On the Formation of Nitrosation Reagents

K. A. JØRGENSEN,* M.T.M. EL-WASSIMY ** and S.-O. LAWESSON

Department of Organic Chemistry, Chemical Institute, University of Aarhus, DK-8000 Aarhus C., Denmark

By use of quantum mechanical perturbation theory developed by Klopman and semi-empirical calculations, the change in perturbation energy for reactions of the nitrosyl ion with anions has been calculated. It is found that the calculated change in perturbation energy correlates with the experimental equilibrium constants for these reactions. The atomic net charges on the nitrogen of some nitrosation reagents have been calculated and found to be inversely proportional to the Pearson's nucleophilicity parameter of the nucleophiles (anions) to which the nitrosyl group is bound. The results are discussed in terms of the Hard and Soft Acids and Bases (HSAB) principle.
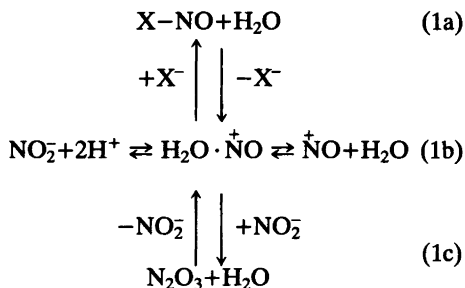
The kinetics of the reaction between nucleophiles and nitrous acid [1-4] or nitrosation reagents [1-5] are complex. Investigations have shown that the nitrosation reagent probably is neither the nitrite ion nor nitrous acid but a species in which the nitrosyl group ($^+$N=O) is free,[6] or bound to a carrier.[1-4] The carrier can be an anion or a neutral species (*e.g.* halide-, nitrite- or thiocyanate ions and alcohols, sulfides or water).

The first step in the formation of nitrosation reagents is protonation of nitrous acid (Scheme 1, 1b); from 1b different routes are possible depending on the reaction conditions.

Anions as chloride, bromide and thiocyanate (1a) are important as catalysts in nitrosation of nucleophiles, and the reaction rate for nitrosation of nucleophiles with anions (X^-) present is given by eqn. (2):[1]

$$X-NO+H_2O \tag{1a}$$

$$+X^- \uparrow \quad \downarrow -X^-$$

$$NO_2^-+2H^+ \rightleftarrows H_2O \cdot \overset{+}{N}O \rightleftarrows \overset{+}{N}O+H_2O \tag{1b}$$

$$-NO_2^- \uparrow \quad \downarrow +NO_2^-$$

$$N_2O_3+H_2O \tag{1c}$$

Scheme 1.

$$\text{Rate}=k_2[\text{Nu}][\text{H}^+][\text{HNO}_2][X^-] \tag{2}$$

which is equivalent to the concentration product eqn. (3):[1]

$$\text{Rate}=k_3[\text{Nu}][X-\text{NO}] \tag{3}$$

In eqn. (2) k_2 contains implicity the equilibrium constants for the formation of $X-NO$ which are known for some nitrosation reagents. For nitrosation with nitrous anhydride (1c) the reaction rate is given by eqn. (4),

$$\text{Rate}=k_4[\text{Nu}][\text{HNO}_2]^2 \tag{4}$$

where k_4 contains the equilibrium constant for the formation of N_2O_3.

By using perturbation theory, Klopman [7] has derived an expression for the energy (ΔE) which is gained or lost when orbitals of one reactant overlap with those of another:

$$\Delta E=- \sum_{ab} (q_a+q_b)\beta_{ab}S_{ab}- \sum_{k<l} \frac{Q_k \cdot O_l}{\varepsilon} \Gamma$$

$$+ \sum_{r}^{\text{occ.}} \sum_{s}^{\text{unocc.}} - \sum_{s}^{\text{occ.}} \sum_{r}^{\text{unocc.}} \frac{2(\Sigma_{ab}c_{ra}c_{sb} \cdot \beta_{ab})^2}{E_r-E_s} \tag{5}$$

In eqn. (5) q_a and q_b are the electron population in the atomic orbitals a and b, β_{ab} is the resonance integral. S_{ab} is the overlap integral. Q_k and Q_l are the total charges on atoms k and l. Γ is $1/R_{kl}$; R_{kl} is the distance between the atoms k and l; c_{ra} is the coefficient of atomic orbital a in molecular orbital r (b,s respectively). E_r is the energy of molecular orbital r, and E_s is the energy of molecular orbital s.

