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Oxygenation of Zinc Dialkyldithiocarbamate Complexes: Isolation, Characterization, and Reactivity of the Stoichiometric Oxygenates

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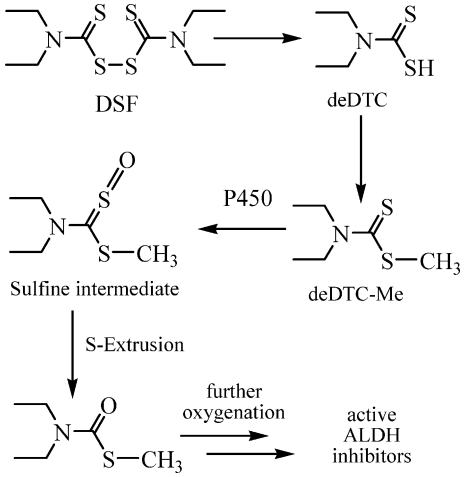
S-oxygenation of dithiocarbamate (DTC) complexes has been implicated in their function as industrial anti-oxidants, as well as in their use as pesticides and most recently in their cumulative toxicity, but little is known of the species generated. Several S-oxygenated derivatives of N,N-disubstituted DTCs have been synthesized, characterized by a variety of methods, and their structure and reactivity examined. Low-temperature reaction of bis(*N*,*N*-diethyldithiocarbamato)zinc(II), Zn(deDTC)$_2$ **1**, with oxygenating reagents (hydrogen peroxide, *m*-chloroperbenzoic acid, urea hydrogen peroxide) yields mono-oxygenated DTC complexes (*N*,*N*-peroxydiethyldithiocarbamato)(*N*,*N*-diethyldithiocarbamato)zin(II), Zn(O-deDTC)(deDTC), **2** and bis(*N*,*N*-peroxydiethyldithiocarbamato)zinc(II), Zn(O-deDTC)$_2$, **3**. The tetraoxygenated derivative bis(*N*,*N*-diethylthiocarbamoylsulfinato)zinc(II), Zn(O$_2$-deDTC)$_2$, **4**, was cleanly obtained by initial reaction of the DTC salts with stoichiometric oxidant prior to complexation with Zn(II). X-ray crystallographic analysis of **2**, **3**, and **4** show that the peroxydithiocarbamate ligands are S,O-bound. Similar derivatives were obtained from the homoleptic dimethyl and pyrollidine DTC Zn complexes. These oxygenated species display unique ^{1}H and ^{13}C NMR variable-temperature spectra, as the symmetry of DTC ligand is broken upon oxygenation; total line shape analysis (TLSA) was used to compare the energetic parameters for rotation about the C–N bond in several derivatives. Compounds **2**, **3**, and **4** were deoxygenated by alkyl phosphine, regenerating the parent dithiocarbamate **1**. The peroxydithiocarbamate complexes were susceptible to base-catalyzed hydrolytic decomposition, giving ligand-based products indicative of S-oxidation and S-extrusion.

Introduction

Dithiocarbamates (DTCs) are strong metal chelators used industrially as pesticides, vulcanization accelerators, and lubricants.[1−5] Disulfiram (DSF), a disulfide derivative of *N*,*N*-diethyldithiocarbamate (deDTC), is clinically used in alcohol aversion therapy because of its inhibition of aldehyde dehydrogenase, a crucial enzyme in the physiological detoxification of ethanol.[6] This activity has been attributed to S-oxygenated derivatives of DSF formed by xenobiotic transformations,[7] Scheme 1. In this *hypothesis*, alkylated

Scheme 1



DTCs are oxygenated within the liver, ultimately generating monothiocarbamates (MTCs) by sulfur extrusion from a sulfine intermediate. Further oxygenation produces sulfoxide and sulfone MTC derivatives (MTC-MeSO and MTC-

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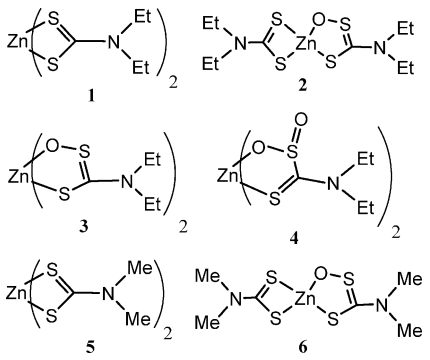
Scheme 2



$MeSO_2$), which substantial evidence implies are the active agents in ALDH inhibition in vivo.[7,8]

Recently, we and others have shown that nanomolar concentrations of DSF induce apoptotic cell death in metastatic melanoma cells,[9] and DSF has shown some success in clinical trials.[10] The anti-melanoma activity of DSF is metal ion dependent, and we have shown that one possible active agent is $Cu(deDTC)_2$, formed by cannibalistic decomposition of DSF.[11]

Previous investigations of the activity of both DSF and other DTC derivatives have focused on biotransformations of the DTC ligand itself, but little consideration was given to what effect metal-uptake might induce.[7,8,12,13] The evidence for the bioactivation of DSF by S-oxygenation is attributed to alkylated forms, and we postulated that similar reactivity may occur upon oxygenation of DTC metal complexes. In a recent report, the reaction of an inert Ru−DTC complex with O-atom transfer agents yielded products of both S-oxygenation and S-extrusion key to the transformations in Scheme 1;[14] a kinetically inert Ru complex was investigated in hopes of trapping and characterizing various intermediates formed from the initial oxygenated intermediates. In this report, we examine synthetic aspects of the S-oxygenation of Zn DTC complexes, as well as forming Zn complexes using pre-oxygenated free DTCs, to assay the stability and reactivity of the resulting products.

Results and Discussion

The oxygenation and oxidative decomposition of metal dithiocarbamate complexes have been previously investigated with regard to their function as antioxidants and vulcanizing agents in polymeric materials, but relatively few oxygenated dithiocarbamate complexes have been reported that are analogous to those described here.[3−5,14−19] Scheme 2 illustrates the compounds identified in this study, which include the peroxydithiocarbamate derivatives Zn(O-deDTC)(deDTC), **2**, $Zn(O\text{-}deDTC)_2$, **3**, the dioxygenated dithiocarbamoylsulfinato $Zn(O_2\text{-}deDTC)_2$, **4**, and analogous derivatives of pyrollidine and dimethyl-substituted dithiocarbamates.

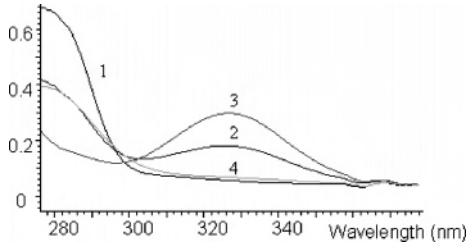


Figure 1. UV−vis absorbance spectra of compounds **1**, **2**, **3**, and **4** at 0.025 mM in CH_2Cl_2.

