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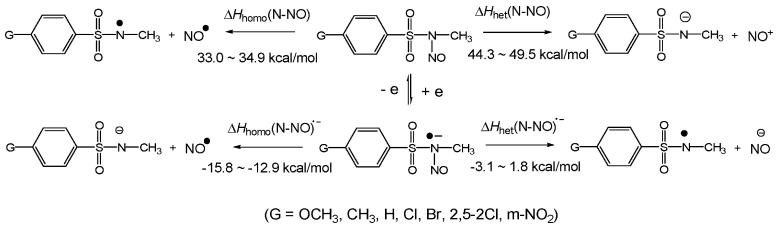

(G = OCH_3, CH_3, H, Cl, Br, 2,5-2Cl, m-NO_2)

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Determination of N−NO Bond Dissociation Energies of *N*-Methyl-*N*-nitrosobenzenesulfonamides in Acetonitrile and Application in the Mechanism Analyses on NO Transfer

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Abstract: The heterolytic and homolytic N−NO bond dissociation energies of seven substituted *N*-methyl-*N*-nitrosobenzenesulfonamides (abbreviated as G-MNBS, G = *p*-OCH_3, *p*-CH_3, *p*-H, *p*-Cl, *p*-Br, 2,5-2Cl, *m*-NO_2) in acetonitrile solution were evaluated for the first time by using titration calorimetry and relative thermodynamic cycles according to Hess' law. The results show that the energetic scales of the heterolytic and homolytic N−NO bond dissociation energies of G-MNBS in acetonitrile solution cover the ranges from 44.3 to 49.5 and from 33.0 to 34.9 kcal/mol for the neutral G-MNBS, respectively, which indicates that *N*-methyl-*N*-nitrosobenzenesulfonamides are much easier to release a NO radical ($NO^{\bullet}$) than to release a NO cation (NO^+). The estimation of the heterolytic and homolytic $(N-NO)^{-\bullet}$ bond dissociation energies of the seven G-MNBS radical anions in acetonitrile solution gives the energetic ranges of −15.8 to −12.9 and −3.1 to 1.8 kcal/mol for the $(N-NO)^{-\bullet}$ bond homolysis and heterolysis, respectively, which means that G-MNBS radical anions are very unstable at room temperature and able to spontaneously or easily release a NO radical or NO anion (NO^-), but releasing a NO radical is easier than releasing NO anion. These determined N−NO bond dissociation energies of G-MNBS and their radical anions have been successfully used in the mechanism analyses of NO transfer from G-MNBS to 3,6-dibromocarbazole and the reactions of NO with the substituted *N*-methyl-benzenesulfonamide nitranions (G-MBSN$^-$) in acetonitrile solution.

Introduction

Since the proven toxicity,[1] carcinogenic,[2] mutagenic,[3] and teratogenic[4] properties of nitrosamines were discovered and identified, great interests have been increasing intently on the chemistry and biochemistry of nitrosamines. A question of general interest is on the course of nitroso group transfer from nitrosamines or to their parent amines. Among all kinds of nitrosamines, *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) has received the most attention of chemists.[5−8] The main reason is that MNTS could not only form the diazomethane to methylate other substrates (in particular, to the methylation of DNA) resulting in organic mutation[9] but also react as an effective transnitrosating agent with the amino nitrogen of secondary amines and amides both in vitro (human gastric juice) and in vivo (rats)[10] to yield *N*-nitroso compounds, which were all known animal carcinogens. Systematic examination of the past reports on MNTS as a NO donor shows that although there are many chemists who devoted much time to the studies on the course of nitroso group transfer from MNTS to second amines, the main attention was limited to the kinetic analysis of the nitroso group transfer.[11] Rather scant attention has been paid to the detailed thermodynamic analysis on the course of the nitroso group transfer, in which the heterolytic and/or homolytic N−NO cleavage of MNTS should be involved. One key reason is that some important thermodynamic data about the heterolytic and homolytic N−NO bond dissociation energies of MNTS and its relative nitroso compounds in solution are difficult to be measured. In fact, the direction and the potential of nitroso group transfer from MNTS to amines are still

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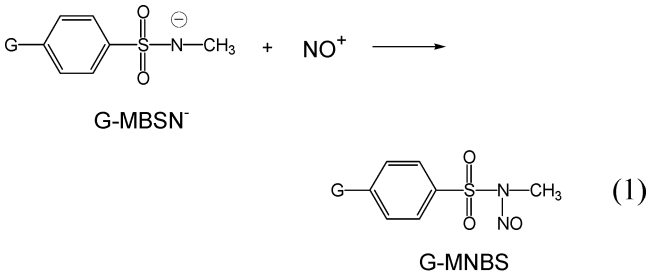
unsolved until now. It is evident that the thermodynamic data of the heterolytic and homolytic N−NO bond dissociation energies of MNTS and its analogues should be very important and urgently required for chemists and biochemists not only to thoroughly elucidate the detailed mechanism of NO transfer from MNTS but also to scientifically design and synthesize suitable and desired nitric oxide releasing agents as NO drugs. Therefore, the development of the N−NO bond energy scale in solution for a series of MNTS compounds has been a strategic goal in our research program for a long time. In this paper, the three following contributions can be provided: (1) The heterolytic and homolytic N−NO bond dissociation energies of seven substituted *N*-methyl-*N*-nitrosobenzenesulfonamides (G-MNBS) in acetonitrile solution were determined by using an experimental method for the first time. (2) The effect of one-electron addition on the N−NO bond activation was estimated quantitatively. (3) The mechanistic steps of the nitroso group transfer from G-MNTS to a second amine 3,6-dibromocarbazole and the combination pathways of NO with the substituted *N*-methylbenzenesulfonamide nitranions (G-MBSN$^-$) in acetonitrile solution were examined in detail and elucidated by using the determined N−NO bond dissociation energies of the substituted *N*-methyl-*N*-nitrosobenzenesulfonamides and their radical anions together with some kinetic parameters of the relative reactions.

Results

The substituted *N*-methyl-benzenesulfonamide nitranions (G-MBSN$^-$) formed by removing a proton from the corresponding parent sulfonamides with KH were treated with nitrosonium perchlorate (NO^+) in acetonitrile solution to yield the corresponding substituted *N*-methyl-*N*-nitrosobenzenesulfonamides (G-MNBS) quantitatively (eq 1), which were identified by MS and ^{1}H NMR. According to the reaction (eq 1), obviously, the



G-MNBS (1)

heterolytic N−NO bond dissociation energy of G-MNBS [ΔH_{het}(N−NO)] is just equal to the reaction enthalpy change (ΔH_{rxn}) of the nitranion G-MBSN$^-$ with NO^+ simply by switching the sign of ΔH_{rxn} (eq 2),

$$\Delta H_{het}(\text{N}-\text{NO}) = -\Delta H_{rxn} \quad (2)$$

and the latter can be directly determined by titration calorimetry, since the combination of NO^+ with the nitranion in acetonitrile solution is fast and quantitative, which is fully suitable for the titration calorimetry. The homolytic N−NO bond dissociation energies [ΔH_{homo}(N−NO)] can be derived indirectly from a thermodynamic cycle shown in Scheme 1 by combining the corresponding heterolytic N−NO bond dissociation energies with suitable redox potentials (eq 3).

$$\Delta H_{homo}(\text{N}-\text{NO}) = \Delta H_{het}(\text{N}-\text{NO}) - \text{F}[E_{1/2}(\text{NO}^{+/0}) - E^\circ_{ox}(\text{G-MBSN}^{0/-})] \quad (3)$$

The latter can be either obtained from literatures or directly measured by second-harmonic ac voltammetry (SHACV) method.[12] The seven enthalpy changes (ΔH_{rxn}) of the reaction (eq 1) and redox potentials of seven substituted *N*-methyl-*N*-nitrosobenzenesulfonamides (G-MNBS) and their corresponding nitranions (G-MBSN$^-$) as well as pK_a's of the corresponding substituted *N*-methyl-benzenesulfonamides (G-MBS) in acetonitrile solution (whichever available) are listed in Table 1. The heterolytic and homolytic N−NO bond dissociation energies of the seven substituted *N*-methyl *N*-nitrosobenzenesulfonamides (G-MNBS) are summarized in Table 2.

Since electron transfer generally occurs in biological and chemical systems and makes a substantial effect on activating chemical bonds,[13−15] the heterolytic and homolytic dissociation energies of N−NO bond for G-MNBS$^{-\bullet}$ in acetonitrile solution were estimated according to eqs 4 and 5,

$$\Delta H_{homo}(\text{N}-\text{NO})^{-\bullet} = \Delta H_{het}(\text{N}-\text{NO}) - \text{F}[E_{1/2}(\text{NO}^{+/0}) - E^\circ_{red}(\text{G-MNBS})] \quad (4)$$

$$\Delta H_{het}(\text{N}-\text{NO})^{-\bullet} = \Delta H_{homo}(\text{N}-\text{NO}) + \text{F}[E^\circ_{red}(\text{G-MNBS}) - E_{1/2}(\text{NO}^{0/-})] \quad (5)$$

which were obtained from the two thermodynamic cycles constructed from the N−NO bond heterolytic and homolytic scission reactions of the neutral G-MNBS in acetonitrile solution as shown in Scheme 2, respectively. The results are also summarized in Table 2.

