Reversible Dimerization of an Acyl Nitroxyl Radical Derived from a Cyclic Hydroxamic Acid

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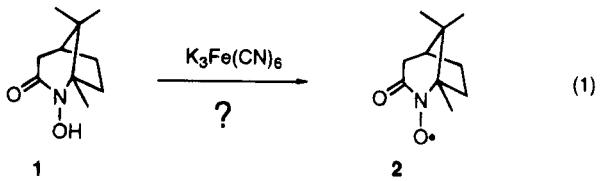
Introduction

Hydroxamic acid **1** is a readily obtainable stable crystalline solid and has been prepared by several methods starting from borneol,[1] isoborneol,[2] or camphor.[3] Oxidation of **1** under conditions developed for acyl nitroxyl radicals was expected to produce nitroxyl **2** (eq 1). In fact, this oxidation was previously reported in 1984



1 **2** (1)

by Lub and de Boer.[3] When this oxidation was carried out independently, a robin egg blue colored crystalline solid was obtained. Analysis of the corresponding solution by ESR did indeed indicate the existence of a nitroxyl radical, which was consistent with that reported earlier. However, surprisingly, the ^{1}H-NMR spectrum was clearly resolved, which is not in accord with the presence of a paramagnetic nitroxyl functionality in the molecule.

Experiments are now described which show that the acyl nitroxyl radical **2** dimerizes reversibly to form the nitroso compound **3**. The identity of the stable dimer was determined by spectroscopic studies including preparation of both the racemic and enantiomerically pure forms of hydroxamic acid **1**, resulting in a mixture of diastereomeric dimers or a single dimer enantiomer, respectively. The propensity of this conformationally restrained cyclic nitroxyl species to dimerize provides evidence for the relative instability of *Z* conformers of acyl nitroxyl radicals.

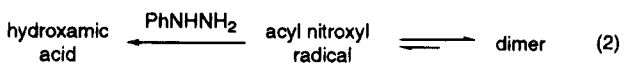
Results and Discussion

The initial studies utilized racemic material derived from *d,l*-borneol. Oxidation of **1**-*rac* using potassium ferricyanide in aqueous sodium hydroxide and dichloromethane resulted in almost instantaneous disappearance of starting material to form a green organic phase. Several aqueous washings removed excess yellow ferric ion to give a clear blue solution. Removal of volatiles, purification by silica gel chromatography, and recrystallization from hexanes resulted in blue crystals. As acyl *tert*-alkyl nitroxides are often isolable blue to green colored compounds,[4] the product was initially assumed to be nitroxyl radical **2**. ESR measurement of the pale blue solution did result in a spectrum consistent with the acyl nitroxyl structure.[5] Oxidation of the hydroxamic acid **1** with silver oxide also provided the same blue ESR-active solution; however, the oxidation was much slower than with ferricyanide and was often incomplete. The crystals were very stable in the solid form. In solution, the blue compound was found to slowly decompose in the presence of light, becoming green in color with loss of a detectable ESR signal, but was stable at room temperature in the dark.

The first indication that the blue compound was not nitroxyl radical **2** came upon examination of the NMR spectra of the recrystallized blue material. The ^{1}H-NMR spectrum showed multiple well-resolved peaks. Notably, the methyl region consisted of a number of singlets of various integral intensities, indicating a mixture of products. However the decoupled ^{13}C-NMR spectrum was much clearer, showing approximately 20 peaks. As the NMR spectra of nitroxyl radicals tend to suffer extreme broadening due to the presence of the unpaired paramagnetic electron, the major compound in solution was clearly not the expected nitroxyl **2**. In addition, attempts to trap **2** with a transient carbon radical failed under conditions that give rise to coupling products with TEMPO ((2,2,6,6-tetramethyl-1-piperidinyl)oxy). Elemental analysis of the blue crystals did confirm the empirical formula expected for nitroxyl **2**.

