Studies on Nitrosation Reagents and Nitrosation Reactions using the Frontier-orbital Approach

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The structure and reactivity of some nitrosation reagents ($^+$NO, H_2O-$^+$NO, ON-Cl, ON-SCN, and ON-OH) are discussed on the basis of Gaussian 80 calculations and Klopman's polyelectronic perturbation theory for closed shell systems. Geometrical optimization and total energy calculations reveal that nitrosation by nitrite in aqueous acid solution probably occurs *via* a nitrosyl cation–water complex, in which the nitrosyl group is bound to water by the Coulomb interaction. The found reactivity of the nitrosation reagents is used to elucidate the observed reactivity in nitrosation of thiols, sulphides, thiocarbonyls, alcohols, and amines.

The chemistry of nitrosation reagents is an important field in organic chemistry. Nitrosation can take place at *e.g.* carbon, nitrogen, oxygen, sulphur, and anions.[1] The most common method for nitrosation involves an interaction of a nucleophile with an $^+$NO species. The nitrosyl cation ($^+$NO) can only be obtained in strong acids (*e.g.* 65% sulphuric acid) or as solid salts (*e.g.* $^+$NOBF$_4^-$). However, $^+$NO is readily available from nitrosation reagents of the type Y-NO, where Y can be regarded as a carrier of $^+$NO. Y can be anions as Cl$^-$, SCN$^-$, OH$^-$, or NO$_2^-$, or a neutral molecule such as H_2O, ROH, R_2NH, RSH, or $R_2C=S$.[1]

The simplest nitrosation system is a solution of sodium nitrite in perchloric acid where the possible nitrosation reagents are (1)—(4). In strong acid solution there has been evidence of the

$$ON^+ \quad ON^+\text{-}OH_2 \quad ON\text{-}NO_2 \quad ON\text{-}OH$$
$$(1) \qquad (2) \qquad (3) \qquad (4)$$
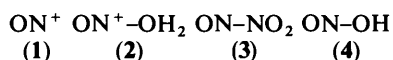
existence of ON$^+$ (1)[2] whereas at lower acidities the nitrous acidium ion (ON$^+$-OH$_2$) (2) has been suggested as the effective nitrosation reagent, although physical evidence is lacking.[1c] In recent times, there has been some discussion concerning the differentiation between ON$^+$ *versus* ON$^+$-OH$_2$ (Scheme 1) as

$$HONO + H^+ \rightleftharpoons H_2O^+\text{-}NO$$

$$H_2O^+\text{-}NO \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H_2O + {}^+NO$$
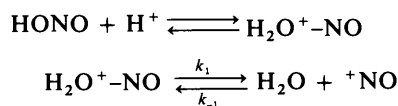
Scheme 1.

the reactive species involved, under conditions where pH is lower than in the nitrogen trioxide mechanism.[1b,c,3] Equation (1) has been established for the observed reaction rate in nitrosation of substrates S which is consistent with reaction *via* ON$^+$-H$_2$O or ON$^+$.[1,3]

$$\text{Rate} = k[HNO_2][H^+][S] \qquad (1)$$

For nitrosation in the presence of anions such as *e.g.* Cl$^-$, Br$^-$, and SCN$^-$, nitrosation occurs with the corresponding nitrosyl chloride (5), nitrosyl bromide (6), or nitrosyl

$$ON\text{-}Cl \quad ON\text{-}Br \quad ON\text{-}SCN$$
$$(5) \qquad (6) \qquad (7)$$
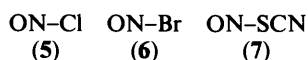
thiocyanate (7), respectively.[1] The reaction rate for the nitrosation of substrates, S, in the presence of anions, X$^-$, follows equation (2):[1] and the catalytic order is usually:

$$\text{Rate} = k_2[HNO_2][H^+][X^+][S] \qquad (2)$$

SCN$^-$ > Br$^-$ > Cl$^-$.[1b–d] The catalytic effect of the anions is related to an increased concentration of ON$^+$ carriers; the equilibrium constants for the formation ON-X (X = Cl, Br, or SCN) at 0 °C are: ON-Cl, 5.6×10^{-4} mol^{-2} l^2; ON-Br, 2.2×10^{-2} mol^{-2} l^2; ON-SCN, 46.3 mol^{-2} l^2.[4] Chloride and thiocyanate catalysis of nitrosation of secondary amines are important reactions from a human point of view, as carcinogenic *N*-nitrosamines might be formed. Chloride and thiocyanate anions are present in gastric juice and thiocyanate anions are also formed in saliva. Thiocyanate anions are present in much higher concentration in smokers and might then represent a risk factor for *in vivo* formation of *N*-nitroso compounds.[5]

