Inorg. Chem. **2007**, *46*, 4515–4522

Metalation of Cyclic Pseudopeptidic Thiosulfinates with Ni(II) and Zn(II) after Ring Opening: A Mechanistic Investigation

Erwan Galardon,[†,‡] Emilie Bourles,[†,‡] Isabelle Artaud,*[,†] Jean-Claude Daran,[§] Pascal Roussel,[||] and Alain Tomas[⊥]

Laboratoire de Chimie et Biochimie Pharmacologique et Toxicologique, Université Paris Descartes, CNRS UMR 8601, 45 rue des Saints Pères, 75270 Paris Cedex 06, France, Laboratoire de Chimie de Coordination, UPR 8241, CNRS, 205 route de Narbonne, 31077 Toulouse Cedex 04, France, Laboratoire de Cristallochimie et Physicochimie du Solide, UMR 8012, CNRS, Université des Sciences et Technologies de Lille et École Nationale Supérieure de Chimie de Lille, BP 108, 59652 Villeneuve d'Ascq Cedex, France, and Laboratoire de Cristallographie et RMN Biologiques, Université Paris Descartes, UMR 8015, CNRS, 4 avenue de l'Observatoire, 75270 Paris Cedex 06, France

Received December 28, 2006

Thiosulfinates are an emerging class of oxidized sulfur species that are frequently supposed to be involved in biochemical processes. Reaction of 12- and 10-membered ring pseudopeptidic thiosulfinates **1a** (4,4,7,7-tetramethyl-1,3,4,7,8,10-hexahydro-5,6,1,10-benzodithiadiazacyclododecine-2,9-dione 5-oxide) and **1b** (3,3,6,6-tetramethyl-1,8-dihydro-4,5,1,8-benzodithiadiazecine-2,7(3*H*,6*H*)-dione 4-oxide) with a Ni(II) salt leads after ring cleavage under alkaline conditions to the isolation of diamidato/thiolato/sulfinato complexes. These two thiolato/sulfinato complexes of nickel, which can also be prepared by dioxygen oxidation of the parent diamidato/dithiolato complexes, were characterized by X-ray crystallography. They show a square-planar geometry with a S-bonded sulfinato ligand. A similar reaction between **1b** and a Zn(II) salt leads to a thiolato/sulfinato complex with an O-bonded sulfinate via the intermediate formation of a mixed thiolato/sulfinic ester. On the basis of ^{1}H NMR, IR, and mass analyses, the sulfinic ester in the intermediate is proposed to be O-bonded to the zinc center. Then, an in-depth study of the cleavage of these thiosulfinates with the oxyanions RO^- and HO^- was performed. This led, after trapping of the open species with CH_3I, to the identification of three polyfunctionalized products containing a methyl thioether, with either an isothiazolidin-3-one *S*-oxide, a methyl sulfone, or a methyl sulfinic ester. All of these products arise from a selective nucleophilic attack at the sulfinyl sulfur, promoted either directly by RO^- or HO^- or by an internal peptidic nitrogen of the thiosulfinate after deprotonation with RO^- or HO^-.

Introduction

Under physiological conditions, cysteines are reversibly oxidized to disulfide. However, they can be further oxidized to sulfenic, sulfinic, or sulfonic acids and, in the case of two thiols, to thiosulfinate or thiosulfonate. There is now evidence that disulfide *S*-oxides have biological implications.[1] Their production could be either mediated by reaction with oxygen or nitrogen species generated under oxidative stress conditions[1] or catalyzed by monooxygenases[2] or dioxygenases.[3] While first limited to glutathione derivatives,[4] it is now suggested that they can also be formed directly in proteins, between two cysteine residues of the same protein or between

* To whom correspondence should be addressed. E-mail: isabelle.artaud@univ-paris5.fr. Tel: +33-1-4286-2189. Fax: +33-1-4286-8387.

† Laboratoire de Chimie et Biochimie Pharmacologique et Toxicologique, UMR 8601, CNRS Université Paris 5.

‡ These authors contributed equally to this work.

§ Laboratoire de Chimie de Coordination, UPR 8241, CNRS.

|| Université des Sciences et Technologies de Lille et École Nationale Supérieure de Chimie de Lille.

⊥ Laboratoire de Cristallographie et RMN Biologiques, UMR 8015, CNRS Université Paris 5.

(1) Jacob, C.; Giles, G. L.; Giles, N. M.; Sies, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4742.

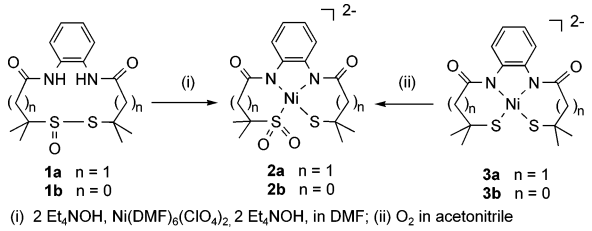
(2) Teyssier, C.; Guenot, L.; Suschetet, M.; Siess, M. H. *Drug Metab. Dispos.* **1999**, *27*, 835.

(3) Boyd, D. R.; Sharma, N. D.; Kennedy, M. A.; Shepherd, S. D.; Malone, J. F.; Alves-Areias, A.; Holt, R.; Allenmark, S. G.; Lemurell, M. A.; Dalton, H.; Luckarfit, H. *Chem. Commun.* **2002**, 1452.

(4) Huang, K.-P.; Huang, F. L. *Biochem. Pharmacol.* **2002**, *64*, 1049.

10.1021/ic062480m CCC: $37.00
Published on Web 04/28/2007

Scheme 1. Synthesis of Nickel Complexes **2a** and **2b**



one cysteine residue of a protein and a free exogenous thiol. The first demonstration of the possible formation of an intramolecular thiosulfinate in a protein was first reported in 1998 in an in vitro study of the reactivity toward oxidants of a peptide corresponding to a zinc finger of a transcription factor.[5] More recently, the reduction of the cysteine−sulfinic acid of mammals' peroxyredoxins involved in their signaling activities has been proposed to proceed through the intermediate formation of a thiosulfinate with a thiol molecule[6] or with a cysteine of a sulfiredoxin.[7] The further reactivity of thiosulfinates with thiols or with nucleophiles is well documented in chemistry[8] and biochemistry.[1,4] However, there are only a few reports on the coordination chemistry of these compounds. Cyclic thiosulfinates were reported to react via oxidative addition with Pt(0) complexes to give the corresponding thiolato/sulfenato complexes platinum-(II).[9,10] Recently, we have shown that a cyclic pseudopeptidic thiosulfinate can react with a Co(III) cation after cleavage of the S(O)−S bond, providing a mixed thiolato/sulfinato complex.[11]

In this paper, we have extended this reaction to Ni(II) and Zn(II) salts. Two new diamidato/thiolato/sulfinato complexes of nickel(II) (S-bonded) complexes have been thoroughly characterized. The zinc derivative enabled us to detail stepwise the formation of the final complex containing a sulfinate O-bonded to the metal cation and has prompted us to study more carefully, in our experimental conditions, the reactivity of these cyclic pseudopeptidic thiosulfinates toward anions acting as bases or nucleophiles.

