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Theoretical investigation of reactivities of amines in the N-nitrosation reactions by N_2O_3

Zhi Sun · Yong Dong Liu · Rugang Zhong

Abstract N-nitrosamine is a class of carcinogenic, muta-genic, and teratogenic compounds, which can be produced from N-nitrosation of amine by nitrosating agents. N-nitrosation of 19 amines (eight acyclic amines, five heterocyclic amines, and six amines with unsaturated groups) by N_2O_3 was investigated at the CBS-QB3 level of theory. The results indicate that generally the heterocyclic amines have the highest reactivities among the three kinds of amines, whereas the reactivities of the amines with unsaturated and electron-withdrawing groups are relatively low. Frontier molecular orbital analysis indicates that the energy gap between the HOMO of an amine and the LUMO of N_2O_3 has a close connection with the reactivity of an amine. A structure-reactivity relationship of amines in the N-nitrosation reactions by N_2O_3 was established using the stepwise multivariate linear regression. The results indicate that the reactivity of an amine has a definite relationship ($R_{adj}^2 = 0.947$) with the heterolytic bond dissociation energy of R_1R_2N-H bond, energy of HOMO, NBO occupancy of the natural lone pair orbital of N atom, the NBO charge of the N atom, and the pyramidalization angle of an amine. This work will be helpful to gain more insight into the N-nitrosation reactions.

Keywords Frontier molecular orbitals ·
N-nitrosation reaction · Reactivities of amines ·
Structure-reactivity relationship

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Introduction

N-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 [1–7]. Furthermore, it is well known that N-nitrosamines are ubiquitous in the environment, and until now, they have been found in air [8], soil [9, 10], water [11–13], food [14–16], cosmetics [17], rubber products [18, 19] as well as many other materials. Therefore, understanding and gaining more knowledge of the reaction mechanism and structure-reactivity relationship of the reactants in the N-nitrosation reactions is of much importance.

As a precursor of N-nitrosamines, amines are widespread with diverse categories in the environment. Protein breaking down is an important source of amines. Therefore, aged, overcooked, processed, and even many raw foods are rich in amines [20–23]. In addition to foods, many other materials, such as tobacco [24], drugs [25], waster water [26], herbicides [27], and pesticides [28], also contain amines or compounds with amine structures. In view of the ubiquity and diversity of amines, the studies for N-nitrosation of different amines have long been of interest. However, most of the research work focused on one or several specific amines, and few studies systematically investigated the structure-reactivity relationship of amines in the N-nitrosation reactions.

As another reactant of N-nitrosation, various nitrosating agents (NAs) have been found such as N_2O_3 [29], N_2O_4 [30], ONCl [31], ONSCN [32]. A theoretical study of the structure-activity relationship of NAs in the N-nitrosation reactions of ammonia has been performed by our previous work [33]. Among the known nitrosating agents, N_2O_3 is a
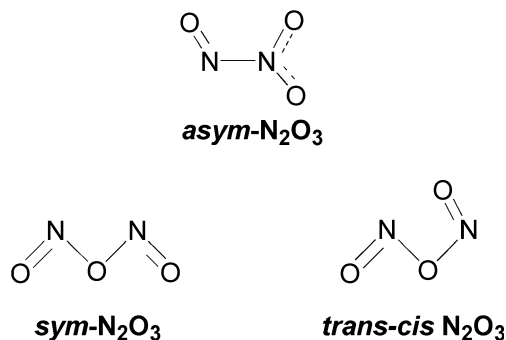
particularly important species, because it not only exerts strong nitrosating ability, but also appears potentially both *in vitro* and *in vivo*. It is well known that it is N_2O_3 rather than nitrous acid as the effective nitrosating agent of *N*-nitrosation of amines in acidic nitrite solution [34–36]. Moreover, recent studies indicate that N_2O_3 can be formed in diverse pathophysiological states, which then could further lead to *N*-nitrosation reaction *in vivo*, and the results of which are probably injurious to biological tissues and disease-related [37, 38].

By now, three main N_2O_3 isomers have been identified [39–43], *i.e.*, asymmetric N_2O_3 (*asym*-N_2O_3), symmetric N_2O_3 (*sym*-N_2O_3), and *trans-cis* N_2O_3 (Scheme 1). The *asym*-N_2O_3 is the most stable configuration thus being the mainly existent conformation [44]. Recent theoretical studies predicted that *N*-nitrosation of ammonia [45] and dimethylamine (DMA) [36] by *asym*-N_2O_3 occurs *via* a five-membered cyclic transition state. Due to the structural similarity of amines, along with ammonia and DMA, it is reasonable to presume that other primary and secondary amines react with *asym*-N_2O_3 *via* a similar mechanism.

Although numerous studies have already been done to investigate *N*-nitrosation of amines, questions on which or what kind of amines has high reactivity, why it has strong reactivity, and what kind of relationship between the structure and reactivity of the amines in the *N*-nitrosation reactions, are not fully understood yet. To address these questions, we attempted to do research herein on the *N*-nitrosation reaction of 19 amines (Fig. 1) including eight acyclic amines, five heterocyclic amines, and six amines with unsaturated group, by the most stable N_2O_3 isomer, *asym*-N_2O_3. The results will elucidate the structure-reactivity relationship of amines in the *N*-nitrosation reactions and will help to in-depth understand *N*-nitrosation reactions.

Theoretical methods

N-nitrosation of amines by N_2O_3 was investigated by density functional theory (DFT) calculations. All structures

of reactants, transition states, and products were fully optimized at the B3LYP/CBSB7 level. Vibrational frequencies were calculated at the same level to characterize the nature of each stationary point. Intrinsic reaction coordinate (IRC) [46] calculation was also performed at the B3LYP/CBSB7 level to confirm that every transition state connects the corresponding reactant and product through the minimized-energy pathway. More reliable energies were obtained at the CBS-QB3 level of theory [47]. All the calculations were carried out with the GAUSSIAN-03 program package [48].

The structure-reactivity relationship analysis for all the amines in the *N*-nitrosation reactions was performed using the statistical software SPSS 12.0 version [49].
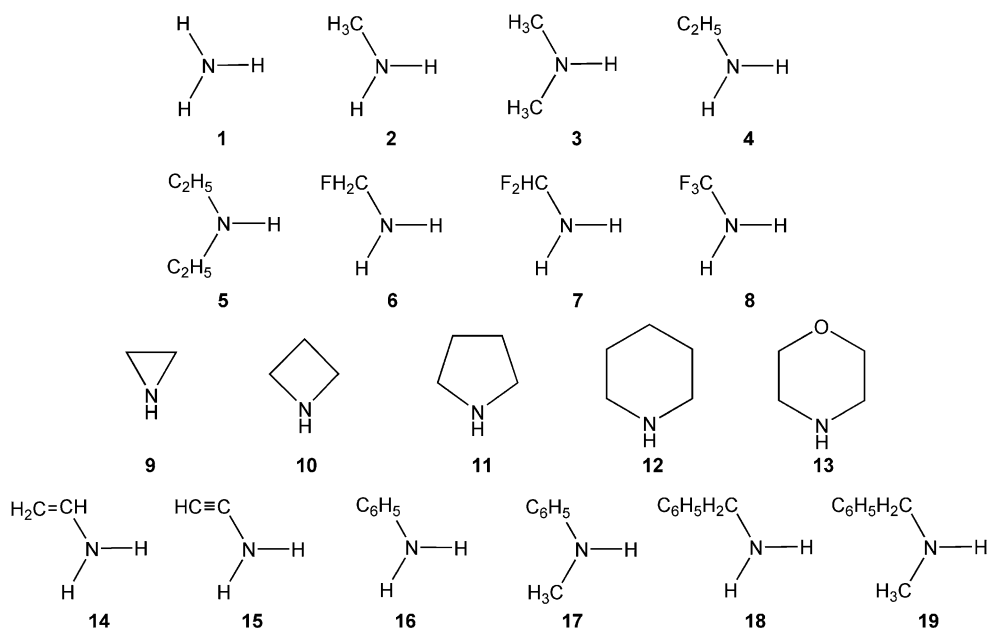
Results and discussion

