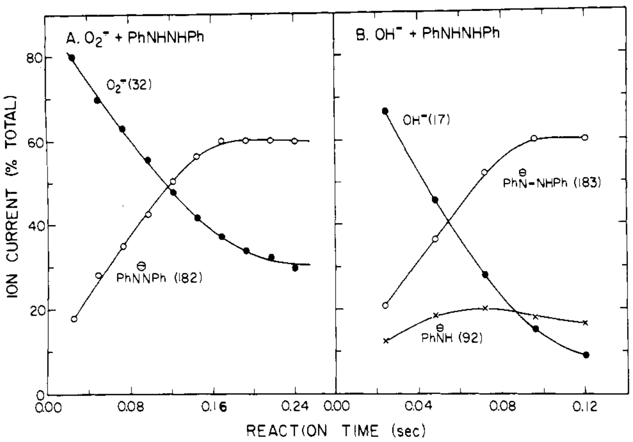

Figure 4. Time-resolved mass spectral intensities for the anions that result from the gas-phase reaction of 1,2-diphenylhydrazine with (A) $O_2^-\cdot$ and (B) ^-OH.

radicals of phenazine (Phen$^-\cdot$) and 3-methyllumiflvanin (3-MeFl$^-\cdot$). These must in turn react with O_2 to give $O_2^-\cdot$ plus phenazine and 3-methyllumiflavin, respectively; the process is analogous to that for the anion radical of azobenzene (PhN$^-\cdot$NPh, eq 3). The oxidation potentials ($E_{p,a}$) for PhN$^-\cdot$NPh (Figure 1), Phen$^-\cdot$,[13] and 3-MeFl$^-\cdot$[13] in Me_2SO are −1.3 V vs. SCE, −1.1 V, and −0.8 V, respectively. Each value is sufficiently negative to reduce O_2 to $O_2^-\cdot$ (−0.7 V vs. SCE in Me_2SO).[18] Hence, the $O_2^-\cdot$-induced autoxidation of PhNHNHPh (eq 4) also is thermodynamically feasible for dihydrophenazine and dihydro-3-methyllumiflavin. The previous results[1] confirm that the sequence of eq 1 and 3 does occur for these two model substrates of reduced flavoproteins. Such an autoxidation reaction sequence may be relevant to the fractional yield of $O_2^-\cdot$ from the flavin-mediated activation of O_2[21] and the autoxidation of xanthine (catalyzed by xanthine oxidase (X.O.), a flavoprotein).[22]

$$\mathrm{Fl} + \mathrm{H_2Sub} \xrightarrow{\mathrm{X.O}} \mathrm{H_2Fl} + \mathrm{Sub} \tag{12}$$

$$\mathrm{H_2Fl} + \mathrm{Fl} \overset{\mathrm{OH^-}}{\rightleftharpoons} 2\mathrm{Fl}^-\cdot + 2\mathrm{H_2O} \tag{13}$$

$$\mathrm{Fl}^-\cdot + \mathrm{O_2} \rightarrow \mathrm{Fl} + \mathrm{O_2}^-\cdot \tag{14}$$

$$\mathrm{H_2Fl} + \mathrm{O_2}^-\cdot \rightarrow \mathrm{Fl}^-\cdot + \mathrm{H_2O_2} \tag{15}$$

Perhaps the most significant aspect of the superoxide-, hydroxide-, or electron-induced autoxidation of donor molecules (1,2-diphenylhydrazine, dihydrophenazine, dihydro-3-methyllumiflavin, and reduced flavoproteins) is the activation of dioxygen to hydrogen peroxide in biological matrices. Thus, within the normal cytochrome P-450 metabolic cycle, either hydroxide ion or an electron-transfer cofactor acts as an initiator (probably to produce Fl$^-\cdot$) and reduced flavoprotein is the donor.[23] In contrast, the introduction of $O_2^-\cdot$ or hydrated electrons (from ionizing radiation or a disease state) into a biological matrix that contains donor molecules leads to the uncontrolled formation of hydrogen peroxide. If reduced metal ions are present Fenton chemistry occurs to give hydroxyl radicals, which will initiate lipid peroxidation[24] and rancidification of stored foodstuffs.

