REGULAR ARTICLE

Structure–activity relationship of nitrosating agents in the nitrosation reactions of ammonia: a theoretical study

Yong Dong Liu · Ru Gang Zhong

Abstract Nitrosating agents (NAs) stimulate the formation of powerful mutagenic and carcinogenic N-nitrosamines. As a model reaction, the nitrosation of ammonia by a series of NAs, i.e., HONO, N_2O_3, N_2O_4, ONOOH, ONCl, ONBr, ONSCN, $ONOCH_3$, $ONOC_2H_5$, ONNC, ONOCl, and $ONOSOCH_3$, was investigated at the CBS-QB3 level of theory. A structure–activity relationship of NAs in the nitrosation reactions of ammonia was established. The results indicate that the nitrosating reactivity of NAs (ON–X) has definite relationship with the heterolytic bond dissociation energies of ON–X and H–X, Mulliken charges of N and X atoms as well as number of the atoms in the ring of the transition state. In light of the established structure–reactivity relationship of NAs, ONNC was found to be a potential powerful nitrosating species.

Keywords Nitrosating agents (NAs) ·
Structure–activity relationship · Nitrosation reaction

1 Introduction

Nitrosation reactions have attracted extensive attention mainly due to the specific properties of their products. N-nitrosamines as products of N-nitrosation of amines are a class of undesired industrial and environmental pollutants, and many of them are highly carcinogenic, mutagenic, and teratogenic [1–8]. Other products such as S-nitrosothiols are considered to play a major role in storing, transporting and releasing nitric oxide in vivo [9, 10]. Furthermore, as it
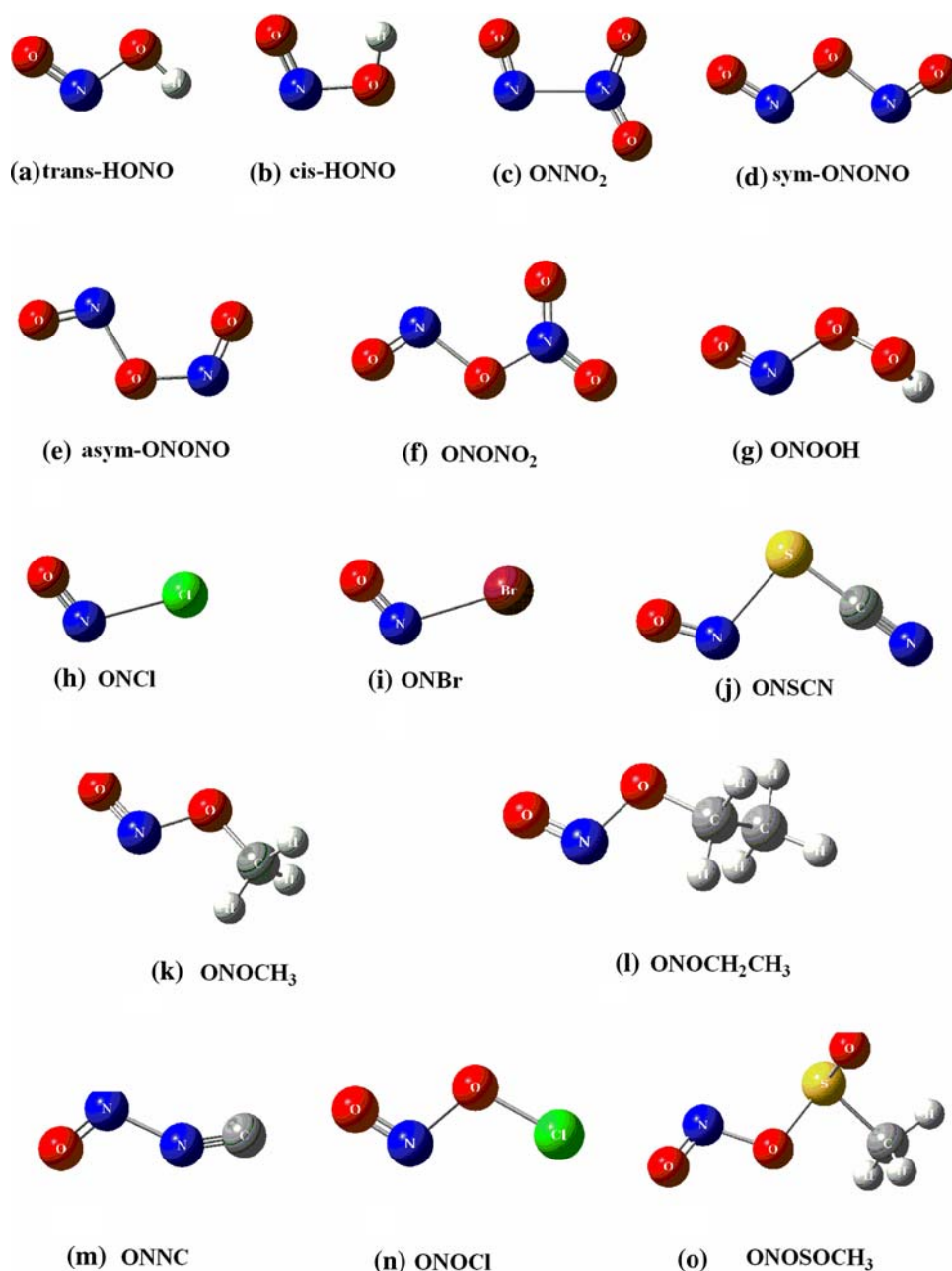
is well known that, along with occurrences in numerous industrial processes and in the environment, nitrosation reactions can also occur in many food products [11] and in the human body [12, 13]. Therefore, understanding and gaining more knowledge of the reaction mechanisms and structure–activity relationship of the reactants in the nitrosation reactions is of much importance.

