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The First O–NO Bond Energy Scale in Solution: Heterolytic and Homolytic Cleavage Enthalpies of *O*-Nitrosyl Carboxylate Compounds

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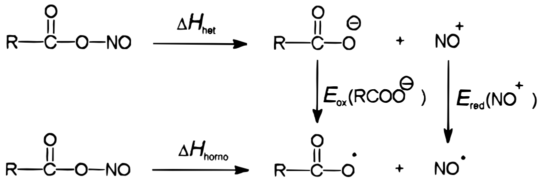
ABSTRACT



The first series of O–NO bond dissociation enthalpies was determined in solution for eight *O*-nitrosyl carboxylate compounds by direct titration calorimetry with a thermodynamic cycle. The derived bond energy data may serve as a quantitative guide to predict the NO binding and releasing abilities of the related amino acids.

In recent years, nitric oxide (NO) has become well-recognized in the field of biology as a very important molecule, being active in regulating blood pressure, transmitting neurostimulation, participating in the immune system to kill tumor cells and intracellular parasites, and so on.[1−4] To understand such a broad range of NO's physiological activities, it is obviously essential to have some knowledge of the chemical fundamentals that govern those functions at the molecular level. It is known that NO, a free radical, cannot exist freely in large quantity in the human body. Therefore, in order for NO to execute its functions, it has to bind to (or be "stored" in) certain carrier molecules first and then, in a suitable environment, be released to another site of the same molecule (intramolecular) or to a different receptor molecule (intermolecular) to finish up a transnitrosation cycle. The driving force for NO to migrate would largely depend on its ability to bind the particular atoms involved in NO transportation. In other words, the Y−NO bond energy (where Y is the atom to which NO is attached) should play a key role in directing NO to migrate. Because of this fundamental importance, NO^+ affinities (i.e., the gas-phase Y−NO heterolysis energies) of quite a number of small molecules have been determined by ion cyclotron resonance (ICR) spectroscopy.[5] However, due to the lack of the means for effectively separating the interference of the secondary bond rupture in gas-phase measurement, essentially no bond information for relatively large organic molecules has been provided in the literature. This has spurred us to initiate research on the Y−NO bond energies of bulky molecules, and the establishment of the first N−NO type bond energy scale in solution (note that most NO-related chemical and biological reactions occur in the condensed phase) for a series

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of *N*-nitroso compounds of relatively large size in solution was reported in a previous communication.[6]

In the present work, we wish to report the first measurement of O−NO bond energies (for both heterolysis and homolysis) of two simple types of *O*-nitroso carboxylate compounds (Figure 1). The biological significance of this kind of information is implicated by the work of Casado et al.,[7] in which they showed that nitrosation of the amino group in amino acids proceeded via the initial formation of nitrosyl carboxylate (−COONO), followed by an intramolecular NO migration from oxygen to nitrogen. The use of nitrite compounds as NO donors in many chemical and biological reaction systems has also long been recognized.[8] It is therefore believed that the quantitative measures of the O−NO bond energies in the present study may serve as a guide for selecting efficient NO donor compounds and for a more insightful understanding of relevant NO-involving reactions.

1

2

X = 4-OMe (a), 4-CH_3 (b), 4-H (c), 4-Br (d), 4-NO_2 (e)

R = CH_3 (a), CH_3CH_2 (b), $(CH_3)_2CH$ (c)

Figure 1. *O*-Nitrosyl carboxylate compounds.

The heterolytic O−NO bond dissociation energies (ΔH_{het}(O−NO)) of **1** and **2** were determined in acetonitrile at 25 °C by titration calorimetry utilizing the general strategy of Arnett,[9] where the heat of reaction (ΔH_{rxn}) of the carbanion with the carbocation was measured in sulfolane and was then converted to ΔH_{het} simply by switching the sign (Scheme 1).