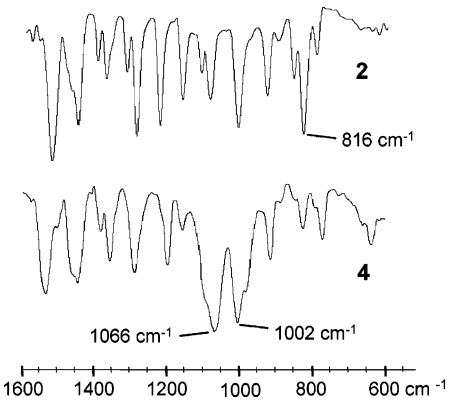


Figure 2. Infrared spectra (KBr pellet) of $Zn(deDTC)(O\text{-}deDTC)_2$, **2**, and $Zn(O_2\text{-}deDTC)_2$, **4**; tentatively assigned ν_{SO} stretching frequencies are indicated.

Electronic and Vibrational Spectra. Shown in Figure 1 are equilmolar absorbance spectra for the isolated complexes **1**, **2**, **3**, and **4** which demonstrate the change in absorbance of DTC derivatives upon sequential oxygenation. The peroxydithiocarbamate complexes have a distinct absorbance at 325 nm, similar to bands observed in other sulfenate metal complexes, M−S(O)R, that have been attributed to the S−O chromophore.[20,21] The band apparent in spectra of the monooxygenate **2**, roughly doubles in that of the homoleptic bis-O-deDTC species, **3**, but disappears in that of the homoleptic bis-O_2-deDTC complex, **4**. A previous kinetic study attributed a distinctive band at ca. 300 nm to the dioxygenated DTC ligand[22] but is not observe for crude or purified samples of **4**.

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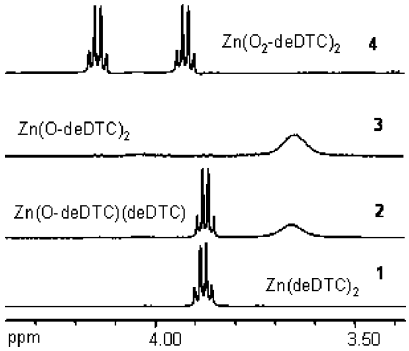

Figure 3. ^{1}H NMR spectra of each isolated diethyl zinc compounds **1**, **2**, **3**, and **4**.

Figure 2 displays infrared spectra obtained for compounds **2** and **4**. Strong vibrational bands in the IR spectrum are expected for the sulfenate (960−1000 cm^{-1}) and sulfinate (1250−1050 and 1080−1030 cm^{-1}) moieties.[14,20−24] The prominent band at 816 cm^{-1} in the spectrum of **2** is not apparent in the spectra of the parent **1** (Supporting Information, S1) and is tentatively assigned to the sulfenic ν(SO) stretch. A similar band at 804 cm^{-1} was reported for the S,O-bound form Ru(bpy)$_2$(O-dmDTC)$^+$; a band at 1030 cm^{-1} was assigned to the sulfenic ν(SO) stretch of the S,S-bound form.[14] Likewise, two strong bands at 1066 and 1002 cm^{-1} are apparent in the spectra of **4** and are attributed to the asymmetric and symmetric ν(SO$_2$) stretches of the sulfinato group. Similar bands at 1144 and 1048 cm^{-1} were assigned to ν(SO$_2$) for the S,S-bound thiocarbamate-sulfinato, Ru(bpy)$_2$(O$_2$-dmDTC)$^+$; the lower-energy absorbances observed for the S,O-bound **4** are expected due to the difference in coordination mode.[14]

^{1}H NMR. ^{1}H NMR spectra can differentiate the degree of oxygenation within the DTC-derived ligands, Figure 3 and Scheme 2, but not between possible mixtures of complexes; the N-alkyl-based signals are unaffected by the nature of the second ligand on the metal ion, i.e., a 1:1 mixture of Zn(O-pDTC)$_2$ and Zn(pDTC)$_2$ is indistinguishable from a sample of Zn(O-pDTC)(pDTC). The parent DTC complexes are known to undergo rapid ligand exchange between metal centers, and such exchange processes are evident in mixtures of the peroxydithiocarbamate complexes (vide supra).

Significant line broadening also makes assignment of product distributions difficult at room temperature, but high- or low-temperature ^{1}H NMR allows better integration to assess the degree of oxygenation. This is illustrated by the methylene peaks of **2**, Figure 4. At −50 °C, three separate quartets are observed at 3.34, 3.83, and 3.89 ppm. The 3.34 and 3.89 peaks coalesce into a broad signal at room temperature (∼25 °C). As the temperature rises to +50 °C, the broad signal sharpens into a quartet peak at 3.67 ppm while the quartet at 3.83 remains relatively stationary. The integration values for these peaks at the two extremes, +50 or −50 °C, allows the degree of oxygenation to be quantified. Similar behavior is observed for the dimethyl peroxydithiocarbamate, **5**, Figure 5, as well as for the Ru-bound peroxydithiocarbamate complex.[14]

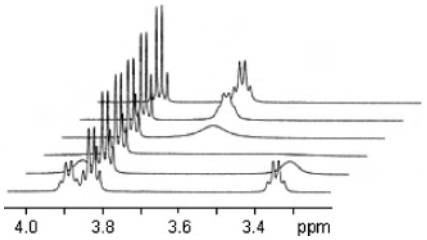

Figure 4. Variable-temperature ^{1}H NMR of Zn(deDTC)(O-deDTC) **2** (+50 to −50 °C, from top to bottom).

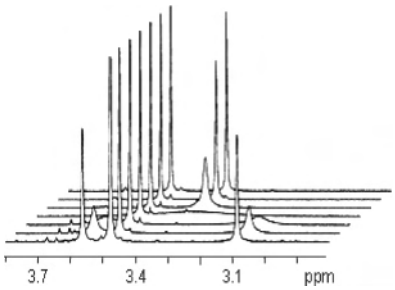

Figure 5. Variable-temperature ^{1}H NMR of Zn(dmDTC)(O-dmDTC), **6** (+60 to −60 °C, from top to bottom).

Scheme 3

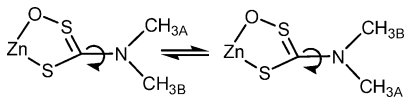

Table 1. Parameters for Zn(deDTC)(O-deDTC) and Zn(dmDTC)(O-dmDTC) Complexes

compound	$\Delta G^‡$ (kcal/mol)	$\Delta H^‡$ (kcal/mol)	$\Delta S^‡$ (kcal/mol)	E_a (kcal/mol)
Zn(O-deDTC)(deDTC), **2**	12.25	15.0	9.2	15.6
Zn(O-deDTC)$_2$, **3**	18.5	12.2	23	12.7
Zn(O-dmDTC)(dmDTC), **6**	11.9	15.9	13.2	16.5

Broadening of the N-alkyl resonances due to hindered rotation about the C−N bond is well documented in DTC complexes, Scheme 3.[25−28] Rate constants for the exchange of N-alkyl groups were determined by total line shape analysis (TLSA) as described in the Experimental Section, and activation parameters obtained from the least-squares straight lines of the log(k/T) vs 1/T and log k vs 1/T (Supporting Information, S2) and given in Table 1. The $\Delta H^‡$ values obtained fall within the range (10−19 kcal) previously reported for rotation about the C−N bond in DTC derivatives.[25−28] The range of $\Delta S^‡$ values is much broader (from −13 to +17 cal), and thus, $\Delta G^‡$ varies accordingly.[25−28] To our knowledge, this is the first time that these parameters have been obtained for oxygenated DTC ligands, and more generally, the first example of such exchange processes being affected by insertion into a ligand-to-metal bond.