Reduction of nitroxyl radicals to the corresponding hydroxylamines using phenylhydrazine is a common method used for NMR characterization.[6] TEMPO type nitroxyls generally undergo reduction in an NMR tube within 15 min in $CDCl_3$ at room temperature. A similar treatment of the blue solution with phenylhydrazine cleanly produced the parent hydroxamic acid **1** as the major product after 4 days and as the exclusive product after a total of 13 days as monitored by ^{1}H-NMR.

It thus appears that nitroxyl **2** is indeed formed upon oxidation of the hydroxamic acid; however, it dimerizes reversibly to form a nonparamagnetic species as the main product. In solution, a small amount of nitroxyl **2** is present, giving rise to a detectable ESR signal. An estimated concentration of the nitroxyl radical was obtained by integration of the very weak signal derived from **2** compared to the signal obtained from standardized samples of TEMPO. The resulting ratio of radical **2** to dimer **3** is 1.7×10^{-4}, indicating that there are approximately 6000 mol of dimer for every mole of radical monomer in solution. This small concentration of nitroxyl radical is reduced by phenylhydrazine to form the parent hydroxamic acid. Gradually the entire sample returns to hydroxamic acid **1** as the equilibrium between dimer and free nitroxyl slowly drains to the left according to Le Chatlier's principle (eq 2).



(2)

Since both the elemental analysis and the phenylhydrazine reduction experiments indicate the formation of

(1) Kabasakalian, P.; Townley, E. R. *J. Org. Chem.* **1962**, *27*, 3562–3565.

(2) (a) Nakazaki, M.; Naemura, K. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 532–535. (b) See ref 1.

(3) Lub, J.; de Boer, Th. J. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 328–332.

(4) (a) Alewood, P. F.; Hussain, S. A.; Jenkins, T. C.; Perkins, M. J.; Sharma, A. H.; Siew, N. P. Y.; Ward, P. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1066–1075. (b) Perkins, M. J.; Berti, C.; Brooks, D. J.; Grierson, L.; Grimes, J. A.-M.; Jenkins, T. C.; Smith, S. L. *Pure Appl. Chem.* **1990**, *62*, 195–200.

(5) (a) Flesia, E.; Surzur, J.-M.; Tordo, P. *Org. Magn. Reson.* **1978**, *11*, 123–126. (b) Aurich, H. G.; Trösken, J. *Chem. Ber.* **1973**, *106*, 3483–3494.

(6) Lee, T. D.; Keana, J. F. W. *J. Org. Chem.* **1975**, *40*, 3145–3147.

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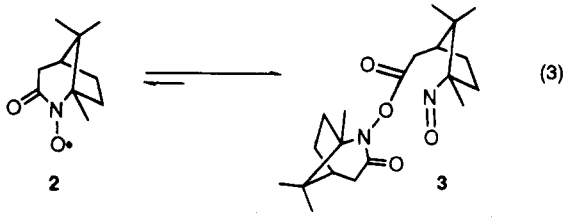
a dimer, it was reasoned that preparation of the hydroxamic acid in optically pure form followed by ferricyanide oxidation would produce a dimer as a single diastereomer. This optically active dimer should differ from the *RR/SS* and *RS/SR* mixture expected from the racemic substrate. Accordingly, optically pure hydroxamic acid was prepared from [(1*S*)-*endo*]-(−)-borneol by the known procedure and oxidized as described for the racemic substrate. The ^{1}H-NMR spectrum was marginally cleaner: at 250 MHz the methyl region displayed six identifiable but not completely resolved singlets, as opposed to the approximately nine singlets of various intensities seen in the racemic case. The ^{13}C-NMR spectrum was even more instructive. Analysis of the decoupled and APT spectra for the *ent* and *rac* series resulted in 20 peaks for the optically pure material and 21 peaks (with one of the quaternary carbon signals slightly split) for the racemic compound. Dilution ^{1}H-NMR experiments on the optically pure dimer in both $CDCl_3$ and CD_3CN showed no change over a range of 0.09 M to 1.8×10^{-4} other than diminished signal to noise ratios. At this point the evidence indicated that the compound was an unsymmetrical dimer of nitroxyl radical **2**; however, the identity of the dimer was as yet unclear. High resolution mass spectroscopy confirmed an M + 1 peak at *m/e* 365: a doubling of the monomer mass.

