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Theoretical Investigation of *N*-Nitrosodimethylamine Formation from Dimethylamine Nitrosation Catalyzed by Carbonyl Compounds

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The carbonyl-compound-catalyzed nitrosation of amines to form carcinogenic nitrosamines under nonacidic condition is different from the classic nitrosation via acidification of nitrite anion. The mechanistic pathways of *N*-nitrosodimethylamine (NDMA) formation by the reactions of dimethylamine (DMA) with the nitrite anion catalyzed by carbonyl compounds have been investigated using the DFT/B3LYP method at the 6-311+G(d,p) level. The computational results show that the energy barriers of the nucleophilic addition reaction, which were calculated as 27−40 kcal/mol, increase significantly with methylation but vary slightly with chloromethylation on the carbonyl group. Comparison of energy barriers of this nucleophilic addition reaction and the electrophilic substitution reaction indicates that the former is the rate-determining step, from which the order of the catalytic activity is obtained as formaldehyde > chloral > acetaldehyde > acetone. Furthermore, analysis of electronic and steric effects on catalytic activity reveals that electron-withdrawing substituents decrease the energy barrier but electron-donating substituents and steric hindrance will block this catalytic reaction. Based on this discovery, fluoral is proposed as a good catalyst for the nitrosation of DMA by nitrite anion, which has a calculated energy barrier of about 26 kcal/mol. The results obtained in this work will help elucidate the mechanisms of formation of nitrosamines.

1. Introduction

Nitrosamines are a class of undesired industrial and environmental pollutants, many of which are carcinogenic, mutagenic, and teratogenic.[1−10] In particular, *N*-nitrosodimethylamine (NDMA), which is the simplest stable nitrosamine, has been demonstrated to be a cause of cancers in various organs, including liver, lung, and kidney, in animals.[11−15] Based on the results on animals, the U.S. Environmental Protection Agency (U.S. EPA) defined NDMA as a probable human carcinogen in 1997.[16]

In the past, NDMA was found in air, soil, water, and food.[17−23] Early studies have reported that the formation of NDMA can take place in physiological systems.[24−26] In view of its universality, numerous experimental and theoretical studies have been done to demonstrate the formation of NDMA,[27−40] and to explore effective methods to inhibit its formation.[41−45] In general, there are two different types of pathways contributing to the NDMA formation: the oxidation of dimethylhydrazine (UDMH) derived from dimethylamine (DMA)[37,39] and the nitrosation of DMA by nitrosating agents including NOCl, N_2O_3, N_2O_4, and $NOBF_4$.[28,32−35]

The reactions of DMA with nitrite anion under acidic conditions have been extensively studied, and the mechanistic pathway involving a N_2O_3 intermediate has been demonstrated using kinetic and theoretical investigations.[27,28,32,33] However, the mechanisms of NDMA formation under neutral and basic conditions, such as in drinking water and most foods, have remained open questions, and much research has been devoted to the formation of NDMA under nonacidic conditions.[31−40] In general, a catalyst is required for the nitrosation of DMA by the nitrite anion. Previously, two types of catalysts were identified. One was the chemicals that activate the nitrite anion, such as HOCl.[33,38] The other was first reported by Keefer and Roller in 1973,[31] and they are formaldehyde and chloral, which can catalyze the reaction of DMA and nitrite anion at pH 6−11. Recently, the authors of this paper theoretically investigated the reaction of DMA with nitrite anion catalyzed by carbon dioxide.[40] It is noteworthy that formaldehyde and chloral as well as carbon dioxide have the common structure of carbonyl group. What features should these catalysts involving a carbonyl group have?

Bearing this question in mind, in this work we elucidate the mechanistic pathways for the formation of NDMA mediated by carbonyl compounds from a theoretical aspect, and analyze the effect of substituents on the catalytic reactivity. The results obtained in this work will help us to better understand the mechanisms of nitrosamines formation.

2. Computation Details

All the structures of reactants, transition states, intermediates, and products were fully optimized by using Becke's three-parameter nonlocal exchange functional with the correlation functional of Lee, Yang, and Parr (the B3LYP method),[46,47] in conjunction with the 6-311+G(d,p) basis set. Previous investigations have demonstrated that although the B3LYP method underestimates the calculated energetic barriers, it provides excellent structures compared with the more sophisticated methods.[48−51] Since the main aim of this work is to elucidate the order of catalytic reactivity and to sum up the common characteristics of carbonyl catalysts, the underestimation of energy barriers calculated by the B3LYP method will not affect the conclusions.