It should be pointed out herein that, in eqs 3−5, free energy changes were used to replace the enthalpy changes for the electron-transfer processes. This treatment is reasonable, since the entropy changes associated with electron transfer have been verified to be small and may be negligible.[12e,19]

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Scheme 1

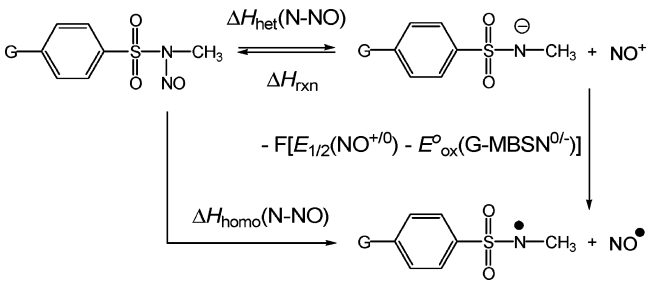


Table 1. Enthalpy Changes of the Reaction (eq 1) and Redox Potentials of the Relevant Species in CH_3CN at 25 °C (V vs $Fc^{+/0}$) Together with the pK_a's of the Corresponding Parent Amines in Acetonitrile

G	ΔH_{rxn}[a]	E°_{ox}(G-MBSN$^-$)[b]	E°_{red}(G-MNBS)[b]	pK_a(G-MBS)[c]
p-OCH_3	−49.5	0.179	−1.844	26.54
p-CH_3	−48.7	0.201	−1.839	26.30
p-H	−47.8	0.305	−1.895	25.94
p-Cl	−46.9	0.261	−1.824	25.29
p-Br	−47.3	0.245	−1.854	
2,5-2Cl	−46.5	0.307	−1.714	
m-NO_2	−44.3	0.411	−1.680	24.03

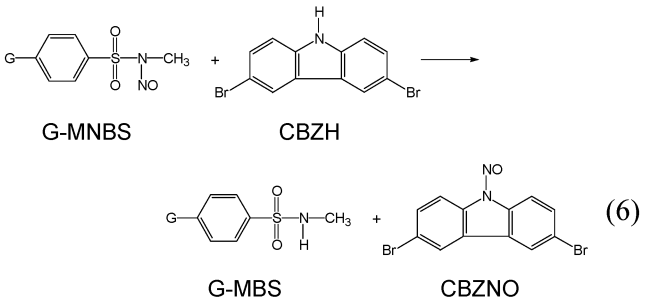
[a] ΔH_{rxn} obtained from the reaction heat of eq 1 by switching the sign of the heat value, the latter was measured by titration calorimetry in acetonitrile at 25 °C. The data in kcal/mol given were average values of at least three independent runs. The reproducibility is ±0.5 kcal/mol. [b] Measured by SHACV in acetonitrile at 25 °C, the unit in volts vs $Fc^{+/0}$ and reproducible to 5 mV or better. [c] The pK_a's of G-MBS in acetonitrile were derived from the corresponding pK_a values in H_2O (11.73, 11.69, 11.43, 11.10, and 10.42 for G: OCH_3, CH_3, H, Cl, and m-NO_2, respectively)[16] by adding the known pK_a difference of the close homologous series in acetonitrile and in water.[17]

Table 2. Heterolytic and Homolytic N−NO Bond Dissociation Energies of G-MNBS and Their Radical Anions in CH_3CN at 25 °C (kcal/mol)

G	ΔH_{het}(N–NO)[a]	ΔH_{homo}(N–NO) [b]	ΔH_{homo}(N–NO)$^{-\bullet}$[b]	ΔH_{het}(N–NO)$^{-\bullet}$[b]
p-OCH_3	49.5	33.7	−12.9	−2.2
p-CH_3	48.7	33.4	−13.6	−2.4
p-H	47.8	34.9	−15.8	−2.2
p-Cl	46.9	33.0	−15.1	−2.4
p-Br	47.3	33.0	−15.4	−3.1
2,5-2Cl	46.5	33.7	−12.9	0.8
m-NO_2	44.3	33.9	−14.3	1.8

[a] ΔH_{het}(N−NO) was obtained from eq 2. [b] ΔH_{homo}(N−NO), ΔH_{homo}(N−NO)$^{-\bullet}$, and ΔH_{het}(N−NO)$^{-\bullet}$ were estimated from eqs 3, 4, and 5, respectively, taking $E_{1/2}(NO^{+/0}) = 0.863$ and $E_{1/2}(NO^{0/-}) = -0.287$ (V vs $Fc^{+/0}$). Relative uncertainties were estimated to be smaller than 1 kcal/mol.[18]

The reaction of G-MNBS with 3,6-dibromocarbazole (CBZH) in dry acetonitrile solution under argon atmosphere yields two products: the substituted *N*-methyl-benzenesulfonamide (G-MBS) and *N*-nitroso-3,6-dibromocarbazole (CBZNO), the latter being separated from the reaction mixture due to the poor solubility of CBZNO in acetonitrile solvent (eq 6). From eq 6,



it is clear that the reaction was carried out by NO transfer from G-MNBS to 3,6-dibromocarbazole. The second-order rate constants of the NO transfer at different temperatures between 15 and 40 °C can be obtained according to the dependence of the yields of *N*-nitroso-3,6-dibromocarbazole on the reaction time, and the details are given in Table 3. Arrhenius activation energy (ΔE_a) and Eyring activation parameters: activation enthalpy ($\Delta H^{\ddagger}$) and activation entropy ($\Delta S^{\ddagger}$) for the reaction 6 are summarized in Table 4, which were derived from Arrhenius plots of ln k_2 and Eyring plots of ln(k_2/T) versus the reciprocal of the absolute temperature ($1/T$), respectively.

Discussion

Heterolytic and Homolytic N−NO Bond Dissociation Energies of G-MNBS in Acetonitrile. Table 2 shows that the energetic scales of the heterolytic and homolytic N−NO bond dissociation energies of G-MNBS in acetonitrile range from 49.5 kcal/mol for G-MNBS (G = *p*-CH_3O) to 44.3 kcal/mol for G-MNBS (G = *m*-NO_2) and from 33.7 kcal/mol for G-MNBS (G = *p*-CH_3O) to 33.9 kcal/mol for G-MNBS (G = *m*-NO_2), respectively. Comparison of the heterolytic N−NO bond dissociation energies with the corresponding homolytic dissociation energies of the N−NO bonds clearly shows that the homolytic N−NO bond dissociation energy is lower than the corresponding heterolytic N−NO bond dissociation energy by 15.8−10.4 kcal/mol, which indicates that homolysis of the N−NO bond to generate the NO neutral free radical (NO$^{\bullet}$) and the corresponding sulfonamide nitrogen free radical is energetically much more favorable than the corresponding N−NO bond heterolysis to generate a pair of ions. This result suggests that, like some *S*-nitroso compounds,[21] the *N*-nitroso compounds G-MNBS should be also easier to release NO$^{\bullet}$ than to release NO^+ in solution by thermolytic dissociation, which is well in line with experimental observation of some *N*-nitroso compounds by pyrolysis at room temperature or at higher temperature. However, it should be pointed out herein that the practical dissociation fashion of G-MNBS and other NO donors in solution, i.e., to release NO$^{\bullet}$ by homolysis or to release NO^+ by heterolysis, could not be dependent only on the relative magnitude of the corresponding dissociation energies of the N−NO bond but should be also on the thermodynamics of the follow-up reactions.

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(18) Although the uncertainties in the absolute values of the N−NO bond dissociation energies are unknown, the relative uncertainties can be estimated from eqs 3−5. According to eqs 3−5, it is clear that the uncertainties of the N−NO bond dissociation energies were contributed by the uncertainty of the heterolytic N−NO bond dissociation energies of G-MNBS and the uncertainties of the redox potentials of the relative species. Since the reproducibility of the determined heterolytic N−NO bond dissociation energies of G-MNBS is ±0.5 kcal/mol, and the reproducibility of the redox potentials of the relative species is less than 5 mV, which is equal to ±0.2 kcal/mol, so the relative uncertainties of the N−NO bond dissociation energies were estimated to be smaller than ±1 kcal/mol.
(19) The entropy change for the redox processes in similar cases has been examined, the result shows that the entropy contribution for the redox processes in the cases should be insignificant (ref. *J. Am. Chem. Soc*. **1998**, *120*, 10266−10267).
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Scheme 2

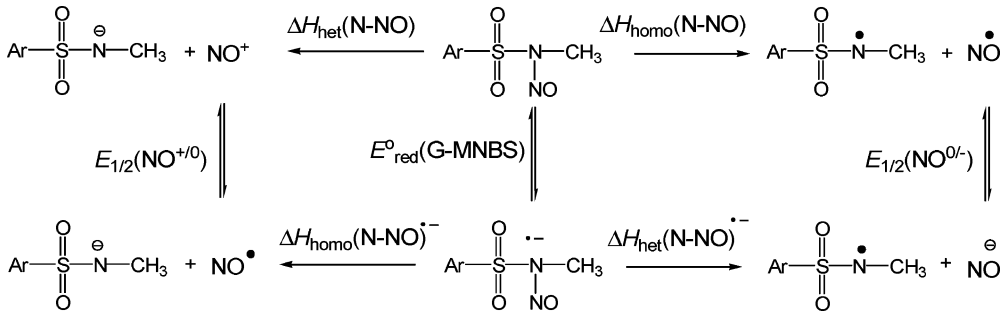


Table 3. Second-Order Rate Constants for the Reaction of G-MNBS with 3,6-Dibromocarbazole at Different Temperatures (15−40 °C)

	$k_2 \times 10^4$ (M^{-1} s^{-1}) [a]					
G	288 K	293 K	298 K	303 K	308 K	313 K
p-OCH_3	0.25	0.38	0.52	0.77	1.26	1.86
p-CH_3	0.38	0.54	0.77	0.99	1.71	2.36
p-H	0.62	0.90	1.15	1.56	2.57	3.68
p-Cl	1.12	1.65	2.07	2.83	4.55	6.13
p-Br	1.13	1.66	2.09	2.88	4.58	6.19
m-NO_2	4.31	5.62	7.80	9.66	14.00	19.03

[a] The second-order rate constants (k_2) for the reaction of G-MNBS with 3,6-dibromocarbazole in acetonitrile solution at different temperatures were obtained by using the equation $k_2 = y/a(100 - y)t$.[20] Therein, y is the percentage yield of the isolated product *N*-nitroso-3,6-dibromocarbazole, a is the initial concentration of the reactant G-MNBS or 3,6-dibromocarbazole (the initial concentration of G-MNBS is equal to the initial concentration of 3,6-dibromocarbazole for the reaction), and t is the reaction time. The detailed values of y, a, and t were offered in the Supporting Information (Table S1).

