Heterolytic and Homolytic Y−NO Bond Energy Scales of Nitroso-Containing Compounds: Chemical Origin of NO Release and NO Capture

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Nitric oxide (NO), known today as the simplest intra- and intercellular signaling molecule, plays key roles in regulating many important physiological functions in living bodies.[1−5] To understand logically and maybe even quantitatively the chemical origins of NO's physiological roles, detailed information regarding quantitative energetic changes in NO-related bonding during its biological transformations has to be disclosed at a molecular level. Since NO is such a small diatomic molecule and is expected not to be too strongly affected by steric or molecule shape-dependent recognition factors that large molecules often encounter, the binding force of NO with a particular active site can therefore be represented by the bond energy of the Y−NO type, where Y is the atom to which NO is actually attached. Here we report the establishment of the first such Y−NO bond energy scale by direct calorimetric measurements combined with relevant electrochemical data for three types of *N*-nitroso compounds, to facilitate the understanding of the driving force for NO release and capture.

Although the NO^+ binding energies for many small neutral organic molecules in the gas phase (also called NO^+ affinities) have been determined by using ion cyclotron resonance spectrometry,[6,7] Y−NO bond energy, where Y is a relatively large organic moiety, is virtually absent from all thermodynamic data bank,[8] because Y is very apt to undergo secondary bond cleavages during the gas-phase bond energy measurement, making the separation of the heats from the primary process essentially impossible. However, the recent development in the bond energy determination utilizing the easily accessible solution thermodynamic quantities[9−15] implies that the problems encountered in the gas phase should no longer be a primary obstacle in solution, as long as the anion (Y^-) and nitrosonium cation can be successfully manipulated in a single solvent at the same time. The thermodynamic cycle in this work to derive the desired Y−NO bonding information is based on Arnett's[9] and Bordwell's[10] work, in which they have shown that the difference between heterolytic bond energy (ΔH_{het}) and homolytic bond energy (ΔH_{homo}) is the enthalpy of electron transfer, which is approximated closely by the free energy of electron transfer (ΔG_{ET}).[16] Thus, ΔH_{het} of Y−NO can be obtained from the heat of combination reaction between Y^- and NO^+, and ΔH_{homo} from ΔH_{het} in combination with the reduction potential (E_{red}) of NO^+ and the oxidation potential (E_{ox}) of Y^- (Scheme 1). Similar approaches were successfully applied recently for deriving C−H bond energies[11] and C_c-C_a (where C_c and C_a represent resonance-stabilized carbocations and carbanions, respectively) bond energies.[9]

Three types of *N*-nitroso compounds, including *N*-nitrosoureas (**1**), *N*-nitrososulfonamides (**2**), and *N*-nitrosophosphoramides (**3**) (Chart 1), were chosen in this work for measurement of Y−NO bond energies. The success of the heat measurement largely depends on two key factors: (i) the combination reactions of NO^+ with anions have to be a quantitative reaction without any side reaction and (ii) the solvent used should be stable to both the strongly electrophilic nitrosonium cation and the strongly basic anion of interest during the entire titration experiment. We found that the chosen reaction systems of this work in acetonitrile met all the criteria for both calorimetric and electrochemical measurements. The cleanness of the combination reactions under calorimetric conditions was confirmed by comparison of the product with the authentic samples specially prepared. The nitrogen anion was generated through the reaction of the parent aniline with potassium hydride. Nitrosonium perchlorate (NO^+-ClO_4^-) served as NO^+ source. The titration experiment was carried out under argon in dry acetonitrile solution at 25 °C using a Tronac 458 calorimeter. After a certain amount of NO^+ solution in MeCN (usually 25 mM in concentration) was titrated through a carefully calibrated motor-driven buret to the reaction vessel containing an excess amount of the nitranion of interest, the heat generation was computer-processed to give the heat of the reaction (ΔH_{rxn}),[9] which can be easily converted to the heat of heterolysis (ΔH_{het}) by switching the sign. The cyclic voltammograms were obtained on a BAS 100B electrochemical analyzer equipped with a three-electrode analytical cell at a sweep rate of 100 mV/s in dried and degassed 0.1 M Bu_4NPF_6−MeCN under argon. The ΔH_{het}s and ΔH_{homo}s of **1**−**3** and the electrochemical data necessary for the evaluations are presented in Table 1. The pK_a[14] and bond dissociation energy (BDEs)[15] of the Y−H parent molecules determined here are listed (whichever available) for comparison.