Results

Trapping with Ni(II). The addition under anaerobic conditions of 2 equiv of a solution of Et_4NOH in methanol to a cooled solution of the cyclic thiosulfinate **1a** or **1b** (Scheme 1) in *N*,*N*′-dimethylformamide (DMF), followed by the addition of 1 equiv of $Ni(DMF)_6(ClO_4)_2$ and of a further 2 equiv of base, provides after crystallization the new complexes **2a** or **2b** (Scheme 1). ORTEP views of **2a** and **2b** are depicted in Figure 1. Crystallographic data are summarized in Table 1, and selected bond angles and lengths are listed in Table 2. The asymmetric unit of **2b** contains, in addition to one anionic moiety and two Et_4N^+, a molecule of acetonitrile. Structures of **2a** and **2b** reveal a nickel center bound to two cis-deprotonated carboxamido nitrogens and two cis sulfurs, one thiolate, and one sulfinate. The geometry around the nickel centers can be described as square planar, with a small tetrahedral distortion (Td = 5.5° and 1.6° for **2a** and **2b**, respectively).[12] For **2a**, occupancy factors of 0.79 for O1 and O2 and 0.21 for O5 and O6 determine two

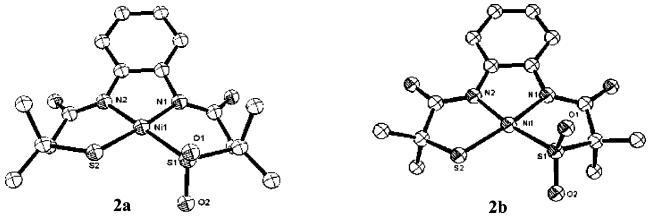


Figure 1. ORTEP views of **2a** and **2b** showing thermal ellipsoids at 50% probability and atom labeling. Hydrogen atoms and Et_4N^+ cations, as well as acetonitrile for **2b**, have been omitted for clarity. For **2a**, only one anionic enantiomer is shown.

Table 1. Crystal Data and Structure Refinements for **2a** and **2b**

	2a	**2b**
formula	$C_{32}H_{60}N_4O_4S_2Ni$	$C_{32}H_{59}N_5O_4S_2Ni$
fw	687.67	700.67
T (K)	120	120
wavelength (Å)	0.710 73	0.710 73
cryst syst	monoclinic	monoclinic
space group	$P2_1/n$	$P2_1/n$
unit cell dimens		
a (Å)	16.833(4)	16.190(2)
b (Å)	11.800(2)	11.3450(10)
c (Å)	19.114(4)	21.092(2)
β (deg)	112.60(3)	109.83 (1)
V (Å^3)	3505.1(1)	3644.4(7)
Z	4	4
d(calcd) (Mg·m^3)	1.303	1.277
abs coeff (mm^{-1})	0.713	0.688
cryst size (mm^3)	0.09 × 0.08 × 0.09	0.08 × 0.075 × 0.08
cryst color	orange	orange
θ range for data collection (deg)	2.08−27.00	2.07−25.00
index ranges	$-21 < h < +20$ $-14 < k < +15$ $-24 < l < +24$	$-19 < h < +19$ $-13 < k < +13$ $-24 < l < +24$
reflns collected	24 233	32 408
indep reflns	7225 [R(int) = 0.037]	6225 [R(int) = 0.051]
completness to θ_{max} (%)	94	97
abs correction	*SADABS*	none
min and max transm	0.938 and 0.951	
refinement methods	*a*	*a*
data/restraints/params	7225/0/496	6225/36/501
GOF on F^2	1.093	1.111
final R indices $[I > 2\sigma(I)]^{b,c}$	R1 = 0.045	R1 = 0.054
	wR2 = 0.114	wR2 = 0.147
R indices (all data)^{b,c}	R1 = 0.065	R1 = 0.075
	wR2 = 0.127	wR2 = 0.160
largest peak and hole (e·Å^{-3})	0.71 and −0.638	1.19 and −0.401

[a] Full-matrix least squares on F^2. [b] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [c] $wR2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}$, where $w = q/\sigma^2(F_o^2) + (qp)^2 + bp$. GOF $= S = \{\sum[w(F_o^2 - F_c^2)^2]/(n - p)^{1/2}\}$.

(5) Xu, Y.; Wilcox, D. E. *J. Am. Chem. Soc.* **1998**, *120*, 7375.
(6) Jeong, W.; Park, S. J.; Chang, T.-S.; Lee, D.-Y.; Rhee, S. G. *J. Biol. Chem.* **2006**, *281*, 14400.
(7) Vivancos, A. P.; Castillo, E. A.; Biteau, B.; Nicot, C.; Ayte, J.; Toledano, M. B.; Hidalgo, E. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 8875.
(8) Kice, J. L.; Liu, C.-C. A. *J. Org. Chem.* **1979**, *44*, 1918.
(9) Weigand, W.; Wunch, R. *Chem. Ber.* **1996**, *129*, 1409.
(10) Wünsch, R.; Bosl, G.; Robl, C.; Weigand, W. *J. Organomet. Chem.* **2001**, *621*, 352.
(11) Boulès E.; Alves de Sousa, R.; Galardon, E.; Giorgi, M.; Artaud, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 6162.
(12) Grapperhaus, C. A.; Mullins, C. S.; Kozlowski, P. M.; Mashuta, M. S. *Inorg. Chem.* **2004**, *43*, 2859.

Table 2. Selected Bond Lengths (Å) and Angles (deg) for Complexes **2a** and **2b**

	2a	2b
Ni−S1	2.166(1)	2.113(1)
Ni−S2	2.169(1)	2.138(1)
Ni−N1	1.928(2)	1.875(3)
Ni−N2	1.923(2)	1.873(4)
S1−O1	1.438(2)	1.482(3)
S1−O2	1.499(2)	1.460 (4)
S2−O5	1.662(8)	
S2−O6	1.323(8)	
N2−Ni−N1	83.9(1)	85.6(1)
S1−Ni−S2	85.07(3)	98.49(5)
N1−Ni−S1	95.88(7)	86.7(1)
N2−Ni−S2	95.38(7)	89.1(1)
O1−S1−O2	113.8(1)	112.4(2)
O5−S2−O6	109.8(5)	

possible oxidation states, thiolate or sulfinate, at S1 and S2. Consequently, as was previously observed with our related cobalt complex,[11] in the solid state, **2a** appears as a disordered mixture of two enantiomers. In contrast, **2b** exists only as one isomer. The $Ni-S_{sulfinate}$ distance (2.113(1) Å) in **2b** is slightly shorter than the $Ni-S_{thiolate}$ distance (2.138(1) Å). As was previously discussed by Darensbourg[13] and Grapperhaus,[12] this shortening of the bond length upon sulfur oxygenation to sulfinate is in agreement with a decrease in the sulfur size and a loss of metal−sulfur π-antibonding interaction, which compensates for a loss of the σ-donating ability of the sulfur. When the metric parameters of **2a** and **2b** are compared (Table 2), it is found that the N−Ni−S bond angles around the nickel ion are slightly greater in **2a** than in **2b** and the Ni−N and Ni−S distances slightly longer, as a result of the greater size of the N,S chelate in the former. In any case, they are in the range of those found in related mixed diamino/thiolato/sulfinato derivatives of nickel(II).[14−17] Complexes **2a** and **2b** are diamagnetic, as was expected for square-planar nickel(II) complexes, and thus only sharp signals between 0 and 10 ppm are observed by ^{1}H NMR. The dissymmetry of **2a** and **2b** is reflected by the spectra, showing two singlets for the methyls as well as for the methylenes. Fourier transform IR (FT-IR) is indicative of deprotonated carboxamido moieties with a set of stretching frequencies between 1600 and 1540 cm^{-1}, while the bands located at 1145 and 1022 cm^{-1} for **2a** and 1148 and 1031 cm^{-1} for **2b** are assigned to the $\nu(SO)_{asym}$ and $\nu(SO)_{sym}$ stretching modes typically observed in S-bonded metal sulfinate complexes.[13,16−18]

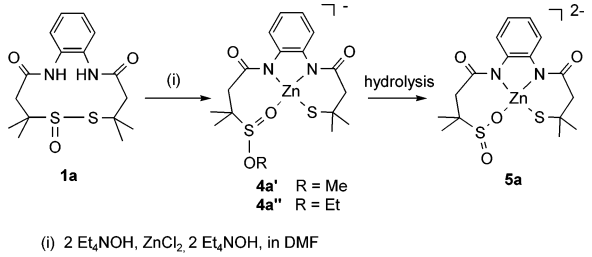
It should be underlined that ^{1}H NMR analysis of the crude mixture obtained after the reaction of **1a** and **1b** with Ni(II) reveals the presence of two major products. However, crystallization only yields pure **2a** and **2b**, without any concomitant increase in the relative amount of the second species present in the mother liquor of crystallization. The electrospray ionization mass spectrometry (ESI-MS) spectra of the crude mixtures display only peaks corresponding to thiolato/sulfinato complexes, while the difference IR spectra between the crude mixture and pure **2a** or **2b** shows a large vibration at 1025 cm^{-1}, typical of O-bonded metal sulfinates. Complexes **2a** and **2b** can also be obtained by dioxygen oxidation of the parent dithiolato complexes **3a** and **3b** in acetonitrile overnight (Scheme 1). Similarly to the experiment run with **1a**, oxidation of **3a** produces the same mixture of two species, which leads to pure **2a** after crystallization.

