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Resonance Description of *S*-Nitrosothiols: Insights into Reactivity

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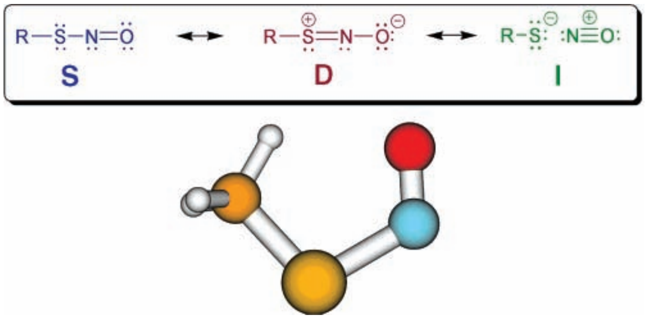
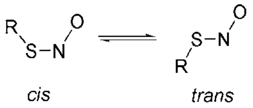
ABSTRACT



A resonance representation of the electronic structure of *S*-nitrosothiols as a combination of the conventional R–S–N═O structure, a zwitterionic structure R–S$^+$═N–O$^-$, and a RS$^-$/NO$^+$ ion pair is proposed. The resonance forms are employed to predict and rationalize the structural and conformational properties of RSNOs, their interaction with Lewis acids, and their overall chemical reactivity.

Despite the growing interest in *S*-nitrosothiols (RSNOs) because of their role in nitric oxide storage and transport in vivo,[1,2] our understanding of their chemical properties, reactivity, and electronic structure is surprisingly poor. Significantly, the nature of the S−N bond in RSNOs remains a matter of controversy.[3,4] Although this bond is relatively weak with a homolytic dissociation energy of ~30 kcal/mol, RSNOs exhibit cis−trans isomerization with an S−N rotation barrier of ≥10 kcal/mol.[2−5]



The planarity of the SNO group generally suggests double-bond character, but the S−N bonds in RSNOs are 1.75−1.8 Å,[6] while S−N double bonds are reported to be ~1.5 Å.[7] The properties of RSNOs can be dramatically altered upon interaction with metals. We have shown computationally[8] that the S−N bond is significantly weakened upon S-coordination of the SNO group to $\mathrm{Cu^I}$, consistent with the known $\mathrm{Cu^I}$-catalysis of RSNO decomposition.[9] In contrast, N-coordination was predicted to strengthen the S−N bond,[10] which was recently demonstrated experimentally.[11] On the

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basis of our current understanding of the electronic structure of RSNOs, these phenomena cannot be fully rationalized.

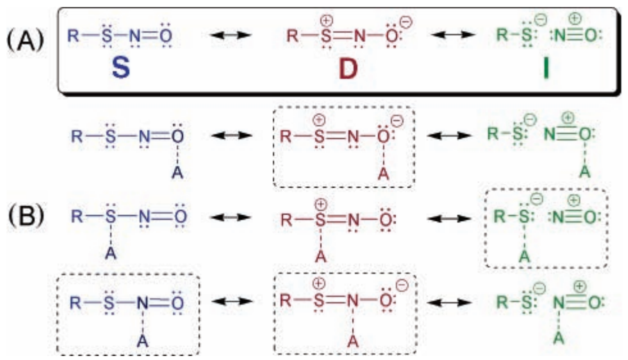

Figure 1. Resonance structures of (A) a free RSNO and (B) its complexes with a Lewis acid A such as a metal ion. Dashed rectangles mark the dominant structures. Both *cis*- and *trans*-RSNOs will exhibit the resonance structures that are shown here with no specific conformation indicated.

Here we describe the electronic structure of RSNOs as a combination of three resonance structures (Figure 1A) that can account for a number of their seemingly contradictory properties. **S** is the conventional RSNO structure with a double N−O bond and a single S−N bond. The zwitterionic structure **D** possesses a double S−N bond and a single N−O bond and would account for RSNO isomerization.[2,3,12] The novel ionic structure **I**, which represents RSNO as a RS$^-$/NO$^+$ ion pair, serves to explain the weak elongated S−N bond. Our qualitative description is further supported by a combination of PBE0/aug-pc-1 density-functional theory calculations[13−15] and natural resonance theory (NRT) analysis[16,17] for CH$_3$SNO and (CH$_3$)$_3$SNO (Table 1). Importantly, NRT analysis not only yields the same three resonance structures proposed above, it also provides an estimate of their relative contributions. **S** is dominant (70 to 80%), **D** is second in importance (~15 to 25%), and **I** makes the smallest, but non-negligible, contribution (~6 to 10%). Also, **S** contributes more to the trans versus cis isomer (Table 1). Notably, the electron distribution in **D** strengthens the S−N bond and weakens the N−O bond, whereas the opposite occurs in **I**. Thus, the electronic structure of RSNO cannot be elucidated solely from bond lengths[4] or total bond orders.