The data in Table 1 show that both *N*-nitrosoureas and *N*-nitrosophosphoramides have ΔH_{het} of 50−62 kcal/mol, while *N*-nitrososulfonamides have considerable lower ΔH_{het} (about 25−35 kcal/mol). The ΔH_{het} correlates linearly with pK_a of the parent compound (Figure 1), indicating that the linear free energy relationship holds in these systems. The Y−NO homolysis energies of the model compounds are substantially lower than the corresponding heterolysis energies and show an opposite trend as being affected by remote substituents. Substituent effect on

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(16) While there is no fundamental reason the entropy changes for redox processes should be insignificant, Arnett has been able to show that mingling of the BDE values with free energy redox terms is valid for an extensive range of cation−anion combinations, because 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 (average uncertainty, 4.0 cal/T).[9,17] Therefore, the same magnitude of uncertainty can be assumed for the present cases because the systems are similar to those in the literature.

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Scheme 1

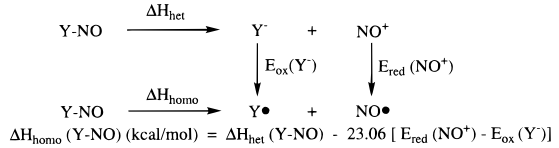

Chart 1

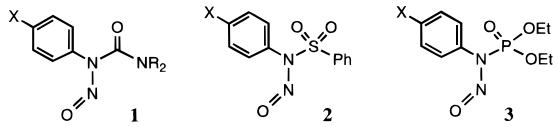

Table 1. ΔH_{Het} and ΔH_{Homo} of Compounds **1**−**3**, pK_as, BDEs of Y−H's, and Related Electrochemical Quantities at 25 °C

substrate	ΔH_{het}[a]	$E_{ox}(N^-)$[b]	ΔH_{homo}[c]	pK_a[d]	$E_{ox}'(N^-)$[e]	BDE[f]
1, R = Me						
X = 4-H	59.5	−0.457	29.1	21.2	−0.435	92.7
4-OMe	62.0	−0.599	28.3	22.1	−0.590	90.4
2-Me	60.0	−0.546	27.5			
4-Me	61.1	−0.542	28.7	21.7	−0.503	91.8
2-Cl	51.3	−0.358	23.1			
4-Cl	58.5	−0.405	29.2	20.0	−0.336	93.4
3-Br	58.1	−0.339	30.3			
4-Br	58.1	−0.380	29.4	19.9	−0.320	93.5
4-I	58.2	−0.392	28.9	19.9	−0.330	93.4
4-COMe	55.3	−0.210	30.5	18.5	−0.182	94.9
4-NO_2	52.4	0.026	33.1	15.9	0.040	96.4
1, X = Me						
R = *i*-Pr	60.4	−0.603	26.6			
CH_2Ph	56.5	−0.489	25.4			
2, X = H	29.1	0.172	13.2	11.9	0.161	92.6
OMe	34.9	−0.112	12.4	12.7	−0.091	89.0
Me	29.9	0.061	11.4	12.5	0.046	91.7
Cl	28.4	0.200	13.1	11.1	0.220	93.8
COMe	25.7	0.376	14.5	10.0	0.346	95.2
NO_2	25.1	0.554	18.0	8.0	0.543	97.1
3, X = H	58.4	−0.149	35.0	18.4	−0.174	94.7
Me	60.4	−0.261	34.5	18.9	−0.261	93.4
Cl	58.1	−0.084	36.2	17.3	−0.066	95.7
Br	57.8	−0.069	36.2	17.3	−0.063	95.7
NO_2	53.3	0.307	40.4	13.8	0.351	100.5

