Ab Initio Calculations Relevant to the Mechanism of Chemical Carcinogenesis by *N*-Nitrosamines. Part 7.[1] The Nitrosation of Amines by Nitrosyl Chloride

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Ab Initio molecular orbital calculations using split-valence 3-21G and 4-31G basis sets are reported on the formation of ONCl from HONO and HCl and on the formation of H_2NNO from NH_3 and ONCl. Both minima and transition structures were fully optimized. The energy barriers for both reactions are low, due in part to the flat nature of the potential-energy surfaces, showing that the reactions proceed readily. The calculations show that both reactions may proceed *via* a low-energy closed shell mechanism without the explicit involvement of water molecules in the transition structure. The calculations also identify the structural features involved in the saddle points for both reactions.

N-Nitrosamines are a series of widely occurring carcinogens. Their widespread occurrence is due both to their ease of formation from amines and to the abundance of nitrosating agents found in the environment.

The usual precursors are amines and nitrite. Nitrite itself is not a nitrosating agent but has to be converted into a carrier of the nitrosonium ion, NO^+. In dilute aqueous solution this may be the nitrous acidium ion,[2] $H_2NO_2^+$, or dinitrogen trioxide,[3,4] N_2O_3. The nitrosating agents were identified as a result of kinetic studies,[3,4] and it was later confirmed that gaseous dinitrogen trioxide is indeed a nitrosating agent.[2,5] The nitrous acidium ion has never been identified experimentally. For that reason we undertook a theoretical study of its structure and reactions.[6,7] The chloride ion is a powerful catalyst in aqueous solution, catalysing both the nitrosation and denitrosation reactions; it functions by increasing the concentration of NO^+ carriers,[5] in this case ONCl. While it is known that gaseous ONCl is a powerful nitrosating agent,[2,5] we undertook a theoretical study of both its formation from nitrite and chloride, modelled by reaction (1), and its reactions with amines, modelled by (2), in order to understand the nitrosation reaction more fully.

$$HONO + HCl \longrightarrow H_2O + ONCl \qquad (1)$$

$$ONCl + NH_3 \longrightarrow HCl + H_2NNO \qquad (2)$$

Methods

The strategy used was to locate all stationary points on the potential-energy surface, both minima and transition states. The energy calculations were performed within the Hartree–Fock framework using the GAUSSIAN suite of programs[8,9] and employed the split-valence 3-21G and 4-31G basis sets.[10–12] The minima studied do not possess expanded valence sets on the chlorine nor were there any linkages from chlorine to other second-row atoms, or multiple linkages to the chlorine (except in $HONCl^+$ which is not the prime focus of this study). For these reasons, and considerations of the cost involved in transition structure location, we did not consider it necessary to use polarization functions on the chlorine.[13] Also for reasons of cost, non-essential methyl groups were replaced by hydrogens.

The location of the four-membered-ring transition structures including chlorine proved to be considerably more difficult than for previous four-membered-ring transition structures studied in this series,[14] due to the flat nature of the surface. In order to obtain a reasonable starting geometry for the transition structure for reaction (1) containing the four-membered HClNO ring, we studied the transition structure for reaction (3) which proceeds *via* the same four-membered ring. This gave