On the basis of their redox thermodynamics and reaction chemistry with $O_2^-\cdot$ in aprotic media, ascorbic acid[19] and some catechols[25] may be subject to an $O_2^-\cdot$-catalyzed autoxidation to dehydroascorbic acid and *o*-quinones, respectively.

Acknowledgment. This work was supported by the National Science Foundation under Grants No. CHE-8212299 and CHE-8208073. Purchase of the FTMS-1000 mass spectrometer was supported under National Science Foundation Departmental Research Instrument Grant No. CHE-8217610. We thank Ms. G. S. Srivatsa and Dr. S. Harmalker of this department for their assistance with the electrochemical measurements of the amines and amine anions and the ESR spectra.

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Studies on the Reaction of NO^+ with SCN^- Using Energy-Weighted Maximum Overlap and ab Initio Calculations

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Abstract: The reaction of the nitrosyl cation with the thiocyanate anion is described in terms of the concept of charge- and frontier-controlled reactions. The thiocyanate anion possesses two sites for nitrosation: the sulfur and nitrogen atoms, giving nitrosyl thiocyanate (**1**) and nitrosyl isothiocyanate (**2**), respectively. By use of energy-weighted maximum overlap calculations and polyelectronic perturbation theory the sulfur atom of thiocyanate is found to be the most reactive in nitrosation reactions. Geometrical optimization (GAUSSIAN 80 (STO-3G basis set)) of nitrosyl thiocyanate and nitrosyl isothiocyanate reveals that the former should be 1.06 eV more stable than the latter. The calculated bond lengths and angles of nitrosyl thiocyanate are found to be in good agreement with those found by X-ray crystallographic investigations of a stable *S*-nitroso compound (2-(acetylamino)-2-carboxy-1,1-dimethyl thionitrite (**3**)). The inefficiency of nitrosyl thiocyanate to act as a nitrosation reagent compared with other nitrosation reagents (as e.g., nitrosyl chloride (**4**)) is described by using the LUMO energy, molecular orbital coefficient, atomic net charge, and the concept of charge- and frontier-controlled reactions, and good agreement with experimental results is found. The decomposition of nitrosyl thiocyanate is described by studying the energy difference of the lowest triplet state as a function of the distance between the NO and SCN groups, and indications are found for the formation of NO and SCN radicals. These radicals can be involved in carcinogenesis in humans.

The thiocyanate anion is interesting from different points of view: it shows reactivity at both nitrogen and sulfur depending on the nature of the electrophile used[1] (Figure 1).

Smokers have increased amounts of the thiocyanate anion in

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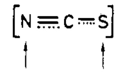

Figure 1.

the saliva, urine, and plasma compared to nonsmokers,[2] and it plays an important role in the formation of *N*-nitroso compounds from nitrite and amines.[3] Certain *N*-nitroso compounds are mutagenic and carcinogenic in animal tests[4] and may be involved in human carcinogenesis. It has been suggested that the nitrosation species of nitrite in aqueous acid solution probably is neither nitrous acid nor the nitrite ion but a derivative such as dinitrogen trioxide or the nitrosyl cation.[3b]

The formation of *N*-nitroso compounds by nitrite in aqueous acid solution is catalyzed by the presence of chloride and thiocyanate anions, and the latter is known to be the most effective.[3b] The ability of thiocyanate to act as a better catalyst than chloride can be accounted for by the equilibrium constants;[3b] while nitrosyl thiocyanate (**1**) is less reactive than nitrosyl chloride (**4**), it is present in much greater extent (the equilibrium constants being 46.5 compared to 5.6×10^{-4} for nitrosyl chloride[1]).

$$\mathrm{NO_2^- + 2H^+ \rightleftharpoons}$$
$$\mathrm{H_2O^+NO\ (\rightleftharpoons H_2O + {}^+NO) \underset{-X^-}{\overset{+X^-}{\rightleftharpoons}} \underset{\mathbf{1,\,4}}{X{-}NO} + H_2O}$$

(X = SCN for **1** and X = Cl for **4**)

On the basis of the ambident character of the thiocyanate anion, soft electrophiles react with the sulfur in thiocyanate through an orbitally controlled process,[5] whereas hard electrophiles undergo a charge-controlled reaction on nitrogen in isothiocyanate. The nitrosyl cation belongs to the borderline/soft electrophiles,[5] and both S- and N-nitrosation of the ambident anion can be expected.

