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REGULAR ARTICLE

Isomerization reactions of RSNO (R=H, C_nH_{2n+1} $n \leq 4$)

Chin-Hung Lai · Elise Y. Li · Pi-Tai Chou

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Abstract We have applied various theoretical methods to gain detailed insights into the isomers as well as the transition states (TSs) along the corresponding reaction pathways for RSNO (R=H, C_nH_{2n+1} $n \leq 4$). On the basis of G2 and G2MP2 results, the relative order of stability for R=H is estimated to be *trans*-HSNO > *cis*-HSNO > HNSO > *cis*-HONS ≈ *trans*-HONS, while it is *cis*-CH_3SNO ≈ *trans*-CH_3SNO > CH_3NSO > *trans*-CH_3ONS > *cis*-CH_3ONS for R=CH_3. A similar trend is also obtained from the B3P86 method with considerably less computing effort if the nearly isoenergetic isomers *cis*-HONS and *trans*-HONS are ignored. Based on the results of B3P86, *cis*-RSNO is more stable than *trans*-RSNO when R=H is replaced by alkyl groups except for R=*t*-Bu. Natural bond orbital analyses allow us to explore whether the high reactivity of S-nitrosothiols is due to the strong negative hyperconjugation ($n_{\pi O} \leftrightarrow \sigma^*_{N-S}$). The mesomeric effect of S-nitrosothiols, although non-negligible, does not cause the breakage of N–O bond due to the compensation of columbic attraction between N and O.

Keywords RSNO · G2 · B3P86 · Negative hyperconjugation · Mesomeric effect

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1 Introduction

S-nitrosothiols (RSNOs) have attracted much attention because species containing an -SNO functional group have been found in vivo as part of the metabolism of nitric oxide (NO), [1–3] an important biological messenger. For a long time, the S-nitrosothiols have been proposed to play a key role in transporting and storing NO within the organism [1–6]. The S-nitrosothiols also exhibit many biological properties similar to those of NO, including vasodilatation of arteries, inhibition of platelet aggregation, smooth muscle cell proliferation, etc. [5,7–11]. Furthermore, the derivatives of S-nitrosothiols, with a form of S-nitrosate cysteine thiols, were found to be involved in Zn^{2+} complexation to disrupt cysteine–Zn^{2+} linkages via a transnitrosation mechanism [12–17]. Unfortunately, the S-nitrosothiols (RSNOs) readily release $NO^{\bullet}$ via thermal agitation [18], radiation [19–21], or reactions catalyzed by certain metal ions [22–33], superoxide [34,35] and seleno compounds [36]. Although the heterolytic cleavage might as well take place, the biological activity of RSNOs has been mostly attributed to the homolytic cleavage of the S–NO bond with the release of $NO^{\bullet}$ [37]. Accordingly, experimental approaches on the RSNOs are rare [38,39], and our current understanding on the physical and chemical properties of this important class of biomolecules is still unsatisfactory.

Alternatively, computational chemistry seems to offer a reasonable access to investigate the reaction pathways of RSNOs. Houk and others have performed some calculations to probe the bond dissociation energy of the N–S bond as well as the energetics of *trans–cis* conformers [40–43]. In a study of primarily photolyzing *cis*-HSNO, forming the unexpected *trans*-HONS,

Nonella et al. have performed an HF calculation in order to extract some possible isomers that can correlate with the experimental results [44]. In another approach, Javakumar and Kolandaivel [45] have applied the maximum hardness principle in an attempt to explain the relative order of stability for various isomers, including HSNO, HONS, HNOS and HOSN. In this paper, we report a comprehensive computational approach on the isomers as well as the corresponding transition states (TSs) along the reaction pathways for RSNOs (R=H, C_nH_{2n+1} $n \leq 4$). On the optimization of theoretical methods, details on structures and thermodynamics of various isomers and TSs are resolved. To the best of our knowledge, this study appears to be the first approach to discuss the corresponding R-shifted isomers regarding S-nitrosothiols.

