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Establishment of Heterolytic and Homolytic Y−NO_2 Bond Dissociation Energy Scales of Nitro-Containing Compounds in Acetonitrile: Chemical Origin of NO_2 Release and Capture

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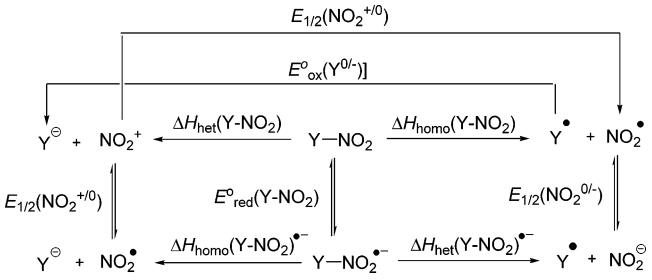

The first heterolytic and homolytic N(O)−NO_2 bond dissociation energy scales of three types Y−nitro (Y = N, O) compounds and corresponding radical anions in acetonitrile were established by using titration calorimetry combined with relevant electrochemical data through proper thermodynamic cycles.

Because of the recent discoveries on the significant roles of nitrogen oxides (N_xO_y) in many important natural processes, the chemistry and biochemistry of N_xO_y have regained tremendous research attention in the last two decades.[1] Among various kinds of N_xO_y, nitric oxide (NO) is certainly the best known "star molecule" for its very broad range of vital roles in human physiological processes.[2] However, the importance of nitrogen dioxide (NO_2) has largely been shadowed or even overlooked during the same period. Nevertheless, the significant functions of NO_2 and nitrite ion (NO_2^-) in mammalian biology have slowly been accumulated,[3] and the research on the functions of NO_2 and NO_2^- has started to draw increasing attention recently.

Nitrogen dioxide has long been known in chemistry as a strong oxidant and nitrating reagent for organic synthesis, but not until very recently was it found to be associated with many destructive processes in living bodies. A wide spectrum of diseases has been suggested to be related to the exogenously and endogenously generated NO_2.[3c,d] Conversely, it is also reported that NO_2^- plays a crucial role in many NO-mediated processes such as hypoxic vasodilation and cytoprotection from cardiac and liver ischemia-reperfusion injury and in gene expression.[4] Nitrite is also suggested to be a potential therapeutic in the treatment of various diseases.[5]

In order to understand the mechanistic details of NO_2 or NO_2^- in chemical or biological processes, the basic information concerning quantitative energetic changes in NO_2-related bond cleavage in solution should be of great value because it provides the necessary information on the thermodynamic driving forces of NO_2-carrier molecules to release, capture, or transfer an NO_2 (or NO_2^-) moiety. However, to our knowledge, no systematic work was reported on experimental determinations of Y−NO_2 bond energies in any solvent system where the NO_2-related chemical and biological activities are likely to take place. The definite and immediate need of the Y−NO_2 bond energy data bank to deepen our understanding of the board range of NO_2-related activities has stimulated us to extend our current research on NO-related bond energetics[6] to cover the equally important Y−NO_2 bond energies. In this work, we report the first series of experimentally determined Y−NO_2 (Y = N, O) heterolytic and homolytic bond energy scales for three representative families of synthetic or biochemical significance (Scheme 1). This kind of bond energy scales should also be useful for the study of stability and shock sensitivity of the Y−NO_2-type energetic materials[7] and for estimating the nitrating ability of

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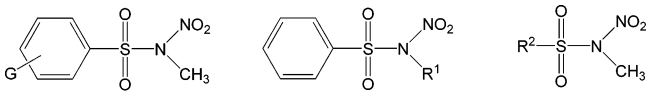
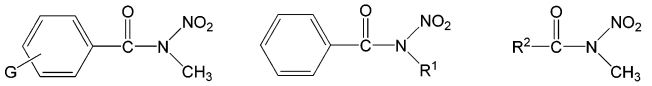
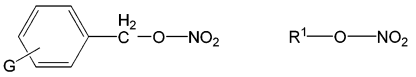
SCHEME 1. Y-Nitro Compounds