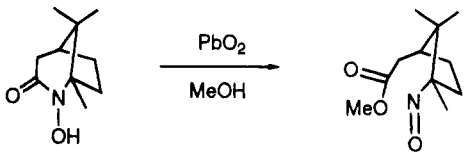
The IR spectrum contained key information for deducing the structure of the dimer. As a CCl_4 solution, the carbonyl region displayed two strong peaks for the dimer at 1687 and 1788 cm^{-1} (1664 and 1783 cm^{-1} in $CDCl_3$). In comparison, the carbonyl of the parent hydroxamic acid **1** absorbs at 1636 cm^{-1} in CCl_4. Thus, the dimer contains a hydroxamic acid-like carbonyl, and an ester-like carbonyl. In addition, the dimer displayed two distinctive peaks of medium intensity at 1549 and 1741 cm^{-1} (only 1534 cm^{-1} is seen in $CDCl_3$). In the previous report claiming preparation of nitroxyl **2**,[3] the IR spectrum taken in CH_2Cl_2 showed "an absorption at 1711 cm^{-1} accompanied by absorptions at about 1800 cm^{-1} and 1680 cm^{-1} of unknown origin." The 1711 cm^{-1} peak is characteristic of α-carbonyl nitroxides. The structure of the dimer is now assigned to be that of nitroso **3** (eq 3),



2 3 (3)

and the peak at 1549 cm^{-1} is attributed to the nitroso N=O stretch.[7] The blue color of the dimer solution is also in accord with the nitroso functionality. Peaks in the UV−vis spectrum recorded in CH_3CN at 228 nm ($\pi \rightarrow \pi^*$ transition), 302 nm (n $\rightarrow \pi^*$ oxygen lone pair transition), and 688 nm (n $\rightarrow \pi^*$ nitrogen lone pair transition) are also consistent with a monomeric aliphatic nitroso compound.[8]

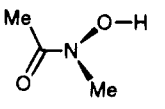
The formation of nitroso compounds by the oxidation of *N*-arylhydroxamic acids has been observed in several studies using periodate,[9] lead tetraacetate,[10] or silver oxide[11] in a disproportionation reaction in which an active acylating species is generated.[12] This same pattern of reactivity is observed with hydroxamic acid **1**; however, the cyclic nature results in this case in the nitroso and acylating species remaining tethered in the same molecule. The intramolecular anchoring of the acyl and nitroso groups in the product is likely to enhance the reversibility of the disproportionation back to the acyl nitroxyl radical, leading to the detectable ESR signal of **2** and the ability to recover the hydroxamic acid with the use of phenylhydrazine. The acylating intermediate can be competitively intercepted by carrying out the oxidation of hydroxamic acid **1** with lead oxide in methanol. Under these conditions, nitroso product **4** bearing a methyl ester is formed as a marginally stable, isoluble monomer (eq 4). Purification by chromatography through neutral



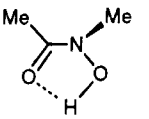
1 4 (4)

alumina provides the nitroso **4** as a blue liquid, in addition to an unidentified yellow fraction. The IR spectrum of **4** shows the distinctive nitroso N=O stretch at 1545 cm^{-1} and an ester carbonyl stretch at 1731 cm^{-1}.