$$HClNO^+ \longrightarrow ClNOH^+ \qquad (3)$$

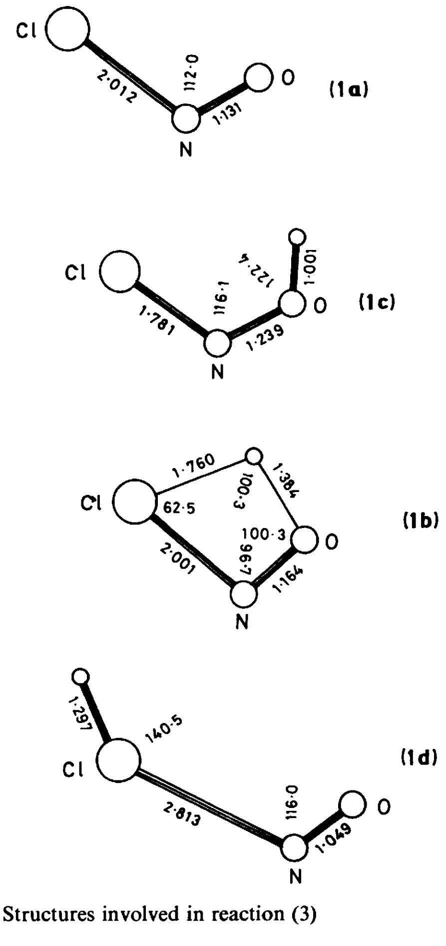

Figure 1. Structures involved in reaction (3)

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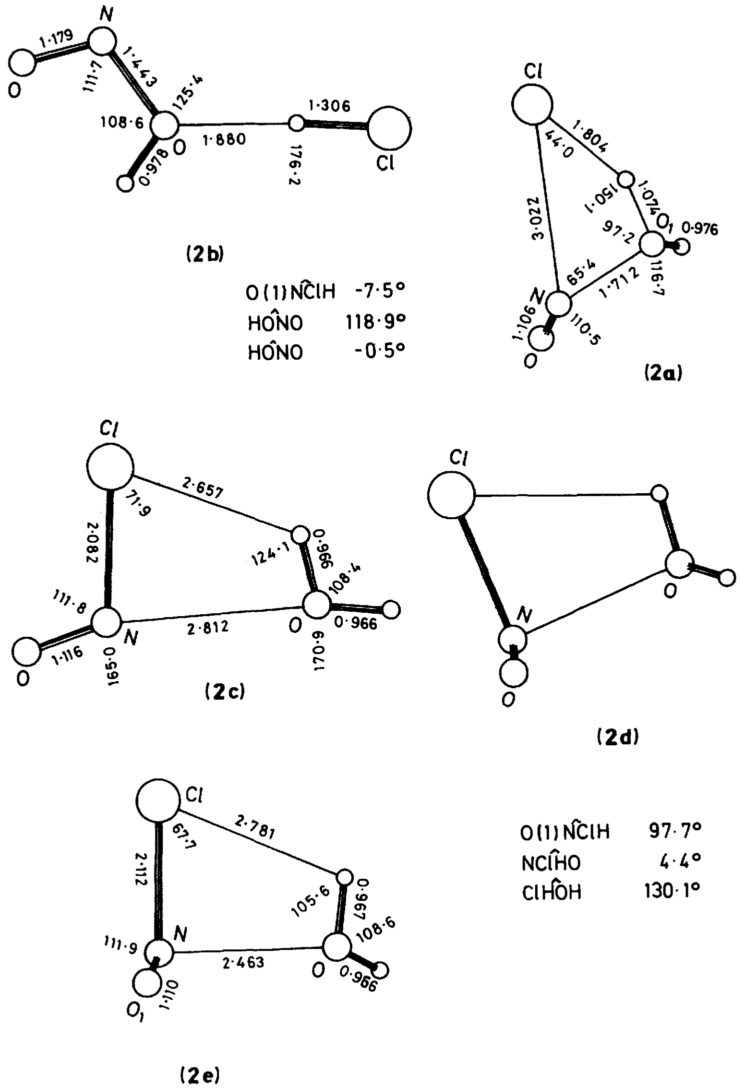

Figure 2. Structures involved in reaction (1)

a reasonable guess at the transition structure bond lengths and angles involving chlorine. The transition structure for reaction (3) was located following a guess at the initial structure and initial hessian obtained by an optimization using analytical second derivatives[15] at every step; a sub-minimal STO-2G basis set[16] was used in these calculations. The optimization alogorithm used was that of Schlegel.[17] The order of the saddle points was confirmed using analytical second-derivative calculations, or numerical ones where large amounts of disk space were required.

Results and Discussion

The energies of all species studied are given in the Table. The RHF/3-21G structures are shown in Figures 1—3; where these are not available, the RHF/4-31G structures are shown. The two basis sets give very similar results.

