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Ab-initio molecular orbital studies on a new mechanism for the interconversion of monomethylnitrosamine and methyldiazohydroxide

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Monomethylnitrosamine and methyldiazohydroxide are two proposed N-nitrosamine metabolites, which are formally related by an N → O 1,3-proton shift. Their possible interconversion is an important reaction to investigate in elucidating the pathways involved in the decomposition of carcinogenic N-nitrosamines. Self-consistent field molecular orbital studies using a 4-21G basis set, in which solvation is treated using the supermolcule approach, have led to the proposal of a new low energy pathway for their interconversion; this mechanism involves protonation and the implicit involvement of at least two molecules of water.

Key words: Molecular orbital — Nitrosamine metabolism — Monomethyl nitrosamine — Methyldiazohydroxide — Mechanism

Introduction

N-nitrosamines are an important class of chemical carcinogens [1, 2], which require metabolic activation in order to show activity [3]. This activation is believed to proceed, in the case of N,N-dimethylnitrosamine, by α-oxidation, and to be catalysed by cytochrome P450 [4, 5, 6]. The resultant α-

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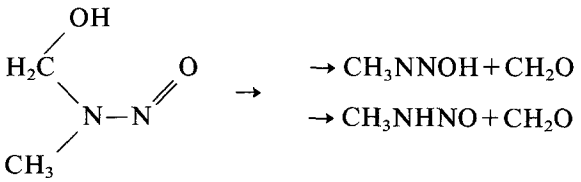
hydroxynitrosamine is very unstable [7–9], and is believed to decompose to either the monomethylnitrosamine [1] or to methyldiazohydroxide.



(1)

The alkylation products are then derived from the diazohydroxide.

The evidence suggests that the α-hydroxynitrosamine decomposes directly to the diazohydroxide [10, 11]. However, studies on the evolution of nitrogen from nitrosamines suggest that not all of the metabolised product decomposes by the same pathway [12, 13, 14]. Moreover, monomethylnitrosamine may be formed in the nitrosation of primary amines; the products (which may include nitrosamines) arise following rearrangmeent to the diazohydroxide [1, 15].

Both the monomethylnitrosamine and the methyldiazohydroxide are highly unstable species; consequently it has not been possible to study their interconversion experimentally. (The monomethylnitrosamine has only been observed at 203 K [16]; the *trans* diazohydroxide has recently been observed by NMR, but the *cis* isomer has not been observed [17]).

The concern about the carcinogenicity of N-nitrosamines has led to recent theoretical studies on their metabolism as a whole, and in particular on the conversion of the monomethylnitrosamine to the methyldiazohydroxide [11, 18, 19]. These studies have attempted to study the proton shift either by the reaction coordinate method [18], or by locating the transition structure [11, 19]. The energy barrier obtained is very high (about 190 kJ mol^{-1}) and is likely to remain so, even if a full treatment of electron correlation is allowed.

This disparity with experimental observation is no doubt due to the neglect of the solvent; this can be seen by including one water molecule in the calculation and determining the transition structure for an H_3O^+ shift – the barrier is considerably reduced (to 74 kJ mol^{-1}) [19]. While this latter approach may be sufficient to explain qualitatively the ease of conversion between the two species, we have found that the proton shift may occur even more readily in protonated molecules provided that at least two molecules of water are included in the calculation.

Methods

Ab-initio Hartree–Fock gradient techniques, as incorporated into Gaussian 80 and Gaussian 82 [20, 21] using a split valence 4-21G [22] basis set have been employed. Full geometry optimisation using the algorithm of Schlegel [23] has been carried out. It has been noted that small basis sets do not necessarily give accurate descriptions of cation-ligand complexes [24, 25]. However, as this study is primarily a comparison of similar cationic complexes, it is believed that these methods are adequate. Hydration has been considered using the supermolecule

Table 1. Energies of molecules at the RHF/4-21G optimised geometry (Energies in atomic units)