Vibrational frequencies of each stationary point were calculated at the same (B3LYP/6-311+G(d,p)) level of theory to characterize the nature of the stationary points and give the zero-point vibrational energy (ZPVE). The minimum-energy path was

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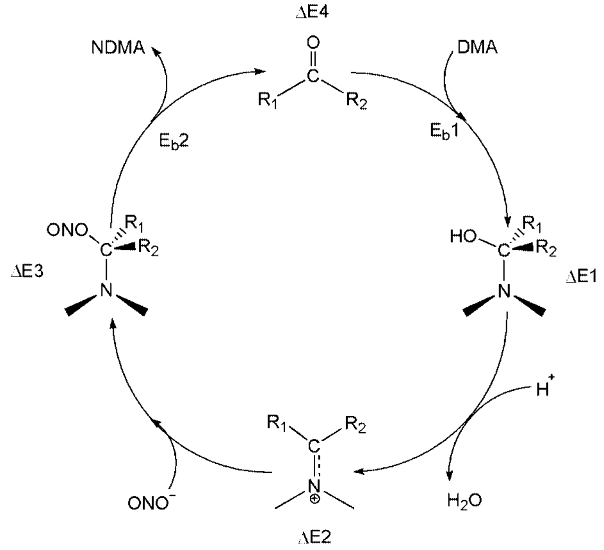
SCHEME 1: Mechanistic Pathway of the Reaction of DMA with Nitrite Anion Catalyzed by Carbonyl Compounds



obtained by using intrinsic reaction coordinate (IRC) calculations to confirm the connection of each transition state with the designated equilibrium species.[52] All the calculations presented in this paper were carried out with the GAUSSIAN-03 program package.[53]

To validate the B3LYP method, a single-point energy calculation has been carried out using the MP2 method. The solvent effect of water on the reactions of NDMA formation was also studied. Based on the optimized geometries at the B3LYP/6-311+G(d,p) level, the single-point energy calculation was performed with B3LYP at the 6-311+G(d,p) level, using the polarizable continuum model (PCM),[54] denoted as PCM−B3LYP/6-311G+(d,p)// B3LYP/6−311G+(d,p). The default dielectric constant (ϵ) of water was taken from the GAUSSIAN-03 program.

3. Results and Discussion

As seen in Scheme 1, which illustrates the mechanistic pathway modified from ref 31, the formation of nitrosodimethylamine (NDMA) by the reaction of dimethylamine (DMA) with nitrite anion catalyzed by carbonyl compounds proceeds via multiple steps. These steps are the nucleophilic addition of DMA with carbonyl compounds, the protonation of nascent adducts and elimination of water, and the reaction of nitrite anion with resulting positively charged intermediates leading to NDMA formation. As the second step of protonation and elimination had no transition state and was found to be barrierless in this work, the authors will give detailed discussions on the calculated results about the nucleophilic addition and the electrophilic substitution reactions in the following subsections.

Figure 1 presents the Mulliken atomic charges for carbonyl groups and some structural parameters in formaldehyde, acetaldehyde, acetone, chloral and fluoral, which will be hereafter denoted as FD, AD, AO, CA, and FA, respectively, for simplicity.

Based on the importance of the free energy profile in the reactions, the relative Gibbs free energies (RG) in the gas phase were also shown in Tables S1 (see Supporting Information). It is found that the values of relative Gibbs free energies in the gas phase are in accordance with those of relative energies (RE). Thus, unless otherwise noted, all energies discussed in the following parts are the calculated adiabatic potential energies (classical potential energy + zero-point energy corrections).

3.1. Nucleophilic Additions. The transition states (TS1-FD, TS1-AD, TS1-AO, and TS1-CA) of these nucleophilic addition reactions of DMA with carbonyl compounds (FD, AD, AO, and CA) were found in this work and shown in Figure 2. In these transition states, the N−H bond has been broken when the bond between the carbon atom of the carbonyl group and the nitrogen atom of the aminyl group is forming. The energy released from the formed bond can compensate somewhat for the requirement of the energy for the breaking bond, which contributes to the majority of the energy barrier of the addition reaction. In view of the relation of structure and energy, the bond lengths of the broken and formed bonds in the transition states are the indicators of the relative energy. As seen from Figure 2, the partially breaking N1−H2 bond lengths were calculated as 1.212, 1.215, and 1.221 Å, in TS1-FD, TS1-AD, and TS1-AO, respectively, whereas the partially formed N1−C12 bond lengths were predicted as 1.568, 1.603, and 1.653 Å. The increasing N1−H2 and N1−C12 bond lengths indicate that increased energies were required for reaching these transition states. The energy barriers were calculated to be 27.0, 32.3, and 39.7 kcal/mol at TS1-FD, TS1-AD, and TS1-AO, respectively.

Figure 2 also shows the geometry of the transition state (TS1-CA) of DMA reacting with CA, where the formed N1−C12 bond length was found to be 1.582 Å and the broken N1−H2 bond length was predicted as 1.241 Å. The energy barrier was calculated to be 28.8 kcal/mol, which is higher than that of FD (27.0 kcal/mol) but lower than that of AD (32.3 kcal/mol). The reason is that although the N1−H2 bond length in TS1-CA is longer than those in TS1-FD (1.212 Å) and TS1-AD (1.215 Å), the N1−C12 bond length in TS1-CA is longer than that in TS1-FD (1.568 Å) but shorter than that in TS1-AD (1.603 Å). After these comparisons, we can conclude that the length of the formed N1−C12 bond has a larger influence on the energy barrier than that of the broken N1−H2 bond.