The Interconversion of Protonated Nitrosyl Chloride.—The structures involved in reaction (3) are shown in Figure 1. $HClNO^+$ is considerably more stable than $ClNOH^+$, by 183 kJ mol^{-1}; it is essentially a complex between HCl and NO^+. Indeed, electrostatic potential maps of ONCl show only slightly negative regions near the oxygen, positive regions around the nitrogen, and large negative regions around the chlorine; this confirms that ONCl is indeed a carrier of NO^+. There is a large energy barrier between $ClNOH^+$ and $HClNO^+$ of 199 kJ mol^{-1}. The transition structure is tight; the imaginary frequency has a magnitude of 2 294 cm^{-1}.

The Formation of Nitrosyl Chloride.—One mechanism for the formation of nitrosyl chloride from HCl and HONO [reaction (1)] is shown in Figure 2. The HONO–HCl complex (**2b**) is 27 kJ mol^{-1} below the reactants. The transition structure (**2a**) is 50 kJ mol^{-1} above reactants, or 77 kJ mol^{-1} above (**2b**). The surface is much flatter than that for reaction (3); the imaginary frequency has a magnitude of only 268 cm^{-1}. While the numerical value of the energy barrier cannot be relied upon, due to the lack of polarization functions in the basis set and the neglect of the correlation energy, it is sufficiently low to suggest that the reaction will proceed readily. (The inclusion of electron correlation often results in a sizeable percentage reduction in the energy barrier.) The reaction is essentially thermoneutral, showing that it may readily proceed both ways. Two structures for the $ONCl–H_2O$ complex are given, (**2c** and **e**). Structure (**2d**) is close in energy to (**2e**); no minima corresponding to (**2d**) could

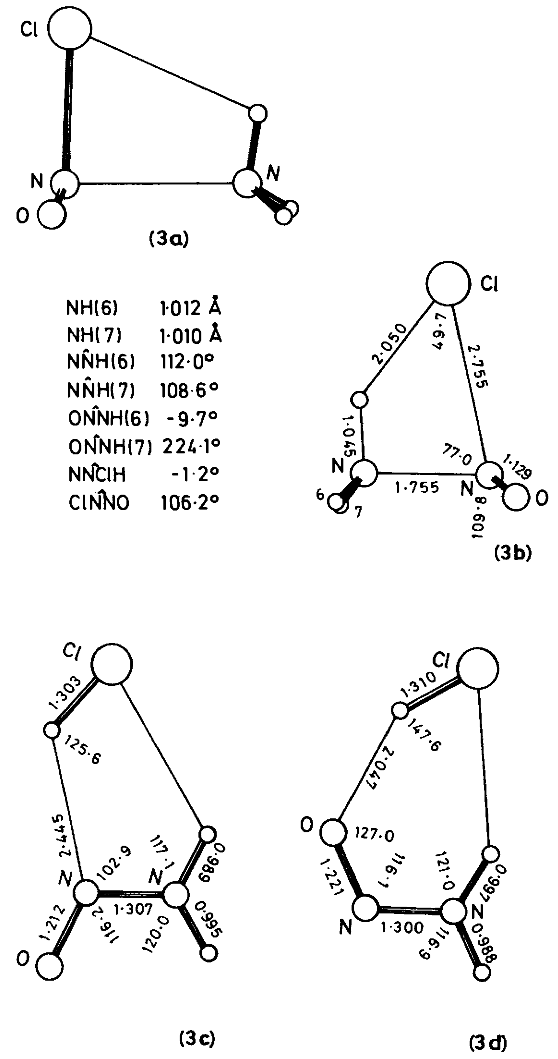

Figure 3. Structures involved in reaction (2)

be found; rather (**2e**) was obtained from the optimization. This again shows the flat nature of the reaction surface.