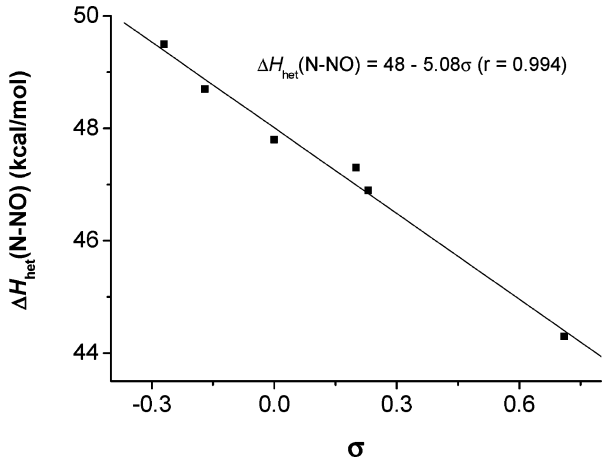


Figure 1. Correlation of the heterolytic dissociation energies of N−NO bonds in G-MNBS with the corresponding Hammett substituent constants σ.

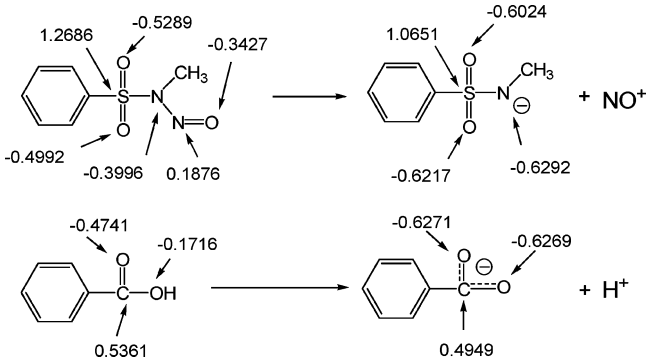
From Table 2, we also found that the value of ΔH_{het}(N−NO) becomes gradually smaller as the *para*-substituent G is going from an electron-donating group (EDG) to an electron-withdrawing group (EWG), which is due to the stabilization effect of EWG and the destabilization effect of EDG on the nitranions of the substituted *N*-methyl-benzenesulfonamides. When the ΔH_{het}(N−NO) was plotted against Hammett constant σ, an excellent straight line with a slope of −5.08 ($r = 0.994$) was obtained (Figure 1). This result implies that distribution of negative charge on the *N*-methyl benzenesulfonamide nitranion should be similar to that of negative charge on the carbanion of benzoate according to the Hammett free energy linear correlation principle,[22] which can be supported by the Mulliken

Table 4. Activation Parameters for the NO Transfer Reaction from G-MNBS to 3,6-Dibromocarbazole

G	ΔE_a[a]	$\Delta H^{\ddagger}$[b]	$\Delta S^{\ddagger}$[c]	$-T\Delta S^{\ddagger}$[d]	$\Delta G^{\ddagger}$[e]
p-OCH_3	14.3 ± 0.5	13.7 ± 0.5	−31.9 ± 1.8	9.5 ± 0.5	23.2 ± 0.5
p-CH_3	13.1 ± 0.7	12.5 ± 0.7	−35.3 ± 2.3	10.5 ± 0.7	23.0 ± 0.7
p-H	12.6 ± 0.7	12.0 ± 0.7	−36.1 ± 2.4	10.8 ± 0.7	22.8 ± 0.7
p-Cl	12.1 ± 0.6	11.5 ± 0.6	−36.1 ± 2.1	10.8 ± 0.6	22.3 ± 0.6
p-Br	12.1 ± 0.6	11.5 ± 0.6	−36.5 ± 2.1	10.9 ± 0.6	22.4 ± 0.6
m-NO_2	10.6 ± 0.4	10.0 ± 0.4	−39.2 ± 1.3	11.7 ± 0.4	21.7 ± 0.4

[a] From the Arrhenius plots, the unit is kcal/mol. [b] From the slope of the Eyring plots, the unit is kcal/mol. [c] From the intercept of the Eyring plots, the unit is cal mol^{-1} K^{-1}. [d] The unit is kcal/mol. [e] From equation $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$, the unit is kcal/mol.

Scheme 3. Charge Distribution Diagram on *N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide, Benzoic Acid and Their Corresponding Anions Derived from Computer Calculation by Using B3LYP/6-31G* Method



charge calculation using the density functional theory (DFT)-B3LYP/6-31G* method[23] about the charge distribution of the nitranion of *N*-methyl-benzenesulfonamide and the carbanion of benzoate as shown in Scheme 3. In a similar way, ΔH_{het}-(N−NO) of G-MNBS was plotted against the pK_a's of the corresponding N−H acids (G-MBS) in acetonitrile also to give an excellent straight line (Figure 2) with a slope of 1.99 ($r = 0.995$), from which an important conclusion can be made that although the enthalpy change for the heterolytic N−NO

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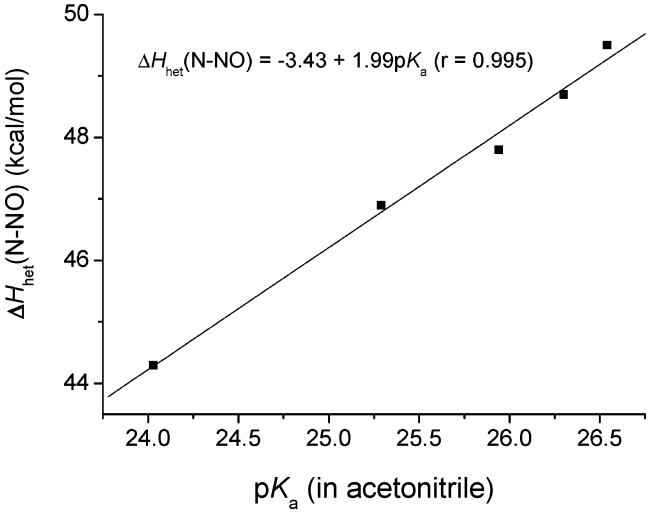

Figure 2. Correlation of the heterolytic dissociation energies of N−NO bonds in G-MNBS with the corresponding pK_a's of their parent N−H molecules.

dissociations of G-MNBS is strongly dependent on the nature of the substituents (G), the entropy change for the heterolytic N−NO dissociations of G-MNBS is not distinctly dependent on the nature of the substituents (G).

Comparing the heterolytic N−NO bond dissociation energies of G-MNBS (44.3−49.5 kcal/mol in acetonitrile solution) with those of the N−NO bonds in other *N*-nitroso compounds, such as *N*-nitrosoacetanilides (54.3−65.4 kcal/mol),[24] *N*-nitrosodiphenylamines (50.2−63.5 kcal/mol),[25] *N*-nitroso-*N*′,*N*′-dimethylphenylureas (52.4−62.0 kcal/mol),[26] and *N*-nitrosophosphoramidates (53.3−60.4 kcal),[26] shows that the N−NO bond heterolytic dissociation energies are generally decreased in the following order of the *N*-nitroso compounds: *N*-nitrosoacetanilides > *N*-nitrosodiphenylamines > *N*-nitrosophenylureas > *N*-nitrosophosphoramidates > *N*-methyl-*N*-nitrosobenzenesulfonamides (see Table 5), which indicates that the substituted *N*-methyl-*N*-nitrosobenzenesulfonamides (G-MNBS) are the best NO^+ donor among the corresponding five types of *N*-nitroso compounds. If NO^+ transfers from the *N*-methyl-*N*-nitrosobenzenesulfonamides to the corresponding acetanilides, diphenylamines, phenylureas or phosphoramidates, the transfer process should be favorable in thermodynamics. This may be the reason many chemists used to use *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) as a NO^+ donor for the nitrosations of many amines. But, by comparing the heterolytic N−NO bond dissociation energies of G-MNBS with those of the O−NO bonds in *O*-nitroso-(para-substituted)benzoates (25.7−32.3 kcal/mol),[27] the S−NO bonds in *S*-nitroso-(*p*-nitro)phenylthiol (39.3 kcal/mol),[28] and those of the Co−NO bonds in T(G)PPCo^{III}-NO (14.1−23.2 kcal/mol in benzonitrile),[29] it is found that the N−NO bond heterolytic dissociation energies of G-MNBS in acetonitrile are not only larger than that of the Co^{III}−NO bonds but also larger than that of the O−NO bonds, and even larger than that of the S−NO bond, which indicates that the NO^+ transfer from *N*-methyl-*N*-nitrosobenzenesulfonamides is unfavorable in thermodynamics to the corresponding (para-substituted)benzoates, T(G)PPCo^{II}, or (*p*-nitro)phenylthiol, but the reverse processes should be favorable. In fact, *N*-methyl-*N*-nitrosobenzenesulfonamide can be easily derived from the parent compound *N*-methyl-benzenesulfonamide by nitrosation using some RONO and RSNO, such as 2,2,2-trichloroethyl nitrites, *S*-nitrosopenicillamine (SPEN), etc., as NO^+ donors.[30]

In a similar analysis manner used above, comparing the homolytic N−NO bond dissociation energies of G-MNBS (33.0−34.9 kcal/mol) with those of *N*-nitrosoacetanilides (36.1−43.8 kcal/mol),[24] *N*-nitrosodiphenylamines (21.4−24.3 kcal/mol),[25] *N*-nitroso-*N*′,*N*′-dimethylphenylureas (28.3−33.1 kcal/mol),[26] and *N*-nitrosophosphoramidates (34.5−40.4 kcal/mol)[26] and those of the O−NO bonds in *O*-nitrosobenzoates (32.5−38.6 kcal/mol),[27] the S−NO bonds in *S*-nitrosophenylthiols (18.6−21.4 kcal/mol),[28] and the Co−NO bonds in both T(G)-PPCo^{III}NO and T(G)PPCo^{II}NO (15.2−17.5 kcal/mol and 21.1−24.6 kcal/mol)[29] demonstrates that the homolytic N−NO bond dissociation energies of G-MNBS are moderate, which indicates that the thermal stability of G-MNBS should be larger than that of the corresponding *N*-nitrosodiphenylamines, *N*-nitroso-*N*′,*N*′-dimethylphenylureas, *S*-nitrosophenylthiols, T(G)PPCo^{III}NO, and T(G)PPCo^{II}NO but smaller than that of *N*-nitrosoacetanilides and *N*-nitrosophosphoramidates. These thermodynamic data obviously are very useful to guide the design and synthesis of some suitable and desired nitric oxide releasing agents as NO drugs with biomedical application.