2 Theoretical methodology

All calculations are done with the Gaussian 03 program [46]. MP2 (full) and various DFT methods are used, including LSDA (SVWN), GGA (BLYP, BP86 and BPW91), and hybrid DFT (B3LYP, B3P86 and B3PW91) methods with the basis set 6-31++G**, except for transition metal [47–53]. For transition metal (Cu^+), we use the relativistic effective core potential (RECP) LANL2 plus DZ basis set, i.e. LANL2DZ [54]. The calculated minima and transition states (TSs) have been carefully checked by frequency analysis to examine whether the number of the imaginary frequency is zero or one. To gain more accurate relative energies among various isomers, G2 and G2MP2 calculations were further performed [55]. All mentioned energetic values are corrected for zero-point vibrational energy (ZPVE). Furthermore, NBO 6.0, implemented in Gaussian 03, is used to perform the natural bond orbital (NBO) analysis [56,57].

3 Results and discussion

We would first like to discuss the optimization of theoretical methods in performing RSNO calculations. Tables S1 and S2 summarize the relative energies and isomerization barriers for *cis*-HSNO and *cis*-MeSNO on various theoretical methods. Note that the optimized structures are similar among different methods applied. If it is assumed that the approaches on higher levels, such as G2 and G2MP2, are more accurate, so that the results can be used as a criterion, the results of the DFT/B3P86 method seem to be better than that of the computationally more expensive method such as MP2 (full) (see Tables S1 and S2). For example, if both results of DFT/B3P86 and MP2 (full) refer to that of the G2 method, the MP2 (full) overemphasizes the stability of RNSO by 5.2 kcal/mol for HNSO and 4.6 kcal/mol for CH_3NSO.

On the above basis, the results and discussion hereafter will mainly rely on B3P86 with the assistance of the NBO analysis. The energetic values and structures of each isomer and TS calculated on B3P86/6-31++G** are listed in Fig. 1 and Fig. S1. Comparing our B3P86/6-31++G** results with respect to those reported by Gauld et al. [21] based on B3P86/6-31++G(3df, 3pd) (see Table S3), it is found that the calculated bond length of N–S (r (N–S)) and N–O (r (N–O)) varies only by 0.02 and 0.01 Å, respectively, while the homolytic bond dissociation energy (BDE) on average differ by as little as 1 kcal/mol for both *trans*-HSNO and *cis*-MeSNO. It is thus not necessary to use 6-311+G(2df,p) or an even larger basis set, to obtain reliable structures or other properties for the cases of RSNO with R groups at least up to C_4H_9.

Thionitrous acid (HSNO) can be viewed as the simplest S-nitrosothiol, the results of which may also provide supplementary information for its alkyl analogues such as CH_3SNO. The calculated results of HSNO, along with those obtained from previous experimental and theoretical works, are collected in Table 1. Based on the G2 results, the relative energies with respect to *cis*-HSNO are -1.1, 4.4, 4.4 and 2.7 kcal/mol for *trans*-HSNO, *cis*-HONS, *trans*-HONS, and HNSO, respectively. In comparison, a similar trend could also be found in previous reports [21,22,24,31,32], except for Bharatam's work [32], who predicted an opposite stability order between *cis*- and *trans*-HSNO. Applying the Hartree-Fock method with various basis sets, Nonella and Huber [44] predicted the relative stability to be on the order of HNSO > HOSN > HSNO > HONS, while a relative energy order of HSNO > HONS > HNOS > HOSN was estimated by Kolandaivel et al. [45] based on the HF/6-31G method. In addition, *trans*-HSNO was more stable than *cis*-HSNO by 0.6 kcal/mol. Although their results vary, depending on the basis sets applied, the prediction that HSNO is more stable than HONS is in mutual agreement and is also consistent with this study (see Table 1).