For nitrosation reagents the following order of reactivity has been observed:[1] ON$^+$ > ON$^+$-OH$_2$ > ON-Cl > ON-Br > ON-SCN $\gg$ ON-OH which is opposite to the overall catalytic effect of added anions when nitrite in acidic solution is used (because of the greater effect on the equilibrium content of ONX formation).

To our knowledge there have been few attempts to describe the properties of nitrosation reagents and nitrosation reactions in terms of MO calculations.[6] This paper presents a study based on the concept of charge and frontier-controlled reactions.[7] A simple form of the second-order perturbation treatment of chemical reactivity is used, in which mainly initial charges, frontier orbital energies, and frontier orbital coefficients are used. The change in energy (ΔE), when orbitals of a nucleophile overlap with those of an electrophile, is given in equation (3)[7] where q_n and q_e are the charges of the nucleophile

$$\Delta E = -\frac{q_n q_e}{\varepsilon \cdot R_{ne}} + \frac{2 \cdot c_n^2 c_e^2 \beta_{ne}^2}{E_{HOMO} - E_{LUMO}} \qquad (3)$$

| Coulomb term | orbital term |

and electrophile, respectively; ε is the dielectric constant of water; R_{ne} is the distance between the nucleophile and electrophile; c_n and c_e are the molecular orbital coefficients of the nucleophile and electrophile, respectively; β_{ne} is the bond integral and E_{HOMO} is the energy of the highest occupied molecular orbital of the nucleophile and E_{LUMO} is the energy of the lowest unoccupied molecular orbital of the electrophile.

For the calculation of the fundamental properties of the nitrosation reagents and some of the nucleophiles, *ab initio* calculations have been performed using a Gaussian 80 program.[8]

Results and Discussion

(a) *Structure and Properties of Positive Nitrosation Reagents* (ON^+ *and* ON^+H_2O).—Geometrical optimization of all bonds in ON^+, OH_2, and ON^+-OH_2, respectively, has been performed using a 4-31 G basis set. The optimized total energies, bond lengths and angles, atomic net charges, LUMO energies, and coefficients for ON^+ and ON^+-OH_2 are given in Table 1.

The properties of the nitrosyl cation have been discussed previously.[6b] Inspection of the results of the nitrous acidium ion in Table 1 shows an unexpected result, the long bond length between the nitrogen in the nitrosyl cation and the oxygen in the water molecule: 2.128 Å, which might be an indication for a Coulomb interaction rather than an orbital interaction. The structure of the nitrous acidium ion complex (8) based on the calculations is shown in Figure 1.
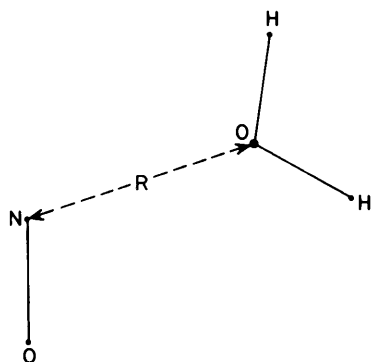
It is noteworthy that the nitrous acidium ion complex (Figure 1) consists of two closed shell systems (the nitrosyl cation and the water molecule) and that the structure of the nitrosyl cation in this complex is very similar to (1) (the N–O bond length is 1.056 Å in the nitrous acidium ion complex compared with 1.048 Å in the nitrosyl cation).

The results in Table 1 show that the main difference between the two nitrosation reagents is the increase in LUMO energy by 1.74 eV for the nitrosyl acidium ion complex relative to the nitrosyl cation, which might account for the difference in reactivity of the two species.[1b]

The results obtained for the optimized structure of the nitrous acidium ion (Table 1 and Figure 1) prompted us to study the total energy functional of this system as a function of the distance between ON and OH_2. The relative change in total energy is shown in Figure 2.