1: *N*-Nitrosulfonamides



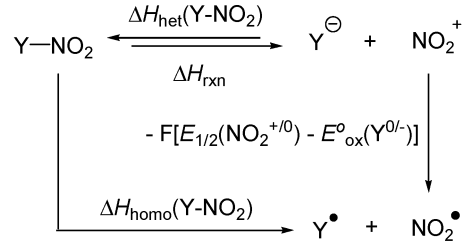
2: *N*-Nitroacylamides



3: *O*-Nitro alcohols

nitro-releasing compounds in synthetic chemistry.[8] Because a rapid cleavage of Y−NO_2 bond (releasing a nitrite) upon one-electron reduction of a nitro compound has been observed for years,[9] in order to gain information concerning the role of electron transfer in activating the N(O)−NO_2 bond rupture, the heterolytic (defined as nitrite ion-releasing) and homolytic (defined as nitro radical-releasing) [N(O)−NO_2]$^{\bullet-}$ bond dissociation energies of the (Y−NO_2)$^{\bullet-}$ radical anions were also determined.

SCHEME 2

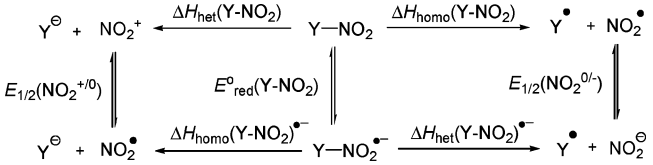


$$\Delta H_{het}(\text{Y–NO}_2) = -\Delta H_{rxn} \quad (1)$$

$$\Delta H_{homo}(\text{Y–NO}_2) = \Delta H_{het}(\text{Y–NO}_2) - F\,[E_{1/2}(\text{NO}_2^{+/0}) - E^{o}_{ox}(\text{Y}^{0/-})] \quad (2)$$

The desired Y−NO_2 bond dissociation energies were derived from the thermodynamic cycle (Scheme 2), which is analogous to that in our earlier studies on NO affinity,[6] where the difference between the heterolytic (ΔH_{het}) and homolytic dissociation energy (ΔH_{homo}) of the Y−NO bond is equal to the enthalpy of electron transfer.[10] As shown in Scheme 2, the ΔH_{het} of Y−NO_2 should be numerically equal to the reaction enthalpy change (ΔH_{rxn}) of the nitranion Y^- with NO_2^+ simply by switching the sign of ΔH_{rxn}(Scheme 2, eq 1). ΔH_{homo} can be derived indirectly from the corresponding heterolytic Y−NO_2 bond dissociation energy with a suitable redox potential through the thermodynamic cycle showed in Scheme 2 (eq 2). The heterolytic and homolytic (Y−NO_2)$^{\bullet-}$ bond dissociation energies in acetonitrile were similarly estimated from eqs 3 and 4, respectively, using the thermodynamic cycle constructed from the Y−NO_2 bond heterolytic and homolytic scission reactions of the neutral Y−nitro compounds combined with certain electrode potentials (Scheme 3).[11] The enthalpy changes of the reactions of Y^- with NO_2^+ (ΔH_{rxn}) and the standard redox potentials[12] of the relevant species are listed in the Supporting Information (Table S2, Figures S1−S3). The heterolytic and homolytic N(O)−NO_2 bond dissociation energies and the (N(O)−NO_2)$^{\bullet-}$ bond dissociation energies of the corresponding radical anion in acetonitrile are presented in Table 1.

