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NO affinity. The driving force of nitric oxide (NO) transfer in biomimetic *N*-nitrosoacetanilide and *N*-nitrososulfoanilide systems

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Abstract Heterolytic and homolytic N-NO bond dissociation energies of six *N*-nitroso-*p*-substituted-benzosulfonanilides and four *N*-nitroso-*p*-substituted-acetanilides were determined respectively by titration calorimetry and by the use of a thermochemical cycle combining heat of heterolysis with the appropriate electrochemical data (Scheme 1). These bond energy data can serve as a good guide in understanding the tendency of NO group transfer in living bodies.

Keywords NO affinity; Thermodynamic driving force; Bond energy; Transnitrosation

Interest in nitric oxide (NO) as an inter- or intra-cellular signaling radical in adjusting many aspects of human life has dramatically increased over the last twenty years.[1] NO has been implicated in very diverse physiological processes, such as vasodilalory and antiplatelet effects, macrophage-induced cytotoxicity , neurotrasomission, and so on.[2] NO has also been found to play a major role in human blood pressure control.[3]

To understand such a broad range of physiological activities of NO as a biological second messenger, the chemical origins of these functions need to be explored. It is conceivable that NO as a free radical certainly could not exist in a large quantity in human body *freely*, so in order to allow it to function as a second messenger effectively, it has to bind to certain carrier molecule first, and then under a suitable environment is released to a nearby receptor molecule to finish up a transnitrosation cycle. Since NO is one of the simplest diatomic molecule, it may behave just like other biologically important diatomic molecules (*e.g.* dioxygen and carbon monoxide) in that when NO is in contact with the active sites in living bodies, it should not be strongly affected by steric or shape-dependent recognition factors that large molecules often encounter. This means that the driving force for NO to transfer from one molecule to another will largely depend on its ability to bind to the molecules involved in the NO transportation. In other words, it is the NO affinity (*i.e.*, binding force), or the bond energy between NO and Y, where Y is the atom in a carrier molecule to which the NO group is attached, that plays a governing role in driving NO to move from one

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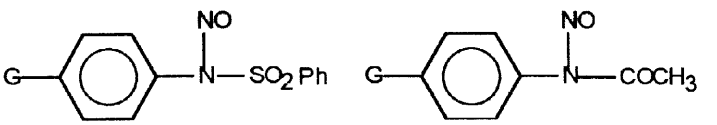
place to another. So, the knowledge about NO binding energy is surely much needed to understand the mechanism of NO transfer inside living bodies. However, till now only the Y-NO bond energies of a few small molecules in the gas phase were determined[4] and virtually no Y-NO bonds of relatively large carrier molecules in solution have been investigated. It is therefore the purpose of the present work to set the first step of this task.

Here we report our recent preliminary work on the measurement of NO affinities in terms of the heterolytic and homolytic Y-NO cleavage energies, determined respectively by direct titration calorimetry and by the use of thermodynamic cycle, a methodology applied before for investigating other types of chemical bonds.[5] Because many *N*-nitroso compounds in which a double bond is attached to the NO-bearing nitrogen showed anti-cancer activity,[6] in this work we selected the simple compounds **1** and **2** to model the structural effect of these types of compounds.



1 2

(G = OCH_3,CH_3, H, Cl, $COCH_3$, NO_2)

NO affinity can be defined as the measure of the strength for a receptor molecule (Y) to bind with the NO group, which is represented by the cleavage energy of the Y-NO bond in three different ways (eqs 1~3):

$$Y\text{-}NO \rightarrow Y^{\cdot} + NO^{\cdot} \quad (1)$$

$$Y\text{-}NO \rightarrow Y^{-} + NO^{+} \quad (2)$$

$$Y\text{-}NO \rightarrow Y^{+} + NO^{-} \quad (3)$$

The first reaction is homolytic, the latter two are both heterolytic. Since the model compounds studied in this work are all bearing a strong electron-withdrawing group at the nitrogen atom to which the NO is attached, so the formation of Y^+ by the second heterolytic way is expected to be extremely unfavorable and thus needs not be concerned here. Therefore, only the energies involved in the first two processes were investigated in the present research.