Effect of Reductive Electron Transfer on N−NO Bond Activation. Since the strength of a chemical bond in molecules is strongly influenced by electron transfer,[31−33] the increase or decrease of electron number in G-MNBS certainly changes the potential of G-MNBS to release a NO radical. To quantitate the effect of reductive electron addition on the N−NO bond activation, the N−NO bond dissociation energies in the radical anions of G-MNBS were estimated as shown in Table 2.

In Table 2, by simply comparing the values of ΔH_{homo}(N−NO) (33.0 to 34.9 kcal/mol) with the values of the corresponding ΔH_{homo}(N−NO)$^{-\bullet}$ (−15.8 to −12.9 kcal/mol), it is found that the value of ΔH_{homo}(N−NO) is larger than that of the corresponding ΔH_{homo}(N−NO)$^{-\bullet}$ by 46 to 51 kcal/mol, which means that the effect of one-electron addition on the N−NO bond homolytic dissociation energy is extremely large, the main reason being that the reduction potentials of G-MNBS in acetonitrile solution are all very negative. Since the values of ΔH_{homo}(N−NO)$^{-\bullet}$ all are quite negative, the radical anions of G-MNBS should be very unstable and easy to release nitric oxide radical spontaneously in acetonitrile solution at room temperature,

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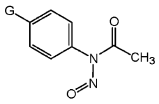
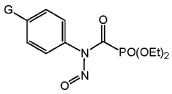
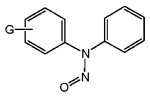
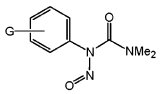
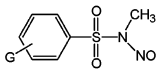
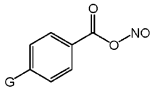
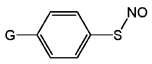
Table 5. Comparison of the Heterolytic and Homolytic Dissociation Energy Scale of X−NO Bonds (X = N, O, S, Co) among Some Typical NO Donors[a] in Acetonitrile Solution (Except Special Note) at Room Temperature (kcal/mol)

Compounds	ΔH_{het}(X-NO)	ΔH_{homo}(X-NO)	Compounds	ΔH_{het}(X-NO)	ΔH_{homo}(X-NO)
					
4-CH_3O	65.4	43.8	4-CH_3O	—	—
4-CH_3	60.4	36.1	4-CH_3	60.4	34.5
4-H	58.7	38.3	4-H	58.4	35.0
4-Cl	57.7	37.6	4-Cl	58.1	36.2
4-NO_2	54.3	39.2	4-NO_2	53.3	40.4
					
4-CH_3O	63.5	21.4	4-CH_3O	62.0	28.3
4-CH_3	62.5	21.4	4-CH_3	61.1	28.7
4-H	62.0	22.6	4-H	59.5	29.1
3-Cl	60.2	24.1	4-Cl	58.5	29.2
4-NO_2	50.2	24.3	4-NO_2	52.4	33.1
					
4-CH_3O	49.5	33.7			
4-CH_3	48.7	33.4			
4-H	47.8	34.9			
4-Cl	46.9	33.0			
3-NO_2	44.3	33.9			
					
4-CH_3O	32.3	32.5	4-CH_3O	53.5	21.0
4-CH_3	31.8	32.8	4-CH_3	52.7	21.4
4-H	30.9	33.9	4-H	49.2	19.4
4-Br	29.5	34.3	4-Cl	47.2	19.2
4-NO_2	25.7	38.6	4-NO_2	39.3	18.6
T(G)PPCo^{III}NO [b]			T(G)PPCo^{II}NO [b]		
4-CH_3O	23.2	17.5	4-CH_3O	—	24.6
4-CH_3	21.9	17.2	4-CH_3	—	24.1
4-H	20.3	16.8	4-H	—	23.4
4-Cl	18.5	16.3	4-Cl	—	22.8
4-NO_2	14.1	15.2	4-NO_2	—	21.1

[a] *N*-Nitroso-acetanilides: ref 24. *N*-Nitroso-diphenylamines: ref 25. *N*-Nitroso-phenylureas: ref 26. *N*-Nitroso-phosphoramidates: ref 26. *O*-Nitroso-(*p*-substituted)benzoates: ref 27. *S*-Nitroso-(*p*-substituted)phenylthiol: ref 28. T(G)PPCo^{III}NO: ref 29. T(G)PPCo^{III}NO: ref 29. *N*-Nitroso-benzenesulfonamides: from this work. [b] In benzonitrile solution. T(G)PPCoNO is the abbreviation of nitrosyl-α,*β*,*γ*,*δ*-tetraphenylporphinatocobalt.

which suggests that the neutral G-MNBS can release nitric oxide radical spontaneously after gaining one electron.

To compare the potentials of G-MNBS radical anions releasing a NO radical and releasing a NO anion (NO^-), the values of $\Delta H_{het}(N-NO)^{-\bullet}$ were also examined; the result shows that the values of $\Delta H_{het}(N-NO)^{-\bullet}$ are either negative or only slightly positive (−3.1 to 1.8 kcal/mol), which indicates that the process of releasing NO^- from G-MNBS radical anions is spontaneous or requires a small amount of energy at room temperature. But by comparing $\Delta H_{het}(N-NO)^{-\bullet}$ with the corresponding $\Delta H_{homo}(N-NO)^{-\bullet}$, it is clearly found that the value of $\Delta H_{homo}(N-NO)^{-\bullet}$ is much more negative than that of the corresponding $\Delta H_{het}(N-NO)^{-\bullet}$, which indicates that releasing neutral NO$^\bullet$ from G-MNBS radical anions is much easier than releasing NO^-. From this result, an interesting and reasonable proposal can be made that the natural NO anion in living body, which is also known as a physiologically active species,[34] is most likely to be derived from the one-electron reduction of NO radical rather than from the N−NO bond heterolytic dissociation of NO^- donors.

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Scheme 4

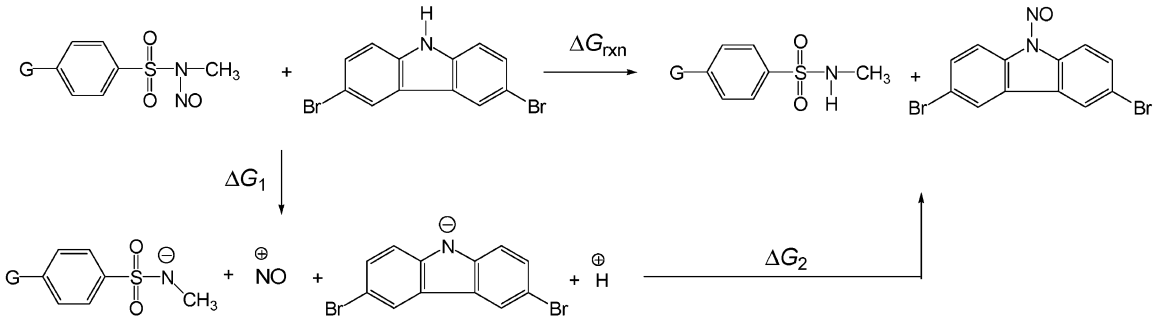


Table 6. Difference of Heterolytic Dissociation Energies of N−NO Bond between G-MNBS and *N*-Nitroso-3,6-dibromocarbazole and Difference of pK_a's between the Corresponding Parent Amines as Well as the Free Energy Changes of NO Transfer from G-MNBS to CBZH (kcal/mol)

G	$\Delta\Delta H_{het}$(G-MNBS − CBZNO)	1.364ΔpK_a(G-MBS − CBZH)[a]	ΔG_{rxn}
p-OCH_3	−2.1	0.22	−1.9
p-CH_3	−2.9	0.55	−2.4
p-H	−3.8	1.04	−2.8
p-Cl	−4.7	1.92	−2.8
m-NO_2	−6.5	3.64	−2.9

[a] pK_a value of CBZH in acetonitrile is 26.7, which was derived from its pK_a value in DMSO (17.1)[36] according to the known relation of pK_a(CH_3CN) = 0.982pK_a(DMSO) + 9.94.[28]

Thermodynamics of NO Transfer from G-MNBS to 3,6-Dibromocarbazole (CBZH). Although the transportation of NO among the different amine molecules widely occurs in many chemical or biochemical reactions, the thermodynamic tendencies of NO transfer among the different amines have been rarely evaluated quantitatively. The main reason is lack of the necessary thermodynamic data of the relative N−NO bond energies. In this work, as the first example, we try to use the determined N−NO bond dissociation energies of G-MNBS to estimate the free energy changes of NO transfer from G-MNBS to 3,6-dibromocarbazole (reaction 6). To efficiently evaluate the free energy changes of NO transfer from G-MNBS to 3,6-dibromocarbazole, a thermodynamic cycle was constructed from reaction 6 as shown in Scheme 4 and from which a formula to evaluate the free energy changes of the NO transfer was derived (eq 7). Since the entropy change of the N−NO bond heterolytic dissociation for G-MNBS would be equal or close to the entropy change of the N−NO bond heterolytic dissociation for *N*-nitroso-3,6-dibromocarbazole in the same solution, eq 7 becomes eq 8 after the neglect of the entropy contribution in the N−NO bond heterolytic dissociations. The differences of the N−NO bond heterolytic dissociation energies between G-MNBS and *N*-nitroso-3,6-dibromocarbazole and the differences of pK_a's between the corresponding two parent amines as well as the free energy changes (ΔG_{rxn}) of NO transfer from G-MNBS to CBZH are listed in Table 6.