Trapping with Zn(II). Following the same procedure as that described above, the cyclic thiosulfinate **1a** can be trapped with $ZnCl_2$ (Scheme 2). After workup, complex **5a** is cleanly isolated as the only product of the reaction. Its ^{1}H NMR spectrum displays the classical splitting of the aromatic protons observed in all of our bis(carboxamido) diamagnetic complexes of zinc[19] and cobalt.[11,20,21] The ortho proton resonances are shifted upfield upon coordination to deprotonated carboxamido nitrogens. Besides frequencies associated with deprotonated carboxamides, the FT-IR spectrum exhibits, in the SO_2 region, only one strong band at 1025 cm^{-1} characteristic of O-bonded sulfinates.[18] Elemental analysis as well as ESI-MS data are also in agreement with the structure proposed in Scheme 2. Unfortunately, all attempts to crystallize **5a** to unambiguously assign its solid-state structure have failed. Interestingly, when using KOH or NaOH as the base instead of Et_4NOH, the ^{1}H NMR spectra remained unchanged, but the IR spectra of the powders show two strong vibrations at 1022 and 966 cm^{-1} or 1027 and 967 cm^{-1}, respectively.

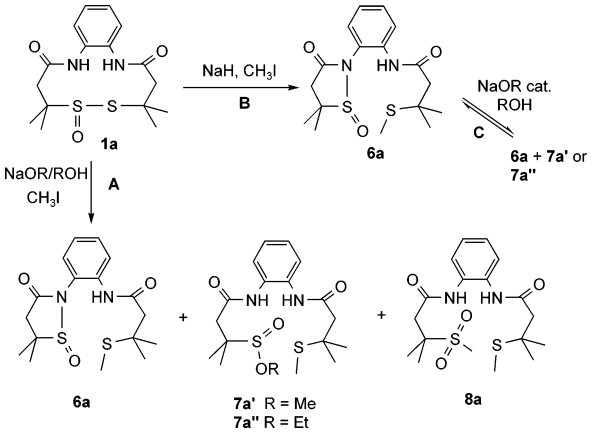
We also detected during the trapping of **1a** with $ZnCl_2$ the formation of an intermediate species **4a′**, which is converted into **5a** over time. When the reaction is stopped just after the addition of the last 2 equiv of Et_4NOH, precipitation into cold diethyl ether affords a mixture containing mainly **4a′**. Its ^{1}H NMR spectrum in CD_3CN shows, in addition to signals similar to those observed for **5a**, a singlet (3H) at 3.74 ppm. Upon prolonged stirring or the direct addition of water, **4a′** is converted to **5a** with the release of methanol, as indicated by the new resonance at 3.28 ppm assigned to free methanol in CD_3CN. The FT-IR spectrum of **4a′** exhibits two bands at 1100 and 1036 cm^{-1} and its MS spectrum (ESI$^-$) a peak at *m*/*z* 447 (100%), corresponding to the mass of **5a** plus one methyl. These results prompted us to propose for this intermediate species the structure shown is Scheme 2. This structure assignment was confirmed by further experiments: (i) an increased amount of **4a′** is obtained when an anhydrous solution of

(13) Buonomo, R. M.; Font, I.; Maguire, M. J.; Reibenspies, J. H.; Tuntulani, T.; Darensbourg, M. Y. *J. Am. Chem. Soc.* **1995**, *117*, 963.
(14) Farmer, P. J.; Solouki, T.; Mills, D. K.; Soma, T.; Russel, D. H.; Reibenspies, J. H.; Darensbourg, M. Y. *J. Am. Chem. Soc.* **1992**, *114*, 4601.
(15) Grapperhaus, C. A.; Darensbourg, M. Y. *Acc. Chem. Res.* **1998**, *31*, 451.
(16) Kaasjager, V. E.; Bouwman, E.; Gorter, S.; Reedjik, J.; Grappenhaus, C. A.; Reibenspies, J. H.; Smee, J. J.; Darensbourg, M. Y.; Derecskei-Kovacs, A.; Thomson, L. M. *Inorg. Chem.* **2002**, *41*, 1837.
(17) Mirza, S. A.; Pressler, M. A.; Kumar, M.; Day, R. O.; Maroney, M. J. *Inorg. Chem.* **1993**, *32*, 977.
(18) Vitzthum, G.; Lindner, E. *Angew. Chem., Int. Ed.* **1971**, *10*, 315.
(19) Alves de Sousa, R.; Galardon, E.; Rat, M.; Giorgi, M.; Artaud, I. *J. Inorg. Biochem.* **2005**, *99*, 690.
(20) Chatel, S.; Rat, M.; Dijols, S.; Leduc, P.; Tuchagues, J.-P.; Mansuy, D.; Artaud, I. *J. Inorg. Biochem.* **2000**, *80*, 239.
(21) Rat, M.; Souza, R. A. d.; Vaissermann, J.; Leduc, P.; Mansuy, D.; Artaud, I. *J. Inorg. Biochem.* **2001**, *84*, 207.

Scheme 2. Synthesis of Zinc Complex **5a** via the Intermediate **4a′** or **4a″**



Scheme 3. Products Distribution Issued from the Cleavage of **1a**



sodium methoxide is used, whereas only **5a** is observed with aqueous sodium hydroxide; (ii) using NaOEt in ethanol instead of NaOMe in methanol enabled us to isolate a mixture of the ethyl analogues of **4a′** (**4a″**), along with **5a**, in a 85:15 ratio. Effectively, MS data show the incorporation of an ethyl group instead of the additional methyl group for **4a′**, and the ^{1}H NMR spectrum shows a new complex multiplet at 4.05 ppm corresponding to the resonances of the two diastereotopic CH_2 hydrogens of the ethyl group. The nonequivalence of the hydrogens is due to the asymmetry of the sulfur atom and implies that the ethyl group is part of a sulfinic ester and not of a sulfone. Again, conversion of **4a″** to **5a** was monitored by NMR, and the disappearance of the signals of **4a″** was associated with the increase of those of free ethanol.