Table 1. Calculated[a] Binding Enthalpies (ΔH_{298}, kcal/mol), NRT Weights of the Resonance Structures (%) and Bond Lengths (Å) for Model RSNOs and *cis*-CH$_3$SNO Lewis Acid Complexes[b]

compound[c]	$-\Delta H_{298}$	**S**	**D**	**I**	r(S−N)	r(N−O)
cis-CH$_3$-SNO		75	15	10	1.820	1.179
trans-CH$_3$-SNO		78	13	9	1.824	1.176
cis-(CH$_3$)$_3$C-SNO		69	25	6	1.785	1.187
trans-(CH$_3$)$_3$C-SNO		79	13	8	1.809	1.182
CH$_3$-SNO(H$^+$)	181.8	31	69	0	1.593	1.291
CH$_3$-S(H$^+$)NO	185.4	49	0	51	2.301	1.108
CH$_3$-SN(H$^+$)O	181.8	60	37	3	1.679	1.192
CH$_3$-SNO(Cu$^{\mathrm{I}}$)	46.0	47	53	0	1.643	1.251
CH$_3$-S(Cu$^{\mathrm{I}}$)NO	54.4	76	4	20	2.142	1.125
CH$_3$-SN(Cu$^{\mathrm{I}}$)O	49.4	73	22	5	1.708	1.198
CH$_3$-SNO(CH$_3$NH$_3$$^+$)	18.3	57	43	0	1.676	1.229
CH$_3$-S(CH$_3$NH$_3$$^+$)NO	11.3	76	10	15	1.941	1.153
CH$_3$-SN(CH$_3$NH$_3$$^+$)O	16.4	62	34	4	1.708	1.207
[IrCl$_4$(CH$_3$CN)N(O)SCH$_3$]$^-$					1.792	1.195

[a] Calculated with PBE0/aug-pc-1. [b] Details in Supporting Information. Natural resonance theory (NRT). [c] The Lewis acids are placed in brackets after the donor atoms except in the N-coordinated Ir complex.

Natural bond orbital (NBO) analysis[16,18] reveals that **D** originates from delocalization from the p-type lone pair of sulfur to the π^*(N−O) orbital. This orbital interaction (Figure 2A) weakens the N−O bond and is responsible for the double-bond character of the S−N bond and the planarity of the SNO group. **I** originates from the even stronger interaction between the p-type lone pair of oxygen and the σ^*(S−N) orbital (Figure 2B), which significantly weakens

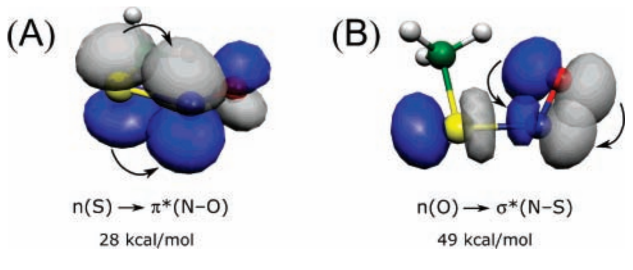

Figure 2. Main orbital interactions in RSNOs and the corresponding delocalization energies suggested by natural bond orbital (NBO) analysis.

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the S−N bond and imparts partial triple-bond character to the N−O bond. Although the n(O) → σ^*(S−N) interaction is ~2-fold stronger than the n(S) → π^*(N−O) interaction[18] (Figure 2B), **I** contributes less than **D** to the electronic structure of RSNO, since the former does not contribute to bonding between the sulfur and nitrogen atoms.

As in previously reported calculations,[4] the S−N bond lengths obtained in this work for the primary and tertiary model RSNOs (1.820 and 1.809 Å, Table 1) are overestimated, compared to the experimental X-ray data obtained for the primary *cis*-RSNO, cysteine ethyl ester hydrochloride (1.769 Å),[6] and the tertiary *trans*-RSNO, *S*-nitroso-*N*-acetylpenicillamine (1.763 Å).[3] However, the contraction of the S−N bond in tertiary versus primary RSNOs is reproduced (calculated, 0.011 Å, vs experimental, 0.007 Å).

The experimentally[3,6] and computationally (Table 1) observed shortening of the S−N bond and the higher stability of tertiary RSNOs[19] agree well with the proposed resonance description (Figure 1). As the substituent R becomes more electron-donating, **D** with its positively charged sulfur is expected to become more favored, whereas **I** with its negatively charged sulfur is expected to be less favored. Indeed, changing the methyl substituent to *tert*-butyl in *cis*-RSNO leads to a 10% increase in the contribution of **D** and a 4% decrease in the contribution of **I**, resulting in significant shortening of the S−N bond (0.035 Å, Table 1). A similar, but less pronounced, effect is seen for *trans*-RSNO.