The detailed reaction pathway for *N*-nitrosation of amines by N_2O_3 is illustrated in Scheme 2. It is shown that the reaction occurs in a concerted step with a five-membered cyclic transition state. Movements of electrons indicate that it is induced by the lone pair electrons of the N atom in amine attacking the nitrogen of the NO moiety in N_2O_3. As the valence shell of nitrogen can accommodate only eight electrons, the N-N bond in N_2O_3 must begin to break while the other N-N bond connecting DMA and NO moiety begins to form. Further movement and rearrangement of electrons lead to the formation of *N*-nitrosamine and HNO_2. Due to the structural similarity, all the selected amines in present study react with N_2O_3 *via* this mechanism.

N-nitrosation of acyclic amines

N-nitrosation of eight acyclic amines, *i.e.*, NH_3, CH_3NH_2, $(CH_3)_2NH$, $C_2H_5NH_2$, $(C_2H_5)_2NH$, FCH_2NH_2, F_2CHNH_2, and F_3CNH_2, was studied at the CBS-QB3 level of theory. Fully optimized geometries for the reactant complex (RC) and transition state (TS) were illustrated in Fig. 2. It is shown that all eight reactions occur *via* similar five-membered cyclic transition states (TS1–TS8). Energy data listed in Table 1 indicate that the reactivities of the eight acyclic amines in the *N*-nitrosation reactions of N_2O_3 are different. Ammonia and its alkyl(electron-donating group)-substituted amines, *i.e.*, NH_3, CH_3NH_2, $(CH_3)_2NH$, $C_2H_5NH_2$, and $(C_2H_5)_2NH$, are going to be first introduced, and then followed by the discussion of FCH_2NH_2, F_2CHNH_2, and F_3CNH_2 to examine the effect of electron-withdrawing group on the reaction.

As shown in Table 1, all the reactions are exothermic, and energy barriers of the *N*-nitrosation of NH_3, CH_3NH_2, $(CH_3)_2NH$, $C_2H_5NH_2$, and $(C_2H_5)_2NH$ by N_2O_3 were calculated to be 70.41, 38.95, 17.90, 38.15, and

Scheme 1 Conformations of the three N_2O_3 isomers

asym-N_2O_3

sym-N_2O_3 *trans-cis* N_2O_3

Fig. 1 Configurations of the 19 amines

20.69 kJ mol^{-1}, respectively. Accordingly, the order of the reactivity for the five amines was predicted as $(CH_3)_2NH$ > $(C_2H_5)_2NH$ > $C_2H_5NH_2$ > CH_3NH_2 > NH_3. Obviously, the reaction barrier is significantly reduced with the alkylation on ammonia, and the primary amines have higher energy barriers than secondary amines. In other words, electron-donating substituents of amines decrease the energy barrier of N-nitrosation reactions. Zhao *et al.* [50] studied the N-nitrosation of amines by NO_2 and NO radicals and predicted the order of the reactivity for amines to be $(CH_3)_2NH$ > CH_3NH_2 > NH_3, which is consistent with the result in present work.

It is well known that the frontier molecular orbitals (FMO), *i.e.*, the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) introduced by Fukui [51], play a dominant role in governing chemical reactions. The energy gap between the HOMO of the nucleophile (electron donor) and the LUMO of the electrophile (electron acceptor) has long been used as a reactivity index [52–55]. In the case of N-nitrosation of amines, the reactivity is probably related to the energy gap between the HOMO of the amine (as nucleophile) and the LUMO of N_2O_3 (as electrophile). Therefore, to better understand the reactivity of amines, the energies of HOMO and LUMO of amines and N_2O_3 were calculated, and the result is depicted in Fig. 3. The HOMO energies of NH_3, CH_3NH_2,

$(CH_3)_2NH$, $C_2H_5NH_2$, $(C_2H_5)_2NH$ were calculated to be −0.430, −0.392, −0.369, −0.391, and −0.366 hartree, respectively, while the LUMO energy of N_2O_3 is 0.008 hartree. Accordingly, the order of the energy gap is NH_3 > CH_3NH_2 > $C_2H_5NH_2$ > $(CH_3)_2NH$ > $(C_2H_5)_2NH$, which basically accounts for the order of the reactivity for the five amines. The only exception is $(C_2H_5)_2NH$, whose energy gap is lower than that of $(CH_3)_2NH$, however, the order of the reactivity is inverse as $(CH_3)_2NH$ > $(C_2H_5)_2NH$. It means that the energy gap of the FMO is probably not a sole factor affecting the reactivity especially when the energy gaps are close to each other. In this case, a steric hindrance is another factor. It is well known that two ethyl groups in $(C_2H_5)_2NH$ have substantially greater steric hindrance than two methyl groups in $(CH_3)_2NH$. Moreover, the energy gap for $(C_2H_5)_2NH$ is close to that of $(CH_3)_2NH$. Therefore, a conclusion can be drawn that the energy gap and steric hindrance together determine the reactivities of amines with electron-donating substituents.

In order to examine the effect of electron-withdrawing group on the reaction, the N-nitrosation of FCH_2NH_2, F_2CHNH_2, and F_3CNH_2 was investigated and the corresponding energy barriers were calculated to be 82.62, 82.81, and 92.98 kJ mol^{-1}, respectively. Obviously, these barriers are higher than that of NH_3 (70.41 kJ mol^{-1}). This indicates that contrary to the electron-donating groups, the

