JOC Articles

Establishment of the C−NO Bond Dissociation Energy Scale in Solution and Its Application in Analyzing the Trend of NO Transfer from *C*-Nitroso Compound to Thiols

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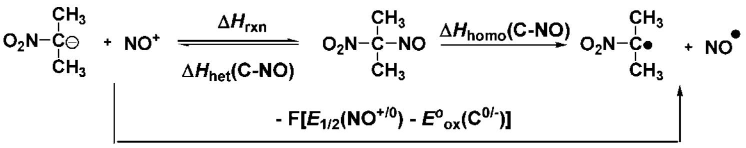

The first set of experimentally determined C−NO bond homolytic and heterolytic dissociation enthalpies in solution is derived by using direct titration calorimetry combined with appropriate electrode potentials through thermodynamic cycles. The homolytic bond dissociation energy scale (BDEs) of the corresponding C−NO bonds in the gas phase was also calculated at the MP2/6-311+G**//B3LYP/6-31G* level and BP86/6-31G*//B3LYP/6-31G* level of theory for the purpose of comparison. The C−NO and S−NO bond thermodynamic parameters were used to predict the trend of NO transfer from *C*-nitroso substrates to thiols in acetonitrile solution.

Introduction

Nitric oxide (NO), now known as the simplest biomessenger in the living body, plays significant roles in many important physiological activities such as transmitting neurostimulation, balancing blood pressure, defending health in the immune system, and so on.[1−4] Consequently, extensive research has been carried out in the last twenty years from the viewpoints of biochemistry, physiology, pharmacy, and chemistry. Because NO is a free radical and cannot exist "freely" in the human body in large quantity, a deeper understanding of its physiological functions should require the knowledge of the NO-carrier compounds (NO donors), which are believed to serve as vehicles for the controlled delivery of NO among biological systems. In this regard, several relevant categories of NO donor compounds such as *S*-nitrosothiols, organic nitrites, metal−NO complexes, etc. have been investigated in recent years.[5] Though substantial progress have already been achieved, one other important NO-carrier molecule, the *C*-nitroso compound, remains almost untouched during the same period.

In the past decade, the *C*-nitroso compounds have received renewed interest from chemists and biochemists due to the recent discoveries of their physiological roles in a number of important bioactivities.[5−7] It is now realized that aliphatic *C*-nitroso compounds can undergo C−NO bond scission to release the

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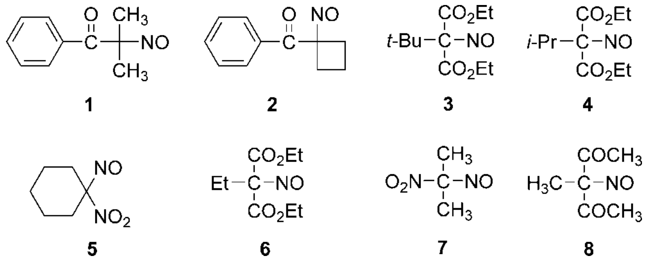
SCHEME 1



NO molecule under photo or thermal conditions,[8] rendering them good candidates to serve as efficient NO donors and thus to affect the life processes. For instance, it was observed that 2-methyl-2-nitrosopropane (MNP) could deliver NO under photochemical conditions and induce relaxation of the preconstricted rat pulmonary artery rings.[9] Some pseudonitroles (e.g., **5** and **7**, in Scheme 1) were found to inhibit aggregation of blood platelets.[10] It was also reported that pseudonitroles are capable of in vitro vasodilatation and raising the basal level of GMP.[11] Without doubt, these interesting properties of C−NO compounds should be associated with their inherent ability to release NO by bond breaking. Though the mechanism of the physiological functions of *C*-nitroso compounds has not yet been fully disclosed, and it should not be expected to be universally simple, the knowledge of their intrinsic ability to deliver NO radical or NO^+ cation upon C−NO bond scission in solution, i.e., the homolytic/ heterolytic BDEs, will, nevertheless, be the key information to study the possible mechanisms and to understand the related biological behaviors of this category of NO donors. Unfortunately, most of the C−NO BDEs known today are those derived in the gas phase and were only determined for bond homolysis of a small number of very simple molecules.[12] For potentially feasible C−NO-type NO donor candidates, there is only one computational study[13] handling the situation in solution and one very recent report on experimental determination of the ΔG value for α-cyano *C*-nitroso compounds in various solvents.[6b] To our knowledge, there was essentially no work on experimental determination of the C−NO BDEs in solution for molecules of relatively large size until now.