Considering the effect of the substituents allows an understanding of the reactivity of the nucleophilic addition reaction of DMA with carbonyl compounds. As presented in Figure 1, the increased Mulliken charges at the carbon atoms of the carbonyl groups with alkylation were calculated as 0.018, 0.180, and 0.183 e in FD, AD, and AO, respectively. However, the carbon atoms attacked by the nitrogen atoms carry an increased negative Mulliken charge with methylation, which were predicated as −0.011, −0.017, and −0.133 e. These opposite electronic effects of methylation in the ground states and in the transition states attribute to the character of the methyl group, which has a higher electronegativity than hydrogen and the electron-donating effect of resonance. Figure 3 illustrates that when the σ molecular orbital of the methyl group partially overlaps the p molecular orbital of the carbonyl group in the ground state, the methyl group shows an electron-withdrawing effect, but when there is a strong hyperconjugation in the transition state, the methyl group is an electron-donating substituent.[55]

The electronic movements in the nucleophilic addition of DMA to the carbonyl group are similar to those in the [4 + 2] pericyclic reaction (see Figure 4), in which occurs a concerted shift of electrons in a cyclic transition state causing σ and π bonds to simultaneously break and form.[56−58] To better understand the reactivity of carbonyl compounds with DMA, a frontier molecular orbital (FMO) analysis was done to elucidate the differences of energy barriers in the addition reactions. According to FMO theory, the reactivity of cycloaddition reaction is

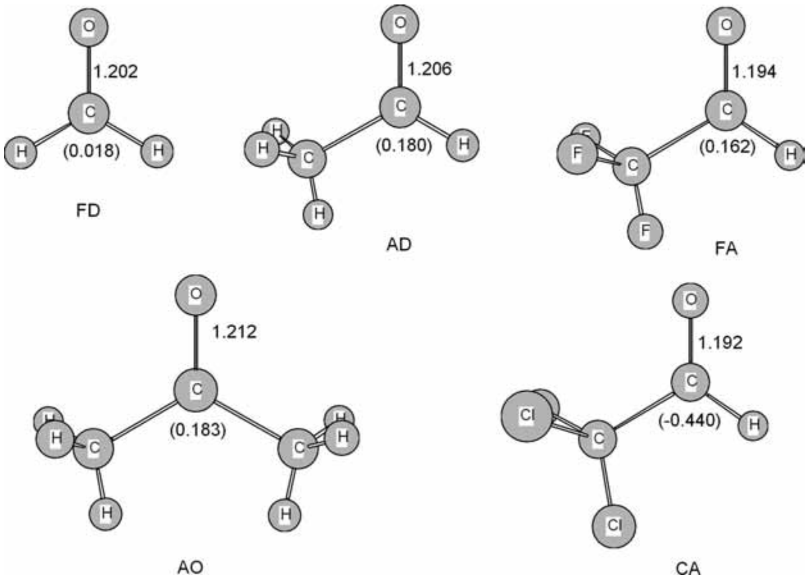


Figure 1. Calculated Mulliken atomic charges for carbonyl groups and some structural parameters in each carbonyl compound.

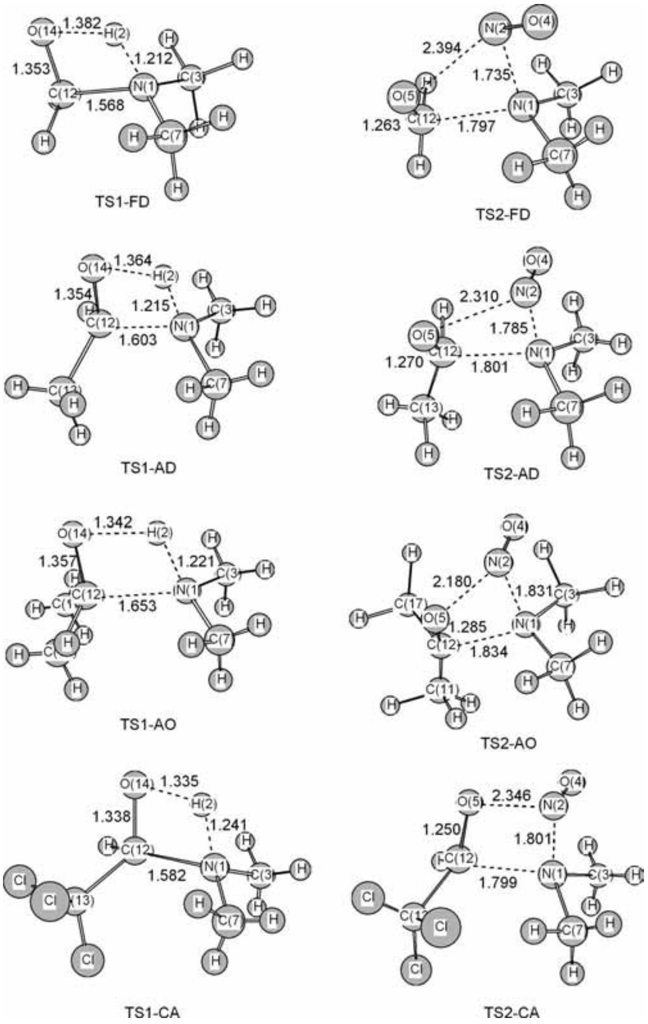


Figure 2. Optimized geometries and main parameters of each transition state encountered in the reaction of DMA with nitrite anion.