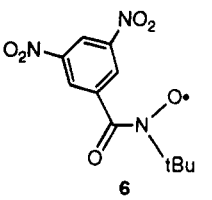
As a number of acyl *tert*-alkyl nitroxyl radicals have been prepared as isoluble compounds, the question arises as to why nitroxyl **2** predominantly disproportionates to form nitroso **3**. The answer is likely due to the constrained *Z* conformation of the acyl nitroxyl group imposed on the molecule by the bicyclic scaffolding. Calculations on *N*-methylacetohydroxamic acid[13] **5** indicates that the *E conformation* is more stable than that of the *Z* by 3.47 kcal mol^{-1}. In the acyl nitroxyl radical,



5
E conformer



5
H-bonded *Z* conformer



6

the energy difference is likely to be even larger, as the *Z* conformer does not have the energetic advantage of hydrogen bonding enjoyed by the parent hydroxamic acid. In acyclic cases, acyl *tert*-alkyl nitroxyls are believed to adopt the lower energy *E configuration*. For example,

(7) Rao, C. N. R.; Bhaskar, K. R. In *The Chemistry of the Nitro and Nitroso Groups*; Feuer, H., Ed.; Interscience Publishers: New York, 1969; Part 1, pp 139−140.
(8) Tapuhi, Y.; Grushka, E. In *The Chemistry of amino, nitroso and nitro compounds and their derivatives*; Patai, S., Ed.; John Wiley & Sons: New York, 1982; Part 2, p 915.
(9) Sklarz, B.; Al-Sayyab, A. F. *J. Chem. Soc.* **1964**, 1318−1320.
(10) Baumgarten, H. E.; Staklis, A.; Miller, E. M. *J. Org. Chem.* **1965**, *30*, 1203−1206.
(11) Forrester, A. R.; Ogilvy, M. M.; Thomson, R. H. *J. Chem. Soc. C* **1970**, 1081−1083.
(12) Perkins, M. J. In *Chemistry and Biology of Hydroxamic Acids*; Kehl, H., Ed.; S. Karger: New York, 1982; Chapter 4.
(13) Fitzpatrick, N. J.; Mageswaran, R. *Polyhedron* **1989**, *8*, 2255−2263.

the X-ray structure of *N-tert*-butyl-3,5-dinitrobenzoyl nitroxide **6** demonstrates that in the solid state, this acyclic nitroxyl adopts the *E* conformation.[4b] Studies based on the correlation of ESR coupling constants also indicate a preference for the *E* conformation.[5] The higher energy of the enforced *Z conformer* of nitroxyl **2** appears to allow the disproportionation pathway to become competitive.

In conclusion, the oxidation of hydroxamic acid **1** produces as the predominate species the disproportionation dimer **3**, a blue crystalline solid, rather than the acyl nitroxyl **2** as previously reported. In solution, dimer **3** exists in equilibrium with a very small amount of acyl nitroxyl radical **2**, which can be detected by ESR. Preparation of both the racemic and enantiomerically pure dimers provided compelling evidence for this conclusion on the basis of subtle but discernible differences in the NMR spectra of the diastereomeric nitroso dimer products. The ease of disproportionation of this cyclic conformationally rigid species provides evidence for the relative instability of *Z* conformers of acyl nitroxyl radicals.

Experimental Section

General. Methanol was distilled from magnesium metal. Flash chromatography was performed using Universal Scientific, Inc., silica gel 63-200. IR spectra were recorded in the indicated solvent. ESR spectra were measured on a Bruker ESP 300 spectrometer operated in continuous wave (CV) mode with a TE_{102} rectangular cavity. Elemental analysis was carried out by M-H-W Laboratories, Phoenix, AZ. Melting points are uncorrected. Mass spectra were obtained using fast atom bombardment (FAB) on a VG ZAB-SE reverse geometry spectrometer with a VG 11/250 data system at the University of Illinois.

