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Theoretical Study of Oxidation Hydroxylation Reaction Mechanism for Nitrosodimethylamine by Oxygen Atom

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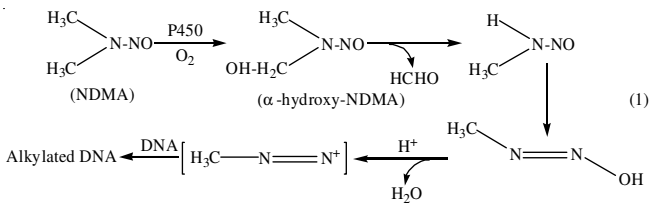
The oxidation hydroxylation reaction mechanism of nitrosodimethylamine (NDMA) by oxygen atom has been theoretically investigated at the B3LYP/6-31G** level. It is found that the path of the oxidation of the CH bond is easier than the path involving a singlet/triplet crossing. The study of the potential surface shows that both solvent effect at B3LYP/6-31G** level and basis set effect at MP2/6-311G** level in the gas phase have no effect on the oxidation hydroxylation reaction mechanism. The oxidation hydroxylation process of nitrosodimethylamine by atomic oxygen is exothermic reaction and easy to occur.

Key Words: Nitrosodimethylamine, Hydroxylation, B3LYP, MP2.

INTRODUCTION

N-Nitrosamines are strong carcinogens for animals and are widely found in our environment. In 1956, Magee and Barnes[1] reported that nitrosodimethylamine (NDMA) could induce liver cancer when it was fed to rats. Afterwards, there were a great deal of experimental studies about the chemical property, metabolism and carcinogenicity of nitrosamines[2-5]. In general, the nitrosamines are not the direct carcinogens[1, 6] but require enzymatic oxidative metabolism to convert into a precursor of the ultimate carcinogen. The most commonly accepted hypothesis for this activation is α-hydroxylation hypothesis. Hydrogens on the α-carbon of nitrosamines can be hydroxylated by a variety of oxidases and oxygenases (such as cytochrome P450-related enzymes). The resultant α-hydroxy-alkyl nitrosamine can finally metabolize into an alkyl diazonium ion and the corresponding carbonyl compound. The diazonium ion is commonly considered to be the putative ultimate carcinogen of possible metabolites[4,7-9]. From the carcinogenic mechanism of nitrosodimethylamine shown in eqn. 1, it can be seen that the hydroxylation of nitrosodimethylamine is the activation path and the formation of alkyl diazonium ion is the key to carcinogenesis of nitrosodimethylamine.