Table 2 summarizes the calculated results on CH_3SNO. For a fair comparison, data obtained from previous results are also collected in Table 2. Based on the G2 results, the relative energies with respect to *cis*-MeSNO are 0.6, 14.4, 13.7 and 4.1 kcal/mol for *trans*-MeSNO, *cis*-MeONS, *trans*-MeONS and MeNSO, respectively. This tendency is qualitatively in agreement with previous reports based on B3LYP and CBS-4M [41–43,60]. Comparing Tables 1 and 2, it can be promptly perceived

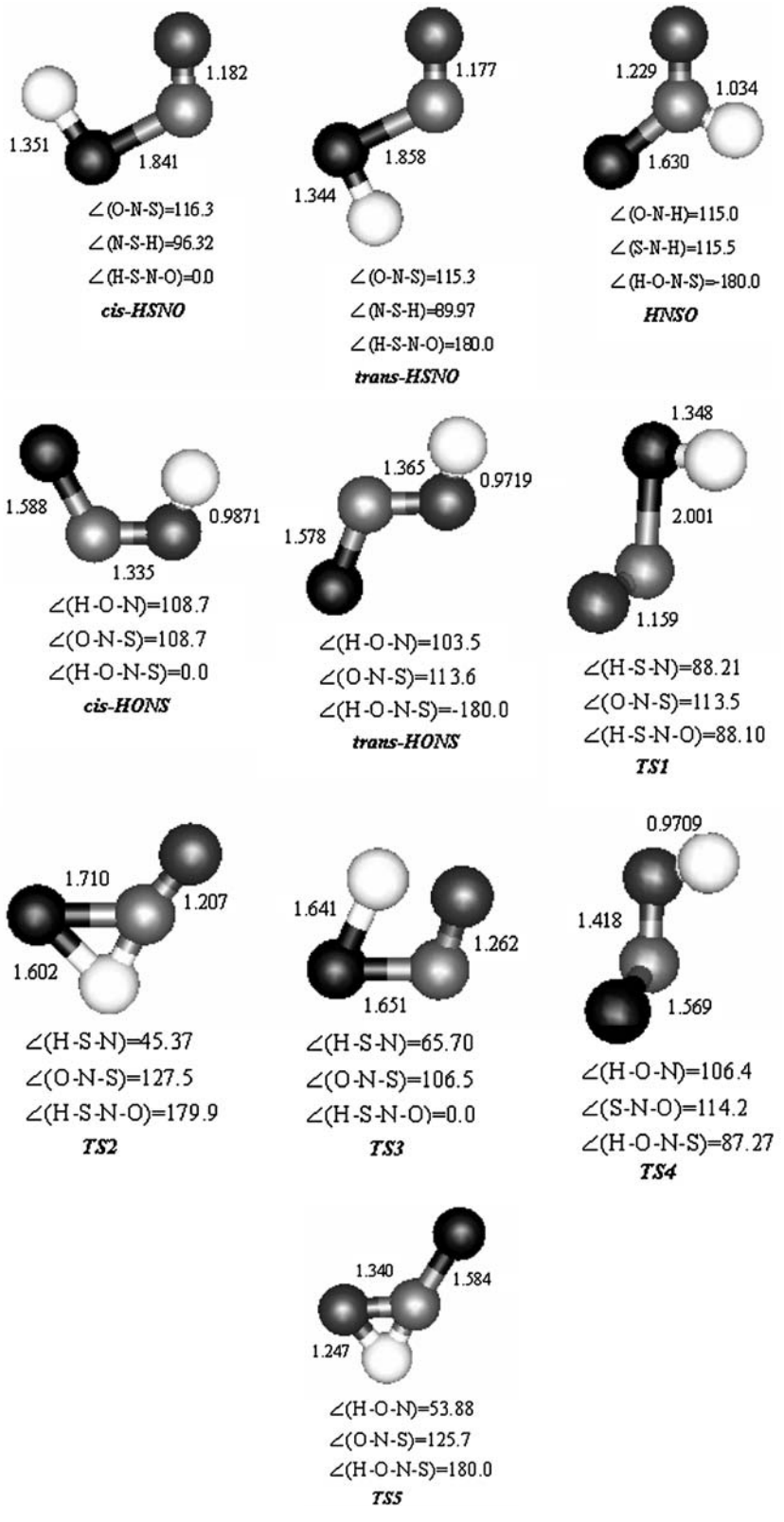


Fig. 1 Structures and relative energetics of various HSNO isomers and the corresponding transition states (H in *white*, N in *ashy*, O in *dark ashy* and S in *black colors*) calculated by B3P86/6-31++G** (energies in kcal/mol, bond lengths in Å, and angles in °)

that both relative energies of isomers and the associated reaction barriers increase as R=H is replaced by a methyl group, despite the relative stability orders being slightly different in these two cases. For R=H, the order of stability is calculated to be *trans*-HSNO > *cis*-HSNO > HNSO > *cis*-HONS ≈ *trans*-HONS, while