The first term in eqn. (5) expresses the first order closed shell repulsion and is derived from the interaction of filled orbitals of one molecule with the filled orbitals of another. This term is ignored here, because the main idea of the frontier orbital theory is to explain features of differential reactivity. The second term in (5) is the Coulomb repulsion or attraction, and the third one is the interaction of filled orbitals of one molecule with the unfilled ones of another. When $E_r - E_s$ is large, the contribution from the third term is neglected and the reaction is said to be charge controlled, whereas if $E_r \simeq E_s$ the third term becomes the important one, and the reaction is said to be frontier orbital controlled.

Eqn. (5) can be approximated to eqn. (6) by using only the HOMO of the nucleophile and LUMO of the electrophile:

$$\Delta E = - \frac{Q_{nucl}Q_{elec}}{\varepsilon} \Gamma + \frac{2(c_{nucl}c_{elec} \beta)^2}{E_{HOMO} - E_{LUMO}} \quad (6)$$

Eqn. (6) is a good approximation of eqn. (5) because the interactions of the other orbitals have all much larger $E_r - E_s$ values and thus make a small contribution to third term in eqn. (6)

The present approach is based on a form of molecular orbital theory, termed energy weighted maximum overlap (EWMO) by Linderberg and Öhrn,[8] and within an electron propagator framework. The model has the attractive features that only atomic orbitals, orbital energy parameters and the molecular geometry enter. Extensive applications of the method show very satisfactory correlation between orbital energies and the ionization potentials.[10,11] Recently the basic ideas behind the model and the applications made so far have been reviewed.[12]

This paper presents an investigation of the formation of nitrosation reagents from protonated nitrous acid and anions, and comparison with experimental results is made. The atomic net charge of some nitrosation reagents has been calculated and discussed in relation to Pearson's nucleophilicity parameter[9] and the hard and soft acids and bases principle.

RESULTS AND DISCUSSION

A new version of an e.w.m.o. program has recently been developed,[13,14] in which atomic parameters, described elsewhere,[14] are stored in the program. The only essential input is the molecular geometry and atomic numbers, while the output gives the atomic net charges, molecular orbitals, molecular energies, etc. As input parameters known structures and mean bond lengths of molecules from the literature are used.

In Fig. 1 the calculated HOMO orbital energies of the anions are used to classify the ions as hard or soft according to Pearson,[8] a hard base having a low value of the occupied frontier orbital, whereas a soft base has a higher value. In other words, softness increases with increased energy of the occupied frontier orbital. A hard acid has a high value of the empty frontier orbital and the hardness will decrease with decreased energy.

Fig. 1 shows the HOMO energy levels for some anions, H_2O, and the LUMO energy levels for the nitrosyl group, free or bound to H_2O. It is
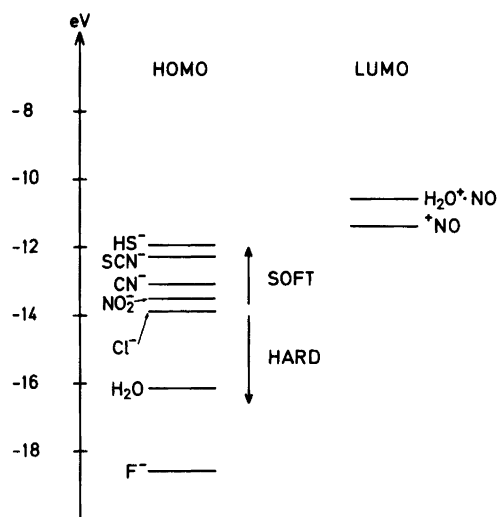

Fig. 1. Schematic representation of the HOMO energy levels in anions and H_2O and LUMO energy levels for the nitrosyl ion free or bound to H_2O.
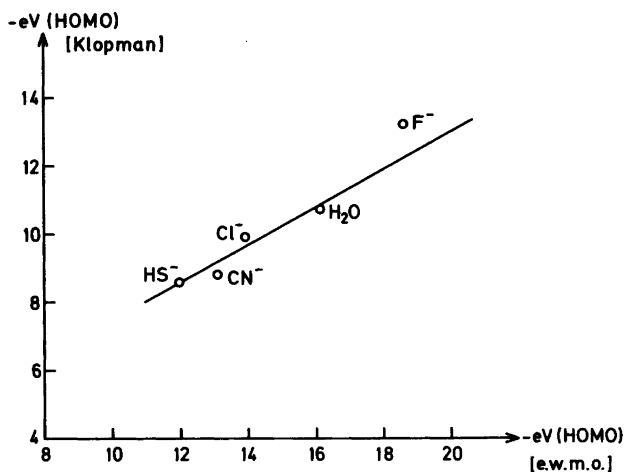
Fig. 2. The correlation between E_{HOMO} calculated by the e.w.m.o. model and E^*_{HOMO} calculated by Klopman.

also seen that the order of the energy of the nucleophiles is in accordance with that calculated by Klopman,[7] using eqn. (7)

$$E^*_{HOMO}=$$

$$-\frac{IP+3EA}{4}+\frac{14.388(q+0.5)}{R_{ion}}\left(1-\frac{1}{\varepsilon}\right) \quad (7)$$

where IP is the ionization potential, EA the electron affinity, R_{ion} the effective ionic radii (in Å), q is the initial charge of the ion and ε is the dielectric constant of the solvent.