Several years ago, this group initiated work on measuring various Y−NO (Y = N, O, S, and metal) bond dissociation energies in solution mainly by experimental approaches. The main purpose of this program is to clarify the thermodynamic driving forces NO delivers in living system and to provide the much needed Y−NO bond dissociation energy information to biochemists and pharmaceutists as a useful tool for their rational research such as designing NO drugs. Consequently, some biologically significant N−NO, O−NO, S−NO, and metal−NO bond dissociation energy scales in solution were established.[14] On continuation of this endeavor, we here report the first C−NO bond heterolytic and homolytic dissociation energy scale of 8 *C*-nitroso compounds in acetonitrile solution (**1**−**8**, Scheme 1). The *C*-nitroso compounds chosen for this study can serve as the models of some archetypal *C*-nitroso compounds which have been used as efficient NO donors.[6,9−11,15] Moreover, we believe that it would be a helpful practice to exemplify how these thermodynamic data can be applied to analyze the trend for NO to transfer among different receptors. In this paper, a detailed thermodynamic analysis of the NO transfer reaction between 2-nitro-2-nitrosopropane and various thiols was conducted in this regard on the basis of the derived energetic data.

Results and Discussion

The heterolytic C−NO bond dissociation energies [ΔH_{het}(C−NO)] of the *C*-nitroso compounds **1**−**8** in acetonitrile solution were directly obtained from the reaction heat (ΔH_{rxn}) measurements of the corresponding parent carbanions (C^-) with NO^+ (ClO_4^- as counterion) at 25 °C in deaerated dry acetonitrile with use of titration calorimetry.[16,17] The homolytic C−NO bond dissociation energies [ΔH_{homo}(C−NO)] were derived from the corresponding ΔH_{het}(C−NO)s combined with relevant electrode potentials through a thermodynamic cycle (eq 3, Scheme 2), where the difference between ΔH_{het} and ΔH_{homo} of the C−NO bond is equal to the enthalpy of electron transfer.[18] The present method, in which the ΔH_{het} values are used in conjunction with redox data to derive the corresponding ΔH_{homo} values, is

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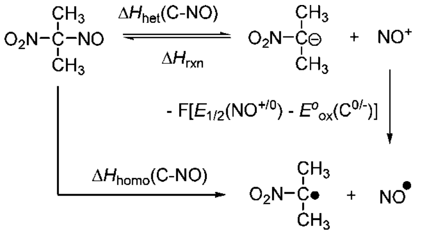
[16] The model compounds studied in this work are all tertiary *C*-nitroso molecules with both sterically bulky and electron-withdrawing groups, which are significantly disfavored for dimerization in solution. Furthermore, the concentration of the *C*-nitroso compounds under the calorimetric titration conditions is very low (<0.005 M), so conjugation of the *C*-nitroso species in solution is negligible. Therefore the contribution from the ΔG of dimerization could be neglected without scarifying accuracy. In a recent report by Toone et al., an approximate range of ca.−0.5 to +2.2 kcal/mol for the ΔG of dimerization of α-cyano *C*-nitroso compound at 1 M concentration at 25 °C was predicted (see ref 6b).

[17] The reaction of carbanions (C^-) (generated upon removing a proton from the parent C−H compound by KH) with nitrosonium perchlorate ($NO^+ClO_4^-$) in acetonitrile solution can yield the corresponding *C*-nitroso compounds quantitatively (the reverse reaction of eq 1, Scheme 2). According to the reaction in eq 1, the heterolytic C−NO bond dissociation energy of the *C*-nitroso compounds [ΔH_{het}(C−NO)] should be equal to the reaction enthalpy change (ΔH_{rxn}) of the carbanion (C^-) with NO^+ simply by switching the sign of ΔH_{rxn} (eq 2, Scheme 2). The latter can be directly determined by titration calorimetry for fast and quantitative reactions as in the present practice.

SCHEME 2



(1)

$$\Delta H_{het}(\text{C-NO}) = -\Delta H_{rxn} \qquad (2)$$

$$\Delta H_{homo}(\text{C-NO}) = \Delta H_{het}(\text{C-NO}) - 23.06[E_{1/2}(\text{NO}^{+/0}) - E^{o}_{ox}(\text{C}^{0/-})] \qquad (3)$$

analogous to that of Arnett for evaluation of the C−C bond energies.[18] Similar approaches to estimate experimentally inaccessible quantities from feasible solution measurements have been widely practiced in the last twenty years in literature.[19] The ΔH_{rxn}, ΔH_{het}(C−NO), and ΔH_{homo}(C−NO) values together with the relevant electrochemical data are summarized in Table 1. The homolytic C−NO bond dissociation energies in the gas phase calculated by DFT method, as well as the literature pK_a[20] values of the corresponding *C*-hydrogen compounds, are also included in Table 1 for the purpose of comparison.