In recent times there has been much research directed at the nitrosation reaction of amines [14–31], especially after the US Environmental Protection Agency (US EPA) defined N-nitrosodimethylamine (NDMA), which is the simplest stable nitrosamine, as a probable human carcinogen in 1997 [32]. Generally, there are two kinds of mechanisms for the nitrosation reaction, which are free radical nitrosation and electrophilic nitrosation [2, 33]. For the free radical mechanism, the nitrosation reaction occurs between nitric oxide and a radical [34]. Thus, as for the nitrosation reaction of amines, the electrophilic nitrosation is the main mechanism. Although the main reaction mechanism has been determined, research results indicate that the nitrosation reaction of amines is still complex, since there are various nitrosating agents generated (Fig. 1) depending upon different reaction conditions.

It is well known that the most general reagent is nitrous acid (HONO) generated from nitrite salt in acidic aqueous solution, as shown in Fig. 1a, b. However, Mirvish et al. [35, 36] and Krula et al. [37] experimentally postulated that, under mildly acidic conditions, it is N_2O_3 species shown in Fig. 1c–e rather than nitrous acid as the nitrosating agent in the nitrosation reactions of dimethylamine and amino acids, and our recent theoretical investigation [26] proves it. So far a number of studies have revealed that reactive nitrogen oxide species (RNOS) are an important and effective class of nitrosating agents. Mack et al. [30] and Lee et al. [31] found that under UV-A irradiation, the

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Fig. 1 Structures of a dozen
common nitrosating agents
(NAs)

(a) trans-HONO   (b) cis-HONO   (c) ONNO₂   (d) sym-ONONO

(e) asym-ONONO   (f) ONONO₂   (g) ONOOH

(h) ONCl   (i) ONBr   (j) ONSCN

(k) ONOCH₃   (l) ONOCH₂CH₃

(m) ONNC   (n) ONOCl   (o) ONOSOCH₃

photolysis of the nitrite ion can produce N_2O_3 and N_2O_4, and they act as the nitrosating agents to stimulate the nitrosation reaction. Choi and Valentine [16, 17] reported that, in neutral and alkaline aqueous solutions, a rapid NDMA formation from DMA in the presence of nitrite and chlorine is presumably via a reactive nitrosating and nitrating intermediate, dinitrogen tetroxide (N_2O_4) in the conformation of ON–ONO₂ as shown in Fig. 1f. Williams [33] investigated the possibilities of peroxynitrous acid (ONOOH, Fig. 1g) acting as a nitrosating agent, and found that ONOOH is hardly a conventional nitrosating agent, however, the nitrogen oxide decomposition products of it can lead to low yields of some nitrosation products. da

