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Negative hyperconjugative interactions in *S*-nitrosothiols: a theoretical study

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Abstract—The S–N interactions are very weak in *S*-nitrosothiols because the $n_O \rightarrow \sigma^*_{S-N}$ negative hyperconjugative interaction weakens the σ bond, though the pπ–pπ interactions are reasonably strong. © 2002 Published by Elsevier Science Ltd.

S-Nitrosothiols are molecules of biological and medicinal interest, which show vasodilation of veins and arteries and inhibition of platelet aggregation, through the release of nitric oxide (NO).[1,2] S–NO bonds are very weak, with an average bond dissociation energy of ~20–28 kcal/mol.[3] The weakness of S–N bonds in *S*-nitrosothiols is clearly evident from their high reactivity.[1,2] The weakness in the S–N bond is also evident from the long S–N bond lengths in *S*-nitrosothiols (1.76–1.79 Å[4] in *S*-nitrosoacetyl-D,L-penicillamine (SNAP) and 1.792 Å in Ph_3CSNO) in comparison to the standard S–N single bond length (~1.70 Å) of sulfenamides[5] RS-NR′$_2$. Even though the S–N interaction is weak, *S*-nitrosothiols show *cis–trans* isomerisation, indicating a strong S–N π bond.[4,6,7] In fact the calculated S–N rotational barrier is of the order of 11–13 kcal/mol.[4b,c] The observation of large rotational barriers in systems with elongated S–N bonds and small S–N bond dissociation energies is very surprising. An ab initio study, reported below, indicates that the weakness of the S–N bond is in its σ bond, due to the $n_O \rightarrow \sigma^*_{S-N}$ second order delocalisation.

Ab initio MO[8] calculations on HSNO (**1**), MeSNO (**2**), PhSNO (**3**), FSNO (**4**) and ClSNO (**5**) indicate that the S–N bond lengths are 1.796, 1.760, 1.891, 1.680 and 1.819 Å, respectively at MP2/6-31+G* level (Fig. 1). The calculated S–N bond lengths in **1**–**5** are much

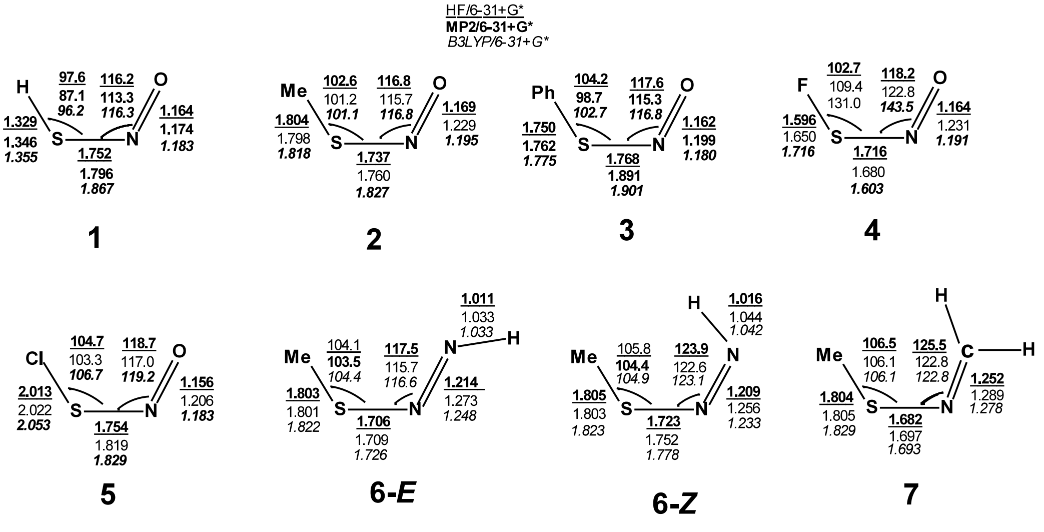

Figure 1. Important geometric parameters (distances in Å and angles in °) for the *cis* isomers of *S*-nitrosothiols **1**–**7**.

