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RESEARCH ARTICLE

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Determination of NO chemical affinities of benzyl nitrite in acetonitrile

Abstract There is an increasing interest in the study of NO chemical affinities of organic nitrites, for the biological and physiological effects of organic nitrites seem to be due to their ability to release NO. In this paper, NO chemical affinities of ten substituted benzyl nitrites were determined by titration calorimetry combined with a thermodynamic cycle in acetonitrile solution. The results show that ΔH_{het}(O–NO)s of benzyl nitrites are substantially larger than the corresponding ΔH_{homo}(O–NO)s, suggesting that these *O*-nitroso compounds much more easily release NO radicals by the O–NO bond homolytic cleavage. It is believed that the structural and energetic information disclosed in this work should be useful in understanding chemical and biological functions of organic nitrites.

Keywords benzyl nitrite, chemical affinity, O–NO bond energy, titration calorimetry

1 Introduction

Organic nitrites are esters between alcohols and nitrous acid. Since they can generate NO in vivo [1], some of them, such as isobutyl nitrite (ISBN), have been clinically used for a long time as vasodilators [2]. In addition, alkyl nitrites have been treated as good NO donors and have been widely used in chemical and biological research in recent years [3]. For example, ISBN inhalation may cause changes in cellular signaling involving tyrosine phosphorylation [3a]. Further, Nicolescu observed that lipid nitrites formed as NO chain termination products have the capacity to further inhibit lipid peroxidation and to release NO [3b].

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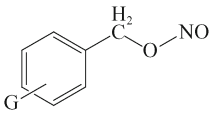
NO chemical affinity, which has been defined as Y–NO bond dissociation energy, could be used to scale NO releasing ability. Early work in our group involved a research on a series of Y–NO (Y=N, O and S) bond dissociation energies [4–8]. Because of the biological and physiological effects of organic nitrites, we have an increasing interest in the study of O–NO bond dissociation energies. Herein, O–NO bond energies of ten substituted benzyl nitrites (Fig. 1) are reported. We also believe that this study will be helpful in understanding the chemical and biological functions of organic nitrites, which include the processes of NO-storage, transport and delivery.



G=4–OCH_3, 4–CH_3, 3–CH_3, H, 4–Cl, 3–Cl, 4–Br, 4–CF_3, 4–NO_2, 3–NO_2

Fig. 1 Substituted benzyl nitrites

2 Experimental Procedures

Substituted benzyl alcohols were purchased from Aldrich. Other 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, Aldrich) was recrystallized from CH_2Cl_2 and was vacuum-dried at 110°C overnight before preparation of a supporting electrolyte solution. Redox potentials were obtained by cyclic voltametry (CV) method on a BAS-100B electrochemical analyzer. The heats of reaction of NO^+ with oxoanions were determined on a 458 titration calorimeter.

2.1 Measurement of redox potentials

All electrochemical experiments were carried out by CV (sweep rate, 100 mV/s) using a BAS-100B electrochemical

apparatus in dry acetonitrile solution under an argon atmosphere at 25°C. *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 of 1.5 mM. The ferrocenium/ferrocene redox couple ($Fc^{+/0}$) was taken as the internal standard. The reproducibility of the potential was smaller than 5 mV.

2.2 General procedure for preparation of anions

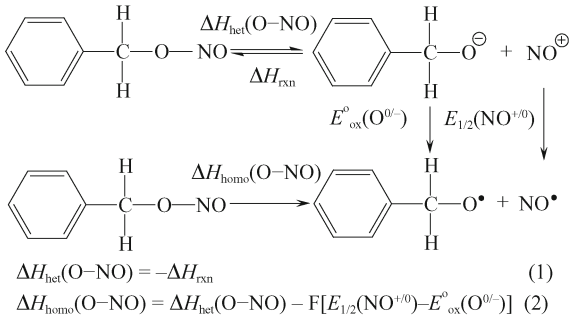
The benzyl alcohol (0.2 mmol) was dissolved in 40 mL of dry acetonitrile, and then a slightly excess amount of KH was added. The mixture was stirred at room temperature for about 20 min and then filtered directly into the reaction vessel. All the operations were carried out in an argon-filled VAC drybox.

2.3 Titration calorimetry

Reaction of NO^+ ($NO^+ClO_4^-$) with oxoanions (K^+ as counterion) in dry CH_3CN was rapid in quantitatively giving the O–NO coupling product. The reaction heat (ΔH_{rxn}) was measured at 25°C by a standard procedure similar to that of Arnett [9]. 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 an 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 oxoanion 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 any 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.