Scheme 2 Reaction mechanism for the N-nitrosation of amines by N_2O_3
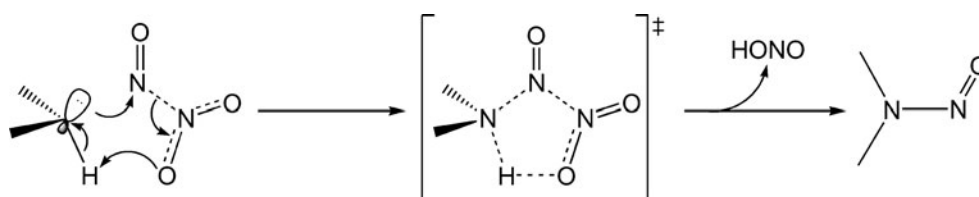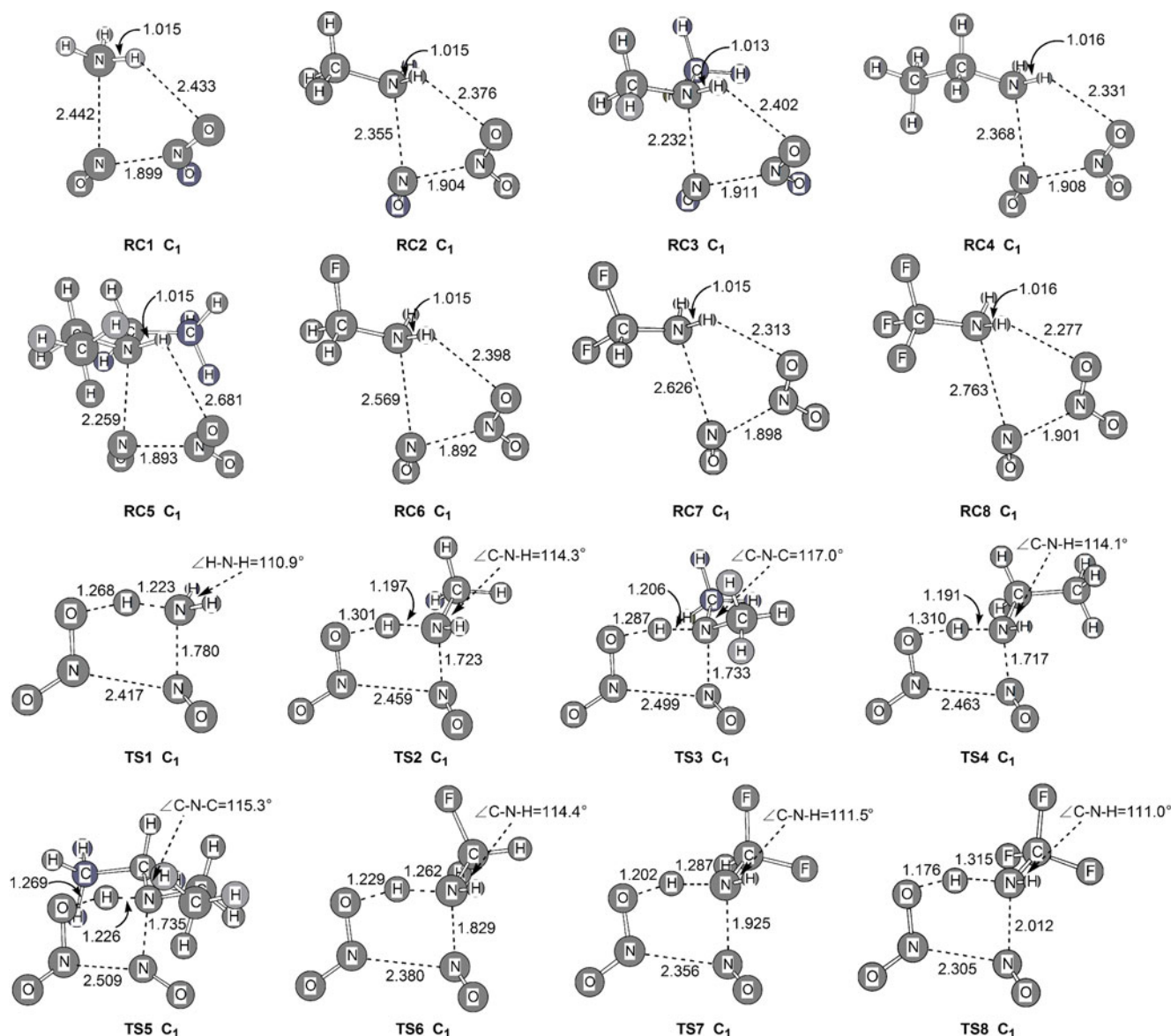
Fig. 2 CBS-QB3 geometries for all the reactant complexes (RC) and transition states (TS) involved in the N-nitrosation of the acyclic amines by N_2O_3 (Distances in Angstroms)

electron-withdrawing groups somewhat increase the energy barrier, thus restraining the N-nitrosation reactions. Furthermore, it can also be found that a substitution with more

electron-withdrawing groups make the energy barrier increase larger. The FMO analysis shows that the energy gaps between the three species, FCH_2NH_2, F_2CHNH_2, and

Table 1 CBS-QB3 energy barriers (E_b, 298 K and 1 atm, in kJ mol^{-1}), reaction energies (ΔH and ΔG, 298 K and 1 atm, in kJ mol^{-1}) for the N-nitrosation of NH_3, CH_3NH_2, $(CH_3)_2NH$, $C_2H_5NH_2$, $(C_2H_5)_2NH$, FCH_2NH_2, F_2CHNH_2, and F_3CNH_2) by N_2O_3 in the gas phase

Reaction	E_b	ΔH	ΔG
$NH_3+N_2O_3 \rightarrow H_2NNO+HNO_2$	70.41	−51.62	−51.77
$CH_3NH_2 + N_2O_3 \rightarrow CH_3NHNO+HNO_2$	38.95	−81.20	−81.92
$(CH_3)_2NH+N_2O_3 \rightarrow (CH_3)_2NNO+HNO_2$	17.90	−95.77	−103.09
$C_2H_5NH_2 +N_2O_3 \rightarrow C_2H_5NHNO+HNO_2$	38.15	−60.58	−67.11
$(C_2H_5)_2NH+N_2O_3 \rightarrow (C_2H_5)_2NNO+HNO_2$	20.69	−85.89	−91.92
$FCH_2NH_2 + N_2O_3 \rightarrow FCH_2NHNO+HNO_2$	82.62	−54.10	−52.51
$F_2CHNH_2 + N_2O_3 \rightarrow F_2CHNHNO+HNO_2$	82.81	−39.54	−37.54
$F_3CNH_2 + N_2O_3 \rightarrow F_3CNHNO+HNO_2$	92.98	−18.43	−18.46

Fig. 3 Schematic profiles for the energies (in hartree) of the HOMO and LUMO of the acyclic amines and N_2O_3
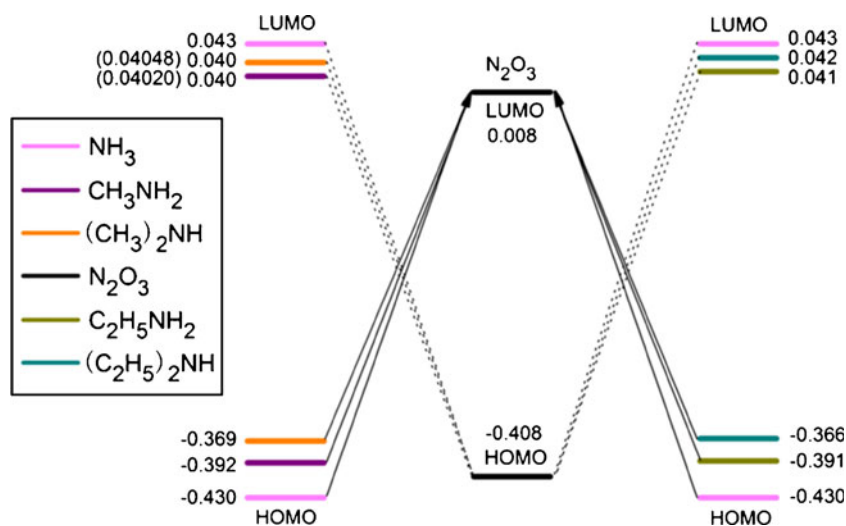
F_3CNH_2, and N_2O_3 are larger than that between NH_3 and N_2O_3 (Table 2), which indicates that these amines have lower reactivities than ammonia. Moreover, the order of energy gap was predicted as $FCH_2NH_2 < F_2CHNH_2 < F_3CNH_2$, which is in good agreement with the order of the energy barriers. In total, correlation analysis for all eight acyclic amines reveals that the energy barrier has a good relationship ($R=0.979$ and $R_{adj}^2=0.951$) with the energy gap between HOMO (amine) and LUMO (N_2O_3).