This paper presents a theoretical study of the reaction of the nitrosyl cation with the thiocyanate anion. The reactivity of the thiocyanate anion is described by use of Klopman's polyelectronic perturbation theory.[5c] Optimized geometries of the nitrosated thiocyanate and the nitrosated isothiocyanate have been calculated, and some properties of the products are elucidated and discussed in relation to the experimental results. The calculations indicate that reactive radicals might be formed from nitrosyl thiocyanate, and these results are discussed in relation to human carcinogenesis.

The work is based on energy-weighted maximum overlap (EWMO) molecular orbital calculations and on ab initio analysis. GAUSSIAN 80 with 4-31G and STO-3G basis sets is used for the geometry optimization and the calculation of the atomic net charges.[6] Orbital energies and molecular orbital coefficients are calculated from an EWMO program.[7] The EWMO molecular orbital method is similar to extended Hückel theory[8] but differs in the treatment of overlap and atomic orbital energies.[7]

Results and Discussion

The geometries of the nitrosyl cation and the thiocyanate anion have been optimized by using a 4-31G basis set. Calculated bond lengths, atomic net charges, molecular orbital coefficients, and the LUMO energy for the nitrosyl cation and the HOMO energy for the thiocyanate anion are presented in Table I. The calculated bond length for the nitrosyl cation compares well with the experimentally determined value, 1.0619 Å,[9] and the atomic net charges seem more probable than those of Yonezawa et al.[10] ($q_N = +0.50$ and $q_O = +0.50$). The ionization potential for NO is 9.54 eV.[11] Our results for the bond lengths in the thiocyanate anion agree well with the structural data of potassium and ammonium thiocyanate (in Å):[1] KSCN $r_{S-C} = 1.689 \pm 0.013$, $r_{C-N} = 1.149 \pm 0.014$; NH$_4$SCN, $r_{S-C} = 1.63$, $r_{C-N} = 1.15$. The atomic net charges of the thiocyanate anion are essentially located on the terminal atoms, with the highest negative charge on nitrogen. Di Sipio et al.[12] have found a more evenly distributed charge ($q_s = -0.48$, $q_c = -0.001$, and $q_N = -0.51$), whereas Klopman[5c] obtains nearly the same results as we do.

Table I. Bond Lengths,[a] Atomic Net Charges,[a] Molecular Orbital Coefficients,[b] and Frontier Orbital Energies[b] of the Nitrosyl Cation and Thiocyanate Anion

$[NO]^+$		$[SCN]^-$	
r_{N-O}[c]	1.0485	r_{S-C}[c]	1.719
q_N	+0.80	r_{C-N}[c]	1.158
q_O	+0.20	q_S	−0.25
c_N	−0.807	q_C	−0.07
c_O	+0.590	q_N	−0.68
E_{LUMO}	−10.75[d]	c_S	0.855
		c_C	0.139
		c_N	−0.444
		E_{HOMO}	−12.27[d]

[a] Calculated by GAUSSIAN 80, using a 4-31G basis set. [b] Calculated by the EWMO program. [c] In Å. [d] In eV.

Two isomers may be formed in the reaction between the thiocyanate anion and the nitrosyl cation **1** and **2**.[13] It is possible

NCS–NO **1** SCN–NO **2**

to compare the interaction of two closed shell molecules in solution by means of Klopman's polyelectronic perturbation theory.