Silva and Kennedy et al. [18, 19] have studied the rate of numerous nitration reactions and put forward new nitro- sating agents composed of an ON moiety and a strong nucleophilic species such as ONCl, ONBr, and ONSCN, as shown in Fig. 1h–j. They also theoretically studied the bonding between the nucleophilic species and the nitroso group [20] and developed an elementary reaction step model of the N-nitrosation reaction of ammonia [21]. Additionally, alkyl nitrites are another group of nitrosating agents, such as ONOCH₃ and ONOCH₂CH₃ shown in Fig. 1k, l, and research on the nitrosation reactions of amines by alkyl nitrites has been done a lot [38–40]. Iglesias et al. [39] experimentally found that the nitrosation

mechanism involving a zwitterionic tetrahedral intermediate in the non-aqueous solvents, whereas Casado et al. [40] suggested that there is a concerted mechanism involving a four-centered transition state in aqueous solution, but recent findings prefer a six-centered transition state in which a water molecule assists the displacement of the alkoxy group.

Based on previous mechanistic studies, there are four main kinds of nitrosating agents, i.e., nitrous acid (HONO), reactive nitrogen oxide species (N_2O_3, N_2O_4, and ONOOH), species composed of an ON and strong nucleophilic moieties (ONCl, ONBr, and ONSCN), and alkyl nitrites (RONO). However, questions on which or what kind of nitrosating agent has high nitrosating ability, why it has strong reactivity, and what kind of relationship between the structure and reactivity of the nitrosating agent in the nitrosation reaction are not fully understood yet.

To address these questions, we attempted to do research herein on the nitrosation reaction of ammonia by various kinds of nitrosating agents including HONO, N_2O_3, N_2O_4, ONOOH, ONCl, ONBr, ONSCN, $ONOCH_3$, $ONOC_2H_5$, ONNC, ONOCl, and $ONOSOCH_3$. The results will elucidate the structure–activity relationship of nitrosating agents in the nitrosation reactions and will help search for new effective nitrosating agents.

2 Theoretical methods

The geometries of all the structures involved in the reaction of ammonia with all the studied reactive nitrosating agents were fully optimized using the hybrid density functional B3LYP method (Becke's three-parameter nonlocal exchange functional [41] with the correlation functional of Lee, Yang, and Parr [42]) with the 6-31+G(d,p) basis set. Vibrational frequencies were calculated at the same level of theory to characterize the nature of the stationary points. The minimum-energy path (MEP) was obtained using intrinsic reaction coordinate (IRC) calculations [43] to confirm the connection of each transition state with the designated isomers. In order to get more reliable energies, re-optimizations of these stationary points were performed with a high level CBS-QB3 method by Petersson et al. [44], which has been used widely because it has high accuracy in prediction of energy but is not time-consuming. All computations were carried out with the GAUSSIAN-03 program package [45].

In order to get the structure–activity relationship of nitrosating agents in the nitrosation reactions, ammonia as the simplest amine was chosen as a model reactant, although the product of this N-nitrosation reaction, H_2NNO, is not stable and may quickly decompose to N_2 and water. The structure–activity relationship analysis

of nitrosating agents in the nitrosation reactions was performed by the statistical software SPSS 11.5 version [46].

3 Results and discussion

Calculated reaction energies and energy barriers at 298 K and 1 atm in the gas phase for the N-nitrosation of ammonia by a dozen common and three possible nitrosating agents (NAs) are listed in Table 1. Table 2 shows the heterolytic bond dissociation energies (HBDE) of ON–X and H–X, the Mulliken charges of N and X atoms in ON–X as well as the number of the atoms in the ring of the transition state for a dozen common and three possible NAs. Scheme 1 illustrates that schematic profile of movements of electrons in the nitration reaction of ammonia. The optimized structures and important geometric parameters of all the transition states involved in the N-nitrosation of ammonia by all the studied NAs are shown in Fig. 2. Figure 3 describes the prediction values of energy barrier (E_b^p) versus the calculated energy barrier (E_b^c) of all the studied NAs.

3.1 Nitrosation of ammonia by the common NAs reactions

The nitrosation reactions of ammonia with an electrophilic nitrosation mechanism by a series of known nitrosating agents, i.e., HONO, N_2O_3, N_2O_4, ONOOH, ONCl, ONBr, ONSCN, $ONOCH_3$, $ONOCH_2CH_3$, were systematically investigated.