Nitrosation by Nitrosyl Chloride.—The mechanism considered in this paper is shown in Figure 3. Solvent assistance has not been studied, so the results are appropriate to the gas phase and organic solvents. It has been suggested that radical mechanisms may be involved in the nitrosation by nitrogen oxides under these conditions,[5] but these have not been studied here. The overall energy barrier for reaction (2) is 3 kJ mol^{-1}; the reaction is exothermic by 35 kJ mol^{-1}. Complex (**3c**), the one formed following reaction (3), is 18 kJ mol^{-1} below the products; complex (**3d**) is 27 kJ mol^{-1} lower in energy than the products. Complex (**3a**) has not been fully optimized but again the results show that the energy barrier is sufficiently low to conclude that the reaction occurs readily by a closed shell mechanism. (This of course does not rule out radical pathways.) Again the low energy barrier may be attributed to the flat nature of the surface.

A Comparison of the Transition Structures.—Structures (**1b**) and (**2a**) both contain a four-membered ONClH ring. However, the N–O bond lengths are very different: structure (**1b**) corresponds to the conversion of an N–O double bond into a triple bond, whereas structure (**2a**) corresponds to the loss of an N–O single bond. The difference in O–H bond lengths may be a result of the difference in N–O bond lengths. The long bonds to the chlorine in (**2a**) almost lead to the saddle point being an $ON{\cdot}OH_2{}^+{\cdot}Cl^-$ complex: (**2a**) was however confirmed as a true saddle point by numerical second-derivative calculations. The hessian has one negative eigenvalue. The difference in N–Cl bond lengths may be due to some double-bond character in (**1c**) which is absent in (**2e**). Both the nitrogen and oxygen atoms have different connectivities in the transition structures. The hydrogen and chlorine atoms, however, have the same connectivities in both (**1b**) and (**2a**). It is therefore not surprising that the H–Cl bond lengths are very similar in both structures.

Table. Energies (hartree) of molecules at their optimized geometry

Molecule		RHF/3-21G Energy	RHF/4-31G Energy
NH_3		−55.872 20	−56.106 69
H_2O		−75.585 96	
H_2NNO		−183.768 07	−184.538 66
c-HONO		−203.468 50	
HCl		−457.869 43	−459.563 41
ONCl	(**1a**)	−585.752 15	−587.978 39
$HClNO^+$ (TS)	(**1b**)	−585.875 90	
$ClNOH^+$	(**1c**)	−585.951 70	
$HClNO^+$	(**1d**)	−586.021 30	
HClNOOH (TS)	(**2a**)	−661.319 01	
HONO·HCl	(**2b**)	−661.348 16	
$ONCl{\cdot}H_2O$	(**2c**)	−661.344 25	
$ONCl{\cdot}H_2O$	(**2e**)	−661.350 64	
$HClNH_2NO$ (TS)	(**3b**)	−641.623 12	
$H_2NNO{\cdot}HCl$	(**3c**)		−644.108 91
$H_2NNO{\cdot}HCl$	(**3d**)		−644.112 32

Structure (**3b**) was confirmed as a true saddle point by analytical second-derivative calculations using the sub-minimal basis set. Owing to the close similarities with (**2a**) and the high cost of second-derivative calculations, this was not repeated with the 3-21G basis set. Structures (**2a**) and (**3b**) are isoelectronic. The transition structure bond lengths and bond angles are therefore very similar. (The concept of transition structure bond lengths and bond angles has been discussed more fully elsewhere[18].) We are not aware of any other work reporting N–Cl bond lengths in *ab-initio* transition structures.

Conclusions.—These calculations show the low energy barriers involved in the formation of ONCl from nitrite and HCl, and also the low energy barriers in both the nitrosation and denitrosation reactions, the reverse of reaction (2). This in itself adds little to our understanding of chloride catalysis in the formation of nitrosamines. However it does show that the reaction need not proceed *via* radical pathways. It also shows that the reaction may proceed by a low energy barrier even without the explicit involvement of a water molecule in the transition structure though such a treatment may lower the barrier still further. We have also identified for the first time the structural features involved in nitrosation by ONCl; this opens the way for the study of other nitrosation reactions by ONCl, including the nitrosation of tertiary amines.

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