The change in energy, ΔE, due to the partial formation of a bond consists of two terms, an electrostatic term (the first term) and a covalent term (the second term):[5c]

$$\Delta E = -\frac{q_s q_t}{\epsilon}\Gamma + 2\sum_{\substack{m\\ \text{occ}}}\sum_{\substack{n\\ \text{unocc}}} \frac{(c_s{}^m c_t{}^n \beta_{st})^2}{E_m{}^* - E_n{}^*} \qquad (1)$$

q_s and q_t are the initial charges on the nucleophile and electrophile, resspectively, Γ is a measure of the Coulomb repulsion term, and ϵ is the dielectric constant of the reaction medium. The covalent term is expressed in terms of the molecular orbital coefficients of the nucleophile, $c_s{}^m$, and electrophile, $c_t{}^n$, the bond integral β_{st}, and perturbed orbital energies $E_m{}^*$ and $E_n{}^*$. The highest occupied molecular orbital of the nucleophile is assigned the energy

$$E_m{}^* = \mathrm{IP_m} + q_s\,(c_s{}^m)^2\frac{\Gamma}{\epsilon} - a^2\left[\mathrm{IP_m} - \mathrm{EA_m} - (c_s{}^m)^2(c_t{}^n)^2\Gamma\left(\frac{2}{\epsilon} - 1\right)\right] - \sum\frac{\chi_s(c_s{}^m)^2}{R_s}\left(1 - \frac{1}{\epsilon}\right)[q_s + 2b^2\chi_s(c_s{}^m)^2] \qquad (2)$$

where IM$_m$ and EA$_m$ are the ionization potential and electron

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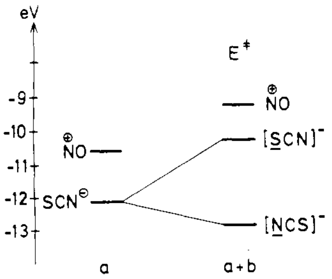


Figure 2. Difference in softness $E^{\ddagger}$ for the sulfur and nitrogen in $[\bar{S}CN]^-$ and the nitrosyl cation by adding the desolvation term, *b*, to the orbital term, *a* (the orbital term for the thiocyanate anion = E_{HOMO} and for the nitrosyl cation = E_{LUMO}).

Table II. ΔE Calculated from Eq 1[a]

	NCS-NO	SCN-NO
electrostatic term, eV	−0.016	−0.063
covalent term, eV	−4.00	−0.20
E, eV	−4.016	−0.263

[a] ϵ = 80 (water), β_{rt} is calculated from $c_rF_{rt}c_t$, R_{st} is obtained from the geometry optimization below, and the other parameters are in the text.

affinity, respectively, for the nucleophile, Γ, is the Coulomb interaction, and *a*, and *b*, χ are given in ref 5c.

From equiation 2 Klopman[5c] has defined an intrinsic parameter $E_m^{\ddagger}$ (softness parameter) independent of the other reagent (Γ = 0):

$$E_m^{\ddagger} = \underbrace{IP_m - a^2(IP_m - EA_m)}_{\text{orbital term (a)}} - \underbrace{\frac{\chi_s(c_s^m)^2}{R_s}\left(1 - \frac{1}{\epsilon}\right)[q_s + 2b^2\chi_s(c_s^m)^2]}_{\text{desolvation term (b)}} \tag{3}$$

The orbital part can be approximated with the HOMO energy of the thiocyanate anion. Calculation of the desolvation term, b_s, for sulfur of the thiocyanate anion gives (using $b^2 = {}^1/_2$,[5c] $q_s = -0.25$, $c_s = 0.885$, $\chi_s = q_s - (q_s - 1)k^{1/2}$, $k = 0.75$,[5c] and $R \simeq 2$ Å) $b_s \simeq 1.8$ eV and for the nitrogen (using $b^2 = {}^1/_4$,[5c] $q_N = -0.68$, $c_N = 0.444$, and $R \simeq 2$ Å) $b_N \simeq -0.51$ eV. Addition of the desolvation term to the orbital term causes a difference in softness of the thiocyanate anion shown in Figure 2, from which it appears that the nitrogen of the thiocyanate anion gets harder and that the sulfur gets softer.

Similarly $E_n^{\ddagger}$ for the nitrosyl cation can be calculated to be −9.35 eV ($b^2 = {}^1/_2$,[5c] $q_N = 0.80$, and $c_N = 0.807$) (Figure 2).

Partial bond formation energies, ΔE (calculated from eq 1 with the covalent term reduced to $2(c_sc_t\beta_{st})^2/(E_m^{\ddagger} - E_n^{\ddagger})$), for the electrostatic term and the covalent term in the reaction of the nitrosyl cation with the thiocyanate anion under formation of nitrosyl thiocyanate (**1**), and nitrosyl isothiocyanate (**2**), respectively, are given in Table II.