related to the energy gap between the highest occupied molecular orbital (HOMO) of the nucleophile and the lowest unoccupied molecular orbital (LUMO) of the electrophile.[59,60] Spino et al. demonstrated that the FMO theory could predict the relative reactivity in the normal electron demand (NED) DA reaction but not in the inverse electron demand (IED) one.[61] For the pericyclic reaction studied in this paper, the energies of the HOMO and LUMO of DMA (as nucleophile) and carbonyl compounds (as electrophile) have been calculated and are depicted in Figure 5. As seen in Figure 5, the energy of the LUMO of FD calculated as −0.064 au is lower than that of AO by about 0.036 au, with that of AD in-between. Thus the authors conclude that the methylation on carbonyl group increases the $HOMO_{DMA}-LUMO_{cat}$ energy gap, and thus results in an increased energy barrier for catalysts FD, AD, and AO. In other words, electron-donating substituents increase the energy barrier of this nucleophilic addition.

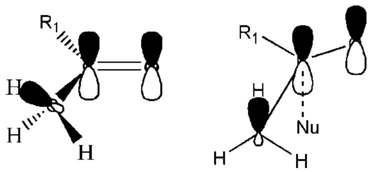
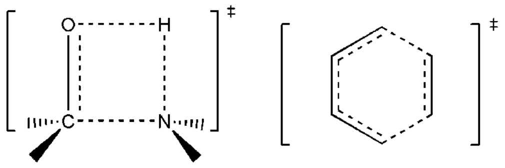


Figure 3. Schematic profile of the resonance of the σ molecular orbital of the methyl group with the p molecular orbital of the carbonyl group in the reactant and transition state.



TS **[4+2]**

Figure 4. Schematic profile of a cyclic transition state.

As seen in Figure 5, the energy of the LUMO of CA was calculated to be −0.091 au, which is significantly lower than that of the corresponding AD by more than 0.050 au. The difference of energy indicates that the chlorination at the methyl group can decrease the $HOMO_{DMA}-LUMO_{cat}$ energy gap and thus lead to the lower energy barrier for the addition of DMA with CA. Therefore, the authors conclude that electron-withdrawing substituents decrease the energy barrier of this nucleophilic addition.

3.2. Electrophilic Substitution. After the protonation of the resulting adducts, a molecule of water is eliminated without a transition state, giving rise to positively charged intermediates.

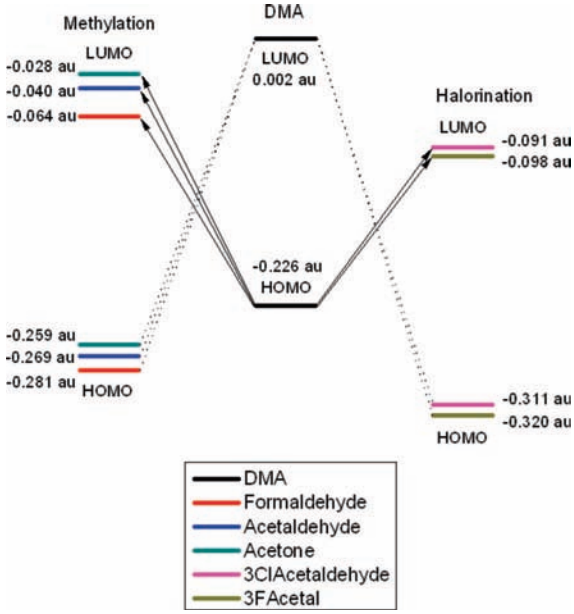


Figure 5. Schematic profiles of the energies of the HOMO and LUMO of DMA and carbonyl compounds.

The nascent intermediates are scavenged by the nitrite anion, leading to the formation of prereactants of electrophilic substitution. The optimized structures of the corresponding transition states of electrophilic substitution are depicted in Figure 2. The partially breaking N1−C12 bond lengths were calculated to be 1.797, 1.801, and 1.834 Å in TS2-FD, TS2-AD, and TS2-AO, respectively. The trend in the N1−C12 bond-length elongation indicates that methylation enhances the leaving ability of the carbonyl compounds. For the electron-donating effect of the methyl group, the positive charge at the carbon atom of the carbonyl group spreads to the methyl group. In addition, an increased steric strain leads to the increased ability of the carbonyl compound to leave with methylation. The energy barriers of the electrophilic substitution were calculated to be 26.0, 21.6, and 21.6 kcal/mol at TS2-FD, TS2-AD, and TS2-AO, respectively. The decreased energy barriers indicate that the order of the reactivity of the electrophilic substitution is PR-FD < PR-AD ∼ PR-AO.

In addition, the electrophilicity of the nitroso group in the prereactants has a significant influence on the reactivity of this electrophilic substitution. As seen in Table 2, the nitrogen atoms of the nitroso groups carried decreased Mulliken charges which were found to be −0.084, −0.068, and −0.052 e in PR-FD, PR-AD, and PR-AO, respectively. In view of the electrophilicity of nitroso group, the same order of the reactivity as above was obtained.