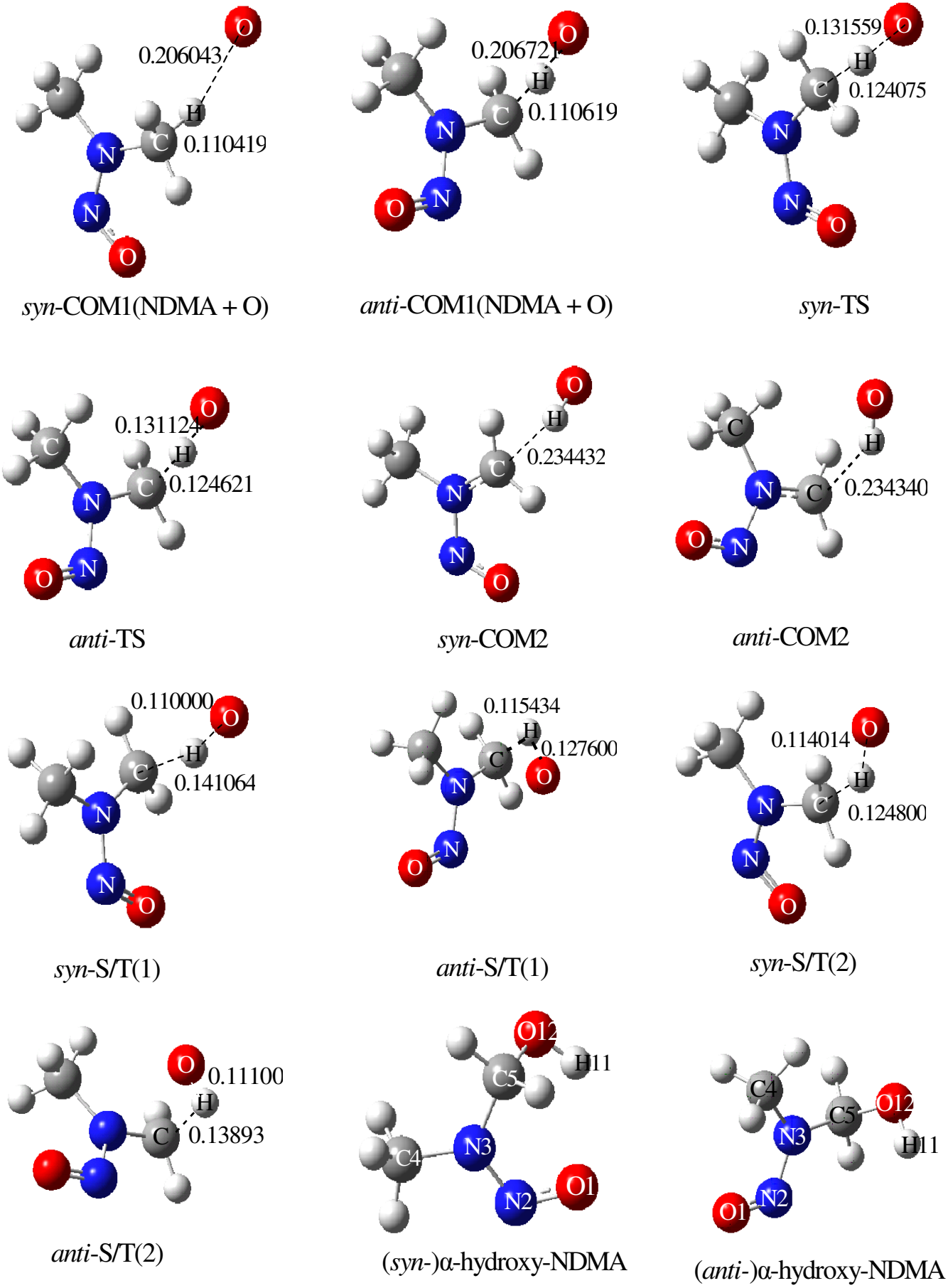
Nitrosodimethylamine is the simplest compound of strong carcinogenic aliphatic nitrosamine compounds. The experimental studies[10-13] have shown the carcinogenic mechanism of the compound, while the key of carcinogenesis of nitrosodimethylamine and its hydroxylation reaction mechanism have not been well studied theoretically up to now. In this paper, the oxidation hydroxylation reaction processes of nitrosodimethylamine are studied by means of the density functional theory (DFT).



(1)

EXPERIMENTAL

All calculations are performed using Gaussian 03 program package at the hybrid Hartree-Fork-density functional theory[14] B3LYP/6-31G**. And for the singlet/triplet crossing, the structures are optimized using the UB3LYP level density functional theory at the same basis set. The molecular systems are geometry optimized in vacuum, followed by vibrational frequency calculations within the harmonic approximation at the same level of theory, in order to characterize the stationary points as either minima or transition states. The key reaction paths are characterized further at the same level of theory, by performing intrinsic reaction coordinate (IRC)[15] from each gas phase optimized transition structure to confirm that they are connected to the corresponding two minima.



syn-COM1(NDMA + O) *anti*-COM1(NDMA + O) *syn*-TS

anti-TS *syn*-COM2 *anti*-COM2

syn-S/T(1) *anti*-S/T(1) *syn*-S/T(2)

anti-S/T(2) (*syn*-)α-hydroxy-NDMA (*anti*-)α-hydroxy-NDMA

Fig. 1. Optimized geometries and some of parameters (bond angles: nm)