Additionally, as shown in Table 2, the NBO charge of the N atom, Q_N, in the amines was found to have a relationship with the reactivity of an acyclic amine. Generally, the acyclic amine with a small absolute value of Q_N has a relatively high reactivity, however, it rules out for the acyclic amines with electron-withdrawing substituents. A similar conclusion was also obtained for the heterolytic bond dissociation energy of R_1R_2N-H bond, E_{N-H}, in which the acyclic amine with low value of E_{N-H} has a high reactivity except for the acyclic amines with electron-withdrawing groups (-F groups). Therefore, it seems that Q_N and E_{N-H} are not good descriptors for the reactivities of the acyclic amines with electron-withdrawing groups.

Population analysis based on NBO theory [56] was performed to check the changes of population due to the introduction of the substitute groups. Generally, it can be found from Table 2 that the appearance of electron-

Table 2 CBS-QB3 energy barrier (E_b, at 298 K and 1 atm, in kJ mol^{-1}), heterolytic bond dissociation energy of R_1R_2N-H bond (E_{N-H}, at 298 K and 1 atm, in kJ mol^{-1}), energy of highest occupied molecular orbital (E_{HOMO}, in hartree), NBO occupancy of the natural lone pair orbital of N atom (LP_N), NBO charge of N atom (Q_N, in e), angle $\angle R_1NR_2$ (α, in degrees), and pyramidalization angle (β, in degrees) of an amine

Species	E_b	E_{N-H}	E_{HOMO}	LP_N (%: s, p) [a]	Q_N	α	β
NH_3	70.41	1688.07	−0.43026	1.998 (24, 76)	−1.033	106.4	118
CH_3NH_2	38.95	1681.51	−0.39246	1.970 (21, 79)	−0.851	110.1	123
$(CH_3)_2NH$	17.90	1644.32	−0.36896	1.937 (17, 83)	−0.709	113.0	127
$C_2H_5NH_2$	38.15	1660.49	−0.39060	1.971 (21, 79)	−0.856	109.7	123
$(C_2H_5)_2NH$	20.69	1623.42	−0.36641	1.938 (17, 83)	−0.716	114.0	127
FCH_2NH_2	82.62	1575.31	−0.44030	1.929 (16, 84)	−0.861	112.3	130
F_2CHNH_2	82.81	1528.89	−0.46290	1.932 (17, 83)	−0.877	111.2	129
F_3CNH_2	92.98	1499.30	−0.48379	1.932 (16, 83)	−0.888	111.5	130
$(CH_2)_2NH$	43.90	1628.36	−0.39484	1.967 (37, 63)	−0.677	60.5	113
$(CH_2)_3NH$	16.60	1645.74	−0.37174	1.949 (21, 78)	−0.724	90.5	127
$(CH_2)_4NH$	12.02	1624.61	−0.36782	1.939 (18, 82)	−0.719	104.9	128
$(CH_2)_5NH$	11.90	1624.64	−0.35498	1.942 (17, 83)	−0.707	112.3	126
$O(CH_2)_4NH$	17.99	1609.96	−0.37437	1.940 (17, 82)	−0.718	111.0	128
CH_2CHNH_2	53.16	1570.94	−0.31861	1.892 (11, 89)	−0.851	115.4	139
$CHCNH_2$	71.22	1507.82	−0.34725	1.893 (12, 88)	−0.854	115.0	138
$C_6H_5NH_2$	47.27	1533.48	−0.29454	1.897 (11, 89)	−0.833	115.1	138
$C_6H_5CH_2NH_2$	44.11	1627.69	−0.32335	1.968 (20, 80)	−0.852	110.3	124
$C_6H_5NHCH_3$	25.23	1522.93	−0.28573	1.849 (6, 94)	−0.691	122.0	149
$C_6H_5CH_2NHCH_3$	21.69	1599.20	−0.32468	1.935 (17, 83)	−0.707	113.4	127

[a] Data in parentheses represent the contribution of s and p components into the natural orbital of lone pair

withdrawing groups (-F) in amine molecules results in a reduction of NBO occupancy for the lone pair of N atom when compared with the amines with electron-donating groups. It indicates that the introduction of electron-withdrawing substitutes may lead to the delocalization of the lone pair. This result could account for the relatively high energy barriers of the amines with electron-withdrawing groups with comparison to those with electron-donating groups, but it cannot give a good explanation for the reactivity of each acyclic amines.

N-nitrosation of heterocyclic amines

Heterocyclic amines are ubiquitous in the human diet, and many of them have been found to be mutagenic and carcinogenic [57, 58]. Therefore, the reactivities of heterocyclic amines to form N-nitrosamines were also examined. Five heterocyclic amines, i.e., $(CH_2)_2NH$ (aziridine), $(CH_2)_3NH$ (azetidine), $(CH_2)_4NH$ (pyrrolidine), $(CH_2)_5NH$ (piperidine), and $O(CH_2)_4NH$ (morpholine) were selected as the nitrosating substrates. Fully optimized geometries for the reactant complex (RC) and transition state (TS) were illustrated in Fig. 4. The result of FMO analysis was summarized in Fig. 5, and the CBS-QB3 energy barriers and reaction energies were listed in Table 3.

As illustrated in Fig. 4, all five reactions occur via similar five-membered cyclic transition states (TS9 to TS13). Table 3 shows that the energy barriers of the N-nitrosation of $(CH_2)_2NH$, $(CH_2)_3NH$, $(CH_2)_4NH$, $(CH_2)_5NH$, and $O(CH_2)_4NH$ by N_2O_3 were calculated to