Scheme 1

$$R^+ + R'^- \rightarrow R\text{-}R' \qquad \Delta H_{rxn}$$

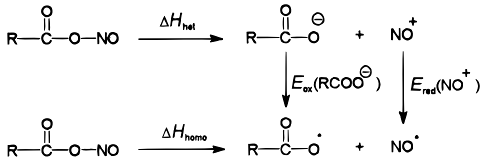
$$R\text{-}R' \rightarrow R^+ + R'^- \qquad \Delta H_{het}$$

$$\Delta H_{het} = -\Delta H_{rxn}$$

In the present work, the carboxylate oxoanions (**1** and **2**) and nitrosonium ion were taken as the interacting anion and cation instead, and acetonitrile took the place of sulfolane as solvent for both the heat and electrochemical measurements. To avoid the interference of the ion-pairing effect on the measured heats, the counterions selected in this work for carboxylates $RCOO^-$ and nitrosonium NO^+ were tetrabutylammonium (n-Bu_4N^+) and perchlorate (ClO_4^-), respectively. Other factors responsible for the validity of the titrimetric heat measurement of organic anion/cation combination reactions are (i) the cleanness of the reactions conducted in the calorimeter reaction vessel and (ii) the stability of oxoanions and NO^+ in the chosen solvent during the entire measurement. By comparison of the isolated titration product with the authentic samples specially prepared under noncalorimetric conditions[10] and by spectroscopic means, we found that all these requirements were met in our reaction systems of interest.

The homolytic O−NO bond dissociation energies (ΔH_{homo}(O−NO)) were derived from a thermodynamic cycle (Scheme 2) similar to that of Arnett[9] utilizing the directly measured ΔH_{het}'s and relevant redox potentials. Similar approaches to derive experimentally inaccessible quantities from feasible solution measurements have been widely applied in the recent literature.[9,11−15] The ΔH_{het}'s and ΔH_{homo}'s determined here, together with the necessary electrochemical data, are presented in Table 1. The homolytic R−H bond dissociation energies (BDE) estimated by the reported method[15a] and the literature pK_a's[16] are also included for the purpose of comparison.

Scheme 2



$$\Delta H_{homo}(\text{O-NO}) = \Delta H_{het}(\text{O-NO}) - 23.06[E_{red}(\text{NO}^+) - E_{ox}(\text{O}^-)] \quad (1)$$

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Table 1. ΔH_{het}(O−NO) and ΔH_{homo}(O−NO) Values of Compounds **1** and **2**, pK_a's, BDE's of RCOOH Compounds, and Related Electrochemical Quantities at 25 °C

substrate	ΔH_{het}-(O−NO)[a]	ΔH_{homo}-(O−NO)[b]	E_{ox}-($RCOO^-$)[c]	pK_a[d]	BDE[e]
$-CH_3O$ (**1a**)	32.3 ± 0.2	32.5	0.87	11.4	109
$-CH_3$ (**1b**)	31.8 ± 0.4	32.8	0.91	11.2	110
−H (**1c**)	30.9 ± 0.5	33.9	0.99	11.0	111
−Br (**1d**)	29.5 ± 0.4	34.3	1.07	10.3	112
$-NO_2$ (**1e**)	25.7 ± 0.3	38.6	1.42	9.0	119
$-CH_3$ (**2a**)	32.5 ± 0.7	35.0	0.97	11.6	112
$-CH_2CH_3$ (**2b**)	35.1 ± 0.5	37.9	0.99	12.3	113
$-CH(CH_3)_2$ (**2c**)	34.6 ± 0.8	36.7	1.00	12.2	113

[a] Measured in MeCN at 25 °C in kcal/mol by titration calorimetry. The data given were average values of at least two independent runs, each of which was again an average value of four to six consecutive titrations. [b] Derived from the equation in Scheme 1 in kcal/mol, taking $E_{1/2}(NO^+)$ = 0.863 V.[6] The uncertainty is estimated to be ≤3 kcal/mol. [c] Measured in MeCN at 25 °C in volts by CV (irreversible) vs the ferrocenium/ferrocene redox couple. The values are reproducible to 10 mV or better. [d] Data from ref 16. [e] Homolytic O−H bond dissociation energy in kcal/mol derived from the equation BDE = 1.364pK_a+ 23.06E_{ox} + 73.6 (kcal/mol).[15] Estimated uncertainty: ≤3 kcal/mol.