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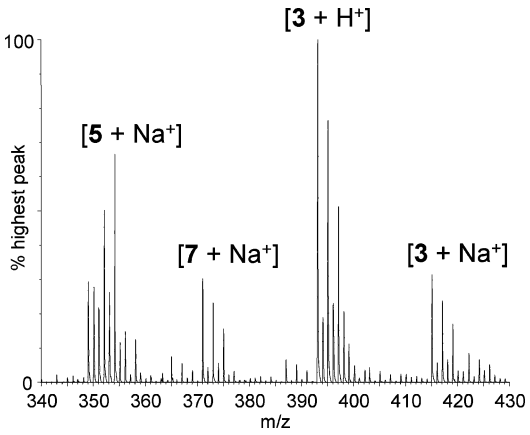


Figure 6. ESI-MS spectra of a ca. 1:1 mixture of $Zn(dmDTC)_2$, **5**, and $Zn(O\text{-}deDTC)_2$, **3**, indicating the presence of a mixed complex, Zn(dmDTC)-(O-deDTC), **7**, formed by ligand exchange.

Mass Spectroscopy. The unique isotopic envelope of Zn allowed ready identification of Zn-containing species in ESI-MS spectra. In the homoleptic complexes, the parent ion peaks were the most abundant (Supporting Information, S3): $M + H^+$ (*m*/*z* 361) for $Zn(deDTC)_2$ **1**; $M + H^+$ (*m*/*z* 393) and $M + Na^+$ (*m*/*z* 415) for $Zn(O\text{-}deDTC)_2$ **3**; and $M + Na^+$ (*m*/*z* 447) for $Zn(O_2\text{-}deDTC)_2$ **4.** However, when an analytically pure sample (by NMR and EA) of the singly oxygenated compound **2** was analyzed, a distribution of peaks obtained corresponding to **2** (plus H^+ and Na^+ at *m*/*z* 377 and 399), **3** (plus H^+ and Na^+ at *m*/*z* 393 and 431) and **4** (plus Na^+ at *m*/*z* 447), with those attributed to the homoleptic compounds more prominent than those of **2** (Supporting Information, S4). Smaller peaks are also apparent that may be rationalized as mixed oxygenates, e.g., *m*/*z* 431 as $M + Na^+$ for [Zn(O-deDTC)(O_2-deDTC)].

Ligand exchange is facile in solutions of DTC metal complexes[29−31] and is also seen for the oxygenated derivatives. ESI MS of equal molar solution of the homoleptic peroxy-diethyldithiocarbamate **3**, $Zn(O\text{-}deDTC)_2$, and the dimethyldithiocarbamate **5**, $Zn(dmDTC)_2$, showed prominent peaks corresponding to the mixed complex Zn(dmDTC)(O-deDTC), **7**, Figure 6.

Solid-State Structures. Crystallographic characterization of the diethyl peroxydithiocarbamate adducts has proved difficult; crystals of homoleptic compound **3** did not diffract, and three structural determinations of purified compound **2**, each showing significant disorder, attributed to partial oxygenation of the second dithiocarbamate ligand. The best refinement, shown in Figure 7, was solved as a 75:25 mixture of dimeric compounds **2** and **3**. Crystallographic disorder was also observed in previous reported structures of peroxydithiocarbamate complexes: the $Cr(deDTC)_2(O\text{-}deDTC)$ has O-atom disordered through three positions in the pseudo-octahedral complex; likewise, three different homologues of the dibutyl-peroxydithiocabamate complex $Zn(O\text{-}dbDTC)_2$ were reported, with similar bond lengths but decidedly

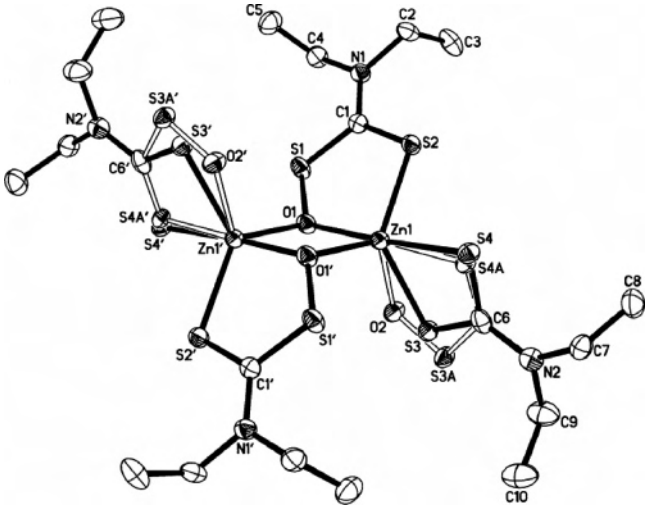
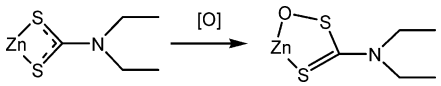


Figure 7. Crystal structure determination solved as a 3:1 mixture of **2** and **3**.

Scheme 4



different bonding angles, labeled in Table 1 as $I\alpha_1$, $I\alpha_2$, and $I\beta_1$, as in the original paper.[14,17−19]

As previously observed, oxygenation of the DTC ligand expands the bidentate chelation from a four-member to a five-member ring, Scheme 4; the S-bound tautomer, which is the apparent kinetic product of oxygenation of the $Ru(bpy)_2(dmDTC)^+$ is not observed in the Zn complexes.[14] The dimeric **2**:**3** is formed by bridging of the sulfenic oxygens between the two metal ions; the Zn_2O_2 core is rectangular with Zn−O bond lengths of 2.12 and 2.05 Å. The parent $Zn(deDTC)_2$ complexes are also dimeric in the solid state,[32,33] with one sulfur of a DTC bridging between two zinc atoms, forming a Zn_2S_2 four-membered ring. All of these dimeric structures have a center of symmetry and crystallize in the $P2_1/n$ space group; a comparison of the crystallographic parameters and Zn−ligand bond lengths are given in the Supporting Information (S5).

The crystal structure of the sulfinato **4** is monoclinic and in the $P2/n$ space group, with two independent half-molecules present in the unit cell. Each molecule is hydrogen-bonded to the next through the Zn-bound water interacting with the noncoordinated sulfinato oxygens. The representation shown in Figure 8 illustrates the hydrogen bonding between the nonbridging sulfinic oxygens and the water molecule coordinated to the complex below, producing linear chains within the crystal lattice. Hydrogen atoms of the coordinated water were located from a difference map and refined. The hydrogen bond ($O-H\cdots O$) H_{water} to O_{DTC} distances are 1.902 and 1.828 Å; the O_{water} to O_{DTC} distances are 2.690 and 2.693 Å. The general form of the chelate is analogous to the recently reported structure for bis-(diisobutyldithiocarbam-