SCHEME 3



$$\Delta H_{het}(\text{Y–NO}_2)^{\bullet-} = \Delta H_{homo}(\text{Y–NO}_2) + F\,[E^{o}_{red}(\text{Y–NO}_2) - E_{1/2}(\text{NO}_2^{0/-})] \quad (3)$$

$$\Delta H_{homo}(\text{Y–NO}_2)^{\bullet-} = \Delta H_{het}(\text{Y–NO}_2) - F\,[E_{1/2}(\text{NO}_2^{+/0}) - E^{o}_{red}(\text{Y–NO}_2)] \quad (4)$$

The data in Table 1 demonstrate that the ΔH_{het}(N−NO_2) and ΔH_{homo}(N−NO_2) bond energies of *N*-nitrosulfonamides (**1**) range from 51.4 to 57.8 kcal/mol and from 36.0 to 38.2 kcal/mol, respectively, while the ΔH_{het}(N−NO_2) and ΔH_{homo}(N−NO_2) bond energies of *N*-nitroacylamides (**2**) range from 60.5 to 69.0 kcal/mol and from 31.9 to 34.9 kcal/mol, respectively. The corresponding ΔH_{het}(O−NO_2)'s and ΔH_{homo}(O−NO_2)'s of *O*-nitro alcohols (**3**) range from 61.2 to 73.7 kcal/mol and from 30.1 to 39.6 kcal/mol, respectively. It is clear that the N(O)−NO_2 heterolytic bond dissociation energies of these three types of nitro compounds in acetonitrile are all greater than the corresponding homolytic bond dissociation energies, which

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$$\text{Y} - \text{NO}_2 \xrightarrow{e} \text{Y} - \text{NO}_2^{\bullet-} \rightarrow \text{Y}^{\bullet} + \text{NO}_2^{-}$$

(10) Arnett has shown that the temperature dependence of the redox processes for resonance-delocalized anions and for the reversible cation-to-radical conversions were experimentally found to be negligible. Then the corresponding entropy changes for redox processes should be insignificant. In this work, we have also examined the temperature effect on the oxidation potentials of the N^- or O^- anions of interest, and found that variation of temperature caused only minimal changes in anion oxidative potentials (see Table S1 in the Supporting Information), suggesting that neglecting the entropy effect for anion electro-oxidation in our thermochemical cycle would not produce remarkable error to the derived bond energy data. 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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TABLE 1. Y−NO_2 Bond Dissociation Energy ΔH_{het}'s and ΔH_{homo}'s of Y-Nitro Compounds and $\Delta H_{het}^{\bullet -}$'s and $\Delta H_{homo}^{\bullet -}$'s of Corresponding Radical Anions in Acetonitrile (kcal/mol)[a]

compd	ΔH_{het}[b]	ΔH_{homo}[c]	$\Delta H_{het}^{\bullet -}$[d]	$\Delta H_{homo}^{\bullet -}$[e]
1				
G = 4-MeO	56.7	37.3	−20.9	−13.2
4-Me	56.0	36.8	−21.3	−13.8
4-H	55.2	36.6	−21.4	−14.6
4-Cl	53.9	36.3	−20.2	−14.4
4-Br	54.2	36.4	−20.2	−14.1
4-NO_2	51.4	36.0	−18.3	−14.6
3-NO_2	51.6	36.1	−18.5	−14.8
R^1 = Et	57.0	37.7	−20.7	−13.1
R^2 = CH_3	57.8	37.1	−21.0	−12.0
CH_3CH_2	57.5	38.2	−20.4	−12.9
2				
G = 4-MeO	67.6	33.6	−22.1	0.1
4-Me	67.1	33.4	−22.1	−0.1
4-H	66.5	33.3	−21.9	−0.5
4-Cl	65.3	32.9	−19.8	0.8
4-Br	65.7	32.7	−19.6	1.6
4-NO_2	64.0	32.6	−17.6	2.1
R^1 = Et	68.1	34.9	−19.9	1.6
Pr	69.0	33.6	−21.8	1.9
R^2 = $ClCH_2$	60.5	31.9	−22.3	−5.5
$ClCH_2CH_2$	68.9	33.2	−24.4	−0.5
3				
G = 4-MeO	65.6	30.1	−32.2	−8.5
4-Me	65.1	30.3	−31.7	−8.7
4-H	64.5	30.4	−30.8	−8.5
4-Cl	63.6	30.8	−30.1	−9.1
4-Br	63.5	31.1	−29.6	−9.0
4-CF_3	62.3	31.4	−26.3	−7.1
4-NO_2	61.2	39.6	−16.0	−6.2
R^1 = CH_3CH_2	73.7	36.5	−27.1	−1.7