Heterolytic and Homolytic C−NO Bond Dissociation Energies in Acetonitrile. Table 1 shows that the ΔH_{het}(C−NO) values of the 8 *C*-nitroso compounds in acetonitrile range from 49.3 to 66.2 kcal/mol, whereas the ΔH_{homo}(C−NO) values range from 26.2 to 31.4 kcal/mol. It is obvious that the C−NO bond heterolytic dissociation energies are considerably greater than the corresponding C−NO bond homolytic dissociation energies by 37.4−21.5 kcal/mol, suggesting that the *C*-nitroso compounds be good NO$^•$ donors. This is similar to the characteristics of the *N*-nitroso and *S*-nitroso compounds in our previous studies,[14] and should explain the observations that NO$^•$ (rather than NO$^+$) was the key player in many physiological processes. The main reason is that oxidation of carbanions is energetically easier than reduction of NO$^+$ (electrode potentials: E_{ox} of −0.760 to −0.068 V vs. E_{red} of 0.863 V, Fc$^{+/0}$ as reference). However, it should be pointed out that in reality the fashion of the Y−NO bond dissociation in solution, i.e., either to release NO$^•$ by homolysis or release NO$^+$ (or NO$^-$) by heterolysis, should not only be governed by the relative magnitude of the dissociation energetics of the corresponding Y−NO bonds, but also be affected by the driving forces of the follow-up reactions.

It is noteworthy that when the ΔH_{het}(C−NO) values of the *C*-NO compounds in acetonitrile are plotted against the pK_a values of the corresponding *C*-H compounds in DMSO,[20] an excellent straight line is obtained (r = 0.999, Figures 1), indicating that the ΔH_{het}(C−NO) values depend mainly on the stability of the carbanions, which, in turn, suggests an alternative way to estimate the C−NO bond heterolysis energy if the corresponding pK_a is available or is more convenient to determine. Similar linear correspondence was also observed in our earlier works on the ΔH_{het} values of *N*-nitrosoureas,[14a] *N*-nitrosodiphenylamines,[14d] *N*-methyl-*N*-nitrosobenzenesulfonamides,[14g] and *O*-nitrosobenzoates.[14c] The much greater energy required for Y−NO (Y = C, N, O) bonds to undergo heterolysis than that of the corresponding Y−H bonds should be mainly attributed to the much lower stability of the nitrosonium ion compared to that of proton in solution. On the other hand, the substantially higher stability of the NO$^•$ radical than that of the H$^•$ radical should be responsible for the huge weakening effect on the Y−NO (ΔH_{homo}) bonds compared to the corresponding Y−H bonds.

Examination of the substituent effect on the heterolytic C−NO bond dissociation energies shows that the strength of the C−NO bonds, i.e. the ΔH_{het}(C−NO), relies heavily on the size of the substituents at the central carbon. For example, among the subseries **3**, **4**, and **6**, which respectively bears *tert*-butyl, isopropyl, and ethyl groups, the bond energy was found to be in a decreasing order: 63.3 kcal/mol > 57.6 kcal/mol > 53.0 kcal/mol. A similar phenomenon was observed between compounds **1** (66.2 kcal/mol) and **2** (65.9 kcal/mol), and between **5** (53.9 kcal/mol) and **7** (52.9 kcal/mol), though the differences are not as large. This may be understood by considering that the large alkyl groups at the central carbon would make its carbanion less solvated so that it becomes less stable. This is also in accordance with the observed decreasing order of oxidation potentials of the related carbanions (Table 1).

Interestingly, the C−NO bond homolytic dissociation energies (ΔH_{homo}) of the same subseries show, however, an opposite order as **3** (27.5 kcal/mol) ≈ **4** (27.6 kcal/mol) < **6** (30.4 kcal/mol). This, again, could be rationalized by considering the size effect of the substituents at the central carbon atom. For radicals of no net charge, the solvation-induced differentiation of stability in solution would be minimized, whereas the size-dependent inhibition to radical dimerization would become a dominant factor in varying radical stability. In such cases, the bulky *tert*-butyl and *i*-Pr should contribute more to the radical stability to cause a decrease in the homolysis energy of the C−NO bond.