The correlation between E^*_{HOMO} from eqn. (7) and E_{HOMO} from e.w.m.o. calculations is linear (Fig. 2) (a=0.54±0.10 and corr.coef.=0.95). The E_{HOMO} values calculated by EWMO are generally found to be lower than those calculated by Klopman.[7]

As the LUMO-energy of $H_2O \cdot \overset{+}{N}O$ is larger than that of $\overset{+}{N}O$ (Fig. 2), $\overset{+}{N}O$ bound to water is the harder species of the two. Our value for E_{LUMO} for $\overset{+}{N}O$ (−11.42 eV) also correlates well with that of Yonezawa *et al.*,[15] (−11.51 eV), calculated by a semi-empirical SCF molecular treatment.

Using eqn. (6) the total perturbation (neglecting the contribution from the change in solvent energy ΔE for the reaction of $H_2O \cdot \overset{+}{N}O$ with X^-) can be calculated using the following constant values: $Q_{elec.}$=+1, ε=80 and $c_{elec.}$=1 and β

obtained from Ref.7. The results are summarized in Table 1.

It is seen from Table 1 that ΔE increases with increased softness of the anions which shows that NO^+ prefers to coordinate with the soft anions rather than with the hard ones.

The effect of X on the atomic net charges of nitrogen (Q_N) of nitrosation reagents has been calculated (Fig. 3).

A good correlation between Q_N and Pearson's nucleophilicity parameter, n,[19] is found. It is observed that Q_N is largest when $\overset{+}{N}O$ is bound to hard species (H_2O), but tends to zero or negative, when $\overset{+}{N}O$ is bound to soft species (SCN^-, HS^-).

When $H_2O \cdot \overset{+}{N}O$ reacts with different nucleophiles either a frontier-controlled or a charge-controlled reaction can occur. The protonated nitrous acidium ion ($H_2O \cdot \overset{+}{N}O$) reacts with the fluoride ion to give nitrosyl fluoride in a charge-controlled reaction because the atomic net charge on the nitrogen changes from +0.80 in the protonated acidium ion to +0.92 in nitrosyl fluoride whereas in the reaction of thiocyanate ion complete charge transfer occurs from +0.80 in the nitrous acidium ion to −0.04 on the nitrosyl nitrogen in nitrosyl thiocyanate. It is also seen from Table 1 that $H_2O \cdot \overset{+}{N}O$ prefers to undergo a frontier-controlled reaction when n increases.

ΔE-values correlate well with the known ex-

Table 1. Calculations of ΔE from eqn. 6. [a,b]

	F⁻	Cl⁻	Br⁻	NO₂⁻	CN⁻	SCN[b]	HS⁻
$R_{X-NO}(\text{Å})$	1.52	1.95	2.14	1.23	1.47	1.70	1.70
$-2\beta_X(\text{eV})$	4.48	4.10	3.60	4.20	3.8	3.9	4.0
$-E_{HOMO}(\text{eV})$	18.60	13.90	13.20[c]	13.54	13.10	12.31	11.97
$\Delta E(\text{eV})$	0.70	1.33	1.46	1.57	1.63	1.85	2.90

[a] The value of E_{LUMO} ($H_2O^+ \cdot NO$) is -10.59 eV. [b] $c_{nucl}=1$, except for SCN⁻, where c_{nucl} is calculated from $\psi_{HOMO}=0.876\,\phi_S+0.142\,\phi_C-0.456\,\phi_N$. The thiocyanate ion is ambident and if the energy gap between the HOMO orbital of thiocyanate and the LUMO orbital of the electrophile is large, then the reaction is charge-controlled. The thiocyanate ion will then prefer to coordinate with a cation through its nucleophilic nitrogen, which carries the highest negative charge. On the other hand, if there is only a minor energy gap between the HOMO and LUMO orbitals, the reaction is orbital-controlled and the cation will seak the largest electronic density pertaining to the highest occupied orbital of SCN⁻. Assuming all other things to be equal, $H_2O \cdot NO$ will then prefer to attack sulfur which carries the highest electronic charge in this particular orbital: $c_S^2=(0.878)^2=0.771$; $c_N^2=(-0.456)^2=0.208$. The value for $c_s^1=0.771$ is then used in the calculation of ΔE for X=SCN. [c] E_{HOMO} for Br⁻ is obtained from Fig. 2 as the program has not been developed for atoms with atomic numbers higher than 17.