TABLE-1
CALCULATED TOTAL ENERGIES (IN HARTREE), ZERO-POINT ENERGIES, RELATIVE ENERGIES (kJ/mol) AND VIBRATIONAL FREQUENCIES (cm^{-1}) (B3LYP/6-31G**)

Species	Total energies	Zero point energies	Relative energies	Frequencies
NDMA+O	-339.5419299	0.0	0.00	
anti-COM1	-339.5451731	0.0032502	-2.04	
syn-COM1	-339.5450451	0.0031222	-1.96	
anti-TS	-339.5415775	0.0003454	0.22	-1012.15
syn-TS	-339.5398480	0.0020749	1.30	-1025.59
anti-S/T(1)	-339.5217389 (T); -339.5217937 (S)		12.67	
anti-S/T(2)	-339.4831375 (T); -339.4831649 (S)		36.89	
syn-S/T(1)	-339.5119398 (T); -339.5119422 (S)		18.81	
syn-S/T(2)	-339.4911584 (T); -339.4911501 (S)		31.86	
anti-COM2	-339.5602042	0.0182803	-11.47	
syn-COM2	-339.5609974	0.0190745	-11.97	
(*anti*-)α-hydroxy-NDMA	-339.6975299	0.1556070	-97.64	
(*syn*-)α-hydroxy-NDMA	-339.6971918	0.1552689	-97.43	

*T the energies of triple state; *S the energies of single state

In order to obtain the more credible result, we have also performed the optimization and vibrational frequency calculations for all energy station points[16-18] at the MP2/6-311G** level. The solvent effect on the present reaction has been investigated by the PCM model[19] at the B3LYP-SCRF/6-31G** level with water solvent(=78.39, 298.15 K). All calculations have been completed on AMD-3800+ computer.

RESULTS AND DISCUSSION

The experiments[20-22] indicate that the source of atomic oxygen in metabolite aldehyde is molecular oxygen during the carcinogenic metabolism process of nitrosamine compounds. Hence, we studied the oxidation hydroxylation of nitrosodimethylamine by atomic oxygen and its subsequent metabolites as a typical process to simplify complex metabolism of organism.

Hydroxylation of nitrosodimethylamine by atomic oxygen: For the hydroxylation reaction of nitrosodimethylamine by atomic oxygen, the optimized geometries of all stationary points and some of the geometrical parameters are displayed in Fig. 1. The total energies, zero point energies, relative energies of corresponding structures and imaginary frequencies of transitional structures are listed in Table-1.

Two possible paths for the hydroxylation reaction of nitrosodimethylamine by atomic oxygen are as follows:

$$\text{Path 1:}\quad \text{NDMA} + {}^3\text{O} \xrightarrow[\text{(crossing point)}]{} \text{S / T} \longrightarrow \alpha\text{-hydroxy-NDMA} \qquad (2)$$

$$\text{Path 2:}\quad \text{NDMA} + {}^3\text{O} \xrightarrow[\text{(transition)}]{} \text{TS} \longrightarrow \alpha\text{-hydroxy-NDMA} \qquad (3)$$

As the ground state of atomic oxygen is a triplet ^{3}P state, the spin multiplicity of reactants (NDMA + O) is accordingly triplet state, while the product of α-hydroxy-nitrosodimethylamine (CH_3CH_2OHNNO, in Fig. 1) is singlet state, we speculate that singlet/triplet crossing might exist in the reaction process, which can be described in path 1. There are many crossing structures[23] on the potential energy surface connecting the reactants with the product. In present study, we found two types of singlet/triplet crossings, namely *anti*-S/T and *syn*-S/T according to CH bond's *anti*- and *syn*- location to nitroso group of nitrosodimethylamine. The energy difference between structures of triplet and singlet state is approximately 10^{-5} Hartree (Table-1). The reaction product *via anti*-S/T and *syn*-S/T is the same, which is α-hydroxy-nitrosodimethylamine. For Path 2, atomic oxygen oxidates the CH bond of nitrosodimethylamine directly and produces triplet state product COM2 ($CH_3CH_2NNO\cdot + OH\cdot$, in Fig. 2). The oxidation reaction has a transition state (TS) (Fig. 1) with a very low energy barrier. It was found that the reactants form a complex compound COM1 (Fig. 1), which lies somewhat lower in energy (*syn*-COM1: -1.96 kJ/mol; *anti*-COM1: -2.04 kJ/mol) than its predecessors. The products of Path 2 are complex COM2 of the two radicals ($CH_3CH_2NNO\cdot + OH\cdot$ in Fig. 1). Full geometry optimization of COM2 leads to the hydroxylation product of α-hydroxy-nitrosodimethylamine.