With the C−NO bond energy scale in hand, it is now possible to compare the feasibility of Y−NO bond breaking in solution with different Y atoms. Comparison of the data derived in this work with those reported earlier by this group[14] reveals that the ease of the homolytic C−NO bond scission is in a decreasing order of Co^{III}−NO bonds (15.2 to 17.5 kcal/mol for T(G)-

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[18] Arnett has shown that the temperature dependence of the redox processes for resonance-delocalized anions and for the reversible cation-to-radical conversions was experimentally observed to be negligible. Then the corresponding entropy changes for redox processes should be insignificant. For previous validation of similar treatment, see: (a) Arnett, E. M.; Amarnath, K.; Harvey, N. G.; Cheng, J.-P. *Science* **1990**, *247*, 423. (b) Arnett, E. M.; Amarnath, K.; Harvey, N. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1990**, *112*, 344. (c) Troughton, E. B.; Molter, K. E.; Arnett, E. M. *J. Am. Chem. Soc.* **1984**, *106*, 6726.

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[22] In this paper, all of the calculations were done with Gaussian 98.[23] The geometry was optimized by using B3LYP/6-31G*, with each optimized structure verified by B3LYP/6-31G* frequency calculations as a real minimum without any imaginary frequency.

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TABLE 1. ΔH_{rxn}, ΔH_{het}(C−NO), and ΔH_{homo}(C−NO) Values of *C*-Nitroso Compounds (kcal/mol), Oxidation Potentials of Corresponding Carbanions (V vs. $Fc^{+/0}$), Theoretical Homolytic BDEs (kcal/mol), and pK_a Values of Corresponding *C*-H Compounds

				ΔH_{homo}				
compds	ΔH_{rxn}[a]	$E^{o}_{ox}(C^{0/-})$[b]	ΔH_{het}[c]	expt[d]	calcd[e]	calcd[f]	solv(MP2)[g]	pK_a[h]
1	−66.2	−0.760	66.2	28.8	29.4	25.4	0.9	26.25
2	−65.9	−0.730	65.9	29.2	33.4	28.3	1.0	26.15
3	−63.3	−0.691	63.3	27.5	30.7	24.6	1.5	24.7
4	−57.6	−0.437	57.6	27.6	30.3	23.8	1.3	20.5
5	−53.9	−0.339	53.9	26.2	29.7	25.6	2.3	17.9
6	−53.0	−0.116	53.0	30.4	34.2	23.9	4.1	16.9
7	−52.9	−0.068	52.9	31.4	33.5	26.7	0.4	15.05
8	−49.3	−0.133	49.3	26.3	26.8	25.5	4.0	-

[a] Measured in CH_3CN at 25 °C by titration calorimetry. The reproducibility is ±0.5 kcal/mol. [b] The standard redox potentials were derived from the corresponding irreversible redox potentials calibrated by using Wayner and Parker's method,[21] respectively. The irreversible redox potentials were measured in acetonitrile solution at 25 °C in volts by CV method vs. ferrocenium/ferrocene redox couple. Reproducible to 5 mV or better. [c] Derived from eq 2 in Scheme 2. [d] Derived from eq 3 in Scheme 2, taking $E_{1/2}(NO^{+/0}) = 0.863$ V (vs. $Fc^{+/0}$). Relative uncertainties were estimated to be smaller than 1 kcal/mol.[14g] [e] Computed at the MP2/6-311+G**//B3LYP/6-31G* level of theory with zero-point energy (ZPE) and thermal corrections to enthalpy at 298 K.[22,23] [f] Computed at the BP86/6-31G*//B3LYP/6-31G* level of theory with zero-point energy (ZPE) and thermal corrections to enthalpy at 298 K. [g] The solvent effect was computed at the MP2/6-311+G**//B3LYP/6-31G* level with the dielectric polarized continuum model (DPCM). [h] From ref 20.

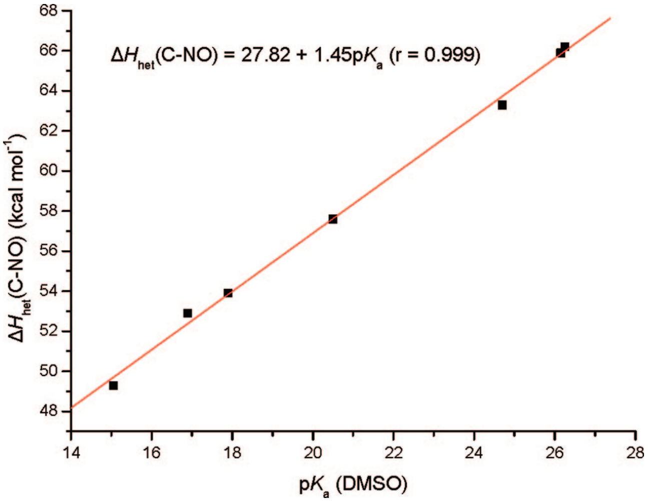

FIGURE 1. Correlation of the C−NO bond heterolytic dissociation energies of the *C*-nitroso compounds in acetonitrile with the corresponding pK_a values of the parent C−hydrogen molecules in DMSO.