These results show that the nitrosyl cation should be most reactive at the sulfur of $[SCN]^-$, which is in good agreement with the kinetic data observed in nitrosation of nitrogen and sulfur.[3b] The S-nitrosation of the thiocyanate anion takes place mainly through an orbital interaction between the $2p_x$ orbital of sulfur in the thiocyanate anion (SCN placed along the *z* axis) and the $2p_x$ orbital of the nitrogen in the nitrosyl cation (NO placed along the *z* axis) giving the large contribution from the covalent term. The N-nitrosation of the isothiocyanate anion takes place through a more charge-controlled reaction, since the charge on nitrogen in isothiocyanate is relatively larger than that on sulfur and the molecular orbital coefficient on nitrogen is smaller than that on sulfur.

Although the results in Table II indicate that the sulfur of the thiocyanate anion is most reactive with the nitrosyl cation, this does not necessarily mean that nitrosyl thiocyanate is the most stable. By use of the STO-3G basis set and geometry optimization of all the bonds in the two compounds (**1**, **2**), the total energy and

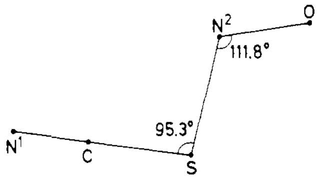


Figure 3. Calculated optimized structure of nitrosyl thiocyanate by use of GAUSSIAN 80 (STO-3G basis set).

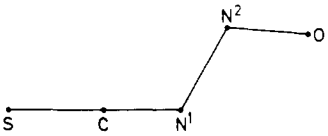


Figure 4. The calculated optimized structure of **2** by use of GAUSSIAN 80 (STO-3G basis set).

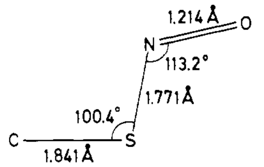
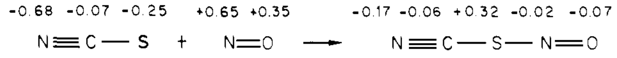


Figure 5. Bond lengths and angles in the *S*-nitroso group in 2-(acetylamino)-2-carboxy-1,1-dimethylpropyl thionitrite.

Table III. Calculated Bond Lengths (Å), Atomic Net Charges, and Total Energies Using GAUSSIAN 80 STO-3G Basis Sets of *S*-Nitrosyl Thiocyanate (**1**) and *N*-Nitrosyl Isothiocyanate (**2**)

	1	**2**
r_{C-S}	1.716	1.534
r_{S-N^1}		1.246
$r_{N^1-N^2}$		1.503
r_{N^2-O}	1.220	1.220
r_{N^1-C}	1.157	
r_{S-N^2}	1.819	
q_{N^1}	−0.17	−0.26
q_{N^2}	−0.02	+0.10
q_O	−0.07	−0.05
q_C	−0.06	+0.04
q_S	+0.32	+0.17
total energy, au	−611.808	−611.769

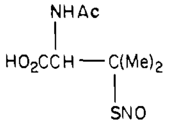
Scheme I



$$\overset{-0.68}{N}\equiv\overset{-0.07}{C}-\overset{-0.25}{S} + \overset{+0.65}{N}=\overset{+0.35}{O} \longrightarrow \overset{-0.17}{N}\equiv\overset{-0.06}{C}-\overset{+0.32}{S}-\overset{-0.02}{N}=\overset{-0.07}{O}$$

atomic net charges have been calculated by using GAUSSIAN 80. The calculated structures of **1** and **2** are shown in Figures 3 and 4, respectively. Bond lengths, atomic net charges, and total energies are given in Table III. There is little change in the N¹–C and C–S bonds in **1** from the starting reactants, but the N²–O bond length increases.