Fig. 4 CBS-QB3 geometries for all the reactant complexes (RC) and transition states (TS) involved in the N-nitrosation of the heterocyclic amines by N_2O_3 (distances in Angstroms)
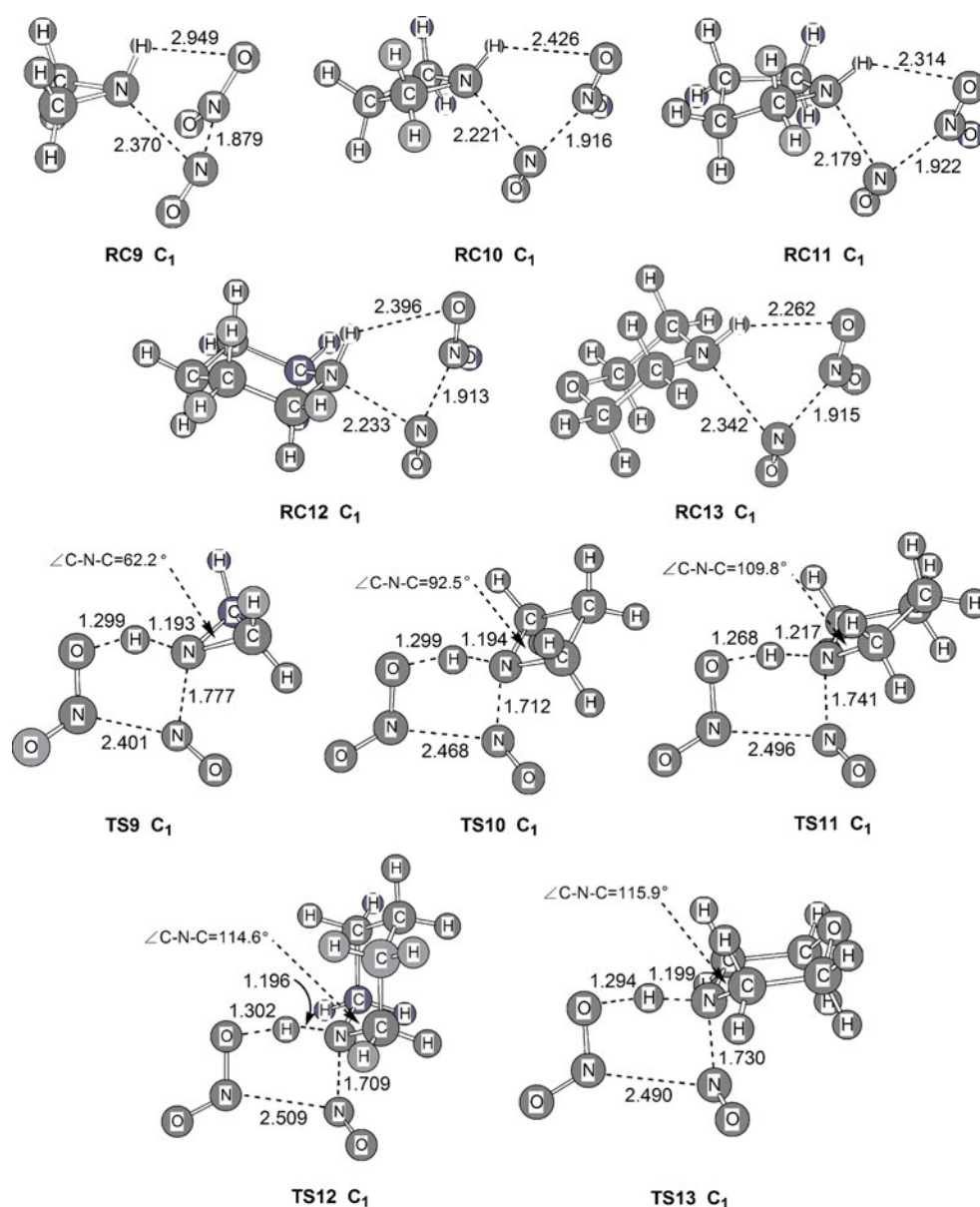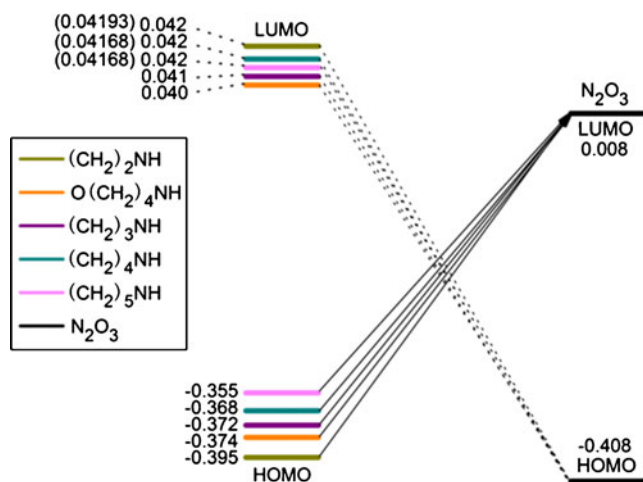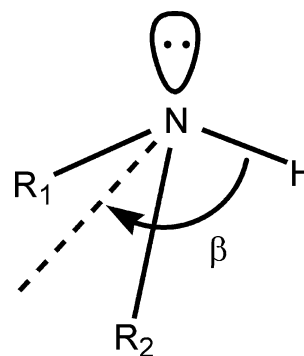
Fig. 5 Schematic profiles for the energies (in hartree) of the HOMO and LUMO of the heterocyclic amines and N_2O_3

Scheme 3 Pyramidalization angle β of amine (defined as the angle between N-H bond and R1-N-R2 plane in present work)

be 43.90, 16.60, 12.02, 11.90, and 17.99 kJ mol^{-1}, respectively. Accordingly, the reactivity order is $(CH_2)_5NH >$ $(CH_2)_4NH > (CH_2)_3NH > O(CH_2)_4NH > (CH_2)_2NH$. In comparison with N-nitrosation reactions of acyclic amines (Table 2), the energy barriers for the heterocyclic amines are somewhat lower. This indicates that N-nitrosation of heterocyclic amines by N_2O_3 occurs more easily than that of acyclic amines.

The FMO analysis in Fig. 5 exhibits a good relationship between the reactivity and energy gap for the heterocyclic amines. The HOMO energies of $(CH_2)_2NH$, $(CH_2)_3NH$, $(CH_2)_4NH$, $(CH_2)_5NH$, and $O(CH_2)_4NH$ were calculated to be −0.395, −0.372, −0.368, −0.355, and −0.374 hartree, respectively. Therefore, the order of the energy gap between the five heterocyclic amines and N_2O_3 (with the $E_{LUMO}=$ 0.008 hartree) is $(CH_2)_5NH < (CH_2)_4NH < (CH_2)_3NH < O$ $(CH_2)_4NH < (CH_2)_2NH$, which is in good agreement with the order of the reactivity. Result of linear regression indicates that the energy barrier correlates linearly (R= 0.923 and $R_{adj}^2=0.802$) with the energy gap between HOMO (amine) and LUMO (N_2O_3).

Additionally, the pyramidalization angles (Scheme 3) of the heterocyclic amines (column β in Table 2) were found to have correlation with the reactivities. As shown in

Table 2, the values of β are 113, 127, 128, and 126° for $(CH_2)_2NH$, $(CH_2)_3NH$, $(CH_2)_4NH$, and $(CH_2)_5NH$, respectively. Basically, a larger pyramidalization angle tends to generate a heterocyclic amine with higher reactivity. This may be rationalized by the reason that the larger pyramidalization angles makes the molecule less pyramidalized and gives the lone pair orbital a larger $2p$ character relative to the original sp^3 hybridized state (this is supported by a systematic increase of p component into the natural bond of lone pair in Table 2), the result of which makes the lone pair being easier to accept the NO moiety of N_2O_3. As for $(CH_2)_5NH$ and $O(CH_2)_4NH$, although they have similar structures both with six-membered ring and the close value of pyramidalization angles, the energy barrier for O $(CH_2)_4NH$ is somewhat higher than that of $(CH_2)_5NH$ by around 6 kJ mol^{-1}. This increased barrier is probably caused by the electron-withdrawing inductive effect of oxygen atom for $O(CH_2)_4NH$, which may decrease the capability of the lone pair orbital accepting the NO moiety of N_2O_3.

In addition, the NBO charge of the N atom (Q_N) and the heterolytic bond dissociation energy of R_1R_2N-H bond (E_{N-H}) of the heterocyclic amine were also taken into consideration to examine their correlations with the reactivity. Unfortunately, different from the case of acyclic amines, there is no definite relationship between the reactivity of the heterocyclic amine and Q_N as well as E_{N-H}.