The calculations for Figure 2 have been carried out with fixed bond lengths and angles for H_2O and by change of the bond length in the nitrosyl group from 1.2 Å at $R = 1.4$ Å [which corresponds to the bond length in nitrous acid (Table 2)] to 1.06 Å at $R = 2.2$ Å, of which the last value is similar to the result in Table 1.

The total energy curve for the nitrous acidium ion system in Figure 2 shows a minimum at R *ca.* 2.1 Å which corresponds to the nitrous acidium ion complex (8) (Table 1 and Figure 1). With $R = 1.40$—1.45 Å between the nitrosyl cation and water, corresponding to bond length in nitrous acid, the total energy is of the same magnitude as the total energy at $R = \infty$.

The formation of the nitrous acidium ion complex (8) from the above results might then be as follows in Scheme 2. The first step in this reaction is a protonation of nitrous acid (4) under formation of the nitrous acidium ion (2) in which an energetically favourable extension of the water–nitrosyl bond takes place, under formation of (8). It should also be noted that the orbital overlap between the nitrosyl cation and water in (8) is nearly equal to zero.

One might also account for (8) from the Hard and Soft Acids and Bases (HSAB) principle:[9] water belongs to the hard bases while the nitrosyl cation is classified as a borderline acid with a tendency to be soft.[6,9] According to the HSAB principle hard acids will tend to complex with hard bases and soft acids tend to complex with soft bases.[9] As the two species are located more or less in different ends of the HSAB scale a Coulomb interaction might be expected.[9]

The presented results do not support the free nitrosyl cation as the effective nitrosation reagent but rather that ON^+-OH_2 is the effective species in a form in which the nitrosyl cation is Coulomb-bound to water. It should also be noted that under

Table 1. Optimized total energies, bond lengths and angles, atomic net charges, LUMO energies and coefficients for ON^+ and ON^+-OH_2 calculated by Gaussian 80 using a 4-31 G basis set

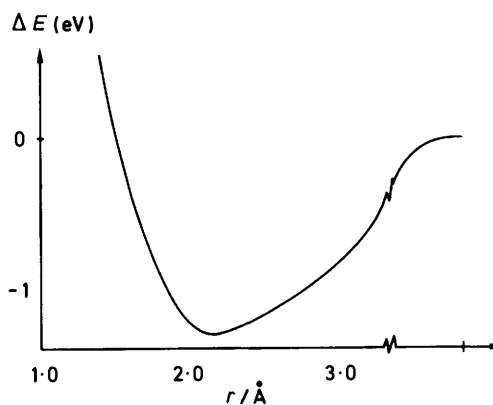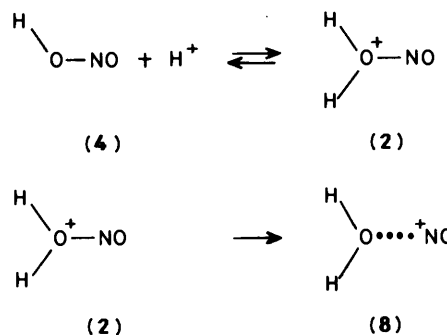|	ON^+	$ON^+ \cdots OH_2$
E_{total} (a.u.)	-128.6697	-204.6267
$r_{N=O}$ (Å)	1.048	1.056
r_{O-N} (Å)		2.128
r_{O-H^1} (Å)		0.957
r_{O-H^2} (Å)		0.956
$\widehat{ONO}$ (°)		105
q_N	0.81	0.79
ε_{LUMO} (eV)	-8.31	-6.57
c_N	0.64	0.64

(8)

Figure 1

Figure 2. The relative change in total energy of the nitrous acidium ion system as a function of the distance between ON and OH_2 using a 4-31 G basis set.

Scheme 2.