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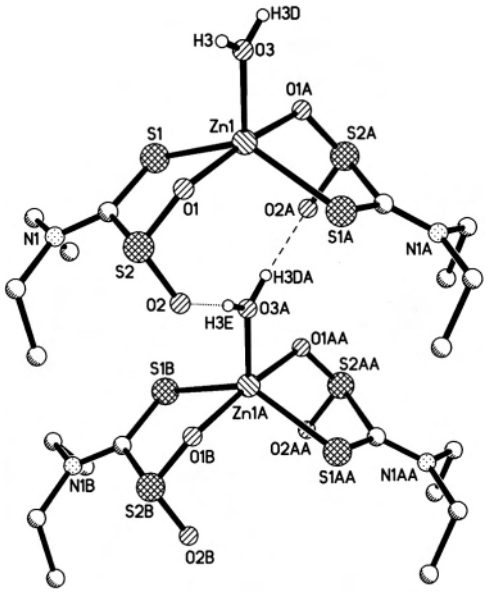


Figure 8. Crystal structure determination of **4** [$Zn(O_2\text{-deDTC})_2(H_2O)$].

oylsulfinato)Zn(II); the sulfinato was S,O-bound to the metal ion but without acoordinated water the Zn was four-coordinate, close to T_d symmetry.[18]

As in the parent complex **1**, the C_2NCS_2 framework remains substantially planar in complexes **2**, **3**, and **4**, indicating significant C−N double bond character remains after S-oxygenation. The sulfenic oxygens of the mono-oxygenated ligands in the **2:3** structures are coplanar with the C_2NCS_2 framework, implying π-delocalization extends through the oxygen. Such planarity is not seen for the sulfinic oxygens of **4**, in which the S−O bonds are ca. 26° from the average C_2NCS_2 plane.

The effect of S-oxygenation on delocalization within the DTC framework may be qualitatively compared by examination of the C−N and C−S bond lengths within the various characterized oxygenated derivatives, limited by the crystallographic disorder. In general, oxygenation lengthens the C−S bond of the oxygenated sulfur, Table 2, and correspondingly shortens the C−S bond of the non-oxygenated sulfur. This effect is larger for the bridging ligands, where the oxygen is further coordinated to two cationic metal ions. The localization of the double bond is even more evident in the dioxygenated sulfinato ligands, and the bonding parameters are similar for both the Zn−S,O-bound complexes as well as the S,S bound tautomer found in $Ru(bpy)_2(N,N'$-dimethylthiocarbamylsulfinate-$S,S)^+$.[14]

Synthetic Routes to the Oxygenated Derivatives. While the oxygenation of dithiocarbamates is facile, controlling the level of oxidation is often difficult, as is purification of the mixtures generated. For the Zn dithiocarbamates studied here, the combination of rapid ligand exchange with decomposition during chromatography on both silica and alumina made obtaining pure compounds challenging.

Two general synthetic routes were used. The reaction of the homoleptic Zn DTC complexes with O-atom transfer reagents typically generated mixtures of products, whereas initial oxygenation of the free DTC ligand prior to complexation gave the best control over oxygenation. The homoleptic peroxydithiocarbamate complex, **3**, could only be obtained by the latter route, and likewise, the highest yields of **4** were obtained by initial ligand oxygenation prior to zinc complexation. For both routes, urea hydrogen peroxide (UHP) proved the superior reagent to cleanly generate the peroxydithiocarbamate derivatives; as a stable solid, it allowed better control over the stoichiometry of oxygenation with decidedly fewer side-products than with *m*CPBA or other oxidants.

Oxygenations of the Zn-bound DTC complexes themselves are more difficult to control. Treatment of **1** with 1 equiv of UHP in chloroform yielded the singly oxygenated complex **2** in greater than 90% yield by ^{1}H NMR; isolated yields are lower, ca. 50−60% as much product is lost during purification. But treatment of **1** with 2 equiv of UHP yielded a mixture of mono- and dioxygenated ligands observable by NMR, Figure 9. Using high-temperature NMR (60 °C) to assay the product mixture gave the distribution as ca. 35% O-deDTC to 25% O_2-deDTC with 40% deDTC unreacted, Supporting Information, Table S6. Identical ligand distributions were obtained by stoichiometric reactions of 1 equiv of UHP with purified **2**. These results are consistent with the initial oxygenation of **1** yielding predominantly the mixed complex, **2**, in which the peroxydithiocarbamates are perhaps

Table 2. Selected Bond Lengths (Å) for S-Oxygenated Dithiocarbamate Derivatives Complexed to Metal Ions

M−ligand	N−C	C−S	C−S_{ox}	S−O
		Bridging		
Iα_1 Zn−(O-dbDTC)[a]	1.338(18)	1.669(9)	1.726(9)	1.586(8)
Iα_2 Zn−(O-dbDTC)[a]	1.334(18)	1.691(9)	1.744(9)	1.581(7)
Iβ_1 Zn−(O-dbDTC)[a]	1.371(19)	1.663(16)	1.733(15)	1.551(11)
2 Zn−(O-deDTC)	1.326(3)	1.709(2)	1.743(2)	1.5973(15)
		Nonbridging		
Iα_1 Zn−(O-dbDTC)[a]	1.309(16)	1.717(9)	1.726(11)	1.45(11)
Iα_2 Zn−(O-dbDTC)[a]	1.343(17)	1.719(9)	1.730(11)	1.543(9)
Iβ_1 Zn−(O-dbDTC)[a]	1.318(18)	1.694(15)	1.742(17)	1.503(17)
Cr−(O-deDTC)[b]	1.324(8)	1.680(6)	1.754(8)	1.53(1)
Ru−(O-dmDTC)[c]	1.350(16)	1.701(12)	1.717(12)	1.588(9)
3 Zn−(O-deDTC)	1.335(3)	1.456(8)	1.835(3)	1.562(6)
		S,O-Bound		
4 Zn−(O_2-deDTC)	1.3098(17)	1.6792(13)	1.8947(13)	1.5068(9)
Zn−(O_2-dbDTC)[d]	1.303(4)	1.676(3)	1.899(3)	1.465(3) 1.509(3)
		S,S-Bound		
Ru−(O_2-dmDTC)[c]	1.286(9)	1.698(8)	1.862(7)	1.470(5)

[a] Iα_1, Iα_2, Iβ_1: three isoforms of $Zn(O\text{-dbDTC})_2$.[19] [b] Cr−(O-deDTC): $Cr(O\text{-deDTC})(deDTC)_2$.[17] [c] Ru−(O-dmDTC): $Ru(bpy)_2(O\text{-dmDTC})(BF_4)$; Ru−($O_2$-dmDTC): $Ru(bpy)_2(O_2\text{-dmDTC})(BF_4)$.[14] [d] Zn−($O_2$-dbDTC): Zn−$(O_2\text{-dbDTC})_2$.[18]

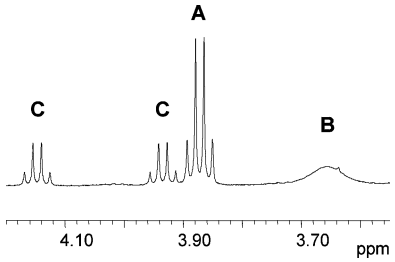


Figure 9. ^{1}H NMR spectra of the products of the reaction of compound **1** with 2 equiv of UHP, which yielded a mixture of the dithiocarbamate (A), peroxydithiocarbamate (B), and thiocarbamoylsulfinate (C) ligands. mono-, and dioxygenated ligands.