PPCo^{III}NO[14f]) > S−NO bonds (18.6 to 21.4 kcal/mol for *S*-nitrosophenylthiols[14e]) > Co^{II}−NO bonds (21.1 to 24.6 kcal/mol for T(G)PPCo^{II}NO[14f]) ≈ N−NO bonds (21.4 to 24.3 kcal/mol for *N*-nitrosodiphenylamines[14d]) > C−NO bonds (26.3 to 31.4 kcal/mol, present work) > O−NO bonds (32.5 to 38.6 kcal/mol for *O*-nitrosobenzoates[14c]) ≈ N−NO bonds (33.0 to 34.9 kcal/mol for *N*-methyl-*N*-nitrosobenzenesulfonamides[14g]) > N−NO bonds (34.5 to 40.4 kcal/mol for *N*-nitrosophosphoramidates[14a]) > N−NO bonds (36.1−43.8 kcal/mol for *N*-nitrosoacetanilides[14b]). Obviously, the C−NO bonds are weaker than O−NO bonds and most N−NO bonds investigated, indicating that the C−NO compounds should be quite promising candidates for good NO donor compounds. The overall spectrum of these Y−NO bond energetic scales should thus provide useful information to guide the design and synthesis of desired NO donor compounds and to understand the mechanisms and the likely trend of NO transfer reactions.

To verify the experimental observations, density functional theory (DFT)[22,23] was used to calculate the homolytic C−NO BDEs in the gas phase for the same *C*-nitroso family studied by experiment. The computation results at the MP2/6-311+G**//B3LYP/6-31G* level and at the BP86/6-31G*//B3LYP/6-31G* level are included in Table 1. It is noted from comparison that the theoretical BDE results, which range from 26.8 to 34.2 kcal/mol with a standard deviation of +2.4 ± 1.9 kcal/mol (by MP2) and from 23.8 to 28.3 kcal/mol with a deviation of −3.0 ± 1.7 kcal/mol (by BP86), agree reasonably well with the experimental values. However, the gaps between theory and experiment observed in this work are notably greater than most of those in the earlier reports (ca. 1−2 kcal/mol),[14e,19a,24] and are believed to be attributed to the complication caused by the bulky structure and the multipolar centers of the present C−NO compounds. The good agreement found between the present ΔH_{homo}(C−NO) of 31.4 kcal/mol for **7** and the reported BDE of 29.2 kcal/mol of a structurally similar α-cyano *C*-nitroso substrate in the vapor phase[6b] also gives credence to the experimental measurements of the current work.

Driving Force Analysis of NO Transfer from C−NO Compound to Thiols. It is well-known that transfer of NO from donors to target species occurs widely in chemical and biochemical processes, and this transportation is believed to be responsible for many biological and physiological effects of NO. Among the NO initiated reactions, transferring NO from a donor compound to thiol has been a focus of interest since the early years of NO research due to the revelation that *S*-nitrosothiols may be an important NO vehicle in vivo. Understanding of the NO transfer process, especially at molecular level, is believed to be crucial for exploring the NO storage and transfer mechanisms in biological systems. However, attention in this regard has only been paid to kinetic aspects by far,[25] and there was almost no energetic study in the literature on the basis of quantitative evaluation of the thermodynamic driving forces for NO transfer reactions.[14h] The main reason is due to the lack of relevant thermodynamic data of the Y−NO (Y= C, N, O, S, metals, etc.) bonds for the interested compounds. In the present study, we chose the

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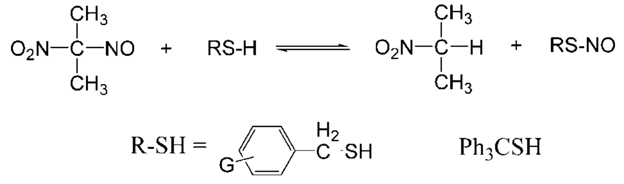
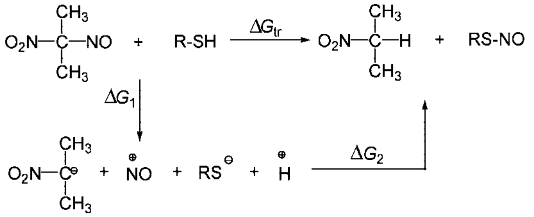
SCHEME 3