[a] Measured in MeCN at 25 °C in kcal/mol by titration calorimetry taking as $-\Delta H_{rxn}$.[9] The data given were average values of at least two independent runs, each of which was again an average value of 4−6 consecutive titrations. The reproducibility is 0.36 ± 0.18 kcal/mol. [b] Measured in MeCN at 25 °C in volts by CV vs ferrocenium/ferrocene redox couple and reproducible to 5 mV or better. [c] Derived from the equation in Scheme 1 in kcal/mol taking $E_{1/2}(NO^+) = 0.863$ V (this work). Uncertainty is estimated to be ≤2 kcal/mol. [d] Measured in DMSO at 25 °C by overlapping indicator titration[14] in this work. Standard deviation <0.05 pK. [e] Same as footnote *b* except the data are in DMSO. [f] Homolytic Y−H bond dissociation energy in kcal/mol derived from the equation[15] BDE = 1.364pK_a(YH) + 23.06$E_{ox}(Y^-)$ + 73.6 (kcal/mol). Uncertainty is estimated to be ≤2 kcal/mol.

the Y−H bond BDEs showing a similar pattern was observed both previously [13,15,18] and in the present work. A closer look of the bond energy data also reveals that the differences between ΔH_{het} and ΔH_{homo} become gradually greater as the *para*-substituent is going from an electron-withdrawing group (EWG) to electron-donating group (EDG). This should be understandable because the EDG tends to stabilize the incipent radical and destabilize the anion (i.e., to weaken the bond when it undergoes homolysis and to strengthen the bond when it undergoes heterolysis), whereas the EWG does just the opposite. It is worth pointing out that, although the heterolysis energy is largely dependent on the solvent in which the measurement is performed, the homolytic BDE in solution is widely observed to match very closely with the corresponding gas-phase value.[19] This implies that the Y−NO BDE in water may be approximated by the BDE obtained from

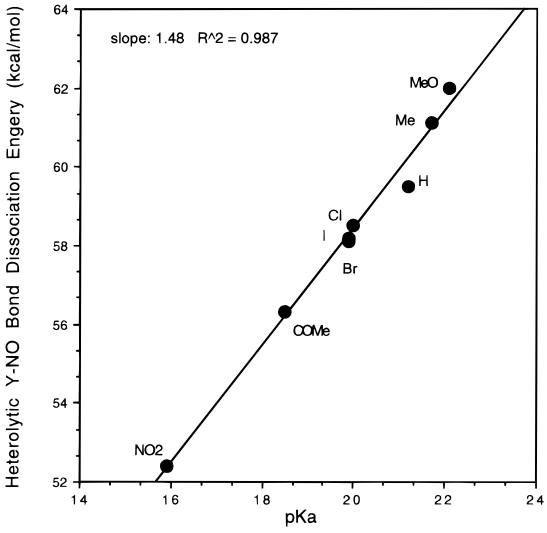

Figure 1. Correlation of hereolytic Y−NO bond dissociation energy of *N*-nitrosoureas with pK_a of Y−H.

other solvent (e.g., acetonitrile as in the present case), validating the application of the BDE scale herein established in the field of biochemistry.

Compounds such as **1**−**3**, in which a double bond is attached to the nitrogen-bearing nitroso group, decompose by two pathways.[20] One path involves nucleophilic attack at the carbon of C═O or C═N− to generate an active diazoate ion. The other path involves nucleophilic attack on the nitrogen of the nitroso group resulting in denitrosation. *N*-Nitrosoureas with relatively high ΔH_{het} of Y−NO bond prefer the first pathway, producing alkylating species which account for their anti-cancer activity.[21] *N*-Nitrososulfonamides, on the other hand, have relatively low ΔH_{het} and prefer the denitrosation pathway to release NO^+ and result in transnitrosation reactions.[22] The NO^+ releasing ability accounts for the potent antimicrobial activity of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS).[23] Other compounds with transnitrosation activities include *N*-nitroso-*N*′-nitroguanindines and *N*-nitroso-*N*′-cyanoguanindines.[24,25]

In summary, an approach to determine the dissociation energy of Y−NO bonds in solution have been established, as exemplified by the Y−NO bond energies of three types of *N*-nitroso compounds. This work is the first step toward establishing a complete data set of Y−NO bond energies for a broader spectrum of organic and inorganic compounds. Such knowledge should be essential in understanding biological functions of nitric oxide.

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