Table 1 The selected geometric parameters, Wiberg-type bond orders and relative energies of isomers and transition states of HSNO calculated by B3P86/6-31++G** (energies in kcal/mol, bond lengths in Å)

	r (N–S)	r (N–O)	BO (N–S)	BO (N–O)	Relative energy
cis-HSNO	1.84	1.18	1.07	1.93	0.0
	1.75[a]	1.17[a]			
trans-HSNO	1.86	1.18	1.06	1.94	−0.9
	1.76[a]	1.17[a]			−0.3[a]
	1.91[e]	1.18[e]			−0.6[b]
					−1.1[c]
					0.9[f]
cis-HONS	1.59	1.34	1.75	1.17	6.9
	1.56[a]	1.31[a]			5.3[a]
					4.8[b]
					7.0[d]
trans-HONS	1.58	1.37	1.80	1.12	6.9
	1.55[a]	1.33[a]			5.1[a]
					4.8[b]
HNSO	1.63	1.23	1.37	1.45	2.6
TS1	2.00	1.16			9.8
	1.85[a]	1.16[a]			10.4[f]
TS2	1.71	1.21			47.3
TS3	1.65	1.26			28.7
					33.5[d]
TS4	1.57	1.42			20.7
	1.54[a]	1.38[a]			
TS5	1.58	1.34			50.8

BO Bond order

[a]Based upon HF/basis (c), see ref. [44]

[b]Based upon HF/6-31G, see ref. [45]

[c]Based upon CBS-4M, see ref. [41]

[d]Based upon B3LYP/6-311G**, see ref. [56,57]

[e]Based upon UB3LYP/6-31G*, see ref. [41]

[f]Based upon B3LYP/6-31+G*, see ref. [58,59]

Table 2 The selected geometric parameters, Wiberg-type bond orders and relative energies of isomers and transition states of MeSNO calculated by B3P86/6-31++G** (energies in kcal/mol, bond lengths in Å)

	r (N–S)	r (N–O)	BO (N–S)	BO (N–O)	Relative energy
cis-MeSNO	1.82	1.19	1.10	1.86	0.0
	1.87[b]	1.19[b]			
	1.86[d]	1.18[d]			
trans-MeSNO	1.82	1.19	1.09	1.89	1.0
	1.86[d]	1.17[d]			0.5[a]
					1.0[c]
					0.8[e]
cis-MeONS	1.60	1.34	1.73	1.17	17.5
trans-MeONS	1.58	1.35	1.77	1.13	16.9
MeNSO	1.64	1.23	1.30	1.49	5.3
TS1	1.96	1.17			14.7
					13.2[c]
TS2	1.71	1.21			67.8
TS3	1.61	1.23			53.4
TS4	1.57	1.41			31.2
TS5	1.60	1.30			76.5

[a]Based upon CBS-4M, see ref. [41]

[b]Based upon UB3LYP/6-31G*, see ref. [41]

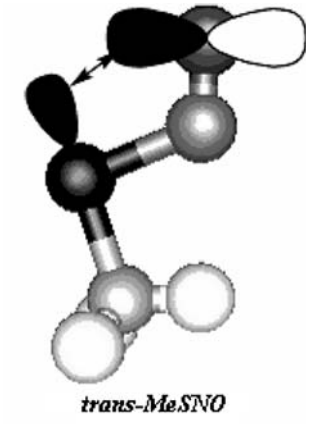
[c]Based upon B3LYP/6-31+G*, see ref. [58,59]