The data in Table 1 indicate that the ΔH_{het}(O−NO)'s of nitrosyl carboxylates (25.7−35.1 kcal/mol) are substantially lower than the ΔH_{het}(N−NO)'s of *N*-nitrosoureas, *N*-nitrosophophoramides, and *N*-nitrosoacetoamides (52.4−62.0 kcal/mol) studied previously,[6] suggesting that these *O*-nitroso compounds are much better NO^+ donors than the mentioned *N*-nitroso compounds. The ΔH_{het}(O−NO)'s are found to correlate linearly with pK_a's of the parent compounds (Figure 2), implying that structural effects on oxoanion stability should be similar in these systems.

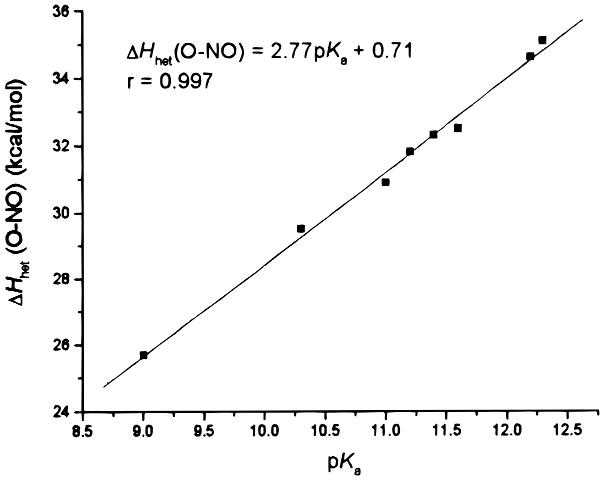

Figure 2. Correlation of heats of heterolytic O−NO bonds with the corresponding pK_a's of their parent molecules.

An inspection of the ΔH_{homo}(O−NO) data in Table 1 shows that these bond energies are either close to or greater than the corresponding ΔH_{het}(O−NO)'s, in sharp contrast to the previous observations of ΔH_{het}'s 10−34 kcal/mol higher relative to ΔH_{homo} for N−NO bond systems. This is mainly attributed to the much greater stability of carboxylate ions relative to nitroanions and suggests that homolytic O−NO bond breaking to deliver an NO radical and heterolytic bond breaking to produce an NO^+ cation should both be energetically feasible. It is also noted that the homolysis energies of the O−NO bonds in series **1** show an opposite trend, being affected by remote electron-donating substituents (EDG) and electron-withdrawing substituents (EWG), which is similar to the pattern showed by the corresponding O−H bond BDE's (Table 1). Correlation of the BDE(O−NO)'s versus BDE(O−H)'s of series **1** demonstrates a good linear relationship with *r* and *s* equal to 0.998 and 0.64 (Figure 3), respectively. The slope of less than unity may reflect relatively small changes in polarity of the O−NO bonds introduced by remote substituents as compared to those of the corresponding O−H bonds. In addition, a comparison of the ΔH_{het} and ΔH_{homo} data shows that the differences between ΔH_{het}(O−NO)'s and ΔH_{homo}(O−NO)'s become gradually greater as the para substituent goes from an EWG to an EDG. These is understandable, since the EDG tends to stabilize the incipient radical and destabilize the anion, whereas the EWG does just the opposite. From the relative ΔH_{homo}(O−NO) data derived here, it can be seen that aromatic *O*-nitroso compounds are generally better NO donors than aliphatic *O*-nitroso compounds and that compounds with EDG are better NO donors than those with EWG. It should be pointed out that though comparisons of BDE's in a relative sense are probably quite reliable, the irreversibility of anion oxidation potentials and neglect of entropy contribution to the electrode process could, of course, introduce substantially greater uncertainty (up to 3 kcal[11,13a]) in the derived absolute BDE data.[17] Therefore, the BDE's listed in Table 1 should be viewed as the upper limits and