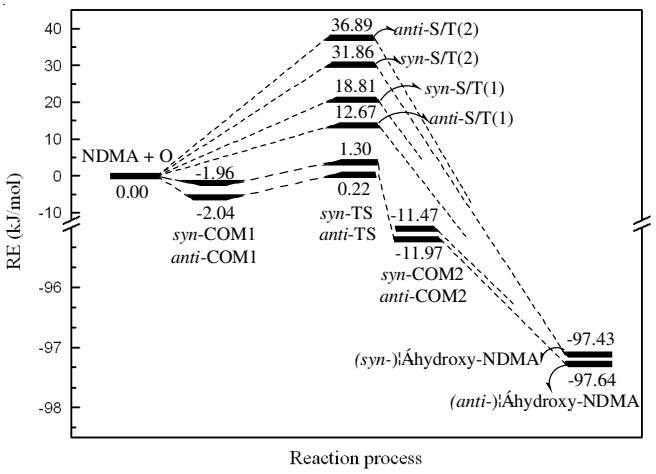


Fig. 2. Schematic potential energy surface of hydroxylation of nitrosodimethylamine

Fig. 2 shows the relative potential energy surface for the hydroxylation of nitrosodimethylamine by atomic oxygen (^{3}P). For Path 1, we found that the Singlet/Triplet crossing must overcome relatively higher energy barriers (*syn*-S/T(1), *syn*-S/T(2), *anti*-S/T(1) and *anti*-S/T(2) are 31.86, 18.81, 36.89 and 12.67 kJ/mol, respectively). However, for Path 2, the energy barriers of oxydation reaction *via syn*-TS and *anti*-TS are both 2.26 kJ/mol. So the oxidation of CH bond is the more advantageous hydroxylation reaction path. By comparing the

TABLE-2
CALCULATED TOTAL ENERGIES (IN HARTREE), ZERO-POINT ENERGIES, RELATIVE ENERGIES (kJ/mol) AND VIBRATIONAL FREQUENCIES (cm^{-1}) (IN THE GAS PHASE:MP2/6-311G**; IN SOLVENT WATER:B3LYP/6-31G**)

Species	Total energies		Zero point energies		Relative energies		Frequencies	
	Gas/MP2	Solvent	Gas/MP2	Solvent	Gas/MP2	Solvent	Gas/MP2	Solvent
NDMA+O	-338.7337684	-339.5532556	0.000	0.00	0.00	0.00		
syn-COM1	-338.7356775	-339.5531037	0.0019091	0.0001519	-1.20	0.10		
anti-COM1	-338.7354527	-339.5535786	0.0016843	0.000323	-1.06	-0.20		
syn-TS	-338.702033	-339.5496486	0.0317354	0.003607	19.91	2.26	-2296.43	-690.923
anti-TS	-338.7025424	-339.5500648	0.031226	0.0031908	19.59	2.00	-2249.31	-603.618
syn-COM2	-338.762549	-339.5786061	0.0287806	0.0253505	-18.06	-15.91		
anti-COM2	-338.7632843	-339.5709239	0.0295159	0.0176683	-18.52	-11.09		
(*syn*-)α-hydroxy-NDMA	-338.8903842	-339.5786061	0.158064	0.1569182	-98.28	-98.47		
(*anti*-)α-hydroxy-NDMA	-338.8918324	-339.713656	0.1566158	0.1604004	-99.19	-100.65		

energy of reactants (NDMA+O) with that of the product (α-hydroxy-NDMA), we found that the reaction of Path 2 appears to be exothermic.