Mechanistic Studies on the Opening of 1a. Reaction of **1a** in DMF with a solution of RONa in ROH (R = Me or R = Et), followed by trapping of the resulting anionic species with methyl iodide, provides a mixture of three products, **6a**, **7a′** (R = Me), **7a″** (R = Et), and **8a** (Scheme 3, path A) in various proportions depending on the experimental conditions. The former product can be cleanly synthesized by the reaction of **1a** with NaH and CH_3I in DMF (Scheme 3, path B) and was characterized by the usual methods. The asymmetry of the sulfur center is reflected in the ^{1}H NMR spectrum by the nonequivalence of the methyl and methylene groups. Since **7a″** was found to be more stable than **7a′** toward hydrolysis, most of the characterizations of the sulfinic esters were carried out using a mixture of this adduct and **6a**. As was anticipated from the results described above, ^{1}H NMR spectra display resonances corresponding to the sulfinic ester groups at 3.87 ppm (s, 3H) for **7a′** and 4.10 ppm (m, 2H) for **7a″**. The FT-IR spectra of **7a′** and **7a″** show the expected vibrations of the amide groups (1685 and 1661 cm^{-1} and 1684 and 1660 cm^{-1}, respectively) and of the sulfinic ester (1112 and 1013 cm^{-1} and 1114 and 1016 cm^{-1}, respectively). When **6a** is dissolved in MeOH (or EtOH) in the presence of a catalytic amount of MeONa (or EtONa), a mixture of **6a** and **7a′** (or **7a″**) is observed (Scheme 3, path C). Variation of the ratio **6a**/**7a′** as a function of the temperature was recorded by ^{1}H NMR in CD_3OD between 300 and 230 K. As shown in Figure 2, $-\ln([\mathbf{6a}]/[\mathbf{7a'}])$ varies linearly with $1/T$ ($R = 0.99434$), as expected for an equilibrium between two species. Back to 300 K, the **6a**/**7a′** ratio reverts to its initial value, confirming that the system is fully reversible. ΔH and ΔS could be calculated by fitting the data to the equation $-\ln([\mathbf{6a}]/[\mathbf{7a'}]) = (\Delta H_{\mathbf{7a'}\rightarrow\mathbf{6a}}/RT) - (\Delta S_{\mathbf{7a'}\rightarrow\mathbf{6a}}/R)$, giving $\Delta H_{\mathbf{7a'}\rightarrow\mathbf{6a}} = 15.3$ kJ·mol^{-1} and $\Delta S_{\mathbf{7a'}\rightarrow\mathbf{6a}} = 43.5$ J·K^{-1}·mol^{-1}.

Discussion

We have recently shown that the anionic species derived from the cleavage of the S−S(O) bond under alkaline conditions could be effectively trapped by Co(III) salts, leading to a mixed thiolato/sulfinato complex, thus providing a new synthetic pathway toward metal complexes containing two sulfur atoms at two different oxidation states.[11] This work now extends this reaction to Ni(II) and Zn(II) salts, and the new mixed thiolato/sulfinato complexes **2a**, **2b**, and **5a** are isolated from the thiosulfinates **1a** and **1b**.

The parent dithiolato complexes of **3a** and **3b** also react with dioxygen to give **2a** and **2b**. While the oxygenation of neutral Ni(N_2S_2) derivatives has been extensively studied this past decade by Darensbourg et al.[14−16,22] and Maroney et al.,[17,23] recent studies on the oxidation Ni(N_2S_2) complexes are now directed toward the reactivity of anionic species. This interest stems from the unexpected discovery, in nickel-containing superoxide dismutase, of two *cis*-thiolate donors along with a deprotonated amide and a N-terminal NH_2 group of a histidine in the coordination sphere of the nickel ion.[24,25] The mechanism of the oxygenation of neutral nickel complexes has been shown to proceed through a direct reaction of the electron-rich thiolate with dioxygen, leading to S-bonded sulfinates, the two oxygen atoms of which arise from a single molecule of dioxygen.[15] Density functional theory calculations have recently shown that introducing deprotonated carboxamido group(s) in the coordination sphere of a nickel ion instead of neutral amino donor(s) switches the reactivity of the complex from sulfur-based to metal-based oxidation.[26,27] The high reactivity of the dianionic complexes **3a** and **3b** toward dioxygen, which is

(22) Grapperhaus, C. A.; Darensbourg, M. Y.; Sumner, L. W.; Russell, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 1791.
(23) Maroney, M. J.; Choudhury, S. B.; Bryngelson, P. A.; Mirza, S. A.; Sherrod, M. J. *Inorg. Chem.* **1996**, *35*, 1073.
(24) Barondeau, D. P.; Kassmann, C. J.; Bruns, C. K.; Tainer, J. A.; Getzoff, E. D. *Biochemistry* **2004**, *43*, 8038.
(25) Wuerges, J.; Lee, J.-W.; Yim, Y.-I.; Yim, H.-S.; Kang, S.-O.; Carugo, K. D. *Proc. Natl. Acad. Sci., U.S.A.* **2004**, *101*, 8569.
(26) Fiedler, A. T.; Bryngelson, P. A.; Maroney, M. J.; Brunold, T. C. *J. Am. Chem. Soc.* **2005**, *127*, 5449.
(27) Mullins, C. S.; Grapperhaus, C. A.; Kozlowski, P. M. *J. Biol. Inorg. Chem.* **2006**, *11*, 617.

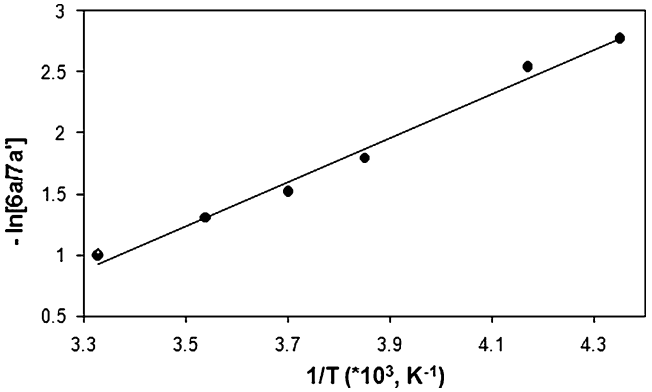
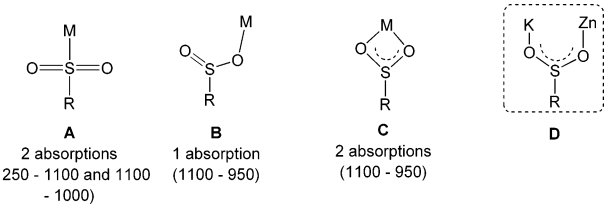


Figure 2. Plot of $-\ln([\mathbf{6a}]/[\mathbf{7a'}])$ vs $1/T$. The two values at $T = 300$ K correspond to the initial and final values.

reminiscent of the rapid oxidation of similar complexes in solution observed by Hegg et al.[28] and which contrasts with the inertness of a closely diamino/dithiolato complex toward ground-state dioxygen,[29] probably results from this switch in the mechanism. This is supported by our results, showing that, as expected for a metal-based mechanism, this oxidation yields an O-bonded sulfinate species, which is slowly converted during crystallization to the thermodynamically favored S-bonded complex. Furthermore, because of the low oxidation potential of the Ni(II)/Ni(III) couple (−0.71 V in acetonitrile vs the ferrocene/ferrocenium redox potential), bulk electrolysis of **3b** allowed the preparation and full characterization of the corresponding stable Ni(III) derivative.[30] Finally, Ni(III)−superoxo intermediates have also been proposed to mediate the ligand oxidation in Ni(II) complexes coordinated to deprotonated carboxamido moieties.[31]

When no clean intermediates were isolated with Ni(II) or Co(III) salts, with Zn(II), the zinc complex of a sulfinic ester, **4a′** (or **4a″**), was isolated and characterized by MS, ^{1}H NMR, and FT-IR. Despite the absence of any crystal structure of such a metal complex in the Cambridge Crystallographic Database, we propose that in **4a′** and **4a″** the sulfinic ester is O-bonded to the zinc center. This hypothetical structure is supported by a comparison of the FT-IR data of **7a″** and **4a″**, which revealed a slight shift of the $\nu(SO_2)$ vibration to lower energy upon zinc binding. Hydrolysis of these intermediates leads to the final complex **5a**. The NMR spectra in dimethyl sulfoxide (DMSO) of salts $\mathbf{(Et_4N)_2}$**-5a**, $\mathbf{(Na)_2}$**-5a**, and $\mathbf{(K)_2}$**-5a** are identical, but their IR spectra in the solid state show different features in the 1200−900 cm^{-1} region. Only one strong vibration is seen at 1025 cm^{-1} for $\mathbf{(Et_4N)_2}$**-5a**, while two bands are observed at 1027 and 967 cm^{-1} and 1022 and 966 cm^{-1} for $\mathbf{(Na)_2}$**-5a** and $\mathbf{(K)_2}$**-5a**, respectively. IR spectroscopy has been widely used to probe the binding mode of oxidized sulfur species in metal complexes. The most common coordination modes of sulfinates are shown in Scheme 4, along with their corresponding expected $\nu(SO_2)$ vibrations.[18] While the nickel complexes **2a** and **2b** show the typical FT-IR spectra of S-coordinated sulfinate species (mode A), the IR spectrum of the zinc derivative **5a** deserves additional comments. The absence of absorption between 1100 and 1200 cm^{-1} in the spectra of $\mathbf{(Na)_2}$**-5a** and $\mathbf{(K)_2}$**-5a** suggests, in contrast to the nickel complexes, the presence of O-bonded rather than S-bonded zinc sulfinato complexes. This is also supported by the absence of S-bonded zinc sulfinato complexes in the literature, when several O-bonded derivatives have been reported and some of them characterized by X-ray crystallography.[32,33] The significant difference noticed in the IR spectra depending on the cation, and the similarity between the spectra of $\mathbf{(Na)_2}$**-5a** and $\mathbf{(K)_2}$**-5a** with those described for O,O′-bonded sulfinates, prompted us to propose for these species the structure D (drawn with K^+) in which the sulfinate is both O-bonded to Zn(II) and O′-bonded to K^+ or Na^+. Such a bis-coordination would be favored with "hard" cations such as K^+ or Na^+ but not with "soft" cations such as ammonium. In a DMSO solution, the sulfinate no longer interacts with K^+ or Na^+ but only with the zinc center and a fast interconversion of the two oxygen atoms is likely, accounting for the only two signals observed for the methyl groups by NMR.