The heat of heterolysis ΔH_{het} can be easily obtained from measurement of the heat of combination reaction (ΔH_{rxn}) of N^- and NO^+ simply by switching the sign of ΔH_{rxn}.[7] The latter quantity is from a titrimetric calorimetry measurement. The titration experiment was carried out under argon in dry acetonitrile (MeCN) at 25 °C using a Tronac 458 calorimeter according to the method of Arnett.[7] After a certain amount of NO^+ solution (in MeCN, 25 mM) was titrated in through a motor-driven burette to the reaction vessel containing a large excess nitranion prepared from a reaction of the correponding aniline with KH in MeCN, heat was evolved and was computer-processed to give a ΔH_{het}. Each final ΔH_{het} value was an average of 2 or more separate runs which was in turn an averaged value of 4~6 consecutive titrations. The homolytic bond dissociation energy ΔH_{homo} is derived from a thermochemical cycle as illustrated in Scheme 1, taking the reaction of $(ArN^-SO_2Ph)^-$ as an example.

The heterolytic and homolytic N-NO bond energies thus derived as well as the electrochemical data necessary for the evaluation for *N*-nitroso-benzenesulfonanilides and *N*-

nitrosoacetanilides are listed in Tables 1 and 2, respectively.

Scheme 1

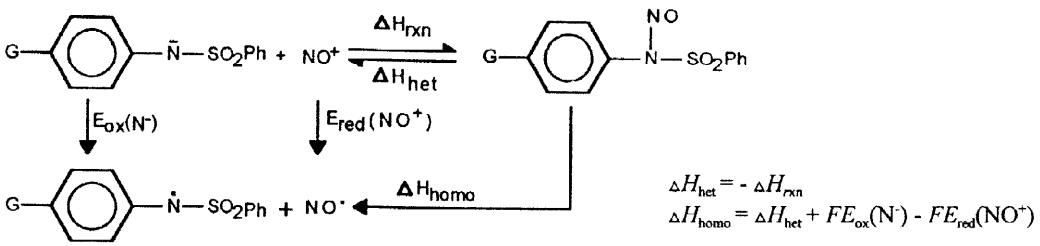


Table 1

The ΔH_{het} and ΔH_{homo} values of the N-NO bonds in *N*-nitroso-benzenesulfonanilides and the E_{ox}s of the corresponding nitranions

Substituent (*G*)	ΔH_{het}(N-NO)[a] kcal/mol		E_{ox}[b] volt	ΔH_{homo}(N-NO)[c] kcal/mol
p-OCH_3	34.9	0.9	-0.112	12.4
p-CH_3	29.9	0.7	0.061	11.4
p-H	29.1	0.1	0.172	13.2
p-Cl	28.4	0.2	0.200	13.1
p-$COCH_3$	25.7	0.2	0.376	14.5
p-NO_2	25.1	0.4	0.554	18.0

a: Measured in acetonitrile at 25 °C by titration calorimetry;
b: Measured in 0.1M *n*-Bu_4NPF_6-CH_3CN vs. Fc^+/Fc under the conditions described in reference 5c;
c: Evaluated from the equation in Scheme 1 using $E_{1/2}(NO^+)$ of 0.863V measured in this work

Table 2

The ΔH_{het} and ΔH_{homo} values of the N-NO bonds in *N*-nitroso-acetanilide and the E_{ox}s of the corresponding nitranions

Substituent (*G*)	ΔH_{het}(N-NO)[a] kcal/mol		E_{ox}[b] volt	ΔH_{homo}(N-NO)[c] kcal/mol
p-CH_3	60.4	0.3	-0.188	36.1
p-H	58.7	1.1	-0.022	38.3
p-Cl	57.7	0.4	-0.011	37.6
p-NO_2	54.3	0.0	0.210	39.2

a: Measured in acetonitrile at 25°C by titration calorimetry;
b: Measured in 0.1M *n*-Bu_4NPF_6-CH_3CN vs. Fc^+/Fc under the conditions described in reference 5c;
c: Evaluated from the equation in Scheme 1 using $E_{1/2}(NO^+)$ of 0.863V measured in this work