[a] Relative uncertainties were estimated to be smaller than or close to 1 kcal/mol. [b] ΔH_{het}(Y-NO_2) obtained from eq 1. [c] ΔH_{homo}(Y-NO_2) derived from eq 2, taking $E_{1/2}(NO_2^{+/0})$ = 0.91 V vs $Fc^{+/0}$.[14] [d] ΔH_{het}(Y-NO_2)$^{\bullet -}$ derived from eq 3, taking $E_{1/2}(NO_2^{0/-})$ = 0.400 V vs $Fc^{+/0}$.[15] [e] ΔH_{homo}(Y−NO_2)$^{\bullet -}$ derived from eq 4, taking $E_{1/2}(NO_2^{+/0})$ = 0.91 V vs $Fc^{+/0}$.[14]

indicates that homolysis of the Y−NO_2 bond to generate the NO_2 radical ($NO_2^{\bullet}$) is energetically much more favorable than the corresponding Y−NO_2 bond heterolysis to generate a pair of ions. Further inspection of the heterolytic bond dissociation energies of these nitro compounds shows that the ΔH_{het} decreases gradually as the remote substituent changes from electron-donating groups (EDG) to electron-withdrawing groups (EWG). This results in a quite good linear correspondence between the ΔH_{het} values and the Hammett σ constants (see Figures S4−S6, where the *r* value equals 0.998, 0.987, and 0.994 for series **1**, **2**, and **3**, respectively). This feature can be understood from the fact that the EDGs are anion-destabilizing (causing an increase in ΔH_{het}) and EWGs are anion-stabilizing (causing a decrease in ΔH_{het}).

Although solvents are known to have a great effect on heterolysis energies, their effect on homolytic BDEs, where only neutral species are formed in solution during the homolysis of neutral molecules, is expected to be small and is indeed observed to be true in the literature where the solution BDEs were found to match the corresponding gas-phase values very closely for many compounds.[16] This feature gives one confidence to apply the BDE scales established in this work to biochemical reactions, since the Y−NO_2 BDEs in water can be well approximated by the data from the present BDE study in acetonitrile. The relative insensitivity of the remote substitiuents on affecting homolytic BDEs as seen from the ΔH_{homo} data is also in consistence with the literature observations.[17]

A closer look at the ΔH_{homo} data further indicates that the pattern of the remote substituents to influence homolysis energies of *N*-nitro compounds (**1**, **2**) differs from that for *O*-nitro compounds (**3**). While in series **3** the remote substituent effect shows a normal O-pattern (i.e., EDG, bond weakening; EWG, bond strengthening) as generally observed for heteroatom-centered radicals in the literature,[18] in series **1** and **2**, the direction is just reversed; i.e., the EDGs are bond-strengthening, whereas EWGs generally bond-weakening. The latter phenomenon, i.e., the so-called counter-O type substituent effect, is rarely observed,[18] but it can be rationalized on the basis of differential solvation of the nitro-containing compounds.

The activation of the Y−NO_2 bond upon one-electron reduction of the nitro compounds to facilitate a rapid release of nitrite is believed to be associated to the numerous physiological and pharmacological functions of the NO_2^- ion.[19] In the present work, the role of electron transfer in activating N(O)−NO_2 bond rupture for species **1**−**3** can be estimated by comparison of the Y−NO_2 bond energies with the corresponding $(Y-NO_2)^{-\bullet}$ bond cleavage energies as determined using the appropriate thermodynamic cycle (Scheme 3).

