The AM1 structures for the cation and the radical of **17** are virtually superimposable on those of **16**, but the single electron in the radical resides primarily in the N−O system. The S^2 value for **17** (1.30) is still not good, but it is much better than for **16**. The predicted oxidation potential of **17**, 664 mV, is in very good agreement with the experimental oxidation potential of **16**, 656 mV.

Conclusions

The AM1-SM2 calculations provide a simple model for the oxidation of nitroxyl radicals to *N*-oxo ammonium ions. The calculated correlation[22] is a good predictor of the oxidation potential, and in most cases the experimental and calculated values fall within 40 mV.[22] Many of the predicted values fall within 10 mV of the experimental values. Problems arise when AM1 nitroxyl radical calculations show significant spin contamination, or when the experimental redox reaction is not reversible. These calculations provide a simple means of predicting redox potentials for nitroxyl radicals.

The oxidation potential of a nitroxyl radical is one important factor in its ability to act as alcohol oxidation catalyst. Another important factor is the stability of the *N*-oxo ammonium ion, the actual oxidant in the catalytic cycle. Both di-*tert*-butyl nitroxide and the doxyl radicals do not form stable *N*-oxo ammonium ions,[23] and are not effective catalysts for this reason.[1] These are not the only structural requirements for effective catalysis. Generally, piperidine-derived nitroxides make good catalysts, but pyrrolidine-derived catalysts do not. Both steric hindrance and torsional strain play a role.[1] Nitroxide **16** is a good catalyst for primary and secondary benzylic alcohols, but it leaves aliphatic secondary alcohols untouched.[4] The nitrogen environment in **16** is significantly more hindered than the corresponding position in TEMPO, which accounts for the greater selectivity of **16**. Although oxidation potential is not the whole story, it is one important factor, and the computational strategy we have described will facilitate the search for new enantioselective oxidation catalysts.

Experimental Section

General Experimental. All reagents were purchased from Aldrich Chemical Co. or Acros and were used as received, unless otherwise stated. The synthesis of nitroxides **9**−**16** is described elsewhere.[4,5]

Voltammetric experiments utilized a BAS 100W electrochemical analyzer with a standard three-electrode cell, consisting of a Pt wire counter electrode, a saturated calomel reference electrode (SCE) connected via Luggin capillary to the analyte solution, and a basal-plane pyrolytic graphite (PG)

(20) Wavefunction, Inc. 18401 Von Karman Ave., Suite 370, Irvine, CA 92612.

(21) (a) Cramer, C. J.; Truhlar, D. G. *J. Computer-Aided Mol. Des.* **1992**, *6*, 629−666. (b) Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 8305−8311.

(22) The best fit line gave the oxidation potential in mV as 34.78-[SM2 energy difference in kcal/mol] + 4164.

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disk working electrode. PG cylinders (Union Carbide) were sealed with epoxy into glass tubes and connected to a wire with Ag paste. In a typical experiment, the electrodes were immersed into solutions containing 0.1 M tetrabutylammonium hexafluorophosphate electrolyte and 2 mM of the nitroxyl analyte, and the solution was purged with purified nitrogen; a nitrogen atmosphere was maintained over the solution throughout the measurements. All electrochemical experiments were performed at room temperature (22 ± 2 °C) in CH_2Cl_2 and calibrated using TEMPO or ferrocene as an internal standard. Digital simulations of voltammograms were performed using the BAS Digisim program.

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