The most striking feature of these tables is that the N-NO homolysis energy is substantially lower than the corresponding heterolysis energy. So the homolytic bond cleavage must be much easier to take place than the other pathway. A close look of the energetic data also reveals that the differences between ΔH_{het} and ΔH_{homo} become gradually greater as the *p*-substituent is going from electron-withdrawing (EWG) to electron-donating (EDG). These could be understood by thinking of the two factors most responsible for the smaller ΔH_{homo} and the variable $\Delta H_{het}/\Delta H_{homo}$ difference: i) the NO radical resulted from homolysis of the N-NO bond is much more stable than the NO^+ cation produced from heterolysis; and as judged from $E_{1/2}(NO^+ \rightarrow NO\cdot)$ of 0.863V (this work), this term alone could contribute nearly 20 kcal/mol bond weakening effect to the homolytic process; ii) The EDG is radical-stabilizing (causing a decrease in ΔH_{homo}) and anion-destabilizing (causing an increase in ΔH_{het}), thus leading to a larger gap between ΔH_{het} and ΔH_{homo}; whereas the effect of an EWG on the $\Delta H_{(het/homo)}$ is just opposite. Therefore the trend for an NO carrier bearing an EDG to undergo homolysis is expected to be much greater than its EWG-bearing partner.

It is noteworthy that while the substituent effect on the ΔH_{het}s is what one could expect, the effect of remote substituents on the ΔH_{homo}s may not be so, because of the numerous evidence in literature showing that both EDG and EWG are radical-stabilizing.[4, 8] However, we have recently found in many cases that when the odd electron in radical is mainly situated at a heteroatom such as N and O, the *p*-EWGs were observed all radical-destablizing.[5a-c,9] The observations that the N-

NO bond is strengthened by an EWG against homolytic cleavage for both the two anilide families studied in this work are just in line with the stability pattern of the nitrogen radicals studied earlier based on the N-H bond dissociation energies (BDE).[5a-c,9]

It would be of a value also to compare the NO affinities obtained in the present work with the pK_a (*i.e.* the solution phase proton affinity) and the BDE data of a compound with similar structure where the NO is replaced by H. Previous N-H bond energy study on the ArNHCOMe molecules[5c] showed that the heterolytic N-H bond cleavage required much less energy (pK_as 29.7-24.1 kcal/mol) than the present heterolytic N-NO bond cleavage (60.4-54.3 kcal), whereas the N-H bonds are much stronger against homolysis (97.1-102 kcal) than the Y-NO bonds (36.1-39.2 kcal). This indicates that the NO transfer is just another energetically favorable process besides the often-seen proton transfer. Also, the fact that MNTS (*p*-$MeC_6H_4SO_2N(NO)Me$) is frequently used as a nitroso-donor in transnitrosation[10] is again in accordance with the weak N-NO bonding observed in the present work for the type **1** model which has a like structure.

Comparison of the bond energy data in Tables 1 and 2 shows that the benzenesulfonanilide anions and radicals are respectively much more stable than the corresponding anions and radicals of the acetanilide family, which is in agreement with the trend observed in a similar comparison of the N-H bond pK_a and BDE values.[5c]

It is worthy of pointing out that like the pK_a values, the ΔH_{het} (Y-NO) should also be largely dependent on solvent properties. However, the Y-H BDE in solution is widely observed to agree very closely with the corresponding gas-phase values,[9c] indicating that the ΔH_{homo} (Y-NO) is virtually solvent independent, therefore should be able to mimic the situation in water.

It is obvious that the larger the Y-NO bond energy value, the higher tendency for Y or Y^- to bind to NO or NO^+. Based on the data of this kind studied in the present work, it can be concluded that the homolytic binding of $NO^·$ with $Y^·$ is usually weaker than the heterolytic binding of Y^- with NO^+ and that the carrier model series **1** must be more apt to release NO than other model series.

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