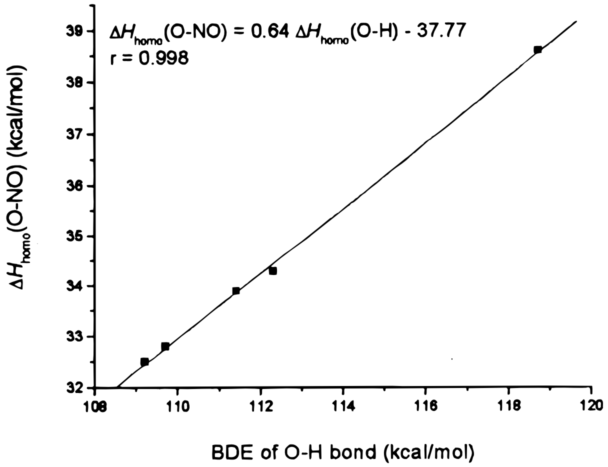

Figure 3. Correlation of energies of homolytic O−NO bonds with the corresponding BDE's of their parent O−H molecules.

one should be cautious if such values have to be used in an absolute sense.

Most of the corresponding O−H bond BDE's in Table 1 are, nevertheless, reported here for the first time (except for acetic acid), which may be of value in serving as a quantitative guide for relevant studies. We already note that replacement of the O−H hydrogen with an NO group has a tremendous effect in reducing the bond strength by an average of 78 ± 2 kcal/mol. However, these relative values of BDE(O−H) versus BDE(O−NO) appear to be not in accordance with the literature ΔBDE of 64 kcal/mol between MeO−H and MeO−NO.[20] This obvious discrepancy of ΔBDE's between the two aforementioned pairs of compounds may be understood by considering that (i) the electron-withdrawing RCO groups are known to be O−H bond strengthening[21] and so should contribute partially to the enlarged BDE gap and (ii) the electron-donating Me group and electron-pulling NO group constitute a push−pull system in Me−O−NO; therefore, its O−NO bond is expected to be stronger than that in RCO−O−NO because no such stabilization exists in the latter system. This, again, could contribute to the variation of the BDE gaps. Our recent ab initio DFT (GAUSSIAN 98) calculations[22] of these two pairs of BDE's gave a relative ΔBDE of 15.3 kcal/mol, which is in excellent agreement with the experimental observation of ΔΔBDE at 14 kcal/mol.

In summary, in this work the first heterolytic and homolytic O−NO bond dissociation energy scales of *O*-nitroso compounds (series **1** and **2**) in solution have been established. The derived energetic data indicate that compounds **1** and **2** are both good $NO^{\bullet}$ donors and good NO^+ donors. We believe that such NO-related bond information should be useful in understanding the biological functions of nitric oxide, especially its reactions with amino acids in vivo.

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(17) Peak potentials of carboxylates in Table 1 were not corrected for irreversibility because of the difficulty in locating all the rate constants of possible follow-up radical reactions (i.e., dimerization, β-scission). However, a maximum cathodic shift of ~120 mV (2.76 kcal) can be estimated using the method of Bard[18] by assuming that the overall rate of radical reactions was nearly diffusion-controlled.[19] For this reason, the derived homolytic BDE's should be viewed as upper limits. On the other hand, while there was no fundamental reason for the common practice of assuming $\Delta G_{\text{redox}} = \Delta H_{\text{redox}}$ in many organic works, Arnett (*J. Am. Chem. Soc.* **1990**, *112*, 344), and many others, did find that temperature effects on redox potentials of delocalized anions and cations were indeed quite small, suggesting that neglect of the entropy effect may not cause large uncertainty and could be acceptable for appropriate systems.

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