G = 4-MeO, H, 4-F, 4-Cl, 4-Br

SCHEME 4



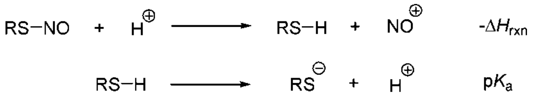
$$\Delta G_{tr} = \Delta G_1 + \Delta G_2 = \Delta\Delta G_{het} + 1.364\Delta pK_a \approx \Delta\Delta H_{het} + 1.364\Delta pK_a \qquad (4)$$

reaction of 2-nitro-2-nitrosopropane (NNP, **7**) with thiols as a model reaction for NO transfer between the C−NO-type donors and SH-containing substrates. We applied the measured C−NO bond energies and the S−NO bond energies together with the pK_a values to derive the driving forces of NO transfer from NNP (**7**) to thiols (Scheme 3).

To evaluate the free energy changes of NO transfer from NNP to thiols, an indirect approach has to be used. The thermodynamic cycle was thus constructed and is shown in Scheme 4. In eq 4 in Scheme 4, ΔG_{tr} represents the free energy of NO transfer, $\Delta\Delta G_{het}$ is the difference between the free energies of the C−NO bond heterolysis and S−NO bond heterolysis, and ΔpK_a is the acidity difference between the corresponding S−H compound and the C−H compound.[24c,26] It should be pointed out that an assumption has to be made there to allow a reasonable use of eq 4 in Scheme 4 to estimate the energetics of NO transfer, that is, the entropy change of the C−NO bond heterolysis of NNP was approximated to be similar to that of the S−NO bond heterolysis of thiols in the same solvent. Then, the corresponding $\Delta\Delta G_{het}$ can be equated to the experimentally determined $\Delta\Delta H_{het}$. Application of the similar assumption was found useful in our earlier study on other types of NO transfer reactions.[14g]

It is obvious that, in addition to the knowledge of ΔH_{het}(C−NO) and the pK_a of the corresponding C−H compound (Table 1), to apply eq 4 in Scheme 4 to estimate the free energy change of NO transfer, determination of the ΔH_{het}(S−NO) and the pK_a values of the related thiols are necessary. However, due to the complication induced likely by formation of the S−S bond when direct calorimetric titration of NO^+ to RS^- was performed, the direct NO^+-to-anion titration in the normal heat measurements should be avoided and a thermochemical cycle that involves the heat of reaction (ΔH_{rxn}) of RSH with NO^+ and the pK_a of the relevant S−H compound (Scheme 5) has to be used instead.[14e] The pK_a values of thiols in DMSO,[27] the measured ΔH_{rxn} values of NO^+ with RSH, and the ΔH_{het}(S−NO) values

SCHEME 5



$$\Delta H_{het}(\text{S-NO}) = 1.364pK_a - \Delta H_{rxn} \quad (\text{kcal/mol}) \qquad (5)$$

of the corresponding RSNOs are summarized in Table 2, together with the evaluated ΔG_{tr} values and other quantities necessary for estimating the free energy changes of NO transfer by eq 4 in Scheme 4.

Table 2 shows that the differences between the C−NO bond heterolysis energy of NNP and the S−NO bond heterolysis energies of *S*-nitrosothiols ($\Delta\Delta H_{het}$) are all negative values, ranging from −4.6 to −0.9 kcal/mol, and become less negative as the para-substituent G is going from electron-donating to electron-withdrawing. This indicates that transferring an NO moiety from carbon to sulfur is energetically feasible for the model reaction in Scheme 4 especially for thiols bearing a strong electron-donating group. Table 2 also shows that the Gibbs free energy changes (ΔG_{tr}) of the NO transfer reactions are from −6.0 to −4.0 kcal/mol. This, again, is indicative of favorable reactions of NO transfer from NNP to thiols.

To further examine the trend of NO transfer, a different approach, i.e., the equilibrium constant (K_{eq}) measurement for the same NO transfer model reaction (Scheme 6), was performed with UV−vis spectroscopy.[28] The results evaluated from eq 6 in Scheme 6 are listed in Table 3.