Molecule	Energy	Molecule	Label	Energy
H_2NNO	−184.366261	$H_2NNOH.H_2O^+$	(1a)	−260.552448
t,t-HNNOH	−184.362004	$H_2O.H_3NNO^+$	(1b)	−260.553463
t,c-HNNOH	−184.364992	$H_2O.H_3NNO^+$	(1c)	−260.554387
c,t-HNNOH	−184.368388	$H_2O.H_2NNOH^+$	(1d)	−260.569563
c,t-CH_3NNOH	−223.318655	$HNN.OH_2.H_2O^+$	(1e)	−260.571024
c-CH_3NHNO	−223.318683	$H_2NNOH.H_2O^+$	(1f)	−260.576535
t-H_2NNOH^+	−184.691956	$H_3NNO.2H_2O^+$	(2a)	−336.419803
c-H_2NNOH^+	−184.666870	$H_2NNO.H_3O.H_2O^+$	(2b)	−336.421657
H_3NNO^+	−184.685281	$HNNOH.H_3O.H_2O^+$	(2c)	−336.437919
$HNN.H_2O^+$	−184.718071	$HNNOH.H_5O_2^+$	(2d)	−336.440580
		$H_2O.H_2NNOH.H_2O^+$	(2e)	−336.443489
		$H_2NNO.H_3O.H_2O^+$	(2f)	−336.446524

approach [26]; as noted above, even the inclusion of one molecule of water can yield valuable information not obtainable by gas phase calculations. This study employs two molecules of water in the supermolecule. Non-essential methyl groups have been replaced by hydrogens in order to save CPU time.

Results

The energies of H_2NNO (the model for monomethylnitrosamine) and HNNOH (the model for methyldiazohydroxide) are given in Table 1, along with those of their protonated and hydrated protonated structures. Due to the large numbers of isomers involved, only a representative selection is given. Also given are various derivatives of H_3NNO^+. The monohydrated and dihydrated structures are shown in Figs. 1 and 2 respectively. The structures of other relevant species are reported elsewhere [19].

Discussion

The *c,t*-isomer of HNNOH is more stable than the model nitrosamine H_2NNO; the energies of the parent molecules are almost identical – see Table 1. The relative stability of the isomers of H_3NNO^+ is: *c*-$H_2NNOH^+ \leq H_3NNO^+ \leq$ *t*-$H_2NNOH^+ \leq HNN.H_2O^+$. As shown in Fig. 1 and Table 1, monohydration can alter the relative stability of the different isomers; *t*-H_2NNOH^+ becomes the most stable. The monohydration energies are about twice those of the neutral molecules. There appears to be an inverse relationship between the monohydration energy and the intermolecular bond length. The structure of $HNN.H_2O^+$ is very interesting. It is actually a transition structure, as characterised by by analytical second derivative calculations [27]; it is discussed more fully elsewhere. The structure (1e) is therefore also likely to be a transition structure.

The dihydrated isomers are, however, far more interesting. The structures are shown in Fig. 2, and were all formed from the monohydrated structures, by