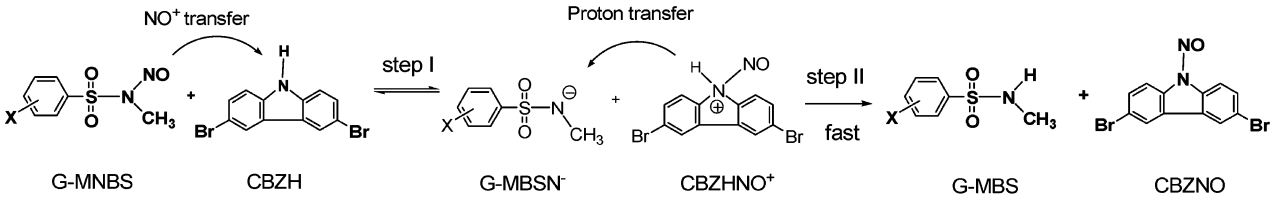
From the thermodynamic data in Table 6, it is clear that Gibbs free energy changes (ΔG_{rxn}) of reaction 6 are all negative quantities, and the values gradually but slightly become more negative as the *para*-substituent G is going from an electron-donating group (EDG) to electron-withdrawing group (EWG), which indicates that reaction 6 is favorable to the NO transfer from G-MNBS to 3,6-dibromocarbazole to form *N*-nitroso-3,6-dibromocarbazole, especially when the *para*-substituent G in G-MNBS is a strong electron-withdrawing group (such as $-NO_2$). The main reason could be that the N−NO bond heterolytic dissociation energy of *N*-nitroso-3,6-dibromocarbazole (51.6 kcal/mol) is quite larger than that of G-MNBS (44.3−49.5 kcal/mol). But, from eq 8, it is worth noting that the Gibbs free energy changes (ΔG_{rxn}) of reaction 6 consist of the two contributions: enthalpy changes and pK_a changes. The enthalpy changes give ΔG_{rxn} the contribution of a negative value, but the pK_a changes give ΔG_{rxn} the contribution of a positive value, the resultant effect making the value of ΔG_{rxn} less negative than that of the differences of the N−NO bond heterolytic dissociation energies between G-MNBS and *N*-nitroso-3,6-dibromocarbazole. Since the increase of the differences of the N−NO bond heterolytic dissociation energies between G-MNBS and *N*-nitroso-3,6-dibromocarbazole is always accompanied by the increase of the pK_a differences between the corresponding parent amines, the Gibbs free energy changes (ΔG_{rxn}) of the NO transfer should be small or close to zero, from which a useful general conclusion can be derived that the transfer of NO between two neutral amines could always be reversible, which, in fact, is well in line with many experimental observations. But, for reaction 6, the reaction can run completely, the main reason being that the product *N*-nitroso-3,6-dibromocarbazole is slightly soluble in acetonitrile and precipitated from the reaction mixture, which makes the reaction equilibrium to move to the side of products.

Mechanism of NO Transfer from G-MNBS to 3,6-Dibromocarbazole (CBZH). As to the mechanism of NO transfer from G-MNBS to 3,6-dibromocarbazole, three possible pathways can be proposed (Scheme 5)[35] according to the reaction products (eq 6) and the distribution of Mulliken charge density on some related atoms in G-MNBS (Table 7) and their nitranions (Scheme 3), which were derived from the calculation by using the Gaussian98 program.[23] In path I, the reaction was initiated by NO^+ transfer and then followed by proton transfer to yield the corresponding substituted *N*-methyl-benzensulfonamide (G-MBS) and *N*-nitroso-3,6-dibromocarbazole. In the path II, the reaction was initiated by proton transfer and then followed

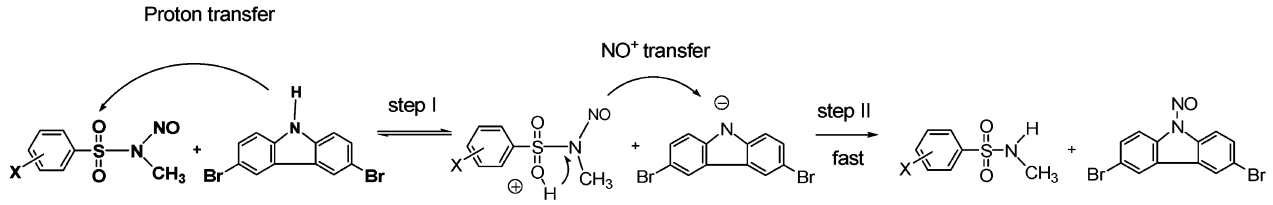
(35) Although many possible mechanisms (at least, more than three) have been proposed in the literature about the nitroso group transfer, only three mechanisms among them as shown in Scheme 5 should be the most likely. As to the concerted pathway that the proton transfers from 3,6-dibromocarbazole to the nitrogen bounded to the nitroso group in *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, the possibility should be very small. The main reason has two points. First, according to the charge distribution diagram on *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, the negative charge density on the SO_2 oxygen (−0.5289) is quite larger than that on the nitrogen atom (−0.399 96), which indicates that the proton transfer from the secondary amine should be more favorable to the SO_2 oxygen than to the nitrogen bounded to the nitroso group. Second, if the proton transfer to the nitrogen bounded to the nitroso group was true, the reaction should have to run in the fashion of four-membered ring (concerted process). It is evident that the construction of the four-membered ring should be more difficult than that of the six-membered ring during the proton transfer to the SO_2 oxygen.

Scheme 5. Possible Mechanisms of Nitric Oxide Transfer from G-MNBS to 3,6-Dibromocarbazole

Path. I :



Path. II :



Path. III :

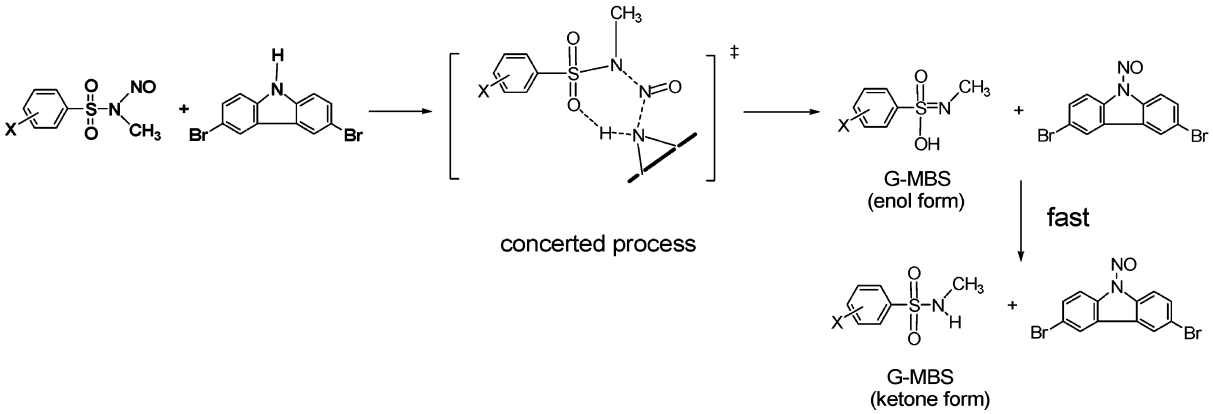
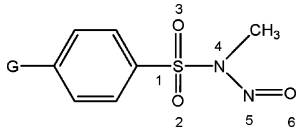


Table 7. Mulliken Charge Density on Some Related Atoms in G-MNBS



	number of the related atoms in G-MNBS					
G	1	2	3	4	5	6
p-OCH_3	1.2615	−0.5020	−0.5313	−0.3965	0.1840	−0.3486
p-CH_3	1.2659	−0.5002	−0.5299	−0.3983	0.1867	−0.3450
p-H	1.2686	−0.4992	−0.5289	−0.3996	0.1876	−0.3427
p-Cl	1.2707	−0.4963	−0.5265	−0.4003	0.1877	−0.3387
m-NO_2	1.2843	−0.4946	−0.5186	−0.4029	0.1880	−0.3327

by NO^+ transfer accompanied with proton 1,3-transfer to form the final products. In path III, the reaction was initiated by synchronous NO^+ transfer and proton transfer in the fashion of a six-membered ring (concerted process) to yield CBZNO and enol form G-MBS, and the formed enol form G-MBS then immediately became the corresponding ketone form isomer by tautomerization (Scheme 5). Obviously, an interesting but difficult question remained of which one is the practical pathway of the NO transfer from G-MNBS to 3,6-dibromocarbazole.