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longer than the S–N bond length in sulfenamides. For example, the S–N bond lengths in (*s-cis*)HSNO (1.796 Å) and (*s-cis*)MeSNO (1.760 Å) are longer than the corresponding (*syn*) sulfenamides, $HSNH_2$ (1.715 Å) and $MeSNH_2$ (1.709 Å), respectively at MP2/6-31+G* level. In **2** (*s-cis*), the S–N bond length is 1.760 at MP2/6-31+G* level, comparable to the experimental reports,[4] but it is 1.827 Å at B3LYP/6-31+G* level. At the B3LYP level the S–N bond lengths for **1**–**5** are slightly overestimated. The S–N rotational barriers in **1**–**5** are 8.53, 11.70, 8.26, 12.52 and 10.89 kcal/mol at MP2/6-31+G* level (Table 1). The calculated S–N rotational barriers are high relative to the S–N single bond rotational barrier in sulfenamides. For example, the S–N rotational barriers in (*s-cis*)HSNO (8.53 kcal/mol) and (*s-cis*)MeSNO (11.70 kcal/mol) are higher than the rotational barriers in (*syn*) $HSNH_2$ (7.63 kcal/mol) and (*syn*) $MeSNH_2$ (10.44 kcal/mol).

Table 1. *cis–trans* Isomerisation energies (ΔE), S–N rotational barriers and bond dissociation energies in **1**–**5** (*cis*) at various levels, all values are in kcal/mol[a]

Molecule	MP2/6-31+G*	B3LYP/6-31+G*
HSNO (1)		
ΔE (*cis–trans*)	0.63	0.88
S–N rotational barrier	8.53	10.39
RSNO BDE	24.16	29.06
MeSNO (2)		
ΔE (*cis–trans*)	1.40	0.99
S–N rotational barrier	11.70	13.17
RSNO BDE	28.07	31.38
PhSNO (3)		
ΔE (*cis–trans*)	1.07	0.40
S–N rotational barrier	8.26	10.31
RSNO BDE	25.21	21.12
FSNO (4)		
ΔE (*cis–trans*)	2.43	4.46
S–N rotational barrier	12.52	16.77
RSNO BDE	24.40	31.32
ClSNO (5)		
ΔE (*cis–trans*)	3.21	2.00
S–N rotational barrier	10.89	12.09
RSNO BDE	24.72	25.83

[a] All the values are ZPE corrected.

Table 2. Second order delocalisation energies ($E^{(2)}$) in **1**–**5** (*cis*) at various levels, all values are in kcal/mol

Molecule	HF/6-31+G*	MP2/6-31+G*	B3LYP/6-31+G*
HSNO (1)			
$n_O \to \sigma^*_{S-N}$	39.51	33.46	48.07
$n_S \to \pi^*_{N=O}$	34.34	31.68	23.54
MeSNO (2)			
$n_O \to \sigma^*_{S-N}$	36.96	29.04	41.59
$n_S \to \pi^*_{N=O}$	41.65	42.86	29.60
PhSNO (3)			
$n_O \to \sigma^*_{S-N}$	45.06	48.15	54.40
$n_S \to \pi^*_{N=O}$	35.73	24.03	23.64
FSNO (4)			
$n_O \to \sigma^*_{S-N}$	40.14	28.41	37.72
$n_S \to \pi^*_{N=O}$	43.80	60.23	46.87
ClSNO (5)			
$n_O \to \sigma^*_{S-N}$	47.04	41.90	49.67
$n_S \to \pi^*_{N=O}$	35.34	29.75	26.14

Natural bond orbital[9] (NBO) analysis shows that there is a strong negative hyperconjugative interaction $n_O \to \sigma^*_{S-N}$ in **1**–**5** (Table 2). For example, the second order energy ($E^{(2)}$) for this interaction in **2** is 29.04 kcal/mol at MP2 level. This interaction weakens the S–N sigma bond and elongates the S–N bond length in *S*-nitrosothiols. **1**–**5** are also characterised by strong $n_S \to \pi^*_{N-O}$ delocalisation, which induces partial π character and is responsible for the S–N bond rotational barriers. For example, the energy ($E^{(2)}$) due to this delocalisation in **2** is 42.86 kcal/mol at MP2/6-31+G* level. This is confirmed by the observation that in the rotational transition state (**2-rts**) the $n_S \to \pi^*_{N-O}$ interaction disappears and the S–N bond length is elongated by 0.206 Å with respect to **2**(*s-cis*). The S–N bond orders calculated using the Atoms in Molecules[10] (AIM) method for **2**(*s-cis*), **2**(*s-trans*), and **2-rts** respectively are 1.235, 1.205, 1.084, clearly supporting the above arguments. The above analysis indicates that the weakness in the S–N sigma bond is due to $n_O \to \sigma^*_{S-N}$ delocalisation and is responsible for the longer S–N bond lengths in *S*-nitrosothiols, though there is a partial double bond and character between S and N.