Oxidation of *dl*-1,8,8-Trimethyl-2-hydroxy-2-azabicyclo-[3.2.1]octan-3-one (1) To Form a Diastereomeric Mixture of Nitroso Dimer 3. To a solution of *dl*-1,8,8-trimethyl-2-hydroxy-2-azabicyclo[3.2.1]octan-3-one (**1**) (120.4 mg, 0.657 mmol) in dichloromethane (13 mL) was added a saturated solution of potassium ferricyanide in 2 N aqueous sodium hydroxide (9.0 mL) and the mixture shaken vigorously in a separatory funnel for 1 min at room temperature. The layers were separated, and the organic layer was washed sequentially with 3 × 20 mL of H_2O followed by 10 mL of saturated sodium chloride solution. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give a blue glassy solid (109.5 mg). Purification by flash column chromatography (2 cm column, 3:1 hexanes:ethyl acetate as eluent) provided 94.5 mg of a light blue solid (78.9% yield). Recrystallization from hexanes provided an analytical sample: mp 170 °C becomes green, 172–173 °C melts; IR ($CDCl_3$) 2969, 1783, 1664, 1534 cm^{-1}; IR (CCl_4) 2965, 1788, 1741, 1687, 1549 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 3.10–1.74 (m, 12H), 1.60–1.42 (m, 2H), 1.24 (s), 1.22 (s), 1.21 (s), 1.18 (s), 1.02 (s), 0.80 (s), 0.78 (s), 0.77 (s), 0.75 (s); ^{13}C-NMR (and APT) (63 MHz, $CDCl_3$) δ 170.8 (C=O), 167.2 (C=O), 110.7 (quaternary), 74.2 (quaternary), 47.9 (split as slight doublet, quaternary), 46.2 (quaternary), 45.1 (CH), 44.9 (CH), 42.7 (CH), 39.2 (CH_2), 36.5 (CH_2), 32.8 (CH_2), 30.7 (CH_2), 27.9 (CH_2), 27.5 (CH_2), 24.5 (CH_3), 24.1 (CH_3), 18.2 (CH_3), 17.7 (CH_3), 17.1 (CH_3), 14.7 (CH_3). UV/vis (CH_3CN) λ_{max} 228, 302, 688 nm. ESR ($CDCl_3$) the spectrum was consistent with a spectrum simulated from the constants reported by de Boer[3] [a^N =7.3, a^{H1}(2H) = 3.3, a^{H2}-(1H) = 1.2 G]; MS (FAB) 365 (MH^+, 5), 198 (1), 184 (100), 183 (8), 182 (5), 168 (29), 166 (4), 155 (40), 154 (11); HRMS calcd for $C_{20}H_{33}N_2O_4$ 365.2440, found 365.2439. Anal. Calcd for $C_{20}H_{32}N_2O_4$: C, 65.91; H, 8.85; N, 7.69. Found: C, 65.72; H, 8.69; N, 7.56.

Integration of the ESR signal was carried out as follows: 28.6 mg of blue dimer **3** was dissolved in 0.55 mL of CCl_4, and the resulting ESR signal was integrated. A 0.0004 M solution of TEMPO (obtained by multiple dilutions) was integrated to give a signal that was 16.9 times larger. Thus, the estimated concentration of radical in the sample is 2.4 × 10^{-5} M as compared the concentration of dimer at 0.142 M.

In an analogous manner, optically active hydroxamic acid **1** prepared from [(1*S*)-*endo*]-(−)-borneol (Aldrich, 99%) was oxidized to give the nitroso dimer **3** as a single enantiomer: ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.90–1.70 (m, 12H), 1.60–1.42 (m, 2H), 1.24 (s, 3H), 1.22 (s, 3H), 1.17 (s, 3H), 1.02 (s, 3H), 0.80 (s, 3H), 0.78 (s, 3H); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 170.8, 167.2, 110.8, 74.2, 48.0, 46.2, 44.9, 42.7, 39.2, 36.5, 32.8, 30.7, 27.9, 27.5, 24.6, 24.1, 18.2, 17.7, 17.1, 14.8.