Nitrous acid (HONO) is believed to be the first and most general nitrosating agent since it is widely generated from nitrite salt in acidic aqueous solution. It is known that there are two conformations of HONO, i.e., trans-HONO and cis-HONO as shown in Fig. 1a, b, and they have similar stabilities [47]. Table 1 shows that the energy barriers of the nitrosation reaction of ammonia by trans-HONO and cis-HONO are 175.7 and 178.3 kJ/mol, respectively, which are in an agreement with the value of 138–146 kJ/mol calculated at the G2M(RCC,MP2)//B3LYP/6-311G(d,p) level [22]. However, these values are so high that the nitrosation reaction hardly occurs directly by nitrous acid. Recent theoretical results [26] reported that the mechanism of the nitrosation reaction of amine by nitrous acid (HONO) is a stepwise pathway, in which two molecules of nitrous acid react first to yield dinitrogen trioxide (N_2O_3), and then N_2O_3 as an effective nitrosating agent reacts with ammonia. This finding is consistent with the experimental results in which the rate of nitrosation reaction is proportional to the square of the concentration of nitrous acid [35–37]. Thus, a conclusion had been drawn that dinitrogen

Reaction	ΔH	ΔG	E_b
NH_3 + trans-HONO → $ONNH_2$ + H_2O	−27.1	−20.8	175.7
NH_3 + cis-HONO → $ONNH_2$ + H_2O	−25.7	−24.9	178.3
NH_3 + $ONNO_2$ → $ONNH_2$ + trans-HONO	−51.6	−51.8	70.4
NH_3 + sym-ONONO → $ONNH_2$ + HNO_2	−48.4	−35.8	75.8
NH_3 + asym-ONONO → $ONNH_2$ + cis-HONO	−73.2	−78.6	23.4
NH_3 + $ONONO_2$ → $ONNH_2$ + HNO_3	−65.3	−74.7	3.4
NH_3 + ONOOH → $ONNH_2$ + H_2O_2	−0.45	6.22	170.3
NH_3 + ONCl → $ONNH_2$ + HCl	−27.7	−26.2	55.6
NH_3 + ONBr → $ONNH_2$ + HBr	4.6	4.7	67.4
NH_3 + ONSCN → $ONNH_2$ + HSCN	−28.4	−34.0	62.2
NH_3 + ON–OCH_3 → $ONNH_2$ + $HOCH_3$	−34.87	−25.81	151.1
NH_3 + ON–OCH_2CH_3 → $ONNH_2$ + $HOCH_2CH_3$	−33.22	−24.13	151.6
NH_3 + ONNC → $ONNH_2$ + HCN	−152.6	−158.1	31.1
NH_3 + ONOCl → $ONNH_2$ + HOCl	−44.8	−33.6	104.1
NH_3 + ON–$OSOCH_3$ → $ONNH_2$ + $HOSOCH_3$	−39.2	−35.4	106.8

Species	HBDE	q(N)	q(X)	N(ring)	Species	HBDE
trans-ON–OH	934.3	−0.03	−0.19	4	H–OH	1,634.0
cis-ON–OH	932.7	−0.02	−0.15	4	H–OH	1,634.0
ON–NO_2	714.0	0.04	0.08	5	t-H–ONO	1,414.2
sym-ON–ONO	713.3	0.03	−0.07	5	H–NO_2	1,381.4
asym-ON–ONO	693.8	0.09	−0.06	6	c–H–ONO	1,412.6
ON–ONO_2	635.2	0.13	−0.07	6	H–NO_3	1,347.3
ON–OOH	898.1	−0.03	−0.03	4	H–OOH	1,570.4
ON–Cl	697.3	0.23	−0.40	4	H–Cl	1,383.8
ON–Br	685.8	0.14	−0.30	4	H–Br	1,347.3
ON–SCN	648.7	0.12	−0.33	6	H–NCS	1,340.8
ON–OCH_3	920.4	−0.01	−0.13	4	H–OCH_3	1,594.9
ON–OC_2H_5	905.5	−0.03	−0.08	4	H–OC_2H_5	1,578.9
ONNC	644.3	0.06	0.02	5	H–CN	1,464.2
ON–OCl	802.9	0.06	−0.05	4	H–OCl	1,484.4
ON–$OSOCH_3$	693.3	0.03	−0.17	5	H–SO_2CH_3	1,372.6