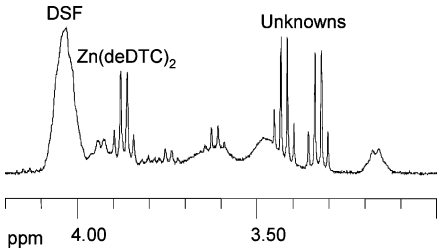
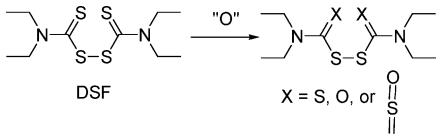


Figure 10. ^{1}H NMR of a reaction mixture of **2** with *m*CPBA left for over a week, substantial conversion back to the starting Zn(deDTC)$_2$ **1** and DSF, along with unknown byproducts.

Scheme 5

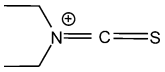


stabilized by bridging between two Zn in the dimeric form seen in the solid state. Comparison of the product yields upon further oxygenation shows that the rate of oxygenation of the O-deDTC is over twice that of deDTC. Thus, the reactivity of the Zn-bound peroxydithiocarbamates varies with its coordination mode, with the nonbridging form much more susceptible to oxygenation than the similarly coordinated dithiocarbamate.

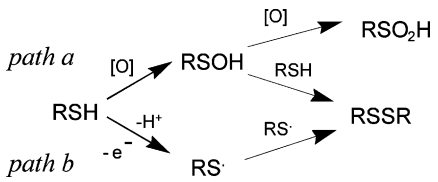
Oxygenations with *m*CPBA proved to be even more problematic. The reaction of **1** with 1 equiv of *m*CPBA yielded the isolated mono-oxygenated **2** in modest yield by ^{1}H NMR, but the reaction mixture was yellow and byproducts were evident. If reaction mixtures were left for long periods of time, substantial conversion back to the starting **1** was observed, Figure 10. Considerable side reactions were observed when more than 1 equiv of *m*CPBA was reacted with **1**; to follow this reactivity, ^{13}C-labeled **1** at the thiocarbonyl Zn(deDTC)$_2$ was reacted and the product mixture followed by ESI MS and ^{13}C and ^{1}H NMR, Supporting Information, S7. The thiocarbonyl peak of starting complex **1** appears in the ^{13}C spectra at 202 ppm, independently synthesized homoleptic peroxydithiocarbamate **3** at 208, and the sulfinato thiocarbamate **4** at 212 ppm. Upon reaction of a 3:1 mixture of *m*CPBA and **1**, the initial formation of **2** is readily identifiable, but DSF and various oxygenated products and sulfur extruded analogues are seen to increase over time, as indicated by multiple peaks from 190 to 130 ppm (typical of monothiocarbamates), as well as corresponding peaks in the ^{1}H NMR between 3 and 3.5 ppm.

Similar yellow byproducts were also observed during purification of isolated peroxydithiocarbamate **2** or **5** on silica chromatography, during washings, or during aqueous workups. ESI-MS spectra of the yellow band shows it to be a mixture of multiple oxygenated and sulfur-extruded versions of the disulfide form of the ligand, characterized by [(deDTC)$_2$ ±16]$^+$ ions, and this is consistent with ^{1}H NMR spectra of these samples. A similar yellow product mixture is generated from 1:1 reaction of DSF with *m*CPBA, Scheme 5.

Scheme 6



Scheme 7



Organic thiosulfinates (RS(O)SR) are known to undergo facile O-atom transfer and disproportionations.[34,35] The unstable *vic*-disulfoxides (RS(O)S(O)R) have only been observed spectroscopically; attempted isolations by chromatography inevitably yield mixtures of disulfides and thiosulfonates. Previous studies of the electron-ionization MS of alkyl dithiocarbamates suggested that formation of a 2,2-diethyl thiooximinium cation, Scheme 6,[36] is catalyzed by carboxylates, e.g., *m*CPBA.[37] Indeed, an ion at *m*/*z* 116 corresponding to the sulfonium is abundant in ESI-MS spectra of yellow byproduct, which shifts to *m*/*z* 117 in samples ^{13}C-labeled at the thiocarbonyl, and this peak is prominent in the ESI-MS of the oxygenated complexes. Promotion of decomposition by O-donor Lewis bases is also supported by the generation of the yellow byproducts upon elution of purified samples of **2** and **3** on silica under both aerobic and anaerobic conditions. As a test for the sensitivity of the Zn−oxygenates to such Lewis base reactivity, exposure of the homoleptic peroxydithiocarbamate complex **3** in $CDCl_3$ to pH 10 borate buffer under biphasic conditions also results in the slow generation of the yellow byproducts, as well as the parent **1**, as characterized by ^{1}H NMR, Supporting Information, S8.

Oxygenation vs Oxidation. The formation of DSF during oxygenations by *m*CPBA, as well as from the base-catalyzed decompositions of the oxygenated products, suggests the possible involvement of S-based radicals, i.e., Scheme 7. Disulfides may be formed by either one- or two-electron oxidation pathways, by coupling of S-radicals, or by nucleophilic attack of a thiol on a sulfenic acid equivalent. For all reactions described here, essentially identical results were obtained in the presence or absence of air, which argues against radical intermediates, Path B. A reviewer requested further investigations of possible radical reactivity; we therefore looked at the oxidation of **1** both electrochemically and by bulk reaction.

The electrochemistry of DTC compounds has been well studied[38] and reviewed.[39] The electrochemical oxidations of the DTCs described here were investigated in MeCN, Figure

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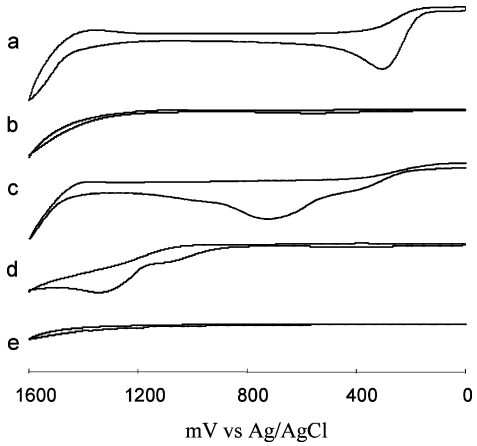
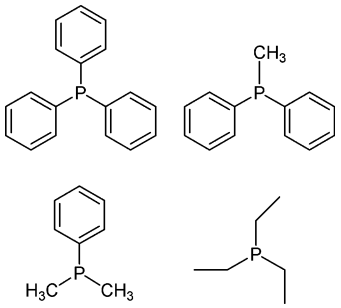
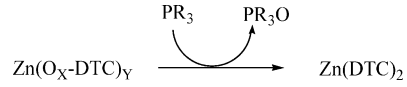


Figure 11. Cyclic voltammograms of DTC derivatives: (a) Na(deDTC); (b) compound **1**; (c) Na(O-deDTC); (d) compound **3**; (e) compound **4**. Conditions: ca. 5 mg sample in MeCN, 0.1 M TBAHFP, 100 mV/s scan rate, PG working electrode, Pt counter electrode, referenced to a Ag/AgCl electrode via a Luggin capillary connector.