Table 2. Optimized bond lengths and angles, atomic net charges, LUMO energies and coefficients for ClNO, NCSNO, and HONO (*trans* and *cis*) calculated by Gaussian 80 using a STO-3G basis set

|	Cl–NO	NCS–NO	HONO (*trans*)	HONO (*cis*)
$r_{N=O}$ (Å)	1.20	1.22	1.22	1.22
r_{X-N} (Å)	1.86	1.82	1.42	1.40
$\widehat{XNO}$ (°)	108	112	111	105
q_N	0.15	−0.02	0.10	0.12
ε_{LUMO} (eV)	3.78	4.80	5.84	5.61
c_N	0.808	0.802	0.802	0.813

X = Cl, S, or O.

Table 3. Calculations of the Coulomb and orbital terms for ON$^+$, ON$^+$ $\cdots$ OH$_2$, ON–Cl, ON–SCN, and ON–OH

	Coulomb term[a] (eV)	Orbital term $(c^2\beta_{ne}^2/eV^{-1})$
ON$^+$	$-0.141q_n$	1.28 $(E_{HOMO} + 8.31)^{-1}$
ON$^+$ $\cdots$ OH$_2$	$-0.138q_n$	1.28 $(E_{HOMO} + 6.57)^{-1}$
ON–Cl	$-0.026q_n$	1.62 $(E_{HOMO} - 3.78)^{-1}$
ON–SCN	$0.004q_n$	1.60 $(E_{HOMO} - 4.80)^{-1}$
ON–OH[b]	$-0.021q_n$	1.63 $(E_{HOMO} - 5.61)^{-1}$

[a] ε = 80 (water). [b] The calculations have been performed for *trans*-nitrous acid.

the experimental conditions other parameters might affect the structure and properties of (**8**), and finally other water molecules may be involved [reaction (4)].

$$ON^+ \cdots OH_2 + nH_2O \rightleftharpoons (ON^+)(OH_2)_{n+1} \quad (4)$$
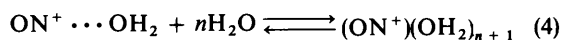
(b) *Structure, Properties, and Reactivity of Nitrosation Reagents.*—Table 2 gives optimized bond lengths and angles, atomic net charges, LUMO energies and coefficients for ClNO, NCSNO, and HONO (*trans* and *cis*).

The optimized structures of nitrosyl chloride and nitrous acid (*trans* and *cis*) with this basis set (STO-3G) are in agreement with recent results.[10] The calculations do also predict *trans*-nitrous acid as more stable than *cis*-nitrous acid by 0.0033 eV. The calculations of nitrosyl thiocyanate have been discussed previously,[6b] and the structure of the thionitrite function (C–S–N=O) of this compound has been found to be in agreement with experimental work.[6b]

Calculations of the Coulomb and orbital term for the nitrosation reagents (ON$^+$, ON$^+$ $\cdots$ OH$_2$, ON–Cl, ON–SCN, and ON–OH) on the basis of equation (3) give the results in Table 3.

The results in Table 3 show the following order of reactivity for the Coulomb interaction: ON$^+$ > ON$^+$ $\cdots$ OH$_2$ > ON–OH > ON–SCN, and for the orbital interaction: ON$^+$ > ON$^+$ $\cdots$ OH$_2$ > ON–Cl > ON–SCN > ON–OH. Thus, the reactivity of the nitrosyl cation, nitrous acidium ion complex, and nitrosyl chloride are in the following order: ON$^+$ > ON$^+$ $\cdots$ OH$_2$ > ON–Cl in agreement with the experimental results.[1] As to the reactivity of nitrosyl thiocyanate and nitrous acid different results are obtained from the Coulomb and orbital terms, respectively. As the orbital interaction is more important than the Coulomb interaction (because of the relatively large molecular orbital coefficient of the nitrosation nitrogen) and the low bond order in nitrosyl thiocyanate relative to nitrous acid (P_{N-S} 0.23 and P_{O-N} 0.52) one might expect nitrosyl thiocyanate to be more reactive than nitrous acid. These results are also in accord

Table 4. Calculation of the orbital term for nitrosation of thiourea (**9**) and cysteine (**11**) by the nitrous acidium ion complex (**8**)[a]

	ΔE^b/eV
Thiourea	−0.68
Cysteine	−0.44

[a] It is assumed that c_n and β_{ne} are more or less of equal size for both compounds. [b] IP (thiourea) 8.50 eV; IP (cysteine) ca. 9.4 eV.