ONA: a,b,g,h,i,k,l,n
ONBB': c,d,m,o
ONCC'C'': e,f,j
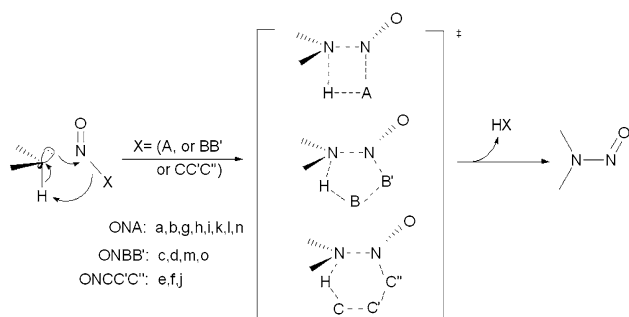
Scheme 1 Schematic profile of movements of electrons in the nitration reaction of ammonia

trioxide (N_2O_3) is the real nitrosating agent in the reaction of amine and nitrous acid.

As for N_2O_3, there are three stable conformations: $ONNO_2$, sym-ONONO, and asym-ONONO as shown in Fig. 1c–e. The essential difference between $ONNO_2$ and sym- or asym-ONONO is the NO moiety bonding to the nitrogen atom or the oxygen atom of the NO_2 moiety. The $ONNO_2$ isomer is more stable than ONONO isomers by approximately 20 kJ/mol at 298 K. Table 1 lists that the energy barrier of the nitrosation reaction of ammonia by $ONNO_2$ is 70.4 kJ/mol, which is in a good agreement with 70.2 kcal/mol at the same level from Morgon et al. [23] and 66 kJ/mol calculated by Nguyen et al. [24]. However,