As CA is the catalyst, the intramolecular electrophilic substitution proceeds via the transition state of TS2-CA. As seen in Figure 2, the partially breaking N1−C12 bond length in TS2-CA was between the lengths of the N1−C12 bond in TS2-FD and TS2-AD, while the partially formed N1−N2 bond length was between the lengths of the N1−N2 bond in TS2-AD and TS2-AO. The energy barrier at TS2-CA was calculated to be 18.9 kcal/mol, lower than that at TS2-AO by 3 kcal/mol. An explanation for this is that the chlorination of methyl group decreased the HOMO−LUMO energy gap from 92.2 kcal/mol in PR-AO to 86.6 kcal/mol in PR-CA; see Table 3.

Comparison of the data presented in Table 1 indicates that the nucleophilic addition reaction is the rate-determining step, for which the energy barriers were calculated as 27.0, 28.8, 32.3, and 39.7 kcal/mol for FD, CA, AD, and AO, respectively. The catalytic activity increases with the decreased energy barriers; therefore, the order of the catalytic activity is FD > CA > AD > AO. This result agrees with that of the early study in which the FD and CA, but not AD, can catalyze the nitrosation of DMA by nitrite anion.[31] In addition, as shown in Table 1, all the steps in the whole catalyzed reaction are exothermic processes, and the second step is the most exothermic one among them.

Analysis of the structure−catalysis relationship of the carbonyl compounds showed that the predicted values of the energy barrier (E_b^p) depend on the dual-variate linear regression equation given as eq 1, where the E_{LUMO}^{cat} means the energy of the LUMO of the catalyst and the V_{cat} represents the volume of the catalyst inside a contour of 0.001 electron/bohr^3 density and was calculated at the B3LYP/6-311+G(d,p) level using the Gaussian-03 program package. The LUMO energy of the catalyst correlates positively (the coefficient of correlation is 0.848) with the electronic effect of the substituents. Figure 6 illustrates that the E_b^p correlates linearly with the calculated energy barrier (E_b^c), with the value of the square of the correlation coefficient (R^2) being 0.9764. Based on the above discussion, therefore, the effect of the substituents is that electron-withdrawing substituents enhance the catalytic activity of carbonyl compounds but electron-donating substituents and steric hindrances block it.

$$E_b^p = 179.683E_{LUMO}^{cat} + 0.165V_{cat} + 33.902 \qquad (1)$$

3.3. Predication of Fluoral as a Catalyst for DMA Reacting with Nitrite Anion. Fluorinated compounds exhibit unique properties[62] and thus are extensively used in pharmaceutical[63] and agrochemical fields.[64] Especially, trifluoroacetaldehyde (fluoral, denoted as FA in this work), which is industrially produced by reduction of trifluoroacetic acid, has rich chemical reactivity. In this work, we propose fluoral to be a good catalyst for the reaction of DMA with nitrite anion, the mechanism of which was elucidated from a theoretical aspect. The encountered transition states in this catalytic process were found to be TS1-FA and TS2-FA for the nucleophilic addition and electrophilic substitution, respectively. TS1-FA and TS2-FA, shown in Figure 7, share the common characteristics of the transition states described above. The energy barriers were calculated as 25.8 and 20.1 kcal/mol at TS1-FA and TS2-FA, respectively; therefore, the nucleophilic addition is the rate-determining step of the reaction of DMA with nitrite anion. As seen in Figure 5, the energy gap of the HOMO of DMA and the LUMO of FA is the lowest, and this is the reason that the energy barrier of FA catalytic reaction is lower than those of FD (27.0 kcal/mol) and CA (28.8 kcal/mol). Consequently, the conclusion can be drawn that FA is a good catalyst for DMA reacting with nitrite anion. This result in turn supports the previous conclusion that the catalysts have the common features of electron-withdrawal and small steric hindrance; see Figure 6.

3.4. The Effects of Solvent. The solvent effect of water on the formation of NDMA was also considered using the PCM-B3LYP/6-311+G(d,p) method. As can be seen from Table 1, in aqueous solvation the energy barriers for nucleophilic addition at TS1-FD, TS1-AD, and TS1-AO were calculated to be 17.1, 23.9, and 32.7 kcal/mol, which were decreased by 9.9, 8.4, and 7.0 kcal/mol compared to those values in the gas phase. The decreased solvent effect of water from TS1-FD to TS1-AO is because the methylation on the carbonyl group decreased the strength of the hydrogen bonds between the water and catalysts. The energy barriers at TS1-CA and TS1-FA, which were calculated as 28.8 and 25.8 kcal/mol in the gas phase, decreased to be 21.2 and 18.4 kcal/mol in aqueous solvation. In addition,