To distinguish the three different mechanisms of the NO transfer, the kinetic isotope effect on reaction 6 was examined by using *N*-deuterated 3,6-dibromocarbazole to replace 3,6-dibromocarbazole to react with MNTS under the same experimental conditions. The result shows that no primary kinetic isotope effect was found ($k_H/k_D = 1.1$ at 25 °C), which indicates that the N−H bond breaking of 3,6-dibromocarbazole in reaction 6 should not be in or in front of the rate-determining step, thus ruling out the involvement of the concerted mechanism (path III) and the mechanism initiated by proton transfer (path II). The NO transfer in reaction 6 should run as pathway I. Since the reaction constant ρ for reaction 6 is a positive value ($\rho = +1.17$) (see Figure 3) and log values of the reaction rate constants are strongly and linearly dependent on the N−NO heterolytic dissociation energies of the NO donors (Figure 4), it is conceived that the N−NO bond heterolytic dissociation of G-MNBS should be in the rate-determining step. Whereas, since the N−NO bond heterolytic dissociation energies of G-MNBS (44.3−49.5 kcal/mol) are much larger than the corresponding activation Gibbs free energy changes (21.7−23.3 kcal/mol) of reaction 6, the N−NO heterolytic dissociation of G-MNBS in the initial reaction step must be in the company of the partial formation of the N−NO bond in the protonized *N*-nitroso-3,6-dibromocarbazole as a reaction intermediate on the basis of a general reaction law that activation free energy change is always larger than the corresponding standard state free energy change for an elemental reaction. Since the ρ value ($\rho = +1.17$) of the present reaction is close to that of the well-known reaction

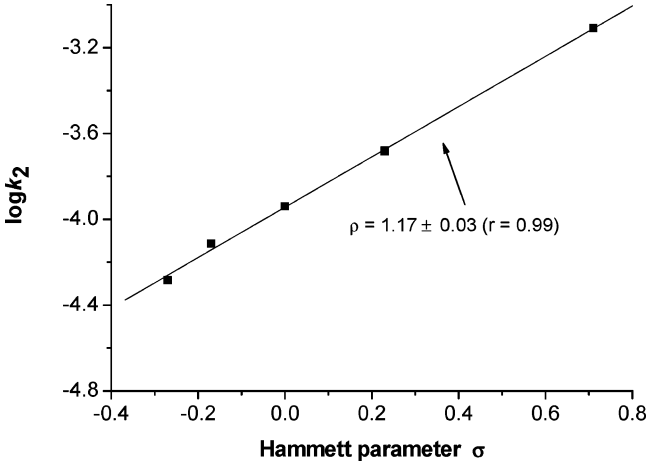


Figure 3. Correlation of log k_2 (at 25 °C) versus Hammett substituent constants σ for the reaction of G-MNBS with 3,6-dibromocarbazole.

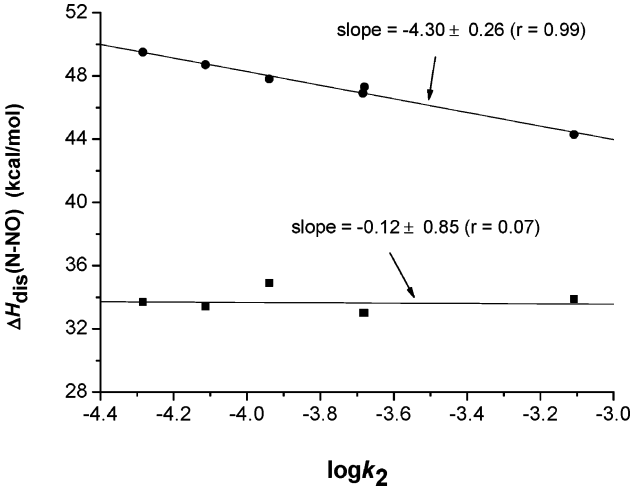


Figure 4. Correlation of the N−NO bond heterolytic (●) and homolytic (■) dissociation energies of G-MNBS against log k_2 (25 °C) for the reaction with 3,6-dibromocarbazole.

$ArCO_2H + H_2O \rightarrow ArCO_2^- + H_3O^+$ ($\rho = +1.00$),[22] it is conceived that the fashion of the NO^+ transfer from G-MNBS to 3,6-dibromocarbazole in reaction 6 in acetonitrile solution should be quite similar to the fashion of proton transfer from $ArCO_2H$ to water.

To further verify the initial NO^+ transfer to be in the limiting step, the state energy changes of the NO^+ transfer in the first step and the proton transfer in the second step for reaction 6 were evaluated, respectively. According to eq 9,

$$\Delta H(NO^+T) = \Delta H_{het}(\text{G-MNBS}) + 1.364pK_a\,(\text{CBZH}) - \Delta H_{het}(\text{CBZNO}) - \Delta Hp \quad (9)$$

which was derived from the thermodynamic cycle in Scheme 6, the state energy changes of the NO^+ transfer in the reaction initial step can be calculated and the results are listed in Table 8. The state energy changes for the proton transfer in the second step can be also easily estimated from the equation $\Delta H(H^+T) = \Delta G_{rxn} - \Delta H(NO^+T)$, where the standard state free energy change was used to replace the standard state enthalpy change for the proton transfer, and the results are also listed in Table 8. Examining the state energy changes of the two reaction steps (NO^+ transfer in the first step and the proton transfer in the second step) shows that the standard state enthalpy changes of the NO^+ transfer are all positive values (14.0 to 8.8 kcal/mol), but the standard state enthalpy changes of the proton transfer are all quite negative values (−15.9 to −11.7 kcal/mol), which indicates that the initial NO^+ transfer should be much more difficult than the proton transfer in the second step. The whole reaction coordinate diagram is shown in Figure 5. According to Figure 5, it is conceivable that the initial NO^+ transfer should be rate-determined in reaction 6. By comparing the value of $\Delta H^‡$ and the value of $-T\Delta S^‡$ for reaction 6, it is clear that the value $-T\Delta S^‡$ is close to or even larger than that of the corresponding $\Delta H^‡$, which indicates the NO^+ transfer in reaction 6 was controlled not only by enthalpy but also by entropy, which means that the transition state for the NO^+ transfer from G-MNBS to 3,6-dibromocarbazole in the first step should be "contacted".

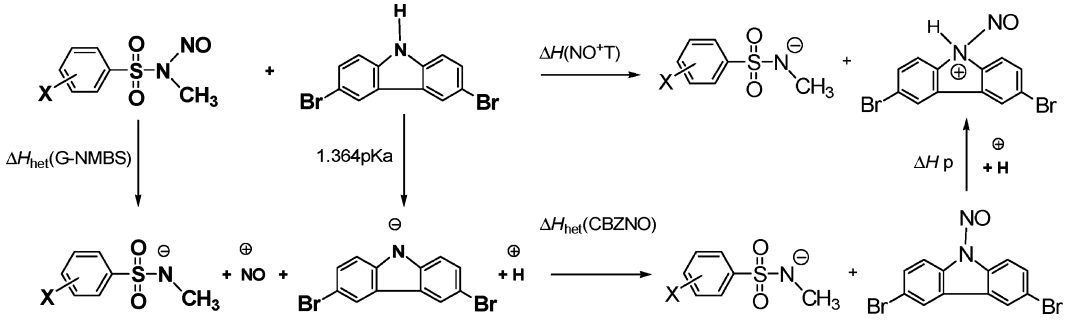
Table 8. Enthalpy Changes of NO^+ and Proton Transfers in the First and Second Reaction Steps, and the State and Activation Free Energy Changes of Reaction 6 (kcal/mol)

G	$\Delta H(NO^+T)^a$	$\Delta H(H^+T)$	ΔG_{rxn}	$\Delta G^{\neq}$
p-OCH_3	14.0	−15.9	−1.9	23.2
p-CH_3	13.2	−15.6	−2.4	23.0
p-H	12.3	−15.1	−2.8	22.8
p-Cl	11.4	−14.2	−2.8	22.3
m-NO_2	8.8	−11.7	−2.9	21.7

[a] The values were derived from eq 9, pK_a of CBZH = 26.7 in acetonitrile, which from the following equation: $pK_a(CH_3CN) = 0.982pK_a(DMSO) + 9.94$, $\Delta Hp = 19.5$ kcal/mol determined in this work, $\Delta H_{het}(CBZNO) = 51.6$ kcal/mol from literature.[37] [b] $\Delta H(H^+T) \approx \Delta G_{rxn} - \Delta H(NO^+T)$.

To elucidate the nature of the transition state of NO^+ transfer in the rate-determining step, the Hammett type plots of the standard state enthalpy change [$\Delta H(NO^+T)$] and the activation enthalpy change ($\Delta H^‡$) for the NO^+ transfer against the Hammett substituent constant σ were examined (Figure 6). From Figure 6, two excellent straight lines were observed with slopes of -5.13 ± 0.22 for the plot of $\Delta H(NO^+T)$ and -3.37 ± 0.51 for the plot of $\Delta H^‡$, respectively. The negative slopes for $\Delta H(NO^+T)$ and $\Delta H^‡$ reflect the negative charge increase at the

Scheme 6



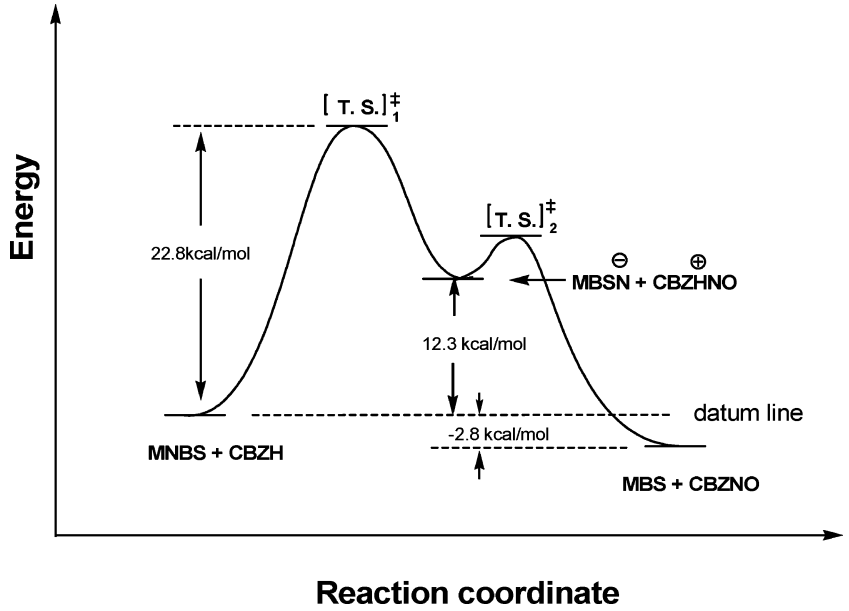


Figure 5. Reaction coordinate diagram for the NO transfer from *N*-methyl-*N*-nitrosobenzenesulfonamide to 3,6-dibromocarbazole in acetonitrile.