Table 3 CBS-QB3 energy barriers (E_b, 298 K and 1 atm, in kJ mol^{-1}), reaction energies (ΔH and ΔG, 298 K and 1 atm, in kJ mol^{-1}) for the N-nitrosation of $(CH_2)_2NH$ (aziridine), $(CH_2)_3NH$ (azetidine), $(CH_2)_4NH$ (pyrrolidine), $(CH_2)_5NH$ (piperidine), and $O(CH_2)_4NH$ (morpholine) by N_2O_3 in the gas phase

Reaction	E_b	ΔH	ΔG
$(CH_2)_2NH+N_2O_3 \rightarrow (CH_2)_2NNO+HNO_2$	43.90	−32.73	−30.93
$(CH_2)_3NH+N_2O_3 \rightarrow (CH_2)_3NNO+HNO_2$	16.60	−90.25	−94.52
$(CH_2)_4NH+N_2O_3 \rightarrow (CH_2)_4NNO+HNO_2$	12.02	−90.87	−96.36
$(CH_2)_5NH+N_2O_3 \rightarrow (CH_2)_5NNO+HNO_2$	11.90	−89.66	−93.92
$O(CH_2)_4NH+N_2O_3 \rightarrow O(CH_2)_4NNO+HNO_2$	17.99	−98.19	−102.41

Fig. 6 CBS-QB3 geometries for all the reactant complexes (RC) and transition states (TS) involved in the *N*-nitrosation of the amines with unsaturated groups by N_2O_3 (Distances in Angstroms, β represents dihedral angle ∠R_1-N-H-R_2)
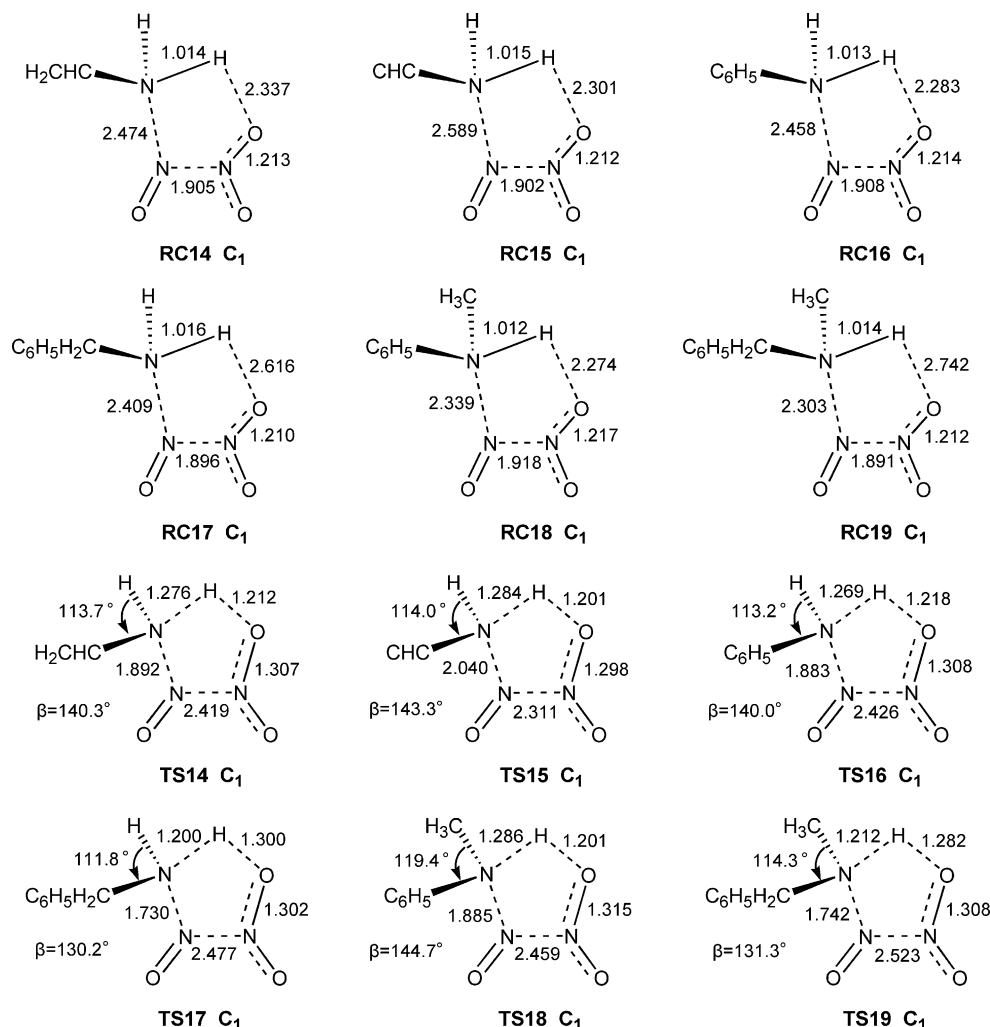
N-nitrosation of amines with unsaturated groups

N-nitrosation of six amines with unsaturated groups, *i.e.*, $CH_2=CHNH_2$, $CH≡CNH_2$, $C_6H_5NH_2$, $C_6H_5CH_2NH_2$, $C_6H_5NHCH_3$, and $C_6H_5CH_2NHCH_3$, by N_2O_3 was also investigated. Fully optimized geometries for the reactant complex (RC) and transition state (TS) were illustrated in Fig. 6. CBS-QB3 energy barriers and reaction energies were listed in Table 4.

The energy barriers calculated for $CH_2=CHNH_2$, $CH≡CNH_2$, $C_6H_5NH_2$, $C_6H_5CH_2NH_2$, $C_6H_5NHCH_3$, and $C_6H_5CH_2NHCH_3$ are 53.16, 71.22, 47.27, 44.11, 25.23, and 21.69 kJ mol^{-1}, respectively. Accordingly, the reactivity order is $C_6H_5CH_2NHCH_3 > C_6H_5NHCH_3 > C_6H_5CH_2NH_2 > C_6H_5NH_2 > CH_2=CHNH_2 > CH≡CNH_2$. Similar to the acyclic amines, the secondary amines with unsaturated group have significantly higher reactivities than the primary amines with unsaturated group. In comparison with the corresponding acyclic and heterocyclic amines, the amines with unsaturated group generally have higher energy barriers.

The HOMO energies of these amines were calculated to be −0.319, −0.347, −0.295, −0.323, −0.286, and −0.325 hartree,

Table 4 CBS-QB3 energy barriers (E_b, 298 K and 1 atm, in kJ mol^{-1}), reaction energies (ΔH and ΔG, 298 K and 1 atm, in kJ mol^{-1}) for the *N*-nitrosation of CH_2CHNH_2, $CHCNH_2$, $C_6H_5NH_2$, $C_6H_5CH_2NH_2$, $C_6H_5NHCH_3$, and $C_6H_5CH_2NHCH_3$ by N_2O_3 in the gas phase

| Reaction	E_b	ΔH	ΔG
$CH_2CHNH_2 + N_2O_3 \rightarrow CH_2CHNHNO + HNO_2$	53.16	−70.23	−68.62
$CHCNH_2 + N_2O_3 \rightarrow CHCNHNO + HNO_2$	71.22	−42.79	−41.18
$C_6H_5NH_2 + N_2O_3 \rightarrow C_6H_5NHNO + HNO_2$	47.27	−95.92	−94.38
$C_6H_5CH_2NH_2 + N_2O_3 \rightarrow C_6H_5CH_2NHNO + HNO_2$	44.11	−79.09	−79.43
$C_6H_5NHCH_3 + N_2O_3 \rightarrow C_6H_5NCH_3NO + HNO_2$	25.23	−75.24	−82.85
$C_6H_5CH_2NHCH_3 + N_2O_3 \rightarrow C_6H_5CH_2NCH_3NO + HNO_2$	21.69	−81.27	−93.59

respectively. Note that the energy gap between the HOMO of amines with unsaturated group and LUMO of N_2O_3 is definitely lower than those of acyclic and heterocyclic amines, which is contrary with previous hypothesis that a lower energy gap leads to a higher reactivity of an amine.