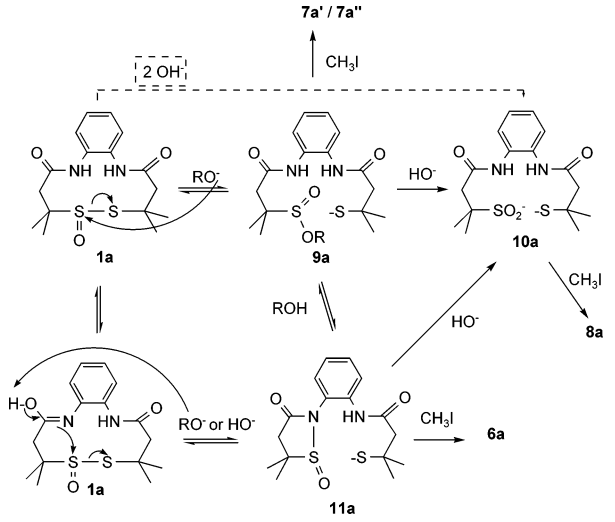
Scheme 4. Sulfinate Coordination Modes and Their Expected IR Characteristics (cm^{-1})



Isolation and characterization of the zinc intermediate species **4a′** and **4a″** led us to investigate more closely the reactivity of the starting cyclic pseudopeptidic thiosulfinate **1a** in DMF toward oxyanions. The reactivity of simple thiosulfinates toward various nucleophiles has been previously studied, and the cleavage of the S(O)−S bond has been shown to depend on the nature of the nucleophile.[34−38] With oxyanions, the nucleophilic attack has been described to occur predominantly[35] or exclusively[37] at the sulfinyl sulfur. The addition of a solution of RONa in ROH to **1a** in DMF and further reaction of the intermediate anionic species with CH_3I led to a mixture of three compounds, **6a**, **7a′** or **7a″**, and **8a**, in a ratio that is highly dependent on the reaction conditions used: the nature of the oxyanion, reaction time, and amount of water present in the solvents. Thereby, the results were not highly reproducible. The formation of the three products may be rationalized as shown in Scheme 5. Because of the presence of water in the solvents, hydroxide

(28) Hatlevik, O.; Blanksma, M. C.; Mathrubootham, V.; Arif, A. M.; Hegg, E. L. *J. Biol. Inorg. Chem.* **2004**, *9*, 238.
(29) Grapperhaus, C. A.; Maguire, M. J.; Tuntulani, T.; Darensbourg, M. Y. *Inorg. Chem.* **1997**, *36*, 1860.
(30) Hanss, J.; Krüger, H.-J. *Angew. Chem., Int. Ed.* **1998**, *37*, 360.
(31) Haas, K.; Dialer, H.; Piotrowski, H.; Schapp, J.; Beck, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 1879.
(32) Bok, T.; Yun, H.; Lee, B. Y. *Inorg. Chem.* **2006**, *45*, 4228.
(33) Brayton, D. F.; Tanabe, K.; Khiterer, M.; Kolahi, K.; Ziller, J.; Greaves, J.; Farmer, P. J. *Inorg. Chem.* **2006**, *45*, 6064.
(34) Kice, J. L.; Liu, C.-C. *J. Org. Chem.* **1977**, *44*, 1918.
(35) Kice, J. L.; Rogers, T. E. *J. Am. Chem. Soc.* **1974**, *96*, 8009.
(36) Kice, J. L.; Rogers, T. E.; Warheit, A. C. *J. Am. Chem. Soc.* **1974**, *96*, 8020.
(37) Oae, S.; Takata, T.; Kim, Y. H. *Tetrahedron Lett.* **1977**, *48*, 4219.
(38) Oae, S.; Yoshikawa, Y.; Tagaki, W. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2899.

Scheme 5. Proposed Mechanism for the Formation of the Alkylated Products **6a**, **7a′**/**7a″**, and **8a**



and alkoxide ions are both present[39] and could react either as nucleophiles (Scheme 5, top pathway) or as bases (Scheme 5, bottom pathway). Nucleophilic attack of RO^- at the sulfinyl center would lead to the sulfinic ester **9a**, which can react either with CH_3I to lead to **7a′** (**7a″**) or with HO^- to give the sulfinate **10a** and then the sulfone **8a** after alkylation. The same reaction using hydroxide as the nucleophile would directly give **10a** and **8a**. If one considers the particular structure of the thiosulfinate, the alkoxide (or hydroxide) acting as a base can deprotonate the amide (or its iminol tautomer), which can further promote by an intramolecular attack of the amidate at the sulfinyl sulfur the cleavage of the S(O)−S bond with release of the thiolate and formation of the cyclic isothiazolidin-3-one *S*-oxide derivative **11a**. Further alkylation of **11a** would lead to **6a**. Although not expected, the formation of 5-membered rings by intramolecular attack of an amide nitrogen on a reactive sulfur center is not unprecedented. Examples include the synthesis of benzisothiazolones,[40] the formation of a sulfenyl amide intermediate observed during the reversible hydrogen peroxide mediated inactivation of protein tyrosine phosphatase 1B[41−43] or the development of new derivatives of the antitumor antibiotic leinamycin by cleavage of a cyclic thiosulfinate[44] by an amide nitrogen included in a NH−C(═O)−C−C−S(═O)−S "sequence" as found in **2a**. This "sequence" would systematically be observed in thiosulfinates in proteins, and an equilibrium between a thiosulfinate and a cyclic sulfinyl amide should be taken into account.

The same competitive reactions are likely to occur with Et_4NOH in a methanol solution because of the presence of both HO^- and MeO^- in this solution,[39] explaining the formation of the intermediate species **4a′**.

In conclusion, even though the ring opening of cyclic pseudopeptidic thiosulfinates is not completely elucidated, all of the mechanisms involve at one step or another the cleavage of the S(O)−S bond by a selective attack of a nucleophile (oxyanion or amidate) at the sulfinyl center. We never observed, in the presence of an alkylating agent or not, the formation of any product arising from a nucleophilic attack at the sulfenyl sulfur. After quenching of the ring-opened species with Ni(II) or Zn(II), the final complex contains a thiolate and a sulfinate S- or O-bonded to Ni(II) or Zn(II), respectively. These results, associated with those previously reported with Co(III), highlight the general reactivity of such disulfide *S*-oxides toward metallic cations under basic conditions.

Experimental Section

Materials. CH_3CN, DMF, and MeOH were dried and distilled prior to use using standard techniques. Dried diethyl ether was purchased from Riedel-de Haën. Solid KOH and NaOH were purchased from SDS and all other products from Fluka, Aldrich, or Acros. The solution of Et_4NOH in MeOH (1.5 M) was diluted 20 times in water and titrated with HCl. The concentration measured and used in the experiments was 1.4 M. The dioxygen cylinder was purchased from Air Liquide.