Scheme 8



Scheme 9



11. The irreversible oxidation of the sodium salt of deDTC occurs at ~300 mV vs Ag/AgCl; by contrast, its Zn complex **1** shows no definable oxidation until ca. 1600 mV. A positive shift in oxidation potential due to thermodynamic stability of the chelate form is predicted by the Nernst equation, the overall binding affinity (β_2) in water has been reported as $10^{11.6}$ mol^{-2},[40] and it is likely larger in MeCN. The mono-oxygenated DTC ligand, as prepared by peroxidation of Na(deDTC) in MeCN, shows a broad, irreversible oxidation with two features at ca. 400 and 700 mV; its homoleptic Zn complex, compound **3**, also shows a two-featured oxidation shifted to 1000 and 1300 mV. The homoleptic Zn complex dioxygenated DTC, **4**, yields no observable oxidation within the solvent window.

Stoichiometric chemical oxidation of **1** with cerium ammonium nitrate, CAN, under aerobic conditions yields only DSF and a white precipitate, presumably $Zn(NO_3)_2$. The reaction is quite slow, but over a 3 day period, the characteristic NMR signals of DSF are seen to grow in, Supporting Information, S9. The slow oxidation rate may be due to low solubility of CAN in $CDCl_3$ or to slow release

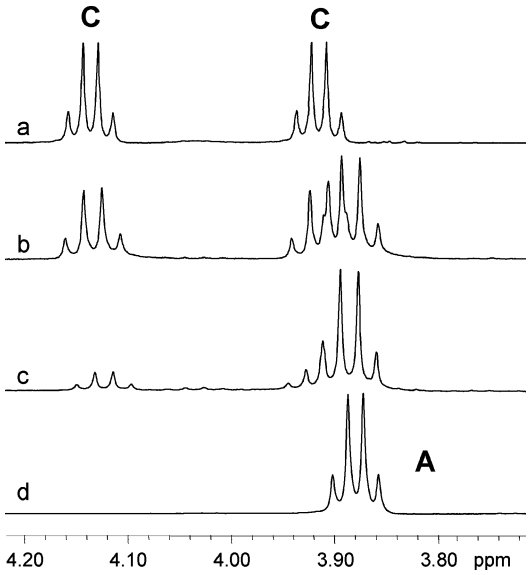


Figure 12. Deoxygenations of **4** by stoichiometric reactions with PEt_3. ^{1}H NMR spectra of product of (a) compound **4**, $Zn(O_2\text{-deDTC})_2$, displaying only resonances of the thiocarbamylsulfinate ligand (C); (b) **4** plus ca. 2 equiv of PEt_3; (c) **4** plus ca. 4 equiv of PEt_3; (d) authentic sample of **1**, $Zn(deDTC)_2$, with a single resonance of the dithiocarbamate ligand (A). No peaks attributable to a peroxydithiocarbamate ligand (ca. 3.65 ppm) were observed in spectra b and c.

of the free deDTC ligand, which would be more susceptible to oxidation. In reactions with excess CAN, in the absence or presence of O-atom donors such as O_2 or $OPPh_3$, no identifiable oxygenates were seen by NMR or ESI-MS. Thus, radical reactivity is not implicated in the formation or reactivity of the S-oxygenated DTC complexes.

O-Atom Transfer Reactivity. The formation of the parent dithiocarbamate **1** during decomposition of the S-oxygenates also implies that these compounds may act as O-atom donors; this ability was assayed against the series of aryl and alkyl phosphines shown in Scheme 8. These test reactions were performed at room temperature on the NMR scale, initiated by stoichiometric addition of the phosphine to the Zn complex in chloroform. Oxygen-exchange was confirmed by observation of the phosphine oxide in the ^{31}P NMR spectra and the appearance of the unoxygenated parent Zn dithiocarbamate complex in the ^{1}H NMR spectra. The oxygen-exchange reactivity was highly dependent on the phosphine: both PPh_3 and PPh_2Me were unable to deoxygenate any of the S-oxygenated compounds. The dependence on phosphine follows the well-characterized trend in basicity of arene and alkyl phosphines.[41−43] However, unexpectedly, relatively little difference in donor ability was seen between the S-oxygenates: both $PPhMe_2$ and PEt_3 stoichiometrically deoxygenates compounds **2** and **3**, as well as the sulfinato derivative **4**. The ease in deoxygenation of the sulfinato **4** was counter to the reactivity of the tautomeric S,S-bound sulfinate in $Ru(bpy)_2$(*N*,*N*′-dimethylthiocarbamoylsulfinato)$^+$, which did not react with PEt_3 under similar conditions.[14]

(40) Scharfe, R. R.; Sastri, V. S.; Chakraba, C. *Anal. Chem.* **1973**, *45*, 413−415.

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Some difference between sulfenic and sulfinic oxygens in O-atom transfers was discernible by following stoichiometric additions of PEt_3 to the sulfinato **4**, Figure 12; the addition of ca. 2 equiv of phosphine to the homoleptic sulfinato **4** generated ca. equal mixtures of **4** with the fully deoxygenated **1**; no evidence of peroxydithiocarbamates **2** or **3** was observed. As the peroxydithiocarbamate ligand should be formed by bimolecular reaction of one phosphine with one sulfinato, the absence of accumulated peroxydithiocarbamate suggests that it reacts with phosphine faster than the corresponding thiocarbamate-sulfinate.

Conclusions. The work shown here introduces a series of new oxygenated DTC compounds and outlines the effect of metal coordination on pathways of ligand oxidation. In addition to crystallographic characterization of structures of both forms of the oxygenated dithiocarbamate complexes, we describe their independent synthesis, characterization, and reactivity, as well identification of several decomposition products.

Many previous studies of Zn DTC oxygenates have focused on their application as antioxidants in rubber formulation and vulcanization accelerants at elevated temperatures.[3−5,15,16] Likewise, it has been long postulated that the bioactivity of dithiocarbamate derivatives such as DSF derives from S-oxygenation and extrusion.[14] The Phoenix-like ability of the oxygenated forms to regenerate the parent DTC complex upon decomposition recalls the recent demonstration that Cu-catalyzed decomposition of the deDTC disulfide, DSF, generates the highly cytotoxic Cu(deDTC)$_2$ in high yield.[11] Similarly, the widely used DTC-based pesticides Ziram, Zn(dmDTC)$_2$, and Thiuram (dmDTC)$_2$, undergo analogous decomposition reactions to those described for the diethyl analogues. The decomposition pathways illustrated here are likely relevant to both the biological and antioxidant activity of these widely used DTC derivatives.

Experimental Section

Abbreviations. DSF, tetraethylthiuram disulfide; deDTC, diethyldithiocarbamate; dmDTC; dimethyldithiocarbamate, UHP, urea hydrogen peroxide; *m*CPBA, *meta*-chloroperoxybenzoic acid; pDTC, pyrrolidinedithiocarbamate; PEt_3, triethylphosphine; $PPhMe_2$, dimethylphenylphosphine; PPh_2Me, methyldiphenylphosphine; PPh_3, triphenylphosphine.

Materials. All common laboratory solvents were reagent grade. KOH, NaOH, and $ZnCl_2$ were purchased from Fisher and used as received. All other chemicals were purchased from Aldrich Chemical Co. Solvents in the nitrogen glovebox were dried using standard techniques. Where anaerobic techniques were required, a dry glovebox and standard Schlenk techniques were used.