Table 3 demonstrated that the K_{eq} values range from 7.07 to 10.22, clearly indicating that there exists a favorable trend for NO to transfer from NNP to all the thiols under the conditions of this study, which is in good accordance with the prediction based on bond energy analysis. This, together with the ΔG_{tr} data in Table 2, suggests that the C−NO compounds, as represented by **7**, could be even better an NO donor than *S*-nitrosothiols, which have been applied so widely as the most famous NO donors in biological studies. The correlation of ΔG_{tr} values vs. K_{eq} values (Figure 2) revealed, though not perfect, a quite good linear relationship (r = 0.968) between the two sets of data of totally different measurements, providing confidence to the overall conclusion about the trend of NO transfer drawn from the bond energy analysis.

In conclusion, the C−NO bond cleavage energies of eight model *C*-nitroso compounds in acetonitrile solution were determined by using titration calorimetry combined with electrochemical measurement. The first quantitative energetic scale of the C−NO bond scission in solution was thus established. Substituent effect on the cleavage energies of the C−NO bonds was rationalized. The homolytic BDEs of

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[26] The factor 1.364 in the 1.364ΔpK_a term is to convert the equilibrium acidity from pK unit to kcal/mol. The application of this expression widely appears in the study of acidity equilibrium. See ref 20 and: (a) Cheng, J. P.; Liu, B.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 7574. (b) Cheng, J.-P.; Liu, B.; Zhao, Y.; Zhang, X. M. *J. Org. Chem.* **1998**, *63*, 7072. (c) Cheng, J.-P.; Lu, Y.; Zhu, X.-Q.; Mu, L. *J. Org. Chem.* **1998**, *63*, 6108.

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[28] In this study, NNP has a maximum absorption at 640 nm, while λ_{max} for *S*-nitrosobenzylthiols is around 540 nm, and λ_{max} for Ph_3CSNO is 590 nm. Transnitrosation between NNP and different thiols can be readily analyzed by using UV−vis spectrometric measurement (Figure S1 in the Supporting Information). UV−vis spectra of the reaction mixtures were obtained by adding an equimolar amount of thiol to a cuvette containing NNP. After the equilibrium was reached, the concentrations of the reactants and products can be calculated from the change of the absorption of NNP at 640 nm according to the Beer−Bouger−Lambert law. The equilibrium constant (K_{eq}) of NO transfer between NNP and different thiols can then be determined from the calculated concentrations as shown in eq 6 in Scheme 6.

TABLE 2. The pK_a Values of Thiols in DMSO, ΔH_{rxn} Values of NO^+ with RSHs in Acetonitrile at 25°C, ΔH_{het}(S−NO) Values of RSNOs (kcal/mol), pK_a Values of RSHs in Acetonitrile, Differences of C−NO Bond Heterolytic Dissocaition Energy of NNP between the S−NO Bond Heterolytic Dissociation Energy *S*-Nitrosothiols and Differences of pK_a Values between the Corresponding Parent Alkane Thiols, As Well As the Free Energy Changes (ΔG_{tr}) of NO Transfer from NNP to Thiols (kcal/mol)

RSNOs, G =	pK_a[a]	ΔH_{rxn}[b]	ΔH_{het}(S−NO)[c]	pK_a(RSH)[d]	$\Delta\Delta H_{het}$	1.364ΔpK_a[e]	ΔG_{tr}[f]
CH_3O	15.8	−22.7	57.5	25.5	−4.6	−1.4	−6.0
H	15.4	−22.0	56.2	25.1	−3.3	−1.9	−5.2
F	15.3	−21.8	55.9	25.0	−3.0	−2.1	−5.1
Cl	15.1	−21.5	55.3	24.7	−2.4	−2.3	−4.7
Br	15.0	−21.5	55.2	24.8	−2.3	−2.5	−4.8
Ph_3CSNO	14.5	−20.8	53.8	24.2	−0.9	−3.1	−4.0

[a] Determined in this work by "overlapping indicator methods" in DMSO,[27] with the uncertainty of ±0.05. [b] Measured in CH_3CN at 25 °C by titration calorimetry. The reproducibility is ±0.5 kcal/mol. [c] Derived from eq5 in Scheme 5. [d] pK_a value of R−SHs in acetonitrile were derived from their pK_a values in DMSO according to the known relation of pK_a(CH_3CN) = 0.982pK_a(DMSO) + 9.94.[14e] [e] The pK_a value of 2-nitropropane in acetonitrile is 26.5, which is derived from its pK_a of 16.9 in DMSO,[20] using the equation in *a*.[14e] [f] Derived from eq4 in Scheme 4.