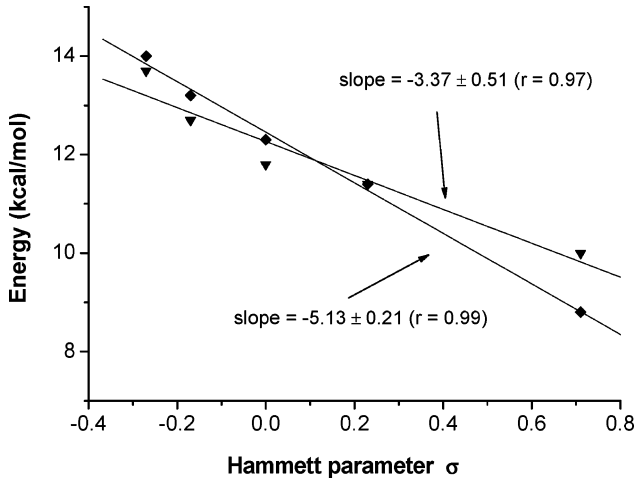
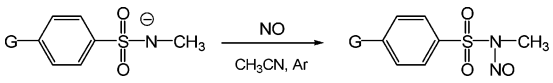


Figure 6. Hammett plots of $\Delta H^{\ddagger}$ (▼) and $\Delta H(NO^{+}T)$ (□) vs Hammett substituent constants. The values of $\Delta H^{\ddagger}$ and $\Delta H(NO^{+}T)$ are listed in Tables 4 and 8, respectively.

nitrogen atom carrying NO group in G-MNBS in going from G-MNBS to G-MBSN^{-} or to the transition state, respectively, and the magnitude of the slope values is a measure for the relative change of the effective charge at the nitrogen atom carrying NO in G-MNBS. To quantitatively evaluate the effective charge on the nitrogen atom carrying NO group in the transition states, we made a definition that the effective charge on the nitrogen atom carrying NO in G-MNBS is zero and the effective charge on the nitrogen atom in G-MBSN^{-} is negative one unit from our basic knowledge of the electronic structures of the neutral G-MNBS and their corresponding nitranions G-MBSN^{-}, which indicates that the slope value of -5.13 for the NO^{+} transfer from the G-MNBS to 3,6-dibromocarbazole [$\Delta H(NO^{+}T)$] is equivalent to a negative charge increase of *one unit* on the nitrogen in going from G-MNBS to G-MBSN^{-}, and from which it is easily available that the slope value of -3.37 for ($\Delta H^{\ddagger}$) is equivalent to negative charge increase of -0.66 on the nitrogen atom in going from G-MNBS to the transition state. Since the effective charge on the nitrogen in G-MNBS has been defined as zero, the effective charge on the nitrogen in the transition state of the G-MNBS should be -0.66 (Scheme 7),[38] which indicates that the nitroso group carries a $+0.66$ positive charge to move far from the parent moiety of G-MNBS in the transition state.

Thermodynamic Analysis on Mechanistic Possibilities for Nitrosation of Nitranions by NO. Since the processes of NO transfer between two amine molecules can directly produce nitranions as the reaction intermediate as described above, the reactions of nitranions with a NO radical should be likely to occur in the reaction system of NO transfer, which indicates that it is necessary to elucidate the reaction mechanism of the nitranions with a NO radical. As an example, when the substituted *N*-methyl-benzenesulfonamide nitranions (G-MBSN^{-}) were treated by NO gas, the corresponding substituted *N*-methyl-*N*-nitrosobenzenesulfonamides (G-MNBS) were formed quantitatively (eq 10). Since a NO radical possesses the two different intrinsic properties, oxidation potential and electrophilicity, the possible mechanisms of the nitrosation of G-MBSN^{-} by a NO radical can be depicted in Scheme 8. Although the exact mechanism of the nitrosation of G-MBSN^{-} by NO is still not fully determined, it is useful and necessary to conduct thermodynamic analysis on mechanistic possibilities for the nitrosation of the nitranions by NO. The standard state enthalpy change for the each elementary reaction step can be evaluated by using the eqs 11−16. The thermodynamic data derived are summarized in Table 9.

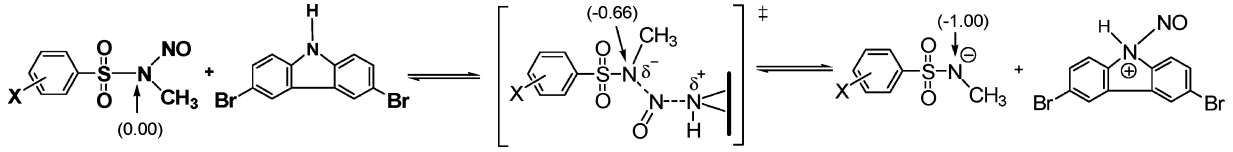


(10)

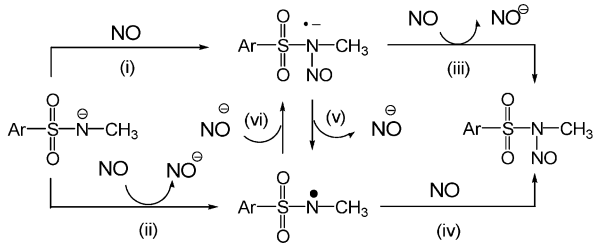
The most eye-catching feature of the thermodynamic data in Table 9 is that the energy changes of the two initial steps (i

(36) Bordwell, F. G.; Zhang, X.-M.; Cheng, J.-P. *J. Org. Chem.* **1991**, *56*, 3216.
(37) Zhu, X.-Q.; Xian, M.; Wang, K.; Cheng, J.-P. *J. Org. Chem.* **1999**, *64*, 4187−4190.
(38) In fact, similar evaluations of effective charge distribution on an active atom in a transition-state structure by using Hammett linear free-energy relationship were extensively reported in the literature. Ref: (a) Page, M., & Williams, A. *Organic and Bio-organic Mechanism*, Addison-Wesley Longman Limited 1997, Chapter 3, pp52−79. (b) Williams, A. *Acc. Chem. Res.* **1984**, *17*, 425. (c) Williams, A. *Acc. Chem. Res.* **1989**, *22*, 387. (d) Williams, A. *Adv. Phys. Org. Chem.* **1991**, *27*, 1. (e) Williams, A. *J. Am. Chem. Soc.* **1985**, *107*, 6335.

Scheme 7. Effective Charge Map on the Rate-Determining Transition State for Reaction 6 in Acetonitrile



Scheme 8



Steps: (i) $\Delta H(\mathrm{i}) = -\Delta H_{\mathrm{homo}}(\mathrm{N\text{-}NO})^{-\bullet}$ (11)

(ii) $\Delta H(\mathrm{ii}) = -F[E_{1/2}(\mathrm{NO}^{0/-}) - E^{\circ}_{\mathrm{ox}}(\mathrm{G\text{-}MBSN}^{-})]$ (12)

(iii) $\Delta G(\mathrm{iii}) = -F[E_{1/2}(\mathrm{NO}^{0/-}) - E^{\circ}_{\mathrm{red}}(\mathrm{G\text{-}MNBS})]$ (13)

(iv) $\Delta H(\mathrm{iv}) = -\Delta H_{\mathrm{homo}}(\mathrm{N\text{-}NO})$ (14)

(v) $\Delta H(\mathrm{v}) = \Delta H_{\mathrm{het}}(\mathrm{N\text{-}NO})^{-\bullet}$ (15)

(vi) $\Delta H(\mathrm{vi}) = -\Delta H_{\mathrm{het}}(\mathrm{N\text{-}NO})^{-\bullet}$ (16)

Table 9. Energetics (kcal/mol) of Each Mechanistic Step Shown in Scheme 8[a]

	ΔH					
G	(i)[b]	(ii)[c]	(iii)[d]	(iv)[e]	(v)[f]	(vi)[g]
			Group I			
2,5-2Cl	12.9	13.7	−32.9	−33.7	0.8	−0.8
m-NO_2	13.5	16.1	−32.1	−34.7	2.6	−2.6
			Group II			
p-OCH_3	12.9	10.7	−35.9	−33.7	−2.2	2.2
p-CH_3	13.6	11.3	−35.8	−33.4	−2.4	2.4
p-H	15.8	13.7	−37.1	−34.9	−2.2	2.2
p-Cl	15.1	12.6	−35.4	−33.0	−2.4	2.4
p-Br	15.4	12.3	−36.1	−33.0	−3.1	3.1

[a] All values were derived in CH_3CN at 25 °C in kcal/mol. [b] From eq 11. [c] From eq 12. [d] From eq 13. [e] From eq 14. [f] From eq 15. [g] From eq 16.

and ii) are all endothermic but the energy changes for their following elementary steps (iii−vi) are all either exothermic or only slightly endothermic. These results indicate that the electron transfer from the substituted *N*-methyl-benzenesulfonamide nitranions (G-MBSN$^-$) to a NO radical or the NO radical electrophilic coupling with the nitranions in the initial steps should be difficult and could be in the rate-determing step during the nitrosation course of the nitranions by NO, but the following reaction steps should be all easy.