Energy profile of hydroxylation reaction: As well known, the content of solvent is over 90 % in body. It is necessary to consider the solvent effect for the model hydroxylation reaction of nitrosodimethylamine. The solvent effect of the reaction has been investigated by the PCM model at the B3LYP-SCRF/6-31G** level with water as solvent. The results are listed in Table-2. Because the influence of larger basis set and method is very important, we have also performed the more credible calculation at the MP2/6-311G** level for the optimized reaction of direct oxidation. The Table-2 shows the optimization result.

In order to explain the energy profile for the hydroxylation reaction, the schematic description of the potential energy surface involving solvent effect and at more credible calculation level is shown in Fig. 3. The obtained results show solvent effect and basis set effect on the hydroxylation reaction of direct oxidation have no effect on the present reaction mechanism. In gas phase, the activation energy of the hydroxylation reaction at the MP2/6-311G** level (*syn*: 20.11 kJ/mol and *anti*: 20.64 kJ/mol) is higher than that calculated at B3LYP/6-31G** level (*syn*:2.2 kJ/mol; *anti*: 2.2 kJ/mol) and also higher than that calculated at B3LYP-SCRF/6-31G** with water solvent (*syn*: 2.16 kJ/mol; *anti*: 2.20 kJ/mol). However, compared with the reaction energies (*syn*: 98.28 kJ/mol; *anti*: 98.47 kJ/mol), activation energies are much lower. Therefore, the analysis of solvent effect and calculations at B3LYP/6-31G** and MP2/6-311G** level indicates that the hydroxylation reaction mechanism of nitrosodimethylamine by atomic oxygen can not be effected either by solvent effect or by calculation methods. It also shows that the hydroxylation of nitrosodimethylamine by atomic oxygen atom has lower activation energy and the reaction is easy to occur. The procession is the same for the hydroxylation of nitrosopyrrolidine (NPYR)[24]. Therefore, it is necessary to avoid production of atom oxygen so as to interrupt the carcinogenic activation of nitrosodimethylamine.

Conclusion

The hydroxylation reaction mechanism for nitrosodimethylamine (NDMA) has been theoretically studied at the B3LYP/6-31G** level. It is found that there are two crossings for each of *anti*-S/T and *syn*-S/T in path 1. In path 2, oxidation reaction to CH bond is easier than Path 1. For the oxidation reaction, the hydroxylation reaction mechanism is not changed no matter in the gas phase at more credible MP2/6-311G** level or considering solvent water at B3LYP/6-31G** level. The oxidation hydroxylation process of nitrosodimethylamine by atomic oxygen is exothermic reaction and easy to occur.

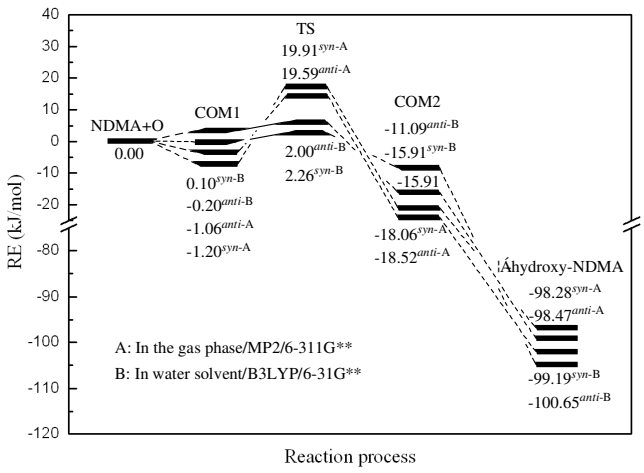


Fig. 3. Schematic potential energy surface of hydroxylation by oxidation

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