Field et al.[14] have prepared a stable *S*-nitroso compound (2-(acetylamino)-2-carboxy-1,1-dimethylethylthionitrite) (**3**), and its molecular structure has been determined by X-ray crystallography.



$$HO_2C\overset{\displaystyle NHAc}{\overset{|}{C}}H-\underset{\underset{\displaystyle SNO}{|}}{C}(Me)_2$$

3

The bond lengths and angles of the *S*-nitroso group in **3** are shown in Figure 5. The differences in bond lengths between **1** and **3** are 0.125 Å for C–S, 0.048 Å for S–N, and 0.006 Å for N–O, and the differences in bond angles are 5.1° for ∠CSN, and

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[14] Field, L.; Dilts, R. V.; Ravichandran, R.; Lenhert, P. G.; Carnahan, G. E. *J. Chem. Soc., Chem. Commun.* **1978**, 249–250.

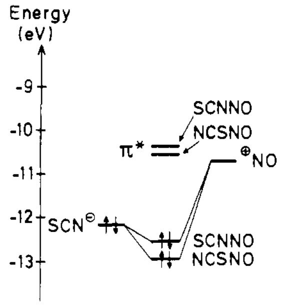

Figure 6. Change in the frontier orbital energy in the reaction of the nitrosyl cation with the thiocyanate anion from the initial state to the final state.

Table IV. LUMO Energies, Molecular Orbital Coefficients, and Atomic Net Charges of *S*-Nitrosyl Thiocyanate and Nitrosyl Chloride

	NCS-NO	Cl-NO
LUMO energy[a]	−11.10	−11.23
c^a	0.670	0.810
net charge on the nitrosation nitrogen[b]	−0.02	+0.21

[a] EWMO calculations. [b] GAUSSIAN 80 calculations (STO-3G basis set).

1.4° for ∠SNO. It might be concluded that our calculations give a reliable estimate of the geometry of **1**.

The reaction of the nitrosyl cation with the thiocyanate anion at sulfur is a typical soft–soft interaction—an orbital-controlled reaction (Scheme I)[5c] which is characterized by a complete charge transfer from the nucleophile to the electrophile.[5c]

The nitrosyl cation, which as a total positive charge of +1.00 in the free state, changes to a total charge at −0.09 in *S*-nitrosyl thiocyanate—a complete charge transfer has taken place. Soft–soft interactions are counterbalanced by the stabilization brought about by the covalent bonding, and the reaction is thus exothermic. Stedman and Whincup[13b] have found that ΔH for nitrosyl thiocyanate is −2.9 kcal/mol.

In the known isothiocyanates (as, e.g., CH_3NCS and H_3SiNCS^1), the bond lengths S–C and C–N differ only 0.034 and 0.036 Å from the corresponding bonds in **2** and the N^2–O bond length in **2** differs only 0.02 Å from the N–O bond in *N*-nitrosodimethylamine.[15]

Our calculations led to a difference in total energy between **1** and **2**, with the former being more stable than the latter by 0.039 au, or 1.06 eV.

The changes in EWMO energy of the highest occupied molecular orbital by reaction of the nitrosyl cation with the thiocyanate anion at the sulfur and nitrogen, respectively, are illustrated in Figure 6. It shows that the energy of the bonding orbital is lowered more in the case of S-nitrosation compared with N-nitrosation, which also can be an indication for a more stable nitrosyl thiocyanate, **1**.

Although the thiocyanate anion is known to increase the reaction rate in nitrosation reactions, nitrosyl thiocyanate is a poorer nitrosation reagent than, for instance, nitrosyl chloride, **4**.[3b] The

Cl—N=O
4

difference can be accounted for by comparing three fundamental parameters: the energy of the lowest unoccupied molecular orbital (LUMO), the molecular orbital coefficient, and the atomic net charge at the nitrosyl group. Table IV gives the molecular orbital coefficients, LUMO energies, and atomic net charges of nitrosyl thiocyanate and nitrosyl chloride.