By detailed examination of the energy changes of the each reaction step in Scheme 8, it is found that the energetic characteristics of the seven reactions all are not exactly the same, however. The grouping suggested in Table 9 was based on their thermodynamic similarity of the reactions. For Group I (G = 2,5-2Cl, *m*-NO_2), the difficulties of the electrophilic combination of NO with the nitranions in step (i) should be all smaller than those of the corresponding competing electron-transfer step (ii) in thermodynamics, and the driving forces of another electron-transfer step (iii) are all greater than those of the alternative path (v). Therefore, the mechanism (i−iii) can be proposed for these reactions. The thermodynamic feature of the Group II reactions (G = OCH_3, CH_3, H, Cl, Br) is quite different from the one described above. It is clear that the driving forces of the direct electron transfer to NO (step ii) and that of the follow-up radical coupling (step iv) are both energetically more favorable than those of the potentially competing alternative routes (i) and (vi). Therefore, the mechanism (ii−iv) would be most suitable for these reactions. Though the scope of the present research limited us from a scrupulous experimental confirmation of all the mechanisms for these seven reactions, the similar energetic analysis for differentiating the mechanistic possibilities of NAD(P)H model reactions was indeed widely supported by experimental observation,[39] giving confidence to the analytical strategy herein applied. Therefore, we believe that the mechanistic guidelines suggested here should be of value in analyzing or predicting the mechanisms of some relevant NO-related transformations.

Conclusions

Four sets of N−NO bond dissociation energies of seven substituted *N*-methyl-*N*-nitrosobenzenesulfonamides and their radical anions in acetonitrile solution were determined. The mechanisms of NO transfer from G-MNBS to 3,6-dibromocarbazole and the reactions of NO with *N*-methyl-benzenesulfonamide nitranion (G-MBSN$^-$) were elucidated by using the determined N−NO bond dissociation energies together with the relative kinetic parameters. The following conclusions can be made: (i) For neutral G-MNBS, the energetic scale of the N−NO bond heterolytic dissociation energies is quite larger than that of the corresponding N−NO bond homolytic dissociation energies, which indicates that G-MNBS should be much easier to release NO$^{\bullet}$ than to release NO$^+$ by thermolysis. (ii) The N−NO bond heterolytic and homolytic dissociation energies of G-MNBS radical anions are negative or slightly positive, which means that G-MNBS radical anions should be unstable at room temperature and able to release either a NO radical or NO$^-$ anion, but to release a NO radical is much easier than to

(39) Cheng, J.-P.; Lu, Y.; Zhu, X.-Q.; Mu, L.-J. *J. Org. Chem.* **1998**, *63*, 6108−6114.

release a NO^- anion, which implies that the natural NO anion (NO^-) in the living body could be produced from the one-electron reduction of a NO radical rather than from the N−NO bond heterolytic dissociation of NO^- donors. (iii) NO transfer between two neutral amines could be reversible, and the direction of NO transfer among different amines could be mainly governed by the entropy increase of the reaction system. (iv) The mechanism of NO transfer between two neutral amines should include two elementary reaction steps: NO^+ cation transfer and the followed proton transfer, but the initial NO^+ transfer is in the rate-determining step. (v) Combination of a NO radical with a nitranion could have two competing pathways to choose from, which is controlled by the oxidation potential of the nitranion.

Experimental Section

All reagents were of commercial quality from freshly opened containers or were purified before use. Reagent grade acetonitrile was refluxed over $KMnO_4$ and K_2CO_3 for several hours and was doubly distilled over P_2O_5 under argon before use. The commercial tetrabutylammonium hexafluorophosphate (Bu_4NPF_6, Aldrich) was recrystallized from CH_2Cl_2 and was vacuum-dried at 110 °C overnight before preparation of a supporting electrolyte solution. The nitrosating reagent $NO^+ClO_4^-$ was prepared according to a literature method.[40] Redox potentials were obtained by a second-harmonic ac voltammetry (SHACV) method on a BAS-100B electrochemical analyzer. The heats of reaction of NO^+ with nitranions were determined on a Tronac 458 titration calorimeter.

General Procedure for Preparation of *N*-Methyl-benzensulfonamides. All substituted *N*-methyl-benzensulfonamides have been synthesized by reaction of the corresponding benzenesulfonyl chlorides with an excess methylamine in water.[16] The product is extracted with dichloromethane and washed with a solution of sodium hydrogen carbonate and with water. After removal of the solvent on a rotator, the residue was recrystallized from 95% ethanol to give pure *N*-methyl-benzensulfonamides. The products were identified by comparison with the authentic values according to their ^{1}H NMR and melting point.

General Procedure for Preparation of *N*-Methyl-*N*-nitrosobenzensulfonamides. *N*-methyl-*N*-nitroso-benzensulfonamides were prepared using a biphasic water−dichloromethane mixture. The aqueous phase containing sodium nitrite and the organic phase containing the corresponding sulfonamide obtained above were mixed together, and then to which concentrated hydrochloric acid (36%) was slowly added. The mixture was stirred for 1 h and separated. The organic phase was washed with water. The crude products were purified by column chromatogram on silica gel with light petroleum−ethyl acetate as eluant to give pure *N*-methyl-*N*-nitrosobenzensulfonamides. The products were identified by ^{1}H NMR spectrum.

General Procedure for Preparation of Anions. The method of E. M. Arnett et al.[41] was followed: The anion precursor (0.2 mmol) was dissolved in 40 mL of dry acetonitrile, and then a slightly excess amount of KH was added. The mixture was stirred at room temperature for about 20 min and then filtered directly into the reaction vessel. All the operations were carried out in an argon-filled VAC drybox.

Preparation of NO Gas. NO gas was produced by reaction of $NaNO_2$ with sulfuric acid in the absence of oxygen and was purified by passing through 10% $NaOH_{aq}$ to remove higher oxides of nitrogen and finally through a solid NaOH dry tube to remove water.[42]

Reaction of G-MBSN$^-$ with NO in Acetonitrile. The flask containing 15 mL of a CH_3CN solution of G-MBSN$^-$ (0.2 mmol) formed by removing a proton from the parent sulfonamide with KH was degassed with argon 3 times by the freeze−thaw method. After it was warmed to room temperature, 25 mL of NO (in excess) was slowly bubbled into the reaction vessel with an airtight Hamilton syringe. The mixture was stirred at room temperature for 30 min, and then dry Ar was bubbled in to expel excess NO. The reaction mixture was worked up to afford the corresponding pure substituted *N*-methyl-*N*-nitroso-benzensulfonamide as the sole product.

General Procedure of Kinetic Measurement. A mixture of G-MNBS (0.25 mmol) and 3,6-dibromocarbazole (0.25 mmol) in 10 mL dry acetonitrile was thermostated at different temperatures (15−40 °C). After an appropriate period of the reaction, the product *N*-nitroso-3,6-dibromocarbazole which formed as a yellow precipitate was centrifuged, separated, and weighed accurately by using an analytic balance ($d = 0.01$ mg) to give the percentage yields of *N*-nitroso-3,6-dibromocarbazole (see Table S1 in Supporting Information). The second-order rate constants of the NO transfer reactions were obtained from the percentage yields of the isolated *N*-nitroso-3,6-dibromocarbazole according to the equation $k_2 = y/(100 - y)at$,[20] therein y is the percentage yield of the isolated product *N*-nitroso-3,6-dibromocarbazole, a is the initial concentration of the reactants, and t is the reaction time.

Measurement of Redox Potentials. All electrochemical experiments were carried out by SHACV (sweep rate, 4 mV/s) using a BAS-100B electrochemical apparatus in dry acetonitrile solution under an argon atmosphere at 25 °C as described previously.[43] *n*-Bu_4NPF_6 (0.1 M) was employed as the supporting electrolyte. A standard three-electrode cell consists of a glassy carbon disk as working electrode, a platinum wire as counter electrode, and 0.1 M $AgNO_3$/Ag (in 0.1 M Bu_4NPF_6−MeCN) as reference electrode. All sample solutions were 1.5 mM. The ferrocenium/ferrocene redox couple ($Fc^{+/0}$) was taken as the internal standard. The reproducibility of the potentials was smaller than 5 mV.

Titration Calorimetry. Reaction of NO^+ ($NO^+ClO_4^-$) with nitranions (K^+ as counterion) in dry CH_3CN was rapid to give N−NO coupling product quantitatively. The reaction heat (ΔH_{rxn}) was measured at 25 °C by a standard procedure similar to that of Arnett.[41] The performance of the calorimeter was checked by measuring the standard heat of neutralization of an aqueous solution of sodium hydroxide with a standard aqueous HCl solution. The MeCN solution of $NO^+ClO_4^-$ (0.1 M) was prepared inside the argon-filled drybox with an analytical balance and volumetric flask before each calorimetric run. The calibrated motor-driven buret, filled with 2 mL of NO^+ solution, and the reaction vessel, containing about 40 mL of a nitranion solution (in excess), were connected to the calorimeter insert assembly. A dry argon atmosphere was maintained at the top of the reaction vessel to protect anions from unexpected reaction. The heat of dilution of nitrosonium perchlorate was small enough to be neglected for heat of reaction measurements. The reported ΔH_{rxn} is the average value of two or three independent runs, which consisted of up to six titrations with the same stock solution.

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Supporting Information Available: The percentage yields of *N*-nitroso-3,6-dibromocarbazole for the reaction of G-MNBS

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with 3,6-dibromocarbazole in acetonitrile solution at different temperatures (15−40 °C), the plots of ln k_2 and ln(k_2/T) against 1/T for the reaction of G-MNBS with 3,6-dibromocarbazole, and English version for the concerned kinetics section of the textbook in the ref 20. This material is available free of charge via the Internet at http://pubs.acs.org.

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