Physical Measurements. ^1H NMR spectra were recorded at 300 K on a Bruker ARX-250 spectrometer, and chemical shifts are reported in ppm downfield from tetramethylsilane. IR spectra were obtained with a Perkin-Elmer Spectrum One FT-IR spectrometer equipped with a MIRacleTM single-reflection horizontal ATR unit (zirconium−selenium crystal). ESI-MS spectra were performed on a Thermo Finnigan LCD Advantage spectrometer. Fast atom bombardment and chemical ionization (CI) were recorded at the ENS-Ulm in Paris. Elemental analyses were carried out by the microanalysis service at Paris VI University or at Gif-sur-Yvette CNRS.

Synthesis. $Ni(DMF)_6(ClO_4)_2$ was prepared as published.[45] The synthesis of *N*,*N*′-1,2-phenylenebis(3-mercapto-3-methylbutanamide) was described previously;[21] the synthesis of *N*,*N*′-1,2-phenylenebis(2-mercapto-2-methylpropanamide) and oxidation of the dithiols to thiosulfinates **1a** and **1b** have been published elsewhere;[46] **$(Et_4N)_2[Ni(N_2S_2)']$ ($(Et_4N)_2$-3b)** was synthetized according to Hanss and Krüger.[30]

$(Et_4N)_2[Ni(N_2S_2)]$ ($(Et_4N)_2$-3a). In a methanolic solution (10 mL) of *N*,*N*′-1,2-phenylenebis(3-mercapto-3-methylbutanamide) (100 mg, 0.29 mmol) was added under argon 2 equiv of Et_4NOH in MeOH (0.420 mL, 0.58 mmol). A degassed methanolic solution of $NiCl_2{\cdot}6H_2O$ (70 mg in 2 mL, 0.29 mmol) was added, followed by a further 2 equiv of Et_4NOH (0.420 mL, 0.58 mmol). After the mixture was stirred for 30 min, the solvent was removed. The crude product was dissolved in acetonitrile (1 mL). Complex **$(Et_4N)_2$-3a** was precipitated in cold diethyl ether and isolated with a yield of 70% (143 mg). Anal. Calcd (found) for $C_{32}H_{60}N_4NiO_2S_2{\cdot}H_2O{\cdot}CH_3OH$: C, 56.16 (56.05); H, 9.43 (9.79); N, 7.94 (7.95). ^1H NMR (δ, CD_3CN): 7.85 (m, 2H), 6.44 (m, 2H), 3.22 (q, 16H, $^3J_{H-H} = 7.3$ Hz), 2.41 (s, 4H), 1.21 (t, 24H, $^3J_{H-H} = 7.3$ Hz), 1.11 (s, 12H).

(39) Komers, K.; Machek, J.; Stloukal, R. *Eur. J. Lipid Sci. Technol.* **2001**, *103*, 359.
(40) Siegemund, A.; Taubert, K.; Schulze, B. *Sulfur Rep.* **2002**, *23*, 279.
(41) Salmeen, A.; Andersen, J. N.; Myers, M. P.; Meng, T.-C.; Hinks, J. A.; Tonks, N. K.; Barford, D. *Nature* **2003**, *423*, 769.
(42) van Montfort, R. L. M.; Congreve, M.; Tisi, D.; Carr, R.; Jhoti, H. *Nature* **2003**, *423*, 773.
(43) Sivaramakrishnan, S.; Keerthi, K.; Gates, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 10830.
(44) Kanda, Y.; Ashizawa, T.; Kakita, S.; Takahashi, Y.; Kono, M.; Yoshida, M.; Saitoh, Y.; Okabe, M. *J. Med. Chem.* **1999**, *42*, 1330.
(45) Van Leeuwen, P. W. N. M.; Groeneveld, W. L. *Inorg. Nucl. Chem. Lett.* **1967**, *3*, 145.
(46) Bourlés, E.; Alves de Sousa, R.; Galardon, E.; Selkti, M.; Tomas, A.; Artaud, I. *Tetrahedron* **2007**, *63*, 2466.

$(Et_4N)_2[Ni(N_2SSO_2)]$ ($(Et_4N)_2$-2a). (a) From Thiosulfinate 1a. 1a (100 mg, 0.28 mmol) was dissolved in DMF (2 mL) under anaerobic conditions and cooled at −30 °C. Et_4NOH in methanol (2 equiv, 0.403 mL, 0.56 mmol) was added. After a few minutes, a degassed solution of $Ni(DMF)_6(ClO_4)_2$ in DMF (196 mg in 1 mL, 0.28 mmol) was added, followed by another 2 equiv of Et_4NOH (0.403 mL, 0.56 mmol). The solution was then allowed to reach room temperature and, after concentration, was transferred into cold diethyl ether (−40 °C) to give an orange precipitate. The complex was crystallized by liquid−liquid diffusion of an acetonitrile solution of **$(Et_4N)_2$-2a** in diethyl ether (94 mg, 50%). **(b) From Dioxygen Oxidation. $(Et_4N)_2$-3a** (50 mg, 0.076 mmol) was dissolved in acetonitrile (5 mL) and stirred in contact with dioxygen overnight. The solvent was removed and the complex purified as above. Anal. Calcd (found) for $C_{32}H_{60}N_4NiO_4S_2 \cdot 1.3H_2O$: C, 54.05 (53.95); H, 8.87 (8.86); N, 7.88 (7.94). MS (ESI^+, *m*/*z*): 816 ([**2a** + $3Et_4N^+$]$^+$, 100%). ^1H NMR (δ, CD_3CN): 7.72 (m, 2H), 6.46 (m, 2H), 3.19 (q, 16H, $^3J_{H-H}$ = 7.3 Hz), 2.47 (s, 2H), 2.27 (s, 2H), 1.25 (t, 24H, $^3J_{H-H}$ = 7.3 Hz), 1.15 (s, 6H), 1.01 (s, 6H). FT-IR (ATR, cm^{-1}): 1585, 1540, 1145, 1022.

$(Et_4N)_2[Ni(N_2SSO_2)']$ ($(Et_4N)_2$-2b). (a) From Thiosulfinate 1b. 1b (50 mg, 0.15 mmol) was dissolved in DMF (1 mL) under anaerobic conditions and cooled to −30 °C. Et_4NOH in methanol (2 equiv, 0.220 mL, 0.30 mmol) was added. After a few minutes, a degassed solution of $Ni(DMF)_6(ClO_4)_2$ in DMF (106 mg in 1 mL, 0.15 mmol) was added, followed by another 2 equiv of Et_4NOH (0.220 mL, 0.30 mmol). The solution was stirred for 1 h at −30 °C and allowed to reach room temperature. After removal of the solvent, the crude product was dissolved in acetonitrile (3 mL) and filtered off. The resulting solution was precipitated in cold diethyl ether. At this stage, the product was contaminated by residual salts, and the yield was calculated by NMR using 1,2-dichloroethane as an internal standard (yield of 52%). **(b) From Dioxygen Oxidation. $(Et_4N)_2$-3b** (47 mg, 0.075 mmol) was dissolved in acetonitrile (2 mL) and the solution was stirred under an atmosphere of dioxygen for 18 h. After removal of the solvent, the orange solid obtained was purified by exclusion chromatography (Sephadex LH-20). The first orange fraction was collected and afforded **$(Et_4N)_2$-2b** (33 mg, 67%). Crystals suitable for X-ray analysis were grown by liquid−liquid diffusion of an acetonitrile solution of **$(Et_4N)_2$-2b** (obtained from either of the two procedures) in diethyl ether. Anal. Calcd (found) for $C_{30}H_{56}N_4NiO_4S_2.1.5\ H_2O$: C, 52.48 (52.57); H, 8.66 (8.65); N, 8.16 (8.37). MS (ESI^-, *m*/*z*): 528 ([**2b** + Et_4N^+]$^-$, 39%), 427 ([**2b** + $Et_4N^+ - Et_3N$]$^-$, 100%). ^1H NMR (δ, CD_3CN): 8.60 (m, 1H), 8.52 (m, 1H), 6.62 (m, 2H), 1.31 (s, 6H), 1.27 (s, 6H). FT-IR (ATR, cm^{-1}): 1589, 1548, 1148, 1031.