Fig. 2 The optimized structures and important geometric parameters of all the transition states involved in the nitrosation of ammonia by all the studied NAs
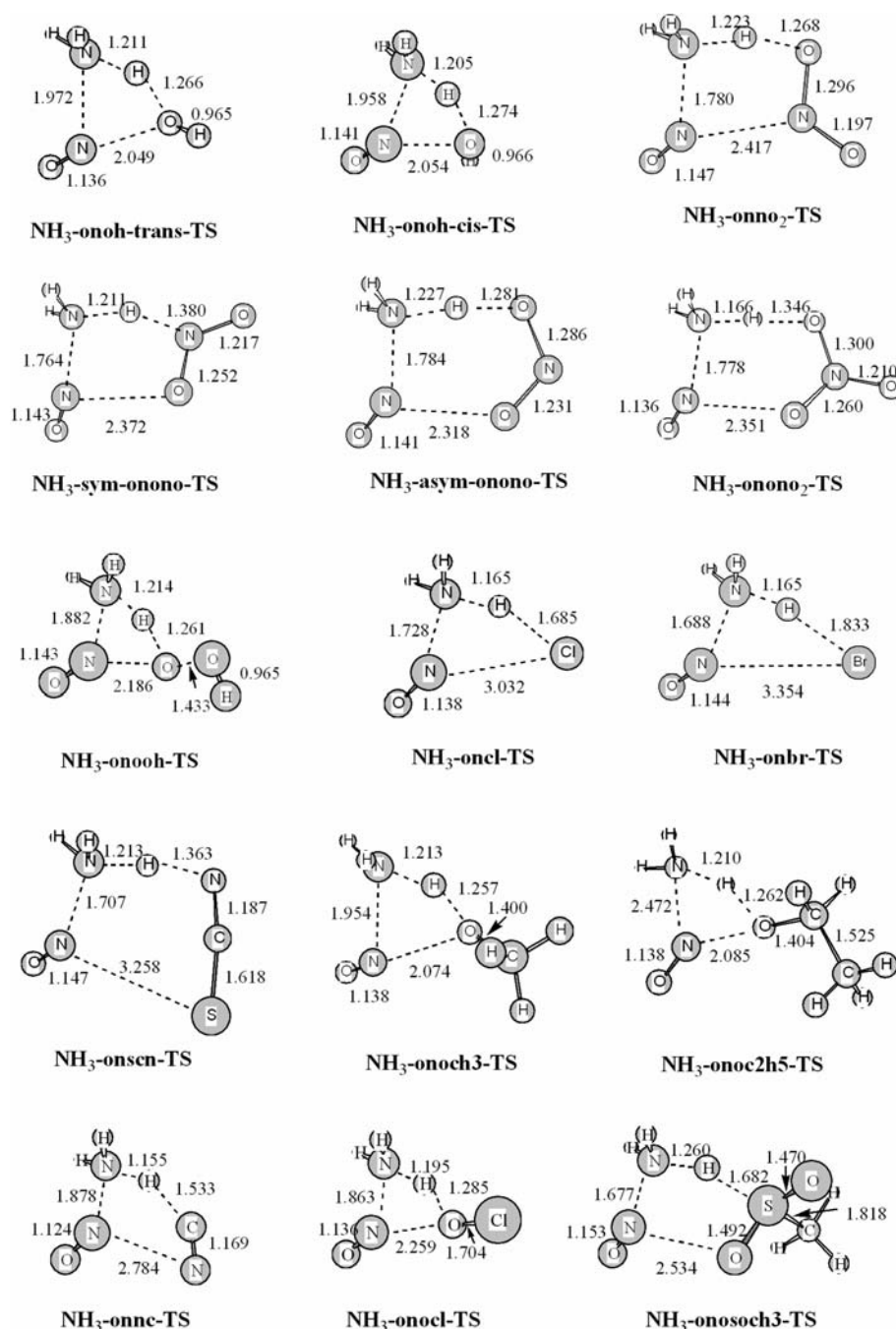
the experimental activation energy for the nitrosation of ammonia by N_2O_3 was calculated as 56 kJ/mol [19]. This value is definitely lower than the energy barrier of the nitrosation of ammonia by $ONNO_2$. A possible reason is that including $ONNO_2$ there are other conformations of N_2O_3 with relatively lower energy barrier accompanying the nitrosation reaction. The calculated energy barriers of the nitrosation reaction of ammonia by sym-ONONO and asym-ONONO are 75.8 and 23.4 kJ/mol, respectively. Therefore, it is inferred that asym-ONONO is another existent conformation in N_2O_3.

The reaction through the transition state sym-NH$_3$-onono-TS, i.e., the nitrosation of ammonia by sym-ONONO, has a higher energy barrier than the nitrosation by asym-ONONO. A similar phenomenon was found by Zhao et al. [25, 48] when they investigated the nitrosation of amine by NO_2; they found that the NO_2 moiety in the trans-conformation transition state is in a relatively higher energy $^2B_2$ electronic state (O-centered radical). The products of these reactions are $ONNH_2$ along with the HNO_2 and cis-HONO. In Table 1, it is also shown that the nitrosation reaction by asym-ONONO is exothermic with the value of 73.2 kJ/mol
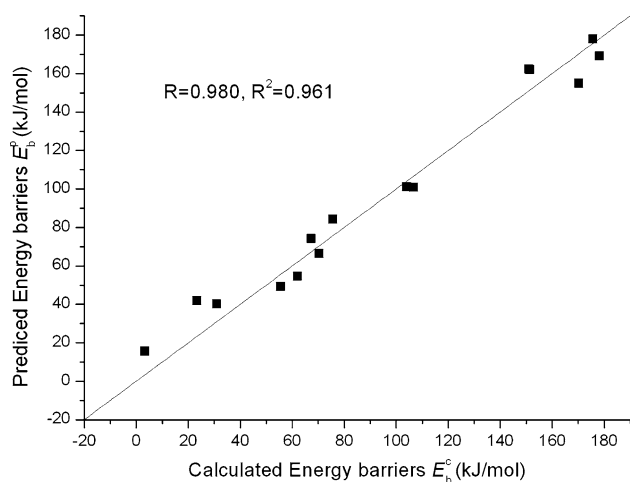
Fig. 3 Prediction values of energy barrier (E_b^p) versus the calculated energy barrier (E_b^c) of the nitrosation of ammonia by all the studied NAs

while that for ON–NO$_2$ is approximately 51.6 kJ/mol. Scheme 1 and Fig. 2 illustrate that the transition states NH$_3$-onno$_2$-TS and NH$_3$-sym-onono-TS are both composed of a five-membered ring, while NH$_3$-asym-onono-TS consists of a six-membered ring. It is known that a six-membered ring is usually more stable than a five-membered ring because of the lower repulsion force. Thus, this is a possible reason why the energy barrier for the nitrosation by asym-ONONO is much lower than those by ONNO$_2$ and sym-ONONO.