Scheme 3.
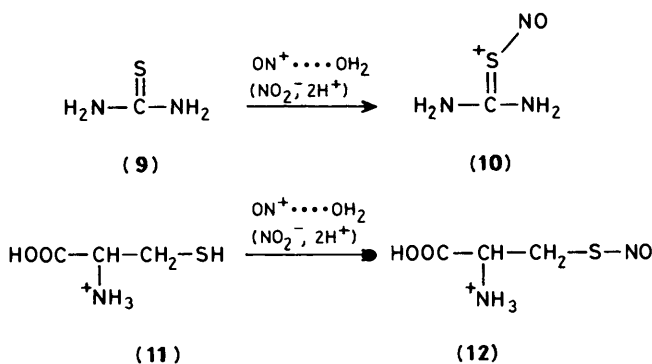
with experimental results,[1] but it should also be noted that nitrous acid is a very poor nitrosation reagent.[1a]

(c) *Nitrosation Reactions.*—In this section nitrosation reactions on sulphur, oxygen, and nitrogen are discussed on the basis of the above results and the concept of charge and frontier-controlled reactions.[7]

Recently there has been an increased interest in nitrosation of thiocarbonyl compounds, thiols, and sulphides.[1c] Stedman *et al.* have studied the *S*-nitrosation of alkylthioureas and cysteine by nitrite in an acidic solution[11] and found that the thiourea derivatives are about an order of magnitude more reactive than cysteine. Thiourea (**9**) forms *S*-nitrosothiourea (**10**) by this reaction, while cysteine (**11**) forms the corresponding thionitrite (**12**) (Scheme 3). The difference in reactivity can be accounted for by the orbital term in equation (3). We use the ionization potentials (IP) for thiourea and cysteine from refs. 12 and 13 as the value of $-E_{HOMO}$[14] and the results for the nitrous acidium ion complex (**8**) in Table 1. The results obtained are given in Table 4.

The values in Table 4 support the observed reactivity.[11] Williams *et al.* have studied the nitrosation of thiols (*e.g.* cysteine) and the corresponding *S*-methylated analogues (*e.g.* *S*-methylcysteine) by *N*-methyl-*N*-nitrosoaniline in an acid solution, where the nitrosation reagent is of the form Y–NO.[15] *S*-Methylation increases the nitrosation rate by a factor of ca. 20. This increase can also be accounted for by studying the change in HOMO energy when going from a thiol to the corresponding methyl sulphide. The IP for cysteine has been found as ca. 9.4 eV[13] and for methionine ca. 8.5 eV;[13] a similar decrease in IP has also been found for some simple thiols and their corresponding *S*-methylated analogues (Figure 3). Using −IP as E_{HOMO} for the nucleophile, a decrease in IP for the methyl sulphides will give a smaller difference in the denominator of the orbital term in equation (3) and thus increase the orbital interaction. These considerations support the increased reactivity of *S*-methylcysteine and methionine (which contain the CH$_2$–S–CH$_3$ group) relative to cysteine and glutathione. It should also be noted that the HOMOs in all the studied compounds are located as non-bonding on sulphur.
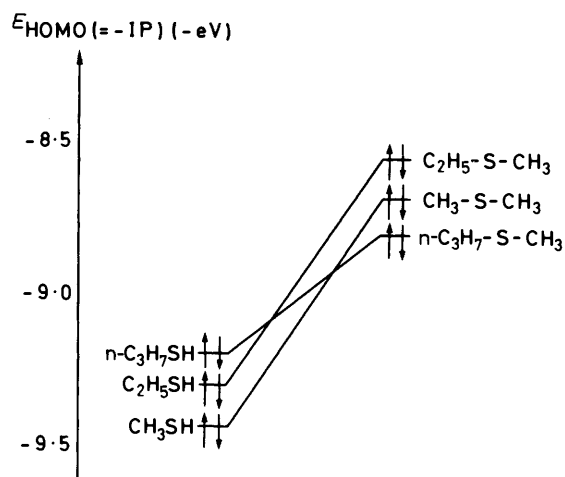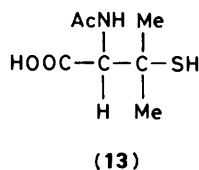
$E_{HOMO}(=-IP)(-eV)$

Figure 3. The change in HOMO energy by methylation of methanethiol, ethanethiol, and propane-1-thiol.