Physical Measurements. Mass spectra were determined by Micromass LCT. UV−vis spectra were recorded by Perkin-Elmer Lambda 900. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded using Bruker Avance 400 and 500 MHz spectrometers. Chemical shifts are referenced via the solvent signal. Infrared spectra were recorded as KBr pellets on Impact 410 from Nicolet. Elemental analyses were performed by Atlantic Microlab, Norcross, GA or Desert Analytics, Phoenix, AZ. All single-crystal X-ray diffraction structures were solved at the X-ray Crystallography Facility at UCI. Voltammetric experiments were performed using Bioanalytical Systems (BAS) CV-50W voltammetric analyzer under PC control. Solutions were prepared with ∼5 mg of each compound in 5 mL of 0.1 M TBAF in dry CH_2Cl_2. A glassy carbon electrode was used for the working electrode, with Pt wire as auxiliary. An $Ag/AgCl_{aq}$ reference electrode was connected to the analyte solution via a Luggin capillary connector. All samples were purged with N_2(g) for 5−10 min before the experiments were preformed.

Synthesis of Zn(OS$_2$NC$_5$H$_{10}$)(S$_2$NC$_5$H$_{10}$), 2. Zn(deDTC)$_2$ (0.500 g, 1.386 mmol) was dissolved in 250 mL of $CHCl_3$, and in a separate round-bottom flask *m*CPBA (0.310 g, 1.386 mmol) was dissolved in a 250 mL 1:1 mixture of $CHCl_3$ and CH_3CN, and both solutions were cooled to 4 °C. The *m*CPBA solution was then added dropwise in an addition funnel to the stirred solution of Zn(deDTC)$_2$. After the mixture was stirred for 10−12 h, the solvent was removed under vacuum. The resulting solid was collected and washed with three 20 mL portions of ice cold CH_3CN to yield 0.412 g (79%) of a white solid. ^{1}H NMR (500.22 MHz, $CDCl_3$): δ 1.28 (t, 3 H, $-CH_3$, $J = 7.2$ Hz), 1.33 (t, 3 H, $-CH_3$, $J = 7.2$ Hz), 3.65 (broad, 2H, $-CH_2-$), 3.87 (q, 2 H, $-CH_2$, $J = 7.1$ Hz). IR(cm^{-1}): 819 (V_{S-O}), 885 (V_{S-O}). Anal. Calcd. for $H_{20}C_{10}ON_2S_4Zn$: C, 31.78; H, 5.33; N, 7.41. Found: C, 31.55; H, 5.20; N, 7.32. Variable-temperature (−40 to +50 °C) ^{1}H NMR was performed for energetic parameters and to confirm the oxidized product.

Synthesis of Zn(OS$_2$NC$_5$H$_{10}$)$_2$, 3. A stirred solution of Na(deDTC) (0.2749 g, 1.605 mmol) in 50 mL of MeOH was cooled in an ice bath, and UHP (0.1478 g, 1.571 mmol) was added after 5 min. Upon UHP dissolution, the mixture turned yellow and $ZnCl_2$ (0.1094 g, 0.802 mmol) was immediately added. Once the mixture was no longer yellow, a white precipitate was collected, washed with 20 mL of MeOH, and dried under vacuum yielding 0.1734 g (56%) of a white solid. ^{1}H NMR at +25 °C (500.04 MHz, $CDCl_3$): δ 3.64 (bs, 2H, $-CH_2-$), 1.29 (t, 3H, $-CH_3$, $J = 7.1$ Hz). ^{1} H NMR at +50 °C: δ 3.66 (q, 2H, $-CH_2$-, $J = 6.8$ Hz), 1.29 (t, 3H, $-CH_3$, $J = 7.0$ Hz). ^{1} H NMR at −50°C (500.04 MHz, $CDCl_3$): δ 3.88 (q, 2H, $-CH_2$-, $J = 7.0$ Hz), 3.34 (q, 2H, $-CH_2$-, $J = 7.0$ Hz), 1.27 (t, 3H, $-CH_3$, $J = 6.8$ Hz), 1.19 (t, 3H, $-CH_3$, $J = 7.0$ Hz). IR (cm^{-1}): 823 (V_{S-O}), 886 (V_{S-O}). Anal. Calcd for $C_{10}H_{20}S_4N_2O_2Zn$: C, 30.49; H, 5.12; N, 7.11. Found: C, 30.27; H, 5.12; N, 6.96.

Synthesis of Zn(O$_2$S$_2$NC$_5$H$_{10}$)$_2$·H$_2$O, 4. A stirred solution of Na(deDTC) (0.500 g, 2.22 mmol) in 10 mL of acetone was cooled to 4 °C, and 30% H_2O_2 (1 mL, 10 mmol) was added dropwise over a 15 min period. The reaction mixture turned yellow and was left to stir for 30 min before being allowed to warm to room temperature. $CHCl_3$ (2 mL), deionized H_2O (2 mL), and $Zn(OAc)_2$ (0.225 g, 1.03 mmol) were added to the reaction mixture and left to stir for another 30 min. Stirring was then stopped, and the mixture was left to stand for 48 h until all the solvent had evaporated. Extractions from the residue with chloroform yielded 0.0877 g (19%) of a white solid. ^{1}H NMR (500.22 MHz, $CDCl_3$): δ 1.40 (t, 3H, $-CH_3$, $J = 3.5$ Hz), 1.42 (t, 3H, $-CH_3$, $J = 3.5$ Hz), 3.92 (q, $-CH_2-$, $J = 7.0$ Hz), 4.14 (q, $-CH_2-$, $J = 7.0$ Hz). IR(cm^{-1}): 1002 (V_{S-O}), 1065 (V_{S-O}). Anal. Calcd for $H_{22}C_{10}O_5N_2S_4Zn$: C, 27.05; H, 4.99. Found: C, 27.22; H, 4.98.

Synthesis of Zn(OS$_2$NC$_3$H$_6$)(S$_2$NC$_3$H$_6$), 6. Zn(dmDTC)$_2$ (0.474 g, 1.540 mmol) was dissolved in 200 mL of $CHCl_3$, and in a separate round-bottom flask *m*CPBA (0.347 g, 1.540 mmol) was dissolved in 200 mL of a 1:1 $CHCl_3$ and CH_3CN mixture, and both solutions were cooled 4 °C. The *m*CPBA solution was then added dropwise in an addition funnel to the stirred solution of Zn(dmDTC)$_2$. After the mixture was stirred for 10−12 h, the solvent was removed under vacuum. The resulting solid was collected and

washed with three 10 mL portions of ice cold CH_3CN to yield 0.170 g (34%) of a white solid. ^{1}H NMR (500.22 MHz, $CDCl_3$): δ 3.31 (broad s, $-CH_3$), 3.48 (s, $-CH_3$), +50 °C: δ 3.31 (s, 3H, $-CH_3$). ^{1}H NMR at −50 °C (500.04 MHz, $CDCl_3$): δ 3.56 (t, 3H, $-CH_3$), 3.48 (s, $-CH_3$), 3.08 (s, $-CH_3$). Anal. Calcd for $H_{12}C_6ON_2S_4Zn$: C, 22.39; H, 3.75. Found: C, 22.61; H, 3.65. Variable-temperature (−40 to +50 °C) ^{1}H and ^{13}C NMR were also done to confirm the oxidized product.