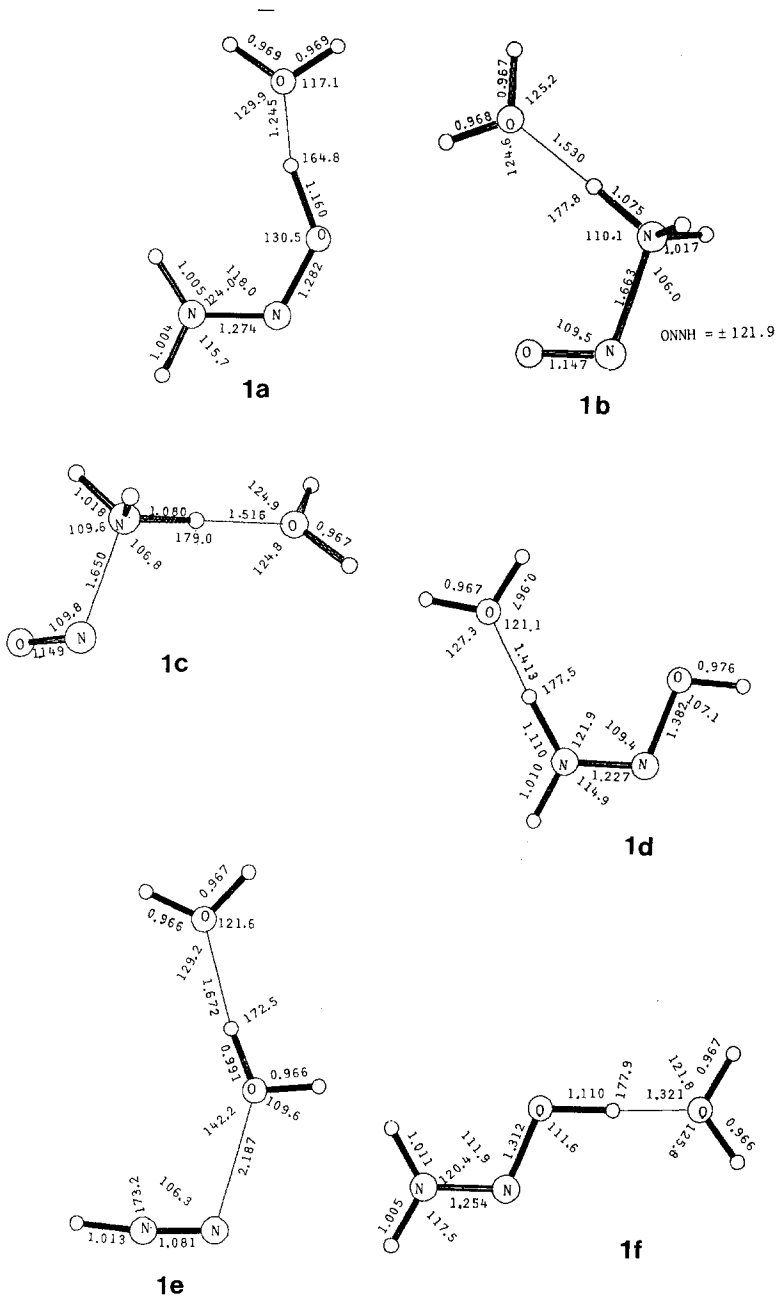


Fig. 1. Structures of monohydrated species

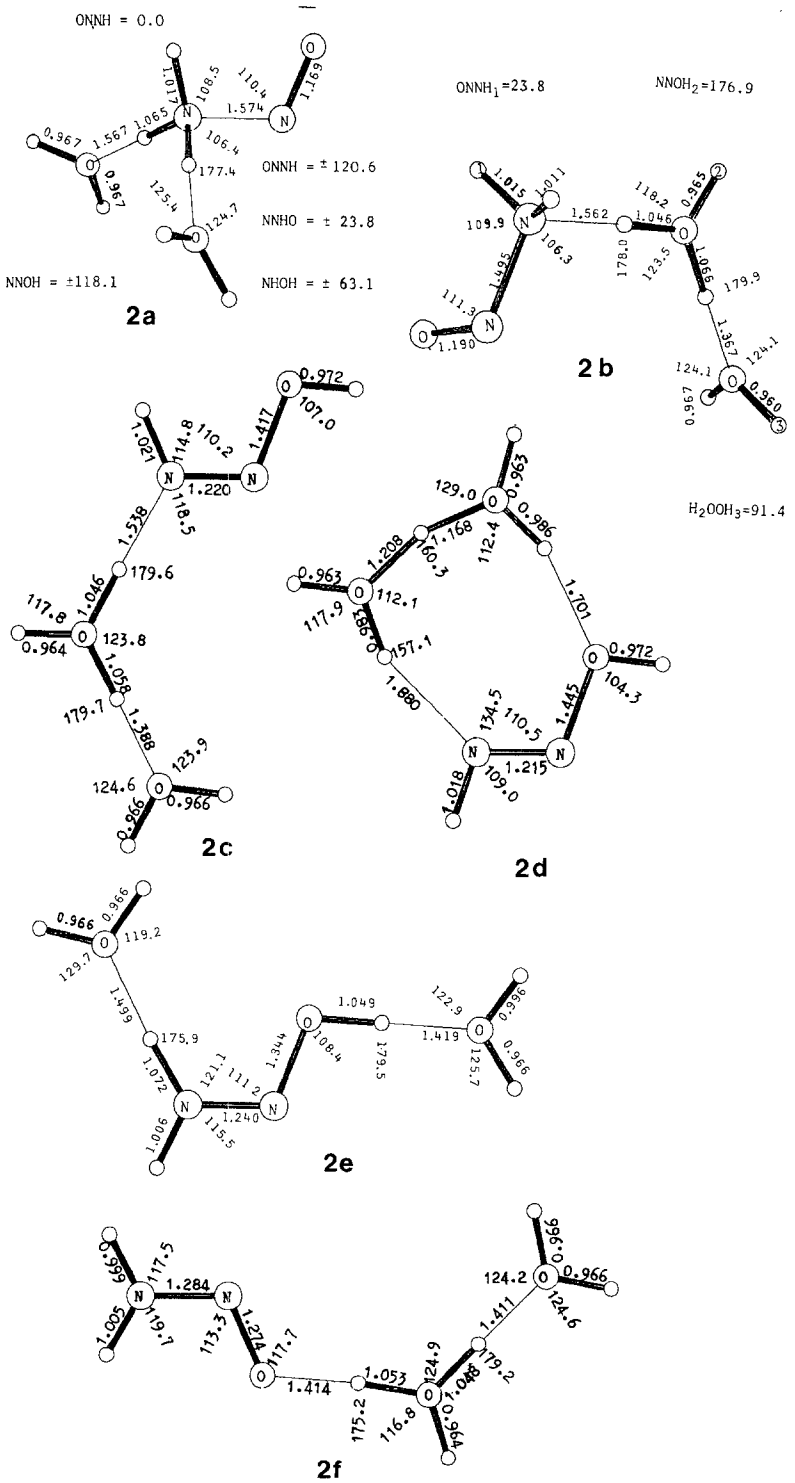


Fig. 2. Structures of dihydrated species

complete geometry relaxation; there was no energy barrier for this process. The structure (2b) is the N-protonated model nitrosamine involved in the formation of nitrosamines from the nitrosation of secondary amines by the nitrous acidium ion [25]. The parent molecule can form only one amino-proton based hydration chain. The structure (2a) could, therefore, be involved only in the nitrosation of primary amines. However, because (2b) is lower in energy than (2a), it appears that primary amine - nitrosonium ion complexes are also likely to be destroyed by a chain of two water molecules, to give the model monoalkylnitrosamine.

The structures (2c), (2d) and (2f) represent three different ways of forming water chains on H_2NNOH^+. The two structures, (2c) and (2d), result in the formation of HNNOH. However, (2f) is more stable than (2c) and (2d) by 23 and 16 kJ mol^{-1} respectively; the structure (2f) results in the regeneration of H_2NNO. Moreover, (2e) is also more stable than (2c) and (2d) by 15 and 8 kJ mol^{-1} respectively. The structures (2c) and (2d) show that the relative stabilities of *c,t*-HNNOH and *t,t*-HNNOH may be reversed in acid solution.

The structure (2d) is quite different from all the other ligand-H_3O^+-H_2O complexes studied in this article and elsewhere [25], as it is better represented as a ligand-$H_5O_2^+$ complex. (This structure may therefore be more sensitive to the inclusion of polarisation functions than the other structures; in the other structures we would expect that primary effect of including *d* orbitals would be to cause the H_3O^+ to become non-planar at its non-bonding hydrogen [28]).

Conclusions

The relative stability of H_2NNO and HNNOH, and their respective protonated complexes, suggests that the equilibrium between H_2NNO and HNNOH is towards the H_2NNO. The energy differences between these molecules are, however, small, and cannot be determined reliably at this level of approximation for either the neutral molecules or the cationic complexes. These calculations do show, however, that there is a low energy pathway between these molecules; this new mechanism involving protonation and dihydration can lead to the interconversion of H_2NNO and HNNOH without any energy barrier - it depends primarily on a rearrangement of the water molecules rather than a rearrangement of the molecule itself. This pathway is therefore more realistic than the formal proton shift (which is often assumed), particularly when the reaction occurs in acidic media - the usual conditions for nitrosation reactions [15, 29]. This mechanism may also be applicable to other formal proton shift reactions involving unstable intermediates.

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