As seen from Table 1, the ΔH_{het}(N−NO_2)$^{\bullet -}$'s and ΔH_{homo}-(N−NO_2)$^{\bullet -}$'s of *N*-nitrosulfonamides (**1**$^{\bullet -}$) range from −18.3 to −21.4 kcal/mol and from −12.0 to −14.8 kcal/mol, respectively; the ΔH_{het}(N−NO_2)$^{\bullet -}$'s and ΔH_{homo}(N−NO_2)$^{\bullet -}$'s of *N*-nitroacylamides (**2**$^{\bullet -}$) range from −17.6 to −24.4 kcal/mol and from 2.1 to −5.5 kcal/mol, respectively, while the ΔH_{het}-(O−NO_2)$^{\bullet -}$'s and ΔH_{homo}(O−NO_2)$^{\bullet -}$'s of *O*-nitro alcohols (**3**$^{\bullet -}$) range from −16.0 to −32.2 kcal/mol and from −1.7 to −9.1 kcal/mol, respectively. A simple comparison of these energetic data with the corresponding bond energies of neutral molecules immediately indicates that both the heterolytic and the homolytic bond dissociation energies of the nitro compound radical anions are substantially lower than those of the corresponding neutral molecules. The main factor contributing to the remarkable bond-weakening effect is that the reduction potential values of *N-(O)*-nitro compounds are all very negative in acetonitrile (see Table S1, Supporting Information). It is also obvious from the data of Table 1 that the ΔH_{het}(N(O)−NO_2)$^{\bullet -}$'s are all much lower than the corresponding ΔH_{homo}(N(O)−NO_2)$^{\bullet -}$'s because the nitrite ion generated in the former bond-breaking process is better solvated than the $NO_2^{\bullet}$ radical and the heterolytic cleavages of the (N(O)−NO_2)$^{\bullet -}$ bond are all exergonic. This feature suggests that these three types of nitro compound radical anions are very unstable at room temperature and able to spontaneously release NO_2^- by heterolytic cleavage. Of these, the *O*-nitro alcohols radical anions seem to be the best NO_2^- donors, since the corresponding ΔH_{het}(Y−NO_2)$^{\bullet -}$ are in the lowest ranges of those evaluated for the nitro radical anions. The opposite influence of remote substituents in varying the ΔH_{het}(N−NO_2)$^{\bullet -}$'s and the ΔH_{homo}(N−NO_2)'s (note that both types of bond rupture generate the same nitrogen radical) can

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be understood in terms of the differential solvation of the starting $(N-NO_2)^{\bullet-}$ radical anion and the nitrogen radical products.

In summary, we here outlined an approach to the bond dissociation energies of the $Y-NO_2$ compounds and their radical anions and have experimentally established, for the first time, all four types of the bond-breaking energy scales for three nitro compound families in acetonitrile. This energetic study should be important in helping chemists and biochemists to understand the mechanistic details of NO_2/NO_2^- release, capture, and transfer. A more inclusive construction of the $Y-NO_2$ bond energy databank is under our immediate research.

Experimental Section

General Procedure for Titration Calorimetry. Reaction of NO_2^+ ($NO_2^+BF_4^-$) with anions (K^+ as counterion) in dry CH_3CN was rapid and gave the $Y-NO_2$ coupling product quantitatively. The titration calorimetry was performed in acetonitrile solution at 25 °C on a CSC 4200 isothermal titration calorimeter. Prior to use, the instrument was calibrated against an internal heat pulse. The reaction heat was determined following eight automatic injections and obtained by area integration of each peak except the first one. The heat of dilution of nitronium tetrafluoroborate was small enough to be neglected for reaction heat measurements. The reported ΔH_{rxn} is the average value of two or three independent runs. Spectroscopic identification of the Y−nitro compounds, for example, *N*-methyl-*N*-nitrobenzamide: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (3H, s), 7.44−7.48 (2H, m), 7.56−7.61 (1H, m), 7.67−7.70 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.9, 128.3, 128.8, 133.2, 133.3, 169.6.

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Supporting Information Available: Experimental procedure, ΔH_{rxn}'s, oxidative potentials of Y^- and $E°_{red}(Y-NO_2)$'s of *Y*-nitro compounds in acetonitrile, and correlation of the heats of heterolysis of $Y-NO_2$ bonds in Y-nitro compounds with σ values. This material is available free of charge via the Internet at http://pubs.acs.org.

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