The S–N bond dissociation energies calculated at MP2/6-31+G* level for **1**–**5** are 24.16, 28.07, 25.21, 24.40, and 24.72 kcal/mol, respectively. These values are very small compared to a simple C–C single bond dissociation energy (~70 kcal/mol) suggesting the weakness of the S–N bond. This can be attributed to the $n_O \to \sigma^*_{S-N}$ interaction, which weaken the S–N bond. The difference (ΔE_{bond}) between the S–N bond dissociation energy and the S–N rotational barrier may be considered as the strength of the σ bond in **1**–**5**, which is 15.63, 16.37, 16.96, 11.88, 13.83 kcal/mol, respectively at MP2/6-31+G* level. This weakness in the σ bond strength facilitates the release of NO from *S*-nitrosothiols. These results compliment the observations made by Bartberger et al., who reported small S–NO dissociation energies.[11]

To confirm that the negative hyperconjugation is indeed responsible for the S–N bond weakening, calculations have been carried out on isoelectronic *s-cis* isomers of CH_3SNX (X=O: **2**, X=NH: **6** and X=CH_2: **7**). The bond dissociation energies for **2**, **6-*Z***, **6-*E*** and **7** at MP2/6-31+G* level are 28.07, 33.89, 40.52,

Table 3. S–N bond dissociation energies and the energy due to second order delocalisations (in kcal/mol) in the *s-cis* isomers of **2**, **6-*Z*** **6-*E*** and **7** at MP2/6-31+G* level

Parameters	MeSNO **2**	MeSN=NH **6-*Z***	MeSN=NH **6-*E***	$MeSN{=}CH_2$ **7**
BDE	28.07	33.89	40.52	55.13
$n_X \to \sigma^*_{S-N}$	29.04	19.82	1.00	–

Table 4. Variation in S–N bond lengths (in Å), S–N bond dissociation energies (in kcal/mol) and second order delocalisation (in kcal/mol) in **1**–**5** in solvent (water) with respect to that in gas phase at B3LYP/6-31+G* level

Molecule	**1**	**2**	**3**	**4**	**5**
Decrease in S–N bond length	0.03	0.04	0.07	0.01	0.04
Decrease in $E^{(2)}$ of $n_O \rightarrow \sigma^*_{S-N}$ delocalisation	4.24	6.42	6.22	0.22	6.04
Increase in BDE	0.24	0.60	0.50	0.08	1.47

and 55.13 kcal/mol, respectively. The negative hyperconjugative interactions due to the lone pair on X are 29.04, 19.82, 1.00 and negligible, respectively (Table 3). The gradual increase in the S–N bond dissociation energies with a decrease in the negative hyperconjugative interactions clearly suggests that there is a direct correlation between negative hyperconjugation and bond dissociation energy in these systems and show the importance of this interaction in *S*-nitrosothiols. The decrease in the S–N bond length at MP2/6-31+G* level in the order **2** (1.760 Å)>**6-*Z*** (1.752 Å)>**6-*E*** (1.709 Å)>**7** (1.697 Å) also supports this observation. Under the polar solvent conditions, the negative hyperconjugation is expected to decrease, which is found to be true for **1**–**5** in water medium according to SCRF calculations (Table 4).[12] The decrease in the S–N bond lengths, increase in the S–N bond dissociation energies for **1**–**5** (in water solvent) correlate well with the decrease in the negative hyperconjugative interactions (Table 4), supporting the importance of these interactions in *S*-nitrosothiols.

The above study shows that negative hyperconjugative interactions play an important role in weakening the S–N σ bond in *S*-nitrosothiols, and are responsible for most of the chemistry of these systems.

Acknowledgements

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