For comparison, the spectra for hydroxamic acid **1** are as follows: IR (CCl_4) 3253, 2963, 1636 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.90 (br s, 1H), 2.73 (br d, J = 17.4 Hz, 1H), 2.29–1.95 (m, 4H), 1.84–1.77 (m, 1H), 1.50–1.42 (m, 1H), 1.33 (s, 3H), 1.06 (s, 3H), 1.00 (s, 3H); ^{13}C-NMR (and APT) (63 MHz, $CDCl_3$) δ 165.7 (C=O), 73.1 (quaternary), 45.3 (quaternary), 42.5 (CH), 37.8 (CH_2), 36.5 (CH_2), 27.7 (CH_2), 24.3 (CH_3), 18.0 (CH_3), 14.3 (CH_3).

Reduction of Nitroso Dimer 3 with Phenylhydrazine To Form *dl*-1,8,8-Trimethyl-2-hydroxy-2-azabicyclo[3.2.1]octan-3-one (1). To a solution of the diastereomeric mixture of nitroso dimer **3** (6.8 mg, 0.019 mmol, derived from *d,l*-hydroxamic acid **1**) in $CDCl_3$ (0.6 mL) was added phenylhydrazine dissolved in $CDCl_3$ (0.64 mL, 0.03 M, 0.019 mmol) in an NMR tube. While not in the spectrophotometer, the NMR tube was wrapped with aluminum foil to protect the reaction mixture from light. The reaction was monitored by ^{1}H-NMR after 17 min, 50 min, 24 h, and for several days during which time the reaction went from clear blue to milky to pink in appearance. After 4 days the hydroxamic acid **1** was clearly the major product and after 13 days the exclusive product observed in the alkyl region.

***d,l*-1-Nitrosocampholancarboxylic Acid Methyl Ester (4).** To a solution of *dl*-1,8,8-trimethyl-2-hydroxy-2-azabicyclo-[3.2.1]octan-3-one (**1**) (58.9 mg, 0.32 mmol) in anhydrous methanol (1.1 mL) was added lead dioxide (154 mg, 0.64 mmol) and 0.44 mg of activated 3 Å molecular sieves. The reaction was stirred under nitrogen at room temperature and monitored by TLC. After 22 h, the mixture was filtered through Celite and washed with methanol. The solvent was removed *in vacuo* to give a green oil, which was filtered through a plug of neutral alumina (Brockmann III). The alumina was washed with ethyl acetate to yield 24.3 mg (35% yield) of the title compound as a blue oil which was marginally stable in dilute solution protected from light, but which decomposed within hours at room temperature as a neat sample. Subsequent washing of the alumina with methanol gave 8.0 mg of an unidentified off-white solid which was insoluble in $CDCl_3$. Title compound: IR ($CDCl_3$) 2973, 1732, 1545 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.52–2.08 (m, 5H), 1.75–1.58 (m, 1H), 1.29–1.15 (m, 1H),1.17 (s, 3H), 0.78 (s, 6H); ^{13}C-NMR (and APT) (63 MHz, $CDCl_3$) δ 173.9(C=O), 110.7 (quaternary), 51.6 (CH_3), 47.9 (quaternary), 45.0 (CH), 35.1 (CH_2), 30.5 (CH_2), 27.9 (CH_2), 23.8 (CH_3), 17.6 (CH_3), 17.3 (CH_3); MS (FAB) *m/z* 214 ([M + 1]$^+$, 25), 183 (31), 154 (100), 139 (52), 136 (96); HRMS exact mass calcd for [M + 1]$^+$ $C_{11}H_{20}NO_3$ 214.1443, found 214.1442.

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Supporting Information Available: Copies of the ^{1}H-NMR and ^{13}C-NMR spectra of both racemic and optically active dimer **3** and nitroso monomer **4**, and actual and simulated ESR spectra of acyl nitroxyl **2** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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