The frontier orbitals, such as the HOMOs, are canonical molecular orbitals which are generally delocalized over the whole molecule. The HOMOs of all 19 amines were illustrated in Fig. 7. It can be found that the distributions of HOMOs for the amines with unsaturated groups are different from those of acyclic and heterocyclic amines. In the case of the acyclic and heterocyclic amines, the HOMO has larger amplitude on the N atom than other atoms; however, in the case of the amines with unsaturated groups,

in addition to the N atom, the HOMO also has considerably larger amplitude on the unsaturated group than that of the N atom. In other words, the reactive position of the HOMO is mainly located at the N atom for the acyclic and heterocyclic amines, whereas two reactive positions are located at the N atom and the unsaturated group for the amines with unsaturated groups. Therefore, for both acyclic and heterocyclic amines, the energy level of HOMO represents the reactivity to react with an electrophile (N_2O_3 in this study), as shown in Scheme 2, since the reaction site for N-nitrosation of amines by N_2O_3 only locates at the N atom. However, as for the amines with unsaturated groups, the energy level of HOMO is mainly attributed from the interaction between the N atom and
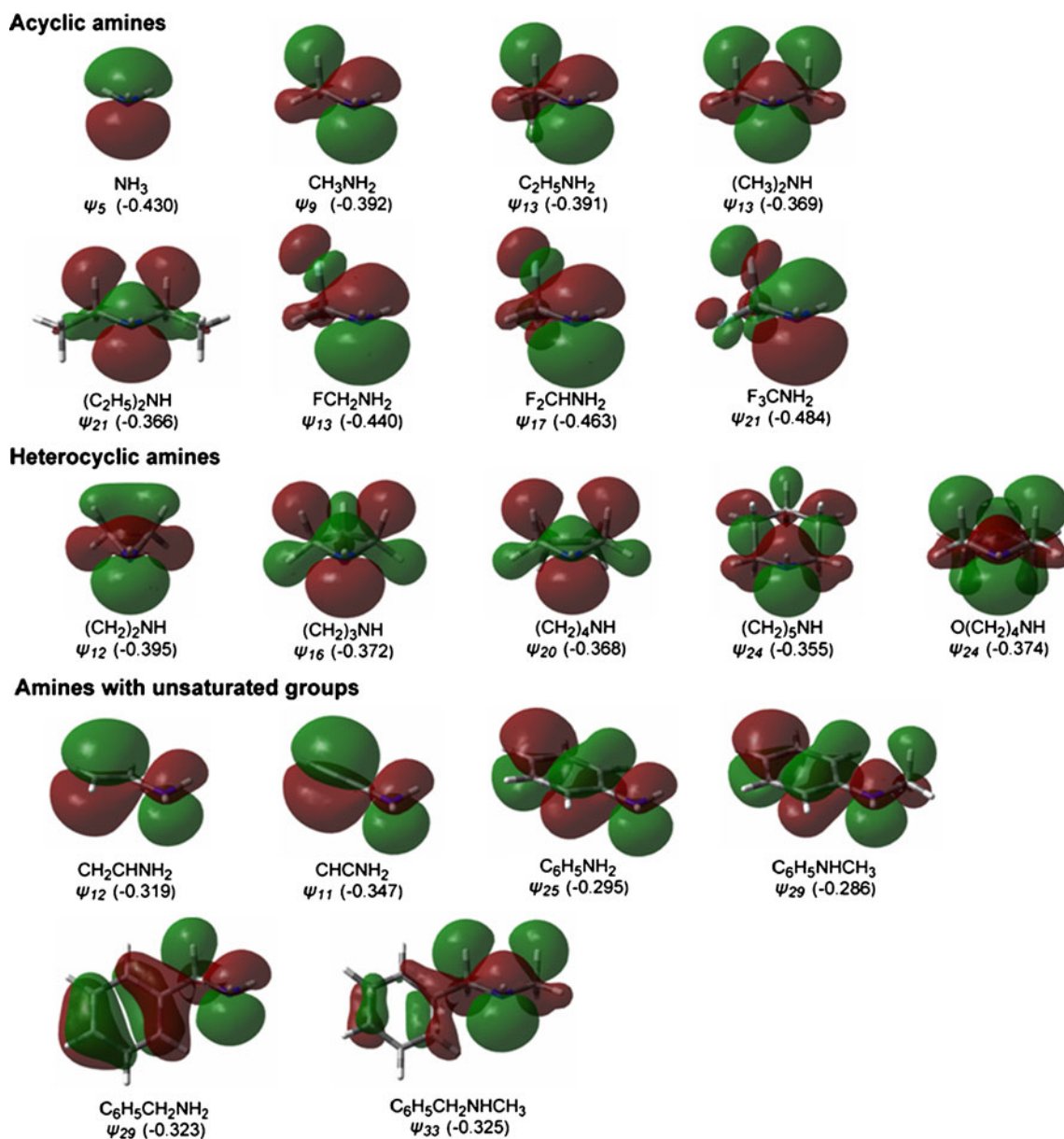
Fig. 7 The HOMOs and the corresponding energies (in parentheses, in hartree, calculated at the CBS-QB3 level) of the 19 amines

unsaturated groups, therefore, it cannot be a representation of the reactivity.

As shown in Table 2 that the appearance of unsaturated groups in amine molecules results in a reduction of NBO occupancy for the lone pair in nitrogen atom when compared with the acyclic and heterocyclic amines. It indicates that the introduction of the unsaturated group may lead to the delocalization of the lone pair. This result somewhat accounts for the relatively high energy barrier of the amine with unsaturated group. In addition, the contribution of s and p components into the natural orbital of lone pair was also taken into account. It is interesting to observe that the contribution of p component into the lone pair orbital generally increases with the introduction of unsaturated group.

As for $CH_2=CHNH_2$, $CH\equiv CNH_2$, and $C_6H_5NH_2$, the order of their reactivities is $C_6H_5NH_2 > CH_2=CHNH_2 > CH\equiv CNH_2$. NBO analysis indicates that $CH_2=CH-$, $CH\equiv C-$, and C_6H_5- are all electron-withdrawing groups because of a lower occupancy (1.892, 1.893, and 1.897) on the lone pair of them than that of NH_3 (1.998). As stated above, electron-withdrawing groups somewhat increase the energy barrier, thus restraining the N-nitrosation reactions. However, in comparison with the barrier of NH_3 (70.41 kJ mol^{-1}), the electron-withdrawing effect of C_6H_5-, $CH_2=CH-$, and $CH\equiv C-$ groups does not increase the reaction barrier, which is inconsistent with the previous conclusion. This inconsistency possibly results from the larger pyramidalization angles β of the three amines, whose values are 139, 138, and 138° for $CH_2=CHNH_2$, $CH\equiv CNH_2$, and $C_6H_5NH_2$, respectively, which are larger than that of NH_3 with the value of 118°. As discussed above, a larger pyramidalization angle β makes an easier reaction. Therefore, in this case, the reactivity of an amine is probably determined by the competition of the electron-withdrawing effect of groups (C_6H_5-, $CH_2=CH-$, and $CH\equiv C-$) with the structural factor pyramidalization angle β.