N$_2$O$_4$ has symmetrical and asymmetrical tautomers of O$_2$NNO$_2$ and ONONO$_2$, in which ONONO$_2$ is an effective nitrosating agent. Pimentel et al. [49] investigated these two isomers and their isomerization, and found that the Gibbs free energy barrier between them is approximately 130 kJ/mol in the gas phase using the DFT/B3LYP/13s8p(2d,1f) method. Table 1 shows that the energy barrier for the nitrosation reaction by ONONO$_2$ through a transition state NH$_3$-onono$_2$-TS is rather low with the value of 3.4 kJ/mol, and the reaction is exothermic by 65.3 kJ/mol. Similar to NH$_3$-asym-onono-TS, the transition state NH$_3$-onono$_2$-TS also consists of a six-membered ring and is geometrically closer to the reactant relative to the product, as shown in Scheme 1 and Fig. 2.

As for peroxynitrous acid (ONOOH), the calculated energy barrier is 170.3 kJ/mol and this value is so high that ONOOH is hardly to be an effective nitrosating agent. This result is consistent with the previous conclusion that a conventional direct nitrosation is not to be expected to occur when peroxynitrous acid acts as a nitrosating agent [33].

Recently, da Silva and Kennedy et al. [18, 19, 21] investigated the effect of added nucleophilic species on the rate of the nitrosation reaction and put forward new nitrosating agents composed of an ON moiety and a strong nucleophilic species such as ONCl, ONBr, and ONSCN, as shown in Fig. 1h–j. As shown in Table 1, the energy barriers for the nitrosation of ammonia by the nitrosating species ONCl, ONBr, and ONSCN are 55.6, 67.4, and 62.2 kJ/mol, respectively. All these calculated values are somewhat lower than the energy barrier of ONNO$_2$. Among these three nitrosating agents, ONCl has the lowest energy barrier, then ONSCN, and ONBr has the highest. This order is in a part agreement with the experimental results [21] in which the rate constants of the reactions of ammonia with ONCl, ONBr, ONSCN, and N$_2$O$_3$ are 5.0×10^7, 2.6×10^7, 8.4×10^5, and 4.3×10^6 M^{-1} s^{-1}, respectively.

Figure 2 describes that the distance of ON–Cl (or Br, SCN) in their corresponding transition states is over 3.00 Å and longer than the bond distance of the corresponding reactant by around 1.00 Å. Table 1 also shows that the nitrosation of ammonia by the nitrosating species ONCl and ONSCN are exothermic but their values are somewhat smaller than those by N$_2$O$_3$ and N$_2$O$_4$, while the nitrosation reaction by ONBr even becomes endothermic. In this case, it seems that the nitrosation by ONBr is thermodynamically not easy to occur in the gas phase.

With respect to alkyl nitrites, ONOCH$_3$ and ONOCH$_2$CH$_3$ shown in Fig. 1k, l were chosen as the nitrosating agent to stimulate the nitrosation reactions of ammonia. As shown in Table 1 that the energy barriers for these two reactions are around 151 kJ/mol. The value is so high that ONOCH$_3$ and ONOCH$_2$CH$_3$ are not effective NAs.

3.2 Three possible NAs

The activities of three possible NAs, i.e., ONNC, ONOCl, and ONOSOCH$_3$ species shown in Fig. 1m–o, were also investigated.

Table 1 shows that ONNC has a rather low energy barrier (31.4 kJ/mol) which is even lower than the known effective NAs, such as ONCl, ONBr, and N$_2$O$_3$, whereas ONOCl and ONOSOCH$_3$ agents have energy barriers of around 100 kJ/mol. The results indicate that ONNC, ONOCl, and ONOSOCH$_3$ are all potential NAs, moreover, ONNC has a powerful nitrosating ability.