The predictive power of the resonance description in Figure 1A becomes apparent when considering the interaction of RSNOs with a Lewis acid, A (Figure 1B). All three atoms of the SNO group have lone pairs in **S** that can be donated to A. O-coordination of RSNO to A would favor **D** with its negatively charged oxygen and disfavor **I** with its positively charged NO moiety (Figure 1B). Thus, oxygen protonation or O-coordination to a metal is expected to significantly strengthen the S−N bond by increasing its double-bond character while weakening the N−O bond. In contrast, S-coordination would favor **I** with its negatively charged sulfur, thereby weakening the S−N bond and strengthening the N−O bond. In the case of N-coordination, **I** is again expected to be disfavored, since coordination of the positively charged NO^+ moiety to A is unlikely. Decreasing the weight of **I** would shorten the S−N bond, which in turn would facilitate the n(S) → π^*(N−O) orbital interaction and increase the importance of structure **D**, thus strengthening the S−N bond.

These conclusions, based on a priori consideration of the three RSNO resonance structures in Figure 1A, are in excellent agreement with quantum-chemical calculations of CH_3SNO complexation with H^+, Cu^I, and $CH_3NH_3^+$ (Table 1). Although the binding enthalpies of the CH_3SNO(A) complexes span 11−185 kcal/mol, the qualitative effects of coordination on the CH_3SNO geometry and the relative weights of the resonance structures remain the same (Table 1). O-, S- and N-coordinated CH_3SNO(A) complexes exhibit similar binding enthalpies with a given A, but the actual order of stability varies with the nature of A.

In the three complexes, O-coordination to A results in 0% contribution of **I** to the electronic structure, in agreement with shortening of the S−N bond and lengthening of the N−O bond (Table 1). **S** remains dominant in complexes with N-coordination but the relative importance of **D** increases at the expense of both the **S** and **I** forms. The S−N bond shortens while the N−O bond elongates, but to a lesser extent than in the O-coordinated complexes (Table 1). Calculations for $[IrCl_4(CH_3CN)N(O)SCH_3]^-$, a model for the recently experimentally characterized $K[IrCl_4(CH_3CN)N(O)SCH_2Ph]$ complex,[11] reveal S−N and N−O bond length changes relative to free CH_3SNO similar to those calculated for N-coordinated $CH_3SN(Cu^I)O$ (Table 1). Consistent with the theoretical results, N-coordination of $PhCH_2SNO$ to Ir^{III} leads to a stable complex, whereas free $PhCH_2SNO$ is highly unstable.[11] Unfortunately, NRT analysis of the Ir complex is not feasible because of its large size.

Upon S-coordination, **I** becomes more dominant and its relative weight depends strongly on the nature of A (Table 1). In each case the S−N bond is significantly elongated, which agrees with our report of the enhanced ionic character of this bond in S-coordinated $RS(Cu^I)NO$ complexes.[8] Experimentally, Hg^{+2} and Ag^+ ions, which exhibit high affinity for sulfur donor atoms, catalyze NO^+ elimination,[9,20] forming the basis of the well-known Saville assay for RSNOs.[21] In contrast, cuprous salts catalyze NO release, suggesting that the nascent NO^+ may be reduced intramolecularly to NO by Cu^I.

In reactions with nucleophiles, attack at the SNO nitrogen would be promoted in **I**. Nucleophilic attack at the sulfur would be favored in **D**, where the sulfur is positively charged, but not in **S**, where the sulfur has two lone pairs (Figure 1A). The products of RSNO thiolysis (trans-S-nitrosation),[22] hydrolysis, and a number of similar reactions[23,24] support nucleophilic attack at the nitrogen atom, in agreement with the predominance over **D** of **S** + **I**, which renders the nitrogen electrophilic. Nonetheless, products (HNO and disulfide) indicative of nucleophilic attack at sulfur have been inferred or observed in the presence of high thiol concentrations,[25] and for unstable mono-S-nitrosated derivatives of adjacent dithiols.[26] Also, at high pH, OH^- may attack RSNOs at the sulfur atom.[24] Under forcing conditions, attack at the sulfur favored by the low-weight resonance structure **D** will occur more frequently, and this will be detected in the products at shorter times. O- and to a lesser extent N-

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coordination of RSNO to A (or H^+) will increase the weight of **D** and hence the electrophilicity of sulfur. This could be the basis for our recent experimental evidence suggesting that nucleophilic attack at sulfur contributes to RSNO hydrolysis at low pH.[27]

Although $CH_3NH_3^+$, a model for basic sites in proteins, binds relatively weakly to CH_3SNO, it induces changes in geometry and resonance-structure weights comparable to those induced by H^+ and Cu^I (Table 1). This underscores the control protein environments could exert over SNO stability and reactivity.

We conclude that the electronic structure of RSNOs is more completely expressed in terms of three resonance structures (Figure 1A). Supported by NRT calculations, this resonance description provides a concise, chemically intuitive representation of the complex electronic structure of RSNOs. More importantly, it can be employed to correctly rationalize and/or predict the structural and conformational properties of RSNOs,[3−5] their interactions with Lewis acids,[8,10,11] and their overall chemical reactivity.[3,23−27]

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Supporting Information Available: Computational details, structures, Cartesian coordinates, and total energies for the molecules reported in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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