Synthesis of $Zn(OS_2NC_5H_8)(S_2NC_5H_8)$. A solution of Zn(pDTC)$_2$ (0.5122 g, 1.431 mmol) was dissolved in 125 mL of CH_2Cl_2 and degassed for 30 min. A solution of UHP (0.1325 g, 1.408 mmol) in 40 mL of MeOH was degassed for 15 min. After the Zn(pDTC)$_2$ was cooled to 4 °C, the UHP solution was added dropwise over a period of 5 min. The reaction was left to stir at 4 °C and periodically monitored in situ by ^{1}H NMR. After 5 days, the reaction solvent was evaporated and an off white solid obtained. A $CHCl_3/H_2O$ extraction was performed; stripping the solvent resulted in white solid which was washed with 20 mL of MeCN and dried by vacuum to give 0.2586 g (49.1%) of a white solid. ^{1}H NMR 25 °C (500.04 MHz, $CDCl_3$): δ 3.91(bs, 2H, $-CH_2-$), 3.76 (t, 2H,-CH_2-), 3.21 (bs, 2H, $-CH_2-$), 2.08 (m, 2H, $-CH_2-$). ^{1}H NMR −50°C (500.04 MHz, $CDCl_3$): δ 3.91(t, 2H, $-CH_2-$), 3.76 (t, 2H, $-CH_2-$), 3.21 (t, 2H, $-CH_2-$), 2.12 (m, 2H, $-CH_2-$), 2.06 (m, 2H, $-CH_2-$), 2.02 (m, 2H, $-CH_2-$). Anal. Calcd for $C_{10}H_{16}S_4N_2OZn$: C, 32.11; H, 4.31; N, 7.49. Found: C, 32.34; H, 54.26; N, 7.75.

Synthesis of $Zn(OS_2NC_5H_8)_2$. A solution of (NH_4)(pDTC) (0.3621 g, 2.204 mmol) was dissolved in 50 mL of MeOH and cooled in an ice bath. UHP (0.2006 g, 2.132 mmol) was then added to the pDTC solution. Once the UHP dissolved and the mixture turned yellow, $ZnCl_2$ (0.1578 g, 1.157 mmol) was added to the mixture. Upon vigorous stirring of the mixture, a white solid precipitated, which was collected by vacuum filtration and washed with 50 mL each of both MeOH and MeCN, yielding 0.3025 g (72.8%) of white solid. ^{1}H NMR 25 °C (500.04 MHz, $CDCl_3$): δ 3.99 (t, 2H), 2.18 (m, 2H), 2.04 (m, 2H). Anal. Calcd for $C_{10}H_{16}S_4N_2O_2Zn$: C, 30.80; H, 4.14; N, 7.19. Found: C, 30.94; H, 4.34; N, 7.08.

Synthesis of ^{13}C-Labeled $Zn(S_2NC_5H_{10})_2$, 1. To an aqueous solution of $(C_2H_5)_2NH$ (0.908 g, 12.4 mmol) and NaOH (0.491, 12.4 mmol), $^{13}CS_2$ (1.000 g, 12.9 mmol) was added dropwise via an addition funnel over a 10 min period. The mixture was allowed to stir for an hour before being frozen in a dry ice−acetone bath and lyophilized overnight. The resulting solid was collected and washed with Et_2O (20 mL), yielding 0.412 g (85%) of an off white solid. Addition of the ^{13}C-labeled deDTC (0.398 g, 1.629 mmol) to a stirred solution of $ZnCl_2$ (0.107 g, 0.790 mmol) in 50 mL of MeOH produced a white solid precipitate, which was collected by vacuum filtration and washed with water, yielding 0.520 g of white solid (90%).

Reactions of 1 and 2 with Stoichiometric UHP. In a typical reaction, an aliquot of UHP (0.025 g, 0.276 mmol) in 20 mL of MeOH was added dropwise at 0 °C to a 50 mL CH_2Cl_2 solution of Zn(deDTC)$_2$ (0.052 g, 0.138 mmol). The reaction mixture was allowed to stir overnight or longer. After the solvent was stripped, the resulting solid was collected and washed with 50 mL of water to yield a white solid. Each solid was analyzed by ^{1}H NMR to identify and determine the yields of oxygenated products. The procedure described above was varied in the amounts of **1**, **2**, and UHP used, as is outlined in the Supporting Information, Table S6.

Reactions of Zn(deDTC)$_2$ with Stoichiometric *m*CPBA. In a typical reaction, aliquots of 1, 2, 3, or 4 equiv of *m*CPBA (each 212 g, 0.949 mmol) in 30 mL of $CHCl_3$ were added dropwise at 0 °C to a 50 mL $CHCl_3$ solution of Zn(deDTC)$_2$ (0.342 g, 0.945 mmol). Upon addition, the reaction mixture turned yellow and the color intensified with increasing equivalents of *m*CPBA. After the reaction was allowed to stir for ∼12 h, the solvent was removed. The resulting solid was collected and washed with three 20 mL portions of ice cold MeCN to yield an off white solid. Each solid was analyzed by ESI-MS and ^{1}H NMR to identify and determine the yields of oxygenated and/or oxidized products.

Reactions of DSF and Stoichiometric *m*CPBA. DSF (0.107 mg, 0.362 mmol) was added to CH_2Cl_2 at 0 °C, and *m*CPBA (0.0801 mg, 0.3622 mmol) in 20 mL of CH_2Cl_2 was added dropwise over 20 min. The reaction turned yellow after the first several drops and slowly intensified upon further addition. The reaction was monitored by ^{1}H and ^{13}C NMR and ESI-MS.

Chemical Oxidation of Zn(deDTC)$_2$ with CAN. An NMR tube charged with Zn(deDTC)$_2$ (0.011 mg, 0.0303 mmol) and CAN (0.016 g, 0.0303 mmol) in $CDCl_3$ was monitored by ^{1}H NMR over the course of a week. Integrating the methylene protons estimates a product distribution at about a 10:9 ratio, DSF to Zn(deDTC)$_2$.

Reactivity with Phosphines. Solutions of PEt_3, PPh_3, $PPhMe_2$, and PPh_2Me were prepared and add to separate solutions of the oxygenated zinc compounds **2**−**6** in $CDCl_3$. The solutions were periodically refluxed for up to 2 weeks and monitored by TLC, ESI-MS, and ^{1}H and ^{31}P NMR. For PPh_3 and PPh_2Me, no reaction or decomposition was ever observed. For PEt_3 and $PPhMe_2$, the O-atom abstraction from zinc compounds **2**−**6** was complete before NMR spectra could be taken. To verify assignments, each phosphine solution was prepared anaerobically in an NMR tube to obtain the PR_3 chemical shift values, then to each sample excess *m*CPBA was added to obtain the corresponding $P(O)R_3$ chemical shift values.

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Supporting Information Available: Total line shape analysis of ^{1}H NMR of compounds **1**, **3**, and **5**; crystallographic and metric parameters for compounds **1**, **2**:**3**, and **4**; ESI-MS spectra for **1**, **2**, **3**, and **4** matched with the isotopic models; NMR characterizations of the reaction of UHP with **3**, the decomposition of **3** when exposed to pH 10 buffer in biphasic mixture; and ^{13}C NMR of the byproduct mixture described in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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