3.3 Structure–activity relationship of all the studied NAs

The structure–activity relationship of a dozen common and three possible NAs was investigated using the single-variate linear regression analysis. The results show that the values of correlation coefficient of the energy barrier depending on *HBDE*(ON–X), *HBDE*(H–X), q(N), q(X), and N(ring) are 0.946, 0.909, 0.826, 0.133, and 0.685, respectively, where the *HBDE*(ON–X) and *HBDE*(H–X) mean heterolytic bond dissociation energies of ON–X and

H–X, the $q(N)$ and $q(X)$ represent the Mulliken charges of N and X atom in ON–X, and $N(ring)$ represents the number of the atoms in the ring of the transition state.

Analysis of the structure–activity relationship of the nitrosating agents (NAs) showed that the predicted values of the energy barrier (E_b^p) depend on five variables which are $HBDE(ON–X)$, $HBDE(H–X)$, $q(N)$, $q(X)$, and $N(ring)$. The E_b^p correlates linearly with the calculated energy barrier (E_b^c) with the values of a correlation coefficient (R) and a square of a correlation coefficient (R^2) being 0.980 and 0.961, respectively, as shown in Fig. 3. This indicates that there is a definite relationship between the nitrosating ability of NA with the heterolytic bond dissociation energies of ON–X and H–X, and the Mulliken charges of $q(N)$ and $q(X)$ as well as the number of the atoms in the ring of the transition state. Moreover, the lower value of $HBDE(ON–X)$ along with the larger values of $HBDE(H–X)$, $q(N)$, $q(X)$, and $N(ring)$, the higher are the activities of NAs as demonstrated in the 5-variate linear regression equation with unstandardized coefficients (Eq. 1). This reveals that the nitrosating activity of NAs is directly proportional to the heterolytic bond dissociation energy of H–X and Milliken charges of N and X atoms in ON–X as well as the number of the atoms in the ring of the transition state, but inversely proportional to heterolytic bond dissociation energy of ON–X.

$$E_b^p = 0.27HBDE(ON-X) - 0.07HBDE(H-X)$$
$$- 404.912q(N) - 109.954q(X)$$
$$- 11.858N(ring) + 54.357 \qquad (1)$$

$$E_b^p = 0.612HBDE(ON-X) - 0.157HBDE(H-X)$$
$$- 0.554q(N) - 0.245q(X) - 0.145N(ring) \qquad (2)$$

In the light of the standardized coefficients (Eq. 2), a conclusion can be drawn that the heterolytic bond dissociation energy of ON–X and Mulliken charge of $q(N)$ make a considerable contribution to the energy barrier, whereas the Mulliken charge of $q(X)$ contributes a little as well as the heterolytic bond dissociation energy of H–X and the number of the atoms in the ring of the transition state $N(ring)$ slightly. It is inferred that the low value of $HBDE(ON–X)$ and high value of $q(N)$ are important basic feature for a powerful nitrosating agent.

4 Summary

The nitrosation reactions of ammonia by a dozen common and three possible nitrosating agents (NAs) were studied at the CBS-QB3 level of theory. A structure–activity

relationship of nitrosating agents in the nitrosation reactions of ammonia was established. Analysis of the structure–activity relationship of the NAs showed that the energy barriers of the nitrosation reactions (E_b^p) have definite relationship with five variables, i.e., $HBDE(ON–X)$, $HBDE(H–X)$, $q(N)$, $q(X)$, and $N(ring)$, which represent the heterolytic bond dissociation energies of ON–X and H–X, the Mulliken charges of N and X atoms in ON–X, as well as the number of the atoms in the ring of the corresponding transition state, respectively. Furthermore, the results indicate that the nitrosating ability of NAs is directly proportional to $HBDE(H–X)$, $q(N)$, $q(X)$, and $N(ring)$, but inversely proportional to $HBDE(ON–X)$. Moreover, the low value of $HBDE(ON–X)$ and high value of $q(N)$ are important basic features for a powerful nitrosating agent. Additionally, ONNC was found to be a potential powerful nitrosating agent as well as ONOCl and $ONOSOCH_3$ to be potential nitrosating agents. The results obtained in this work will help search for new effective nitrosating agents.

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