(13)

Table 5. Rate constants for nitrosation by Y–NO, at 25—31 °C, of MeOH, RSH, and $C_6H_5NH_2$.[1c] The HOMO energies are taken from ref. 12 and LUMO energies from Table 2

Reagent	E_{HOMO}/ eV	Substrate	E_{HOMO}/ eV	k/ l mol^{-1} s^{-1}
ClNO	3.78	MeOH	−10.84	2.1×10^5
BrNO		MeOH	−10.84	2.0×10^4
ClNO	3.78	RSH^a	−9.4	2.6×10^6
BrNO		RSH^a	−9.4	1.4×10^5
NCSNO	4.80	RSH^a	−9.4	3.0×10^3
ClNO	3.78	$C_6H_5NH_2$	−7.7	2.2×10^9
BrNO		$C_6H_5NH_2$	−7.7	1.7×10^9
NCSNO	4.80	$C_6H_5NH_2$	−7.7	1.9×10^8

^{a} Cysteine.

The S-nitrosation of N-acetylpencillamine (13) has been studied kinetically in the presence of anions.[15] Nitrosyl chloride should, according to the results in Table 3, be a better nitrosation reagent than nitrosyl thiocyanate, in support of the experimental results as the reaction constants are 2.6×10^6 and 3.0×10^3 dm^3 mol^{-1} s^{-1}, respectively.[15]

It is rather difficult to compare nitrosation of alcohols with thiols, as the former reaction is reversible and the latter is virtually irreversible (it is possible to denitrosate thionitrites only at very high acidities).[16] The experimental results indicate that S-nitrosation is much more favoured than O-nitrosation. As the HOMO energies of alcohols are generally lower than those of thiols the denominator in the orbital term in equation (3) is larger for nitrosation of alcohols compared with thiols, giving the observed difference.

Table 5 gives a series of collected rate constants for nitrosation by Y–NO of methanol, N-acetylpenicillamine (13) and aniline [1c,17] together with HOMO and LUMO energies.
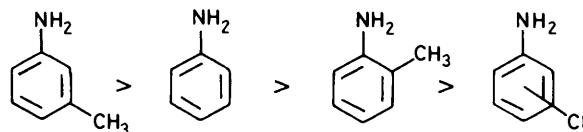
The results for the reactivity of the different nitrosation reagents with the substrates shown in Table 5 fit with the expected reactivity on the basis of the orbital term in equation (3). One should be aware of the fact that aniline is extensively protonated in the dilute acid solution usually employed for these nitrosations, which affects the overall reactivity, whereas methanol and N-acetylpenicillamine are not.

Nitrosation of secondary amines to N-nitrosamines has received considerable attention since the discovery by Magee and Barnes that N-nitrosodimethylamine is carcinogenic in rats.[18] Amines are more basic than the sulphur and oxygen compounds discussed above, and, depending on pH, various amounts of protonated amine will be present. This property makes it more difficult to obtain overall reactivity for nitrosation reactions, but the orbital term indicates a difference in nitrosation rate of aliphatic and aromatic amines. Our results for the nitrous acidium ion complex (8) in Table 1 and the IP for dimethylamine and aniline give −0.63 and −2.11 $c_n^2\beta_{ne}^2$ eV^{-1}, respectively. These values indicate that nitrosation of

aniline will be the faster reaction in agreement with experimental results.[19] The frontier orbital analysis might also to some extent elucidate the observed nitrosation rates of aniline and some of its derivatives. The reactivity order is based on E_{HOMO} and the orbital term in equation (3)[20] and correlates with the observed reactivity.[19a]

We conclude that the difference in reactivity of nitrosation reagents and nitrosation reactions can be accounted for by the frontier orbital method. Studies of the total energy function of the nitrosyl–water cation system reveals that the nitrosation reagent is probably a species in which the nitrosyl cation is bound to a water molecule through Coulomb interactions.

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