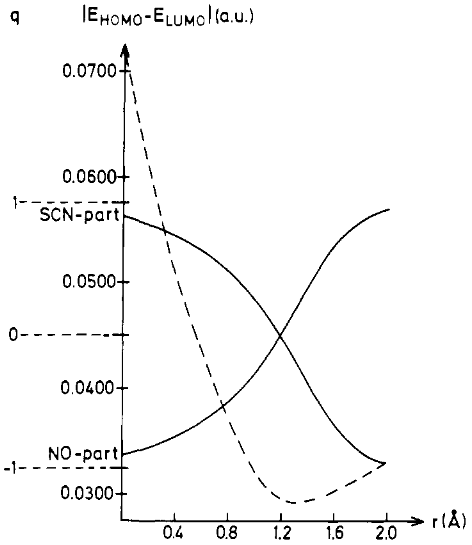

Figure 7. Energy difference $\Delta\epsilon = |E_{HOMO} - E_{LUMO}|$ (au) in nitrosyl thiocyanate plotted as a function of the stretching of the S–N bond (dotted line). The full line shows the atomic net charge (calculated by EWMO) of the NO and SCN parts.

By use of the results in Table IV in eq 1 with $E_m^* = E_{HOMO}$ for the nucleophile and $E_n^* = E_{LUMO}$ for the electrophile, this equation is reduced to eq 4 for the nitrosation of a nucleophile, S, with the atomic net charge q_s, molecular orbital coefficient c_s, and the energy of the highest molecular orbital E_{HOMO} with nitrosyl thiocyanate

$$E(\text{NCS–NO}) = \frac{0.02q_s}{\epsilon}\Gamma + \frac{0.898c_s^2\beta_1^2}{E_{HOMO} + 11.10\ \text{eV}} \tag{4}$$

and for nitrosation of the same nucleophile, S, with nitrosyl chloride

$$E(\text{Cl–NO}) = -\frac{0.21q_s}{\epsilon}\Gamma + \frac{1.312c_s^2\beta_1^2}{E_{HOMO} + 11.23\ \text{eV}} \tag{5}$$

A nitrosation reaction of a nucleophile, S, with X–NO (X = Cl, NCS) is of the following type:

$$\text{X–NO} + \text{S} \xrightarrow{k} \text{S–}^{+}\text{NO} + \text{X}^- \tag{6}$$

with the corresponding second-order rate constant

$$\text{rate} = k_0[\text{S}][\text{X–NO}] \tag{7}$$

Rate constants for a variety of nitrosation reactions with nitrosyl chloride and *S*-nitrosyl thiocyanate on different nucleophiles, S, are known,[3b] and they have shown that the reactivity of Cl–NO is greater than that of NCS–NO.[3b] These findings are in good agreement with our results from eq 4 and 5. For the electrostatic term (the first term), nitrosyl thiocyanate will decrease the reaction rate compared with nitrosyl chloride as the atomic net charge at the nitrosyl group in nitrosyl thiocyanate has a small negative charge and therefore gives a positive contribution to the total perturbation energy, whereas the nitrogen in nitrosyl thiocyanate has a positive atomic net charge and then gives a negative contribution. For the orbital-controlled reaction term (the second term) nitrosation with nitrosyl chloride vs. nitrosyl thiocyanate gives the following ratio:

$$\frac{\Delta E'(\text{Cl–NO})}{\Delta E'(\text{NCS–NO})} = 1.46\,\frac{E_{HOMO} - 11.10\ \text{eV}}{E_{HOMO} - 11.23\ \text{eV}}$$

which also indicates that nitrosyl chloride is more reactive than *S*-nitrosyl thiocyanate. Combination of these considerations and the experimental results[3b] gives satisfactory explanation for the difference in reaction rate of nitrosation of nucleophiles by nitrosyl chloride and nitrosyl thiocyanate (a question which to our knowledge has not been elucidated until now).

It was stated above that a complete charge transfer takes place from the thiocyanate anion to the nitrosyl cation in the S-nitrosation of the thiocyanate anion. We attempt to decribe the chemical properties of nitrosyl thiocyanate by studying the energy difference, $\Delta\epsilon$, between the energy of the lowest triplet state as

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a function of the distance between the SCN and NO species of nitrosyl thiocyanate. The triplet states are in the EWMO model represented by the LUMO and HOMO energy difference[16] $\Delta\epsilon = |E_{\mathrm{HOMO}} - E_{\mathrm{LUMO}}|$, and the single state should be located 1–2 eV above the triplet state. The results are shown in Figure 7 where $\Delta\epsilon$ is plotted as a function of the stretching of the S–N bond. The total atomic net charge on the SCN and NO parts are given as well.