Table 2. ΔE compared with the experimental equilibrium connstants for the same reaction.

	Cl–NO	Br–NO	O₂N–NO	NCS–NO
$\Delta E(\text{eV})$	1.33	1.46	1.57	1.85
K	$5.6\times10^{-4a,16}$	$2.2\times10^{-2b,17}$	$0.2^{c,18}$	$46^{d,19}$

[a, b, d] at 0 °C; [c] At 20 °C.

perimental equilibrium constants and illustrate the semiquantitative agreement between the calculated and observed reactions of various nucleophiles with $H_2O \cdot \overset{+}{N}O$ (Tables 1 and 2).

The reaction between a nucleophile and an electrophile can be either ionic or frontier orbital controlled. If E_{HOMO} has a large negative value and E_{LUMO} a large positive value, the stable
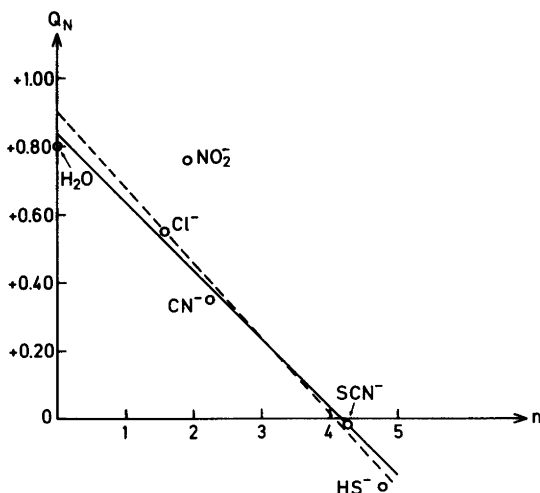

Fig. 3. Plot of Q_N (the atomic netto charge at the nitrosation nitrogen) as a function of n (Pearson's nucleophilicity parameter). *Full line:* without Q_N of NO₂⁻: $Q_N=0.84-n \cdot 0.20$ [$s(Q_N^0)=0.048$ and $s(n)=0.016$]. *Dotted line:* with Q_N of NO₂⁻: $Q_N'=0.91-n \cdot 0.22$ [$s(Q_N^0)=0.091$ and $s(n)=0.032$].
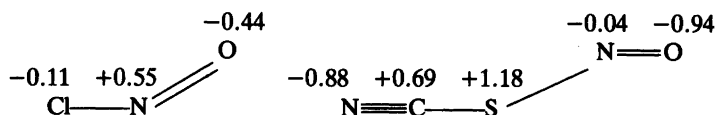
Fig. 4. Calculated atomic net charges on the atoms in nitrosyl chloride and nitrosyl thiocyanate.

hard—hard interaction can take place, whereas if E_{HOMO} has a small negative value and E_{LUMO} a large negative value, a soft—soft interaction can occur. Hard—hard interactions take place because of favourable entropy and soft—soft combinations due to favourable enthalpy. The interaction between the nitrosyl group and thiocyanate ion is then a typical soft—soft combination ($\Delta H = -2.9$ kcal/mol)[19] and the interaction of the nitrosyl group with the chloride ion is more of a hard—soft (borderline) interaction ($\Delta H = 5.4$ kcal/mol). The hard—hard bonding should then be electrostatic and the soft—soft one covalent. Fig. 4 shows the atomic net charges of Cl—NO and NCS—NO calculated by the EWMO model (observe that the values calculated "too high" which is due to an exaggerated polarization in the calculation by EWMO).

The values in Fig. 4 also indicate that a charge transfer takes place from the thiocyanate ion to the nitrosyl ion, which is typical for soft–soft interactions, whereas in nitrosyl chloride the bonding is more electrostatic.

CONCLUSION

The change in perturbation energy for the reaction of the protonated nitrous acidium ion with anions has been calculated. Correlation between the stabilization energy and the equilibrium constant is found. The atomic net charge of the nitrogen in the nitrosation reagent is found to be inversely proportional to the Pearson's nucleophilicity parameter of the anions.

Addendum. After this manuscript was accepted for publication a quite recent paper was published: *Ab Initio Studies of a Proposed Mechanism for* N-*Nitrosamine Formation.*[22]

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