3 Discussion

According to the reaction in Scheme 1, obviously, the heterolytic O–NO bond dissociation energy (ΔH_{het}(O–NO)) of benzyl nitrite is just equal to the reaction enthalpy change of the oxoanion with NO^+ simply by switching the sign of ΔH_{rxn} (equation (1)). The homolytic O–NO bond dissociation energy (ΔH_{homo}(O–NO)) was derived from equation (2), which came from a thermodynamic cycle (Scheme 1) [9]. The ΔH_{rxn}s, ΔH_{het}(O–NO)s and ΔH_{homo}(O–NO)s determined here, together with the necessary electrochemical data, are presented in Table 1, and dates of the Hammett σ constants [10] are also included for the purpose of discussion.



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

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

Scheme 1 Thermodynamic cycling process

Table 1 shows that the ΔH_{het}(O–NO)s of these *O*-nitroso compounds (248.7 ~ 277.6 kJ/mol) are substantially larger than the corresponding ΔH_{homo}(O–NO)s (140.9 ~ 151.7 kJ/mol), suggesting that the studied benzyl nitrites are good NO donors rather than NO^+ donors, just like *N*-nitroso compounds [4,6,8] and *S*-nitroso compounds [7]. It is suggested that NO-releasing is much easier than NO^+-releasing in these organic nitrites in dry acetonitrile solution by thermolytic dissociation. This feature can be seen as a powerful evidence for the fact that NO (rather than NO^+) plays a key role in many chemical and biological systems. From the dates in Table 1, we also observe that ΔH_{het}(O–NO)s are found to correlate line-

Table 1 ΔH_{het}s, ΔH_{homo}s of benzyl nitrites, related electrochemical quantities at 25°C, and dates of Hammett σ constants

G-PhCH$_2$ONO	ΔH_{rxn}[a] /(kJ/mol)	ΔH_{het}(O–NO)[b]/(kJ/mol)	$E_{ox}(O^-)$[c] (V vs Fc^+/Fc)	ΔH_{homo}(O–NO)[d] /(kJ/mol)	σ[e]
G = 4-MeO	−277.6	277.6	−0.554	140.9	−0.27
4-Me	−274.6	274.6	−0.526	140.9	−0.17
3-Me	−272.1	272.1	−0.466	144.2	−0.07
4-H	−269.6	269.6	−0.416	146.3	0
4-Cl	−261.2	261.2	−0.271	151.7	0.23
3-Cl	−254.6	254.6	−0.225	149.6	0.37
4-Br	−262.9	262.9	−0.295	151.3	0.23
4-CF_3	−251.2	251.2	−0.181	150.5	0.54
4-NO_2	−248.7	248.7	−0.147	151.3	0.78
3-NO_2	−249.5	249.5	−0.162	150.9	0.71

[a]Measured in CH_3CN at 25°C by titration calorimetry; [b] Derived from the equation (1); [c] Measured by cyclic voltametry (CV) in CH_3CN at 25°C. Reproducibility = 0.005 V; [d] Derived from the equation (2), taking $E_{1/2}(NO^+)$ = 0.863 V. Estimated uncertainties are 2 kal/mol; [e] Date from Ref. [10]

arly with Hammett σ constants of the parent compounds (Fig. 2), implying that substituent effects should appear in these systems.

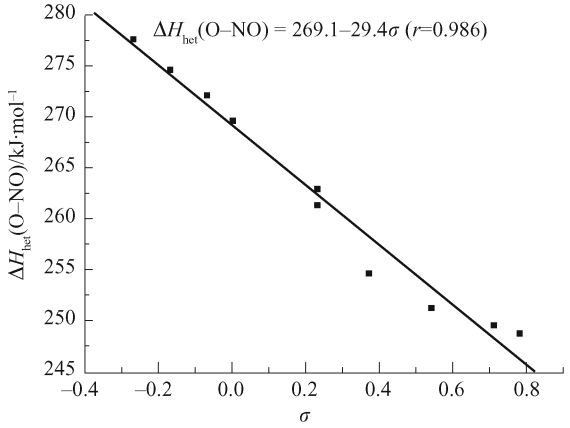


Fig. 2 Correlation of ΔH_{het}(O–NO)s of benzyl nitrites with Hammett σ constants

A close look at the energetic data also reveals that the differences between ΔH_{het} and ΔH_{homo} ($\delta\Delta H$) increases gradually as the remote substituent goes from electron-pulling to electron-pushing, which results in a quite good linear correspondence between the