TABLE 1: Energy Barriers (E_b) and Reaction Energies (ΔE) with Zero-Point Energy Corrections for Each Step (in Scheme 1) in the Cycle of Catalyzed Reactions in the Gas Phase and Water Calculated at the B3LYP/6-311+G(d,p) Level, in kcal/mol[a]

	in the gas phase						in water					
cat	E_b1	E_b2	$\Delta E1$	$\Delta E2$	$\Delta E3$	$\Delta E4$	E_b1	E_b2	$\Delta E1$	$\Delta E2$	$\Delta E3$	$\Delta E4$
FD	27.0(23.4)	26.0(23.7)	−8.3	−218.0	−120.7	−10.4	17.1	17.1	−11.1	−289.2	7.4	−14.2
AD	32.3(26.2)	21.6(20.8)	−1.3	−227.1	−109.7	−19.9	23.9	13.5	−3.4	−294.7	14.7	−25.4
AO	39.7(29.8)	21.6(20.8)	7.0	−233.9	−103.0	−27.4	32.7	14.8	5.8	−298.4	17.7	−31.9
CA	28.8(22.6)	18.9(15.8)	−3.2	−210.1	−126.0	−19.6	21.2	11.2	−6.3	−279.0	1.4	−25.8
FA	25.8(21.6)	20.1(16.8)	−7.5	−202.9	−132.6	−13.0	18.4	11.2	−9.4	−276.1	−1.0	−18.3

[a] For comparison, the energy barriers calculated at the MP2/6-311+G(d,p) level based on the B3LYP/6-311+G(d,p) optimized structures are also presented in parentheses.

TABLE 2: Mulliken Atomic Charges at C12 and N2 in Some Transition States

species	C12	species	N2
TS1-FA	−0.011	TS2-FA	−0.084
TS1-AD	−0.017	TS2-AD	−0.068
TS1-AO	−0.133	TS2-AO	−0.052

TABLE 3: Energies of the HOMO and LUMO as Well as the HOMO−LUMO Energy Gaps, in kcal/mol, in Prereactants of Electrophilic Substitution

species	E_H	E_L	E_{H-L}
PR-FD	−150.6	−57.7	92.9
PR-AD	−145.0	−52.7	92.3
PR-AO	−143.7	−51.5	92.2
PR-CA	−153.7	−67.1	86.6
PR-FA	−156.9	−69.7	87.2

the solvent effect of water decreased the energy barriers of electrophilic substitution reactions by 6∼9 kcal/mol.

It is notable that the ionic intermediates (the reactants) of the electrophilic step were stabilized in water and the formation of prereactants was changed from exothermic process (−103.0∼−132.6 kcal/mol) in the gas phase to endothermic process (1.4∼17.7 kcal/mol) in water except when FA was a catalyst (−1.0 kcal/mol). The comparison of the energy barriers of each step shows that the nucleophilic addition is the rate-determining step in aqueous solvation, which is in good agreement with the results in the gas phase.

It is important to remark that the PCM as an implicit solvent model gives excellent results in treating the strong long-rang solute−solvent interactions which dominate many solvation phenomena but it does not satisfactorily consider the mediation of solvent in reactions. Therefore, a further investigation will be devoted to test if the water is involved in the transition states or not.

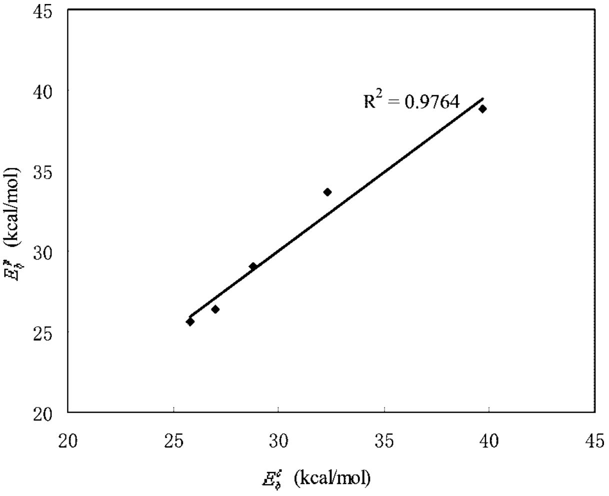


Figure 6. Prediction values of energy barrier (E_b^p) versus the calculated energy barrier (E_b^c).

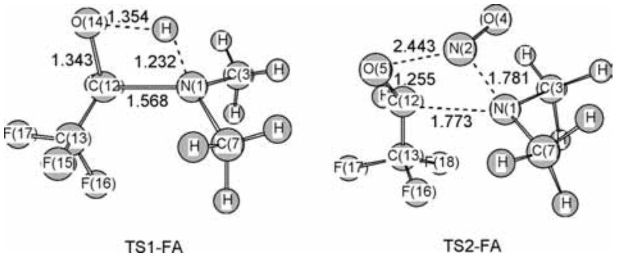


Figure 7. Optimized geometries and main parameters of the transition states of the reaction of DMA with nitrite anion catalyzed by FA.