The dotted curve in Figure 7 which represents the triplet excitation energy in nitrosyl thiocyanate reaches a minimum at a stretching length of 1.2 Å. This is evidence of an avoided crossing of the molecular orbital energies. The full line which represents the total atomic net charge on the SCN and NO parts, respectively, tends to zero at $r = 1.2$ Å. These simple considerations indicate the presence of a biradical state close in energy, and it can be concluded that nitrosyl thiocyanate might dissociate to NO and SCN radicals. Seel and Wesemann[17] have shown that nitrosyl thiocyanate decomposes to nitrogen oxide and thiocyanogen (**5**); the decomposition probably takes place via SCN radicals.

$$2\mathrm{ON{-}SCN} \rightarrow 2\mathrm{NO} + \underset{\mathbf{5}}{\mathrm{NCS{-}SCN}}$$

Smokers secrete ca. 200 mg of thiocyanate per day more than nonsmokers.[2b] The thiocyanate secreted in saliva must be reabsorbed in the alimentary tract and secreted again in the saliva. Nitrite can be present in the stomach from bacterially reduced nitrate or from nitrite added to food. The acidic conditions in the stomach might cause nitrite to form the nitrosyl cation which can react with the thiocyanate anion under formation of nitrosyl thiocyanate. The higher content of thiocyanate in the saliva of smokers may then accelerate the rate of formation of *N*-nitrosamines as stated earlier or it might cause formation of reactive NO and SCN radicals which can be involved in the carcinogenesis in the stomach or in the alimentary tract. On the other hand, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine affords after incubation in rat liver homogenate an ESR spectrum with a *g* value of 2.035,[18] due to a cysteine–ferrous ion–nitrogen oxide complex which is known to inhibit the binding of carcinogens to proteins. Since nitrogen oxide has a pronounced tendency to couple with free radicals, it might be released in the liver and quench the carcinogenic free radicals and, thereby, inhibit their action.

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Registry No. 1, 3985-25-9; **2**, 90991-48-3; $\mathrm{NO^+}$, 14452-93-8; $\mathrm{SCN^-}$, 302-04-5; nitrogen, 7727-37-9; sulfur, 7704-34-9.

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Skewed Exchange Spectroscopy. Two-Dimensional Method for the Measurement of Cross Relaxation in ^{1}H NMR Spectroscopy

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Abstract: A theoretical treatment of the two-dimensional measurement of nuclear magnetic cross relaxation leads to a method in which all rates are obtained through the back-transformation of a matrix of NOESY mixing coefficients. The theory of a two-dimensional pulse sequence, skewed exchange spectroscopy, is also developed. This experiment is applicable to the study of nuclear Overhauser effects in ^{1}H NMR spectroscopy. *J*-coupling effects are absent, and spectral crowding along the diagonal is avoided by the projection of diagonal-peak information onto the cross peaks. The back-transformation method is used to identify a relay NOE in a three-spin system.

I. Introduction

The nuclear Overhauser effect (NOE) is an important exchange phenomenon which can be studied by both one-dimensional (1-D) and two-dimensional (2-D) NMR spectroscopy.[1,2] Its importance stems from the fact that NOE's are used to determine the structure and dynamics of molecules in solution. In proton NMR spectroscopy, NOE's are usually absent when nuclei are more than 500 pm apart, and thus the mere occurrence of an NOE provides valuable information on connectivity[3] and structure.[4,5] Quantitative information, however, is obtained only by the measurement of cross relaxation rates between interacting nuclei. The rates are normally measured by 1-D techniques in which the buildup of the NOE is plotted as a function of saturation time.[6,7] In these experiments, measurements must be restricted to the regime of short saturation times to avoid the effects of multispin exchange, which arise in the steady state.

An efficient way to study cross relaxation is found in the NOESY experiment, which was first described by Jeener et al.[8] Unlike 1-D methods, NOESY allows the simultaneous observation of all exchange phenomena in one experiment and is free of the problems associated with selective irradiation. Semiquantitative analysis of the relaxation pathways obtained from NOESY has

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