SCHEME 6

$$R_1C\text{-}NO + R_2SH \xrightleftharpoons{K_{eq}} R_1CH + R_2SNO$$

$$K_{eq} = [R_1CH][R_2SNO]/[R_1CNO][R_2SH] \qquad (6)$$

TABLE 3. Equilibrium Constant of NO Transfer Reaction between NNP and Thiols

RSH, G =	K_{eq}[a]
CH_3O	10.22
H	9.56
F	9.30
Cl	8.67
Br	8.80
Ph_3CSH	7.07

[a] Derived from eq 6 in Scheme 6.

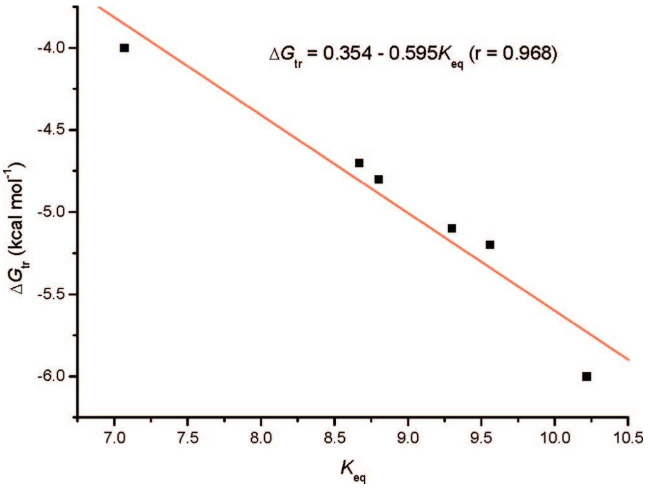

FIGURE 2. Correlation of the equilibrium constants (K_{eq}) of the NO transfer reaction between 2-nitro-2-nitrosopropane and thiols with the Gibbs free energy changes (ΔG_{tr}) of the transfer reaction.

the C−NO bond in these *C*-nitroso compounds were also computed and the calculated results agreed reasonably well with the experimental observations. In addition, the derived C−NO bond energy was applied to estimate the trend of NO transfer from NNP to thiols in solution, and the prediction drawn from thermodynamic driving force analysis was found to correspond quite well with the spectraphotometrically determined equilibrium constants.

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 distilled over P_2O_5 under argon before use. The commercial tetrabutylammonium hexafluorophosphate (Bu_4NPF_6) 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.[29] Redox potentials were obtained by the CV method on an electrochemical analyzer. The heats of reaction of NO^+ with carbanions and NO^+ with thiols were determined on a titration calorimeter. UV−visible measurements were carried out on a UV−visible spectrometer.

Titration Calorimetry for *C*-Nitroso Compounds. Reaction of NO^+ ($NO^+ClO_4^-$) with carbanions (K^+ as counterion) in dry CH_3CN was rapid and gave the C−NO coupling product quantitatively. The reaction heat (ΔH_{rxn}) was measured at 25 °C by a standard procedure similar to that of Arnett.[18] 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 carbanion 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.

Measurement of Redox Potentials. All electrochemical experiments were carried out by CV (sweep rate, 100 mV/s) in dry acetonitrile solution under an argon atmosphere at 25 °C as described previously. *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 1.0 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 for *S*-Nitrosothiols. The heats of reactions (ΔH_{rxn}) of thiols with NO^+ (as from a $NO^+ClO_4^-$−MeCN solution) were measured under argon by titration calorimetry in dry acetonitrile at 25 °C. After a certain amount of MeCN solution of $NO^+ClO_4^-$ was titrated in through a carefully calibrated motor-driven buret to the reaction vessel containing an excess amount of thiol, heat was generated and was computer-processed to give the heat of nitrosation (ΔH_{rxn}). The ΔH_{het} values of the S−NO bond (i.e., NO^+ affinities) can then be calculated from eq 5 in Scheme 5.

Equilibrium Study of Transnitrosation between 2-Nitro-2-nitrosopropane and Thiols. The equilibrium constants (K_{eq}) for transnitrosation were determined by reacting equimolar amounts of thiols and 2-nitro-2-nitrosopropane. Briefly, 2-nitro-2-nitrosopropane in acetonitrile was placed in a quartz cell at 25 °C. The absorption at 640 nm was monitored for 60 min to obtain the slow decomposition rate. An equimolar amount of thiol was added and the exchange reaction was monitored until equilibrium was reached. K_{eq} was then calculated based on the change of the UV absorption. Experiments were repeated at least once.

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Supporting Information Available: Experimental procedures, UV−vis spectra of $PhCH_2SNO$ and Ph_3CSNO, and detailed results of theoretical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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