$(Et_4N)_2[Zn(N_2SSO_2)]$ ($(Et_4N)_2$-5a). 1a (100 mg, 0.28 mmol) was dissolved in DMF (1.5 mL) and cooled at −40 °C under anaerobic conditions, and Et_4NOH in MeOH (2 equiv, 0.120 mL, 0.56 mmol) was added. $ZnCl_2$ (38 mg, 0.28 mmol) dissolved in the minimum amount of DMF was added under argon via a cannula followed by KOH in MeOH (1 M, 2 equiv, 0.560 mL, 0.56 mmol). After the mixture was stirred for 1 h at −40 °C and then for 3 h at room temperature, the solvents were removed under vacuum. The product was dissolved in acetone (0.5 mL) and was precipitated in cold diethyl ether (50 mL). After dissolution of the product in a minimum amount of dichloromethane and centrifugation to eliminate the salts, the pure complex was isolated after removal of the solvents (152 mg, 78%). Anal. Calcd (found) for $C_{32}H_{60}N_4O_4S_2Zn \cdot 2H_2O$: C, 52.62 (52.38); H, 8.83 (8.80); N, 7.67 (7.67). MS (ESI^-, *m*/*z*): 562 ([**5a** + Et_4N^+]$^+$, 100%). MS (ESI^+, *m*/*z*): 822 ([**5a** + 3 Et_4N^+]$^+$, 100%). ^1H NMR (δ, DMSO-d_6): 8.58 (m, 1H), 8.25 (m, 1 H), 6.52 (m, 2H), 3.21 (q, 16H, $^3J_{H-H}$ = 7.3 Hz), 2.28 (s, 2H), 2.17 (s, 2H), 1.25 (s, 6H), 1.20 (t, 24H, $^3J_{H-H}$ = 7.3 Hz), 0.91 (s, 6H). FT-IR (ATR, cm^{-1}): 1590, 1545, 1025, 791. **5a-$(K)_2$** and **5a-$(Na)_2$** were obtained following the same procedure using either KOH (1 M in MeOH) or NaOH (1 M in MeOH) as the base. The salts were eliminated by precipitation in acetone and centrifugation. ^1H NMR spectra of **$(K)_2$-5a** and **$(Na)_2$-5a** are identical with that of **$(Et_4N)_2$-5a**. **$(Na)_2$-5a.** FT-IR (ATR, cm^{-1}): 1599, 1533, 1027, 967. **$(K)_2$-5a.** MS (ESI^-, *m*/*z*): 471 ([**5a** + K^+]$^+$, 100%). IR (ATR, cm^{-1}): 1598, 1540, 1022, 966.

(K)[$Zn(N_2SS(O)OMe)$] and (Na)[$Zn(N_2SS(O)OEt)$] ((K)-4a′ and (Na)-4a″). A procedure similar to that described for the synthesis of **$(K)_2$-5a** was followed using KOH in MeOH or NaOH in EtOH, but the reaction was stopped just after the addition of the last 2 equiv of the base. The mixture in DMF was transferred dropwise via a cannula in cold diethyl ether (−50 °C). A white precipitate containing a mixture of **(K)-4a′** and **$(K)_2$-5a** or **(Na)-4a″** and **$(Na)_2$-5a** was collected. **(K)-4a′** was characterized from a 70:30 mixture of **(K)-4a′** and **$(K)_2$-5a**. MS (ESI^-, *m*/*z*): 447 ([**4a′**]$^-$, 100%). ^1H NMR (DMSO-d_6): 8.49 (m, 1H), 8.06 (m, 1H), 6.53 (m, 2H), 3.71 (s, 3H), 2.20 (s, 2H), 2.15 (m, 2H), 1.25 (s, 6H), 0.91 (s, 6H). FT-IR (ATR, cm^{-1}): 1588, 1544, 1100, 1036. **(Na)-4a″** was characterized from a 85:15 mixture of **(Na)-4a″** and **$(Na)_2$-5a**. MS (ESI^-, *m*/*z*): 461 ([**4a″**]$^-$, 100%). ^1H NMR (δ, DMSO-d_6): 8.51 (m, 1H), 8.06 (m, 1H), 6.53 (m, 2H), 4.05 (dq, 1H, $^2J_{H-H}$ = −10.7 Hz, $^3J_{H-H}$ = 6.9 Hz), 4.00 (dq, 1H, $^2J_{H-H}$ = −10.7 Hz, $^3J_{H-H}$ = 6.9 Hz), 2.64 (d, 1H, $^2J_{H-H}$ = −14.7 Hz), 2.53 (d, 1H, $^2J_{H-H}$ = −14.7 Hz), 1.36−1.15 (m, 15H); one of the CH_2 signals, probably hidden under the residual peak of the solvent, has not been assigned. FT-IR (ATR, cm^{-1}): 1594, 1537, 1104, 1017.

***N*-[2-(5,5-Dimethyl-1-oxido-3-oxoisothiazolidin-2-yl)phenyl]-3-methyl-3-(methylthio)butanamide (6a). 1a** (150 mg, 0.42 mmol) was dissolved in DMF (6 mL), and CH_3I (1.2 equiv, 0.032 mL, 0.51 mmol) was added. After the mixture was stirred at −40 °C for 15 min, NaH (1.2 equiv, 0.012 mg, 0.51 mmol) was added. After being stirred at −40 °C for 20 min, the mixture was slowly allowed to reach room temperature, and the solvent was removed. After the addition of dichloromethane (20 mL) and filtration of the salts, the crude product was purified by column chromatography [silica gel, 50:50 (v/v) CH_2Cl_2/EtOAc mixture] to give **6a** as a white powder (116 mg, 75%). Anal. Calcd (found) for $C_{17}H_{24}N_2O_3S_2$: C, 55.41 (55.53); H, 6.56 (6.29); N, 7.60 (7.31). HRMS (CI^+, CH_4, *m*/*z*). Calcd (found) for $C_{17}H_{25}N_2O_3S_2$: 369.1307 (369.1304). ^1H NMR (δ, CD_3OD): 9.14 (s, 1H), 7.95 (m, 1H), 7.48 (m, 1H), 7.35 (m, 2H), 3.17 (d, 1H, $^2J_{H-H}$ = −17.1 Hz), 2.81 (d, 1H, $^2J_{H-H}$ = −17.1 Hz), 2.59 (s, 2H), 2.11 (s, 3H), 1.56 (s, 3H), 1.54 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H). FT-IR (ATR, cm^{-1}): 1738, 1697, 1608, 1596, 1058, 988.