4. Summary

In this work, we have carried out a theoretical investigation of the mechanistic pathway of the reactions of DMA with nitrite anion catalyzed by carbonyl compounds. A multiple-step process, involving the nucleophilic addition of DMA with carbonyl compounds, the protonation of nascent adducts and elimination of water, and the reaction of nitrite anion with resulting positively charged intermediates leading to NDMA formation, has been examined. The computational results show that the energy barriers of the nucleophilic addition reaction, which were calculated as 27∼40 kcal/mol, significantly increase with alkylation but slightly vary with chloromethylation on the carbonyl group. Comparison of energy barriers of this nucleophilic addition reaction and the electrophilic substitution reaction indicates that the former is the rate-determining step. Thus, the order of the catalytic activity is obtained as formaldehyde (FD) > chloral (CA) > acetaldehyde (AD) > acetone (AO), which reasonably explains the early results that formaldehyde and chloral but not other carbonyl compounds are the catalysts of this reaction.

Furthermore, analysis of the electronic and steric effects on catalytic activity reveals that electron-withdrawing substituents can decrease the energy barrier but electron-donating substituents and steric hindrance will block this catalytic reaction. Based on this discovery, the authors propose that fluoral (FA), which has an electron-withdrawing substituent and a small hindrance, is also a good catalyst for the reaction of DMA with nitrite anion, which has a calculated energy barrier of about 26 kcal/mol. These results will be helpful in elucidating the mechanisms of formation of nitrosamines and discovering efficient inhibitors.

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Supporting Information Available: The optimized structures and main parameters of the reactants, intermediates, and products; the energies and the lowest harmonic vibrational frequencies (LHVF) of the species in the formation of NDMA at the B3LYP/6-311+G(d,p) level; geometries (*x*, *y*, *z* coordination). These materials are available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Wolf, Th.; Niehaus-Rolf, C.; Luepke, N.-P. *Food Chem. Toxicol.* **2003**, *41*, 561.

(2) Mittal, G.; Brar, A. P. S.; Soni, G. *Exp. Toxicol. Pathol.* **2008**, *59*, 409.

(3) Mirvish, S. S. *Cancer Lett.* **1995**, *93*, 17.

(4) Dennehy, M. K.; Loeppky, R. N. *Chem. Res. Toxicol.* **2005**, *18*, 556.

(5) Mijal, R. S.; Loktionova, N. A.; Vu, C. C.; Pegg, A. E.; Peterson, L. A. *Chem. Res. Toxicol.* **2005**, *18*, 1619.

(6) Hecht, S. S. *Chem. Res. Toxicol.* **1998**, *11*, 559.

(7) Lin, H. L.; Hollenberg, P. F. *Chem. Res. Toxicol.* **2001**, *14*, 562.

(8) Goto, Y.; Matsuda, T.; Ito, K.; Huh, N. H.; Thomale, J.; Rajewsky, M. F.; Hayatsu, H.; Negishi, T. *Mutat. Res.* **1999**, *425*, 125.

(9) Anderson, L. M.; Souliotis, V. L.; Chhabra, S. K.; Moskal, T. J.; Harbaugh, S. D.; Kyrtopoulos, S. A. *Int. J. Cancer* **1996**, *66*, 130.

(10) Barnes, J. M.; Magee, P. N. *J. Cancer* **1956**, *10*, 114.

(11) Barnes, J. M.; Magee, P. N. *Adv. Cancer Res.* **1967**, *10*, 163.

(12) Mizgireuv, I. V.; Majorova, I. G.; Gorodinskaya, V. M.; Khudoley, V. V.; Revskoy, S. Y. *Toxicol. Pathol.* **2004**, *32*, 514.

(13) Fukushima, S.; Wanibuchi, H.; Morimura, K.; Nakae, D.; Tsuda, H.; Imaida, K.; Shirai, T.; Tatematsu, M.; Tsukamoto, T.; Hirose, M.; Furukawa, F. *Cancer Lett.* **2005**, *222*, 11.

(14) Tanaka, A.; Hisanaga, A.; Inamasu, T.; Hirata, M.; Ishinishi, N. *Food Chem. Toxicol.* **1988**, *26*, 847.

(15) Anderson, L. M.; Carter, J. P.; Logsdon, D. L.; Driver, C. L.; Kovatch, R. M. *Carcinogenesis* **1992**, *13*, 2107.

(16) http://www.epa.gov/iris/subst/0045.htm.

(17) Charrois, J. W. A.; Arend, M. W.; Froese, K. L.; Hrudey, S. E. *Environ. Sci. Technol.* **2004**, *38*, 4835.

(18) Tomkins, B. A.; Griest, W. H. *Anal. Chem.* **1996**, *68*, 2533.

(19) Zhao, Y.-Y.; Boyd, J.; Hrudey, S. E.; Li, X.-F. *Environ. Sci. Technol.* **2006**, *40*, 7636.

(20) Yurchenko, S.; Mölder, U. *Food Chem.* **2006**, *96*, 325.

(21) Gloria, M. B. A.; Barbour, J. F.; Scanlan, R. A. *J. Agric. Food Chem.* **1997**, *45*, 1816.

(22) Haruta, S.; Chen, W. P.; Gan, J.; Šimůnek, J.; Chang, A. C.; Wu, L. S. *Ecotoxicol. Environ. Saf.* **2008**, *69*, 374.