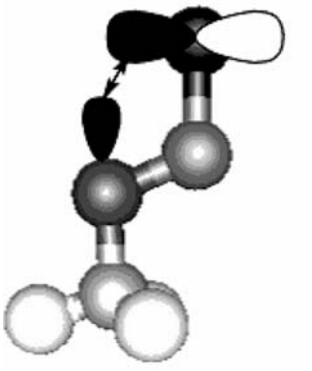
[d]Based upon B3LYP/6-311+G*, see ref. [42,43]

[e]Δ Grel in ref. [42,43]

it is *cis*- $CH_3SNO \approx$ *trans*- $CH_3SNO > CH_3NSO >$ *trans*- $CH_3ONS >$ *cis*- CH_3ONS for R=CH_3. This result might be due to the fact that both N–S and N–O bonds possess a double bond character in NOS, whereas the strength of π_{N-S} is weaker than that of π_{N-O}. As a result, substituents R (R=H, Methyl) prefer to attach to the N–S bond, especially on the S center. For R=H, there might exist another important factor to influence the relative order, namely the strength of hydrogen bonding from e.g. O–H. . . .S, O–H. . .N, etc. Our results indicate that the RSNO appears to be the most stable form among its isomers, regardless of the *trans* or *cis* form. Table 3 lists the results obtained from B3P86/6-31++G**, so that a fair comparison can be made of the relative energies between *cis*- and *trans*-RSNO, in which R=ethyl, n-propyl and iso-propyl, n-butyl, iso-butyl and tert-butyl. In all cases (R=H ∼ *t*-C_4H_9), r (N–S) in *trans*-RSNO is longer than that in *cis*-RSNO, whereas the r (N–O) in *trans*-RONS is longer than that in *cis*-RONS. These tendencies could be qualitatively rationalized by the repulsion of lone pair electrons between sulfur and oxygen in *trans*-RSNO as well as in *trans*-RONS (see Scheme 1, *trans*-MeSNO and *trans*-MeONS were taken as examples). Furthermore, as shown in Table 3, except for R= *t*-Bu, the *cis* form is more stable than the *trans* form when R=H is replaced by alkyl groups. The anomalous tendency for R=*t*-Bu could be attributed to the significant steric hindrance between *tert*-butyl and oxygen atom in the *cis* form.

As supported by Table 3, the quantity of the relative energy is around 0.6 kcal/mol for primary S-nitrosothiols (R=Et, *n*-Pr, *n*-Bu), and 1.2 kcal/mol for the tertiary one (R=*t*-Bu), while it is wider for secondary ones, being 0.2 kcal/mol for *i*-PrSNO and 0.6 kcal/mol for *i*-BuSNO. Furthermore, the rotational barriers of *cis*-EtSNO, *cis*-*i*-PrSNO and *trans*-*t*-BuSNO have been calculated by B3P86/6-31++G**, and the results are summarized in Table 4. Note that these three reactions are all endothermic. Interestingly, independent of the quantity of endothermicity, the rotational barriers are close in these three reactions, being calculated to be 14.4, 13.7, 13.2 kcal/mol for *cis*-EtSNO, *cis*-*i*-PrSNO and *trans*-*t*-BuSNO, respectively. Based on the method developed by Wiberg [33] the bond orders for some critical bonds are listed in Table 2. The bond order for N–S





Scheme 1 Simple illustration of the repulsion in *tran*-RONS and *trans*-RSNO, respectively (H in *white*, C in *light ashy*, N in *ashy*, O in dark ashy and S in black colors)

Table 3 The relative energies and bond lengths of *cis*- and *trans*-RSNO for R=Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu (energies in kcal/mol, bond lengths in Å)

R=		r (N–S)	r (N–O)	Relative energy
Et	*cis*	1.81[a]	1.19[a]	0.0
		1.86[b]	1.18[b]	
	trans	1.82[a]	1.19[a]	0.5[a]
		1.86[b]	1.18[b]	0.5[c]
n-Pr	*cis*	1.81[a]	1.19[a]	0.0
	trans	1.82[a]	1.19[a]	0.6[a]
i-Pr	*cis*	1.81[a]	1.19[a]	0.0
	trans	1.82[a]	1.19[a]	0.2[a]
				0.1[c]
n-Bu	*cis*	1.81[a]	1.19[a]	0.0
	trans	1.82[a]	1.19[a]	0.6[a]
i-Bu	*cis*	1.81[a]	1.19[a]	0.0
	trans	1.82[a]	1.19[a]	0.6[a]
t-Bu	*cis*	1.78[a]	1.20[a]	0.0
		1.82[b]	1.19[b]	
	trans	1.80[a]	1.19[a]	−1.2[a]
		1.84[b]	1.18[b]	−1.2[c]