Methyl 2-Methyl-4-[(2-{[3-methyl-3-(methylthio)butanoyl]-amino}phenyl)amino]-4-oxobutane-2-sulfinate (7a′) and Ethyl 2-Methyl-4-[(2-{[3-methyl-3-(methylthio)butanoyl]amino}phenyl)-amino]-4-oxobutane-2-sulfinate (7a″). 6a (22 mg, 0.06 mmol) was dissolved in anhydrous methanol or ethanol (2 mL). A catalytic amount of MeONa in MeOH or EtONa in EtOH (5−10%) was added, and the mixture was stirred overnight. The solvent was finally removed, and the residue was analyzed by ^1H NMR, as a mixture of **6a** and **7a′** or **7a″**. **7a′.** ^1H NMR (δ, $CDCl_3$): 8.72 (s, 1H), 8.60 (s, 1H), 7.63 (m, 1H), 7.47 (m, 1H), 7.21 (m, 2H), 3.87 (s, 3H), 2.76 (d, 1H, $^2J_{H-H}$ = −14.9 Hz), 2.64 (s, 2H), 2.58 (d, 1H, $^2J_{H-H}$ = −14.9 Hz), 2.15 (3H, s), 1.49 (6H, s), 1.40 (s, 3H), 1.38 (s, 3H). FT-IR (ATR, cm^{-1}): 1685, 1661, 1112, 1013. **7a″.** HRMS (CI^+, CH_4, m/z). Calcd (found) for $C_{19}H_{31}N_2O_4S_2$: 415.1725 (415.1722). ^1H NMR (δ, CD_2Cl_2): 8.52 (s, 1H), 8.38 (s, 1H), 7.68 (m, 1H), 7.54 (m, 1H), 7.24 (m, 2H), 4.23 (dq, 1H, $^2J_{H-H}$ = −10.2

Hz, $^3J_{H-H}$ = 7.0 Hz), 4.16 (dq, 1H, $^2J_{H-H}$ = −10.2 Hz, $^3J_{H-H}$ = 7.0 Hz), 2.80 (d, 1H, $^2J_{H-H}$ = −14.2 Hz), 2.67 (s, 2H), 2.57 (d, 1H, $^2J_{H-H}$ = −14.2 Hz), 2.17 (3H, s), 1.49 (6H, s), 1.40 (s, 3H), 1.39 (t, 3H, $^3J_{H-H}$ = 7.0 Hz), 1.38 (s, 3H). FT-IR (ATR, cm^{-1}): 1684, 1660, 1114, 1016.

3-Methyl-*N*-(2-{[3-methyl-3-(methylthio)butanoyl]amino}-phenyl)-3-(methylsulfonyl)butanamide (8a). To a solution of **1a** (70 mg, 0.20 mmol) in DMF (4 mL) at −35 °C was added 2 equiv of a solution of KOH in ethanol (0.58 M, 0.68 mL, 0.40 mmol). After the solution was stirred for 1 h at −35 °C, CH_3I (4 equiv, 0.050 mL, 0.80 mmol) was added. Then, the solution was allowed to reach room temperature over 2 h. After removal of the volatiles, the crude product was dissolved in acetone (10 mL) and filtered off. The product was purified by column chromatography [silica gel, 50:50 (v/v) CH_2Cl_2/EtOAc mixture) to give **8a** as a white solid (40 mg, 51%). Anal. Calcd (found) for $C_{18}H_{28}N_2O_4S_2$: C, 53.97 (53.86); H, 7.05 (6.85); N, 6.99 (6.83). MS (ESI, *m*/*z*): 423 ([**8a** − Na$^+$]$^+$, 100%). ^{1}H NMR (δ, $CDCl_3$): 8.64 (s, 1H), 8.48 (s, 1H), 7.70 (m, 1H), 7.45 (m, 1H), 7.19 (m, 2H), 2.91 (s, 3H), 2.81 (s, 2H), 2.67 (s, 2H), 2.17 (s, 3H), 1.64 (s, 6H), 1.49 (s, 6H). FT-IR (ATR, cm^{-1}): 1661, 1290, 1106.

A modified protocol leads to a mixture of **6a**, **7a′**, and **8a**, as shown by ^{1}H NMR: to 30 mg of **1a** (0.085 mmol) in DMF (2 mL) at −35 °C was added a solution of KOH in methanol (1 M, 0.17 mL, 0.170 mmol). After the solution was stirred for 5 min at −35 °C, CH_3I was added (0.020 mL, 0.340 mmol), and the solution was allowed to reach room temperature over 30 min. After removal of the volatiles, the crude product was analyzed by ^{1}H NMR.

NMR Study of the Equilibrium between 6a and 7a′. 6a (10 mg, 0.0270 mmol) was dissolved in CD_3OD (0.50 mL). A catalytic amount (10%) of NaOMe in MeOH was added. The ^{1}H NMR spectra were recorded at different temperatures (300, 280, 270, 260, 240, and 230 K), and the ratio **6a**/**7a′** was determined by integration of the SMe peaks at 2.12 ppm (**6a**) and 2.16 ppm (**7a′**). The data −ln([**6a**]/[**7a′**]) = $f(1/T)$ were fitted to the equation $y = 1.8426x - 5.2305$ ($R = 0.99434$). ΔH and ΔS values were calculated using $R = 8.32$.

X-ray Data Collection and Structural Determination. Crystal data and experimental conditions are listed in Table 1. Data collection on **2a** was carried out on a Bruker Smart CCD 1K system using monochromated Mo Kα radiation (λ = 0.710 73 Å). The *SMART*[47] software package was used to acquire a total of 24 233 reflections to $2\theta_{max}$ = 54.00°. Frame data were processed using *SAINT*[48] to determine the monoclinic unit cell parameters: a = 16.833(4) Å, b = 11.800(2) Å, c = 19.114(4) Å, β = 112.60(3)°, V = 3505.1(1) Å^3, Z = 4, and d(calcd) = 1.303 Mg·m^3. The semiempirical method *SADABS*[49] was applied for absorption correction. The structure was solved by direct methods in the space group $P2_1/n$ using *SHELXS-97*[50] and refined by least-squares methods on F^2 using *SHELXL-97*.[51] Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were placed in their geometrically generated positions and allowed to ride on their parent atoms with isotropic parameters equal to 1.2 times those of the attached atoms. For all 7225 unique reflections, the final anisotropic full-matrix least-squares refinement on F^2 for 496 variables converged at R1 = 0.045 and wR2 = 0.114 with a GOF of 1.093. The anionic moiety of **2a** is a disordered mixture of two isomers corresponding to the two possible sulfur oxidation sites. The refinement yields occupancy factors of 0.79 for O1 and O2 (sulfinate group S1) and 0.21 for O5 and O6 (sulfinate group S2). The crystal structure of **2a** is completed by two molecules of Et_4N^+. One is disordered: C25, C26, C27, C28, C29, C30, C31, and C32 (and their corresponding hydrogen) are located over two sites denoted by the suffix A or B (occupancy factor 0.46/0.54).

Data collection for **2b** was performed with monochromated Mo Kα radiation (λ = 0.710 73 Å) on a Stoe IPDS detector at 120 K, with data collection and reduction using the Stoe and Cie IPDS program package.[52] A monoclinic unit cell [a = 16.190(2) Å, b = 11.345(1) Å, c = 21.092(2) Å, β = 109.83(1)°, V = 3644.4(7) Å^3, Z = 4, and d(calcd) = 1.277 Mg·m^3] yielded 32 408 total reflections to $2\theta_{max}$ = 50.00°. The structure was solved by direct methods in the space group $P2_1/n$ using *SHELXS-97*[50] and refined by least-squares methods on F^2 using *SHELXL-97*.[51] Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were calculated for idealized geometries and refined as a riding model as described above for **2a**. For all 6225 unique reflections, the final anisotropic full-matrix least-squares refinement on F^2 for 501 variables converged at R1 = 0.054 and wR2 = 0.147 with a GOF of 1.111. The drawings of the molecules were realized with the help of ORTEP III.[53] Copies of the data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information Available: Crystallographic data for **2a** and **2b** in CIF format. This material is available free of charge via the Internet at http:/pubs.acs.org.

IC062480M

(47) *SMART*, version 5.054; Bruker AXS: Madison, WI, 1998.
(48) *SAINT*, version 6.45A; Bruker AXS: Madison, WI, 2003.
(49) *SADABS 2004−1*; Bruker AXS: Madison, WI, 2004.
(50) Sheldrick, G. M. *SHELXS-97, Program for crystal structure solution*; University of Göttingen: Göttingen, Germany, 1997.
(51) Sheldrick, G. M. *SHELXS-97, Program for crystal structure refinement*; University of Gottingen: Göttingen, Germany, 1997.
(52) Stoe&Cie, *IPDS Manual (version 2.75) and XRED (revision 1.08*); Stoe & Cie: Darmstadt, Germany, 1996.
(53) Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.