(23) Andrzejewski, P.; Kasprzyk-Hordern, B.; Nawrocki, J. *Water Res.* **2008**, *42*, 863.

(24) Ohsawa, K.-I.; Nakagawa, S.-Y.; Kimura, M.; Shimada, C.; Tsuda, S.; Kabasawa, K.; Kawaguchi, S.; Sasaki, Y. F. *Mutat. Res.—Gen. Toxicol. Eng.* **2003**, *39*, 65.

(25) Krul, C. A. M.; Zeilmaker, M. J.; Schothorst, R. C.; Havenaar, R. *Food Chem. Toxicol.* **2004**, *42*, 51.

(26) Huang, Y. G.; Ji, J. D.; Hou, Q. N. *Mutat. Res.—Fundam. Mol. M.* **1996**, *358*, 7.

(27) Mirvish, S. S. *J. Natl. Cancer Inst.* **1970**, *44*, 633.

(28) Mirvish, S. S. *Toxicol. Appl. Pharmacol.* **1975**, *31*, 325.

(29) Margerum, D. W.; Schurter, L. M.; Hobson, J.; Moore, E. E. *Environ. Sci. Technol.* **1994**, *28*, 331.

(30) Andrzejewski, P.; Barbara, K. H.; Nawrocki, J. *Desalination* **2005**, *176*, 37.

(31) Keefer, L. K.; Roller, P. P. *Science* **1973**, *181*, 1245.

(32) Lv, C. L.; Liu, Y. D.; Wang, Y. H.; Zhong, R. G. *Acta Chim. Sin.* **2007**, *65*, 1568.

(33) Choi, J.; Valentine, R. L. *Environ. Sci. Technol.* **2003**, *37*, 4871.

(34) Zhao, Y. L.; Garrison, S. L.; Gonzalez, C.; Thweatt, W. D.; Marquez, M. *J. Phys. Chem. A* **2007**, *111*, 2200.

(35) Lv, C. L.; Liu, Y. D.; Zhong, R. G. *J. Phys. Chem. A* **2008**, *112*, 7098.

(36) Choi, J.; Valentine, R. L. *Water Res.* **2002**, *36*, 817.

(37) Mitch, W. A.; Sedlak, D. L. *Environ. Sci. Technol.* **2002**, *36*, 588.

(38) Schreiber, I. M.; Mitch, W. A. *Environ. Sci. Technol.* **2005**, *39*, 3811.

(39) Schreiber, I. M.; Mitch, W. A. *Environ. Sci. Technol.* **2006**, *40*, 6007.

(40) Lv, C. L.; Liu, Y. D.; Wang, Y. H.; Zhong, R. G. *J. Mol. Struct. (THEOCHEM)* **2007**, *802*, 1.

(41) Choi, S. Y.; Chung, M. J.; Sung, N. J. *Food Chem. Toxicol.* **2002**, *40*, 949.

(42) Wu, Z. Y.; Wang, H. J.; Ma, L. L.; Xue, J.; Zhu, J. H. *Micropor. Mesopor. Mater.* **2008**, *109*, 436.

(43) Plumlee, M. H.; López-Mesas, M.; Heidlberger, A.; Ishida, K. P.; Reinhard, M. *Water Res.* **2008**, *42*, 347.

(44) Chung, M. J.; Lee, S. H.; Sung, N. J. *Cancer Lett.* **2002**, *182*, 1.

(45) Hiramoto, K.; Ryuno, Y.; Kikugawa, K. *Mutat. Res.—Gen. Toxicol. Eng.* **2002**, *520*, 103.

(46) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(47) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(48) Musaev, D. G.; Hirao, K. *J. Phys. Chem. A* **2003**, *107*, 1563.

(49) Bach, R. D.; Gluhkovtsev, M. N.; Canepa, C. *J. Am. Chem. Soc.* **1998**, *120*, 775.

(50) Musaev, D. G.; Geletii Yu., V.; Hill, C. L.; Hirao, K. *J. Am. Chem. Soc.* **2003**, *125*, 3877.

(51) Shustov, G. V.; Spinney, R.; Rauk, A. *J. Am. Chem. Soc.* **2000**, *122*, 1191.

(52) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154.

(53) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas,O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, revision C.02*; Gaussian, Inc.: Wallingford, CT, 2004.

(54) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027.

(55) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 6th ed.*; Wiley & Sons: New York, 2007.

(56) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed.* **1969**, *8*, 781.

(57) Peña-Gallego, A.; Rodríguez-Otero, J.; Cabaleiro-Lago, E. M. *Tetrahedron* **2007**, *63*, 4937.

(58) Bushweller, C. H.; Ross, J. A.; Lemal, D. M. *J. Am. Chem. Soc.* **1977**, *99*, 629.

(59) Epiotis, N. D.; Cherry, W. *J. Am. Chem. Soc.* **1976**, *98*, 5432.

(60) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience: New York, 1976.

(61) Spino, C.; Rezaei, H.; Dory, Y. L. *J. Org. Chem.* **2004**, *69*, 757.

(62) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3.

(63) Filler, R.; Kobayashi, Y.; Yagulpolskii, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993.

(64) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994.

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