[a]Based upon B3P86/6-31++G**

[b]Based upon B3LYP/6-311+G*, see ref. [42,43]

[c]Δ Grel in ref. [42,43]

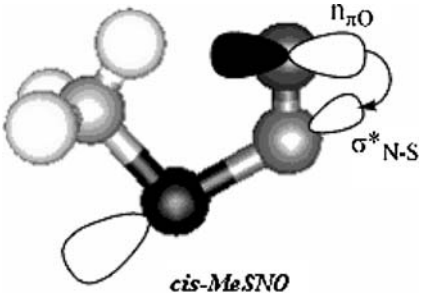
is calculated to be 1.09 and 1.10 for *trans*-MeSNO and *cis*-MeSNO, respectively, the result of which agrees with the conclusion (single bond character) made by Gauld and co-workers [40]. Furthermore, the calculated N–S bond orders (BO (N–S)) are 1.73 and 1.77 for *cis*-MeONS and *trans*-MeONS, respectively. The BO (N–O) is 1.86 and 1.89 for *cis*-MeSNO and *trans*-MeSNO, respectively. The results lead us to conclude that both N–S in MeONS and N–O in MeSNO possess double bond characters. These are in consistence with that of the previous reports [40,41]. Note that a similar double bond character is found by HSNO isomers. For example, BO (N–S) is calculated to be 1.80 and 1.75 for *trans*- and *cis*-HONS. Likewise, the bond order of N–O (BO (N–O)) for *trans*- and *cis*-HSNO is estimated to be 1.94 and 1.93.

As for the transition state (TS), as shown in Fig. 1 and Table 4, r (N–S) is lengthened and r (N–O) is shortened among *cis* and *trans* forms analogues in all TS1, the structures of which are depicted in Fig. S1. The energy difference between *cis* and *trans* conformers, i.e. |E(*trans*)–E(*cis*)|, was ∼0.6 kcal/mol for 1° S-nitrosothiols and 1.2 kcal/mol for 3° S-nitrosothiol (*t*-BuSNO). Moreover, the rotational barrier is calculated to be 14.4 and 13.9 kcal/mol for *cis*-EtSNO and *trans*-EtSNO, respectively. Thus, *trans*- and *cis*- forms of primary S-nitrosothiols should interconvert quickly and reversibly at ambient temperature. Conversely, the rotational barrier is 13.2 and 12 kcal/mol for *trans*-*t*-BuSNO and *cis*-*t*-BuSNO, respectively. From both thermodynamic and kinetic viewpoints, 3° S-nitrosothiols is less prone to undergo *trans* $\Longleftrightarrow$ *cis* isomerization reaction. According to the above comparison, the relative stability order is 3° S-nitrosothiols > 1° S-nitrosothiols. This viewpoint is in agreement with two experimental evidences. Firstly, it has been reported that primary S-nitrosothiols are typically unstable and could be characterized only by transient spectroscopy [62,63], whereas tertiary ones have been successfully isolated and have indefinite stability [64,65]. Secondly, 1° S-nitrosothiols typically produce shorter-lived biological effects than 3° [66]. The results of relative energetics based on B3P86/6-31++G** are very close to those obtained by Houk et al. based on the B3LYP/6-311+G* method [42,43].

In yet another approach, Bharatam has proposed that the high reactivities of S-nitrosothiols are due to a negative hyperconjugation, i.e. $n_{\pi O} \Longleftrightarrow \sigma^*_{N-S}$ (see Scheme 2, *cis*-MeSNO taken as example) [60,67], and has accordingly proven this viewpoint by calculating $CH_3SN{=}X$ (X=O, NH, CH_2) systematically. Their results showed that upon the replacement of O with

Table 4 Comparison of the structures and energies of *cis*-, *trans*- and TS of RNSO for R = Et, *i*-Pr, *t*-Bu calculated by B3P86/6-31++G** (energies in kcal/mol, bond lengths in Å and angles in °)

R		r (N–S)	r (N–O)	r (S–C)	∠ (C–S–N)	∠ (S–N–O)	∠ (C–S–N–O)	Energy
Et	*cis*	1.81	1.19	1.81	102.5	117.1	−0.70	0.0
	trans	1.82	1.19	1.82	94.75	116.4	178.68	0.5
	TS	1.96	1.17	1.83	94.00	113.2	88.55	14.4
i-Pr	*cis*	1.81	1.19	1.82	103.2	117.5	−0.11	0.0
	trans	1.82	1.19	1.83	95.03	116.4	−179.99	0.2
	TS	1.95	1.17	1.85	93.42	114.1	83.85	13.7
t-Bu	*cis*	1.78	1.20	1.86	109.1	118.9	−0.19	0.0
	trans	1.80	1.19	1.86	97.31	115.7	−179.97	−1.2
	TS	1.94	1.17	1.87	98.10	113.8	84.27	12.0



Scheme 2 The illustration of negative hyperconjugation in S-nitrosothiols (H in *white*, C in *light ashy*, N in *ashy*, O in *dark ashy* and S in black colors)

NH and CH_2 step by step, the number of lone pair electrons decrease along with an increase of the BDE of the N–S bond, hence the decrease in r (N–S). By NBO analysis, we also find this orbital interaction in either *cis*-RSNO and *trans*-RSNO (R=H, Me). For example, the $E^{(2)}$ values regarding this interaction are 44.0 and 42.8 kcal/mol for *trans*-MeSNO and *cis*-MeSNO, respectively. On comparing HF and B3P86 [44] as shown in Table 1, it could be promptly found that electron correlation is necessary to describe the negative hyperconjugation interaction. Otherwise, a shorter r (N–S) would be gained. Note that if the bond length correlates well with BDE, a higher BDE for N–S bond is predicted without electron correlation.

From the NBO analysis, it appears that there exists another strong orbital interaction between $n_{\pi S}$ and π^*_{N-O}, namely the mesomeric effect [69] and $E^{(2)}$ values regarding this interaction are calculated to be 25.5 and 32.3 kcal/mol for *cis*-HSNO and *cis*-MeSNO, respectively. Bharatam et al. [60] also noted this interaction but without discussing whether this effect facilitate or inhibit the negative hyperconjugation [67]. To clarify this, we calculate the energetics and N–S bond length of the complexes formed by *cis*-HSNO and Lewis acid, BH_3, at O and S sites, namely the O complex and S complex (see Table 5). Doctorovich and coworkers synthesized and

Table 5 The comparison of O complex and S complex by BH_3 or Cu^+ of *cis*-HSNO (energies in kcal/mol, bond lengths in Å)

	BDE[a]	r (N–S) [b]	Complexation energy[c]
BH_3			
O complex	38.4	1.70	−8.0
S complex	13.6	1.98	−10.4
N complex	35.4	1.76	−22.0
Cu^+			
O complex	50.2	1.66	−33.9
S complex	30.9	2.22	−42.2
N complex	42.2	1.721.71[d]	−35.6

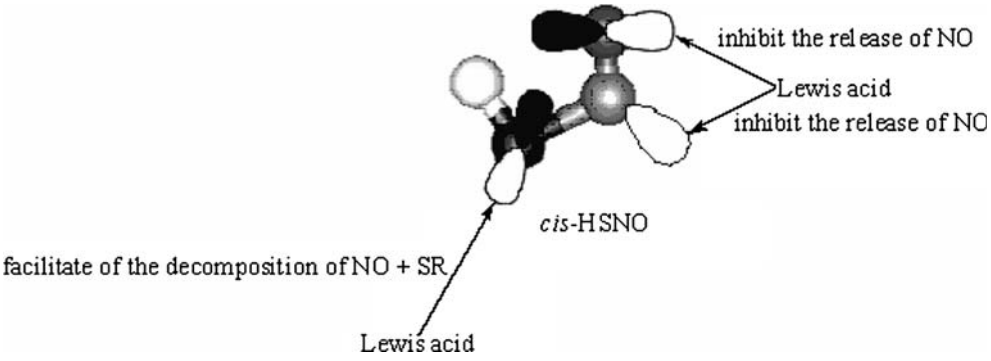
[a]Original BDE of N–S = 30.6 kcal/mol

[b]Original r (N–S) = 1.84 Å

[c]Complexation energy = E (O, S complex, or N-complex)- E (*cis*-HSNO)- E (BH_3 or Cu^+)

[d]Based upon B3P86/6-311+G(2df,p), see ref. [31]

calculated a stable Ir–PhSNO complex [70]. According to their reported X-ray crystal structure and theoretical result, they found that the Ir center was coordinated by the N atom. They proposed that this stabilization was probably due to the electrophilicity of the Ir center, as shown by their DFT calculations. Likewise, we also consider this condition, namely N complex. As revealed in Table 5, the formation of O and N complex stabilizes *cis*-HSNO and shortens the N–S bond, whereas the formation of S complex lengthens the N–S bond as well as lowers the BDE of the N–S bond. This result can be rationalized by the basicity of N atom and the rivaling between the negative hyperconjugation effect and the mesomeric effect depicted in Scheme 3. Note that the O-atom and S-atom induce a negative hyperconjugation (destabilization) and mesomeric (stabilization) effects, respectively, to RSNO. The addition of BH_3 to the O-site, in part, removes the negative hyperconjugation, resulting in the stabilization of the O complex. Conversely, mesomeric effect is ridden by accommodating the S-atom lone pair electron (via the Lewis acid BH_3) destabilizes the S complex. Note that although the



Scheme 3 The possible site of RSNO attacked by Lewis acid (H in *white*, C in *light ashy*, N in *ashy*, O in *dark ashy* and S in *black* colors)

mesomeric effect obviously weakens π_{N-O}, there exists a columbic attraction between N and O in the form of N^+-O^-. The mutual compensation does not cause the breakage of N–O bond in S-nitrosothiols. On the contrary, the electronegativities of N and S are close to each other, so that one would expect their columbic interaction to be weaker than that of N and O. Once the N–S bond is weakened, decomposition takes place spontaneously.

We believe that a similar mechanism is also applicable to other Lewis acids. For example, if ions, such as Cu^+ or Fe^{2+}, acting as a Lewis acid, attack the S site (see Scheme 3), the net result should cause the destabilization of S-nitrosothiols and consequently accelerate the release of NO. To prove this, we chose Cu^+ ion as an instance. The results are also listed in Table 5. According to our results, we find Cu^+ has similar effect as BH_3. This gives an explanation why some ions could catalyze the decomposition of S-nitrosothiols on attaching RSNOs [22–33]. However, an intriguing thought then comes up to be what if the Lewis acid attacks the O-site, the net effect should increase the BDE of the N–S bond and consequently inhibit the NO formation.

4 Conclusion

In conclusion, we have carefully investigated the energetic minima and TSs on isomeric potential energy surfaces of S-nitrosothiols (RSNOs). Based on the results of B3P86, *cis*-RSNO is more stable than *trans*-RSNO when R = H is replaced by alkyl groups (C_nH_{2n+1} $n \leq 4$) except for R = *t*-Bu. Considering relative computational resources and accuracy, B3P86 turns out to be the most suitable method to describe the relative thermodynamics as well as the isomerization process among various theoretical methods used. We could thus summarize our results as follows:

1. The energy of TS1 of the studied S-nitrosothiols is independent of the endothermicity of the reaction.
2. The order of stability is concluded to be 3° > 1° S-nitrosothiols from both thermodynamic and kinetic viewpoints.
3. The S-nitrosothiols are possibly unstable due to the negative hyperconjugation ($n_{\pi O} \iff \sigma*_{N-S}$) effect that strongly weakens the σ_{N-S} bond [58,59,67]. Accordingly, a plausible mechanism as for the role played by the metal ions in stabilizing or destabilizing the RSNOs is proposed and depicted in Scheme 3.

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