According to the electron-donating effect, substitution of a CH_3- group in $C_6H_5NH_2$ (i.e., $C_6H_5NHCH_3$) remarkably reduces the energy barrier from 47.27 to 25.23 kJ mol^{-1}. Similarly, due to the electron-withdrawing effect of C_6H_5- group, the energy barriers of the N-nitrosation of $C_6H_5CH_2NH_2$ and $C_6H_5CH_2NHCH_3$ are slightly higher than those of CH_3NH_2 and $(CH_3)_2NH_2$.

In addition, the NBO charge of the N atom, Q_N, and the heterolytic bond of R_1R_2N-H bond, E_{N-H}, were also taken into consideration to examine their correlations with the reactivity of the amine with unsaturated groups. Similar to the acyclic amines, generally, the amine with unsaturated groups with a small absolute value of Q_N has a relatively high reactivity. However, there is no definite relationship between the dissociation energy E_{N-H} and the reactivity, which is probably due to the electron-withdrawing effect of the unsaturated substituents.

Structure-reactivity relationship analysis

The structure-reactivity relationship of the amines in the N-nitrosation by N_2O_3 was investigated using the stepwise multivariate linear regression (MLR). The descriptors used for the MLR were listed in Table 2, where the E_b, E_{N-H}, E_{HOMO}, LP_N, Q_N, α, and β represents the energy barrier, the heterolytic bond dissociation energy of R_1R_2N-H bond, the energies of the highest occupied unoccupied molecular orbital, NBO occupancy of the natural lone pair orbital of N atom, the NBO charge of the N atom, the angle $\angle R_1NR_2$ and pyramidalization angle of an amine, respectively.

The stepwise multivariate linear regression was performed with all the descriptors in Table 2. The final regression model was obtained as Eq. 1. The model shows that the predicted energy barrier (E_b^p) depends on five descriptors E_{N-H}, E_{HOMO}, LP_N, Q_N, and β, while the descriptor angle α was excluded due to failing to meet the criteria for P≤0.05. Figure 8 shows that the predicted energy barrier (E_b^p) correlates linearly with the calculated energy barrier (E_b^c) with a correlation coefficient (R) and adjusted determinate coefficients (R_{adj}^2) being 0.981 and 0.947, respectively. Accordingly, there is a definite relationship between the reactivity of an amine with heterolytic bond dissociation energy of R_1R_2N-H bond, energy of the highest occupied molecular orbital, NBO occupancy of the natural lone pair orbital of N atom, NBO charge of N atom, and pyramidalization angle of an amine. Furthermore, the regression model reveals that the energy barrier correlates negatively with all five descriptors. In light of the standardized coefficients (Eq. 2), it leads to a conclusion that the LP_N, Q_N, and β make a considerable contribution to the energy barrier, whereas the E_{N-H} and E_{HOMO} contribute a little. This predicts that the high values of the NBO occupancy of the natural lone pair orbital, the NBO charge of the N atom, and
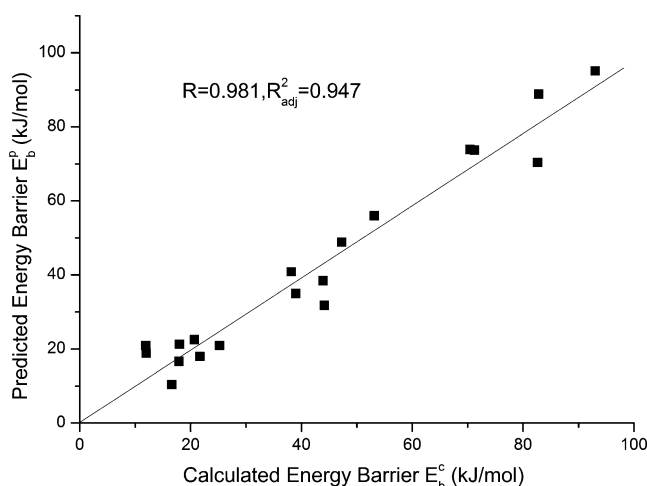
Fig. 8 Predicted energy barriers (E_b^p) versus the calculated energy barriers (E_b^c) for the N-nitrosation of amines by N_2O_3

pyramidalization angle of an amine are important basic features for a highly reactive amine.

$$E_b^p = -0.167E_{N-H} - 123.921E_{HOMO} - 838.242LP_N$$
$$- 237.443Q_N - 3.491\beta + 2146.372 \quad (1)$$

$$E_b^p = -0.369E_{N-H} - 0.253E_{HOMO} - 1.096LP_N$$
$$- 0.863Q_N - 1.064\beta \quad (2)$$

Conclusions

N-nitrosation of 19 amines (eight acyclic amines, five heterocyclic amines, and six amines with unsaturated group) by N_2O_3 was investigated at the CBS-QB3 level of theory. In the case of the acyclic amines, the reaction barrier is decreased with alkylation on ammonia. Furthermore, a conclusion is drawn that the electron-donating substituents of amines facilitate the *N*-nitrosation reactions, whereas the electron-withdrawing substitutions somewhat restrain the reactions. As for the heterocyclic amines, they generally have the highest reactivities among the three studied kinds of amines. It was found that the larger the pyramidalization angle of the heterocyclic amines is, the higher the reactivities would be. For the amines with unsaturated groups, the reactivity was found to be probably determined by the competition of the electron-withdrawing effect of substituents (C_6H_5-, $CH_2=CH$-, and $CH\equiv C$-) with the structural factor pyramidalization angle β. Frontier molecular orbital analysis indicates that the energy gap between the HOMO of an amine and the LUMO of N_2O_3 is an important factor predicting the reactivity of an amine only when the reactive position of the HOMO mainly located at the N atom of the amines, otherwise it is not. This is the case for the acyclic and heterocyclic amines but not for the amines with unsaturated groups, because the HOMO of the amines with unsaturated group is attributed from the interaction between the N atom and unsaturated group of the amines rather than the N atom itself.

A structure-reactivity relationship model was established using a stepwise multivariate linear regression. The model shows that the energy barriers have a definite relationship (R= 0.981 and R_{adj}^2=0.947) with five descriptors E_{N-H}, E_{HOMO}, LP_N, Q_N, and β, which represent the heterolytic bond dissociation energy of R_1R_2N-H bond, the energies of the highest occupied molecular orbital, NBO occupancy of the natural lone pair orbital of N atom, the NBO charge of N atom, and the pyramidalization angle of an amine, respectively, and they are inversely proportional to the five descriptors. The results will elucidate the structure-reactivity relationship of

amines in the *N*-nitrosation reactions and will help to gain an in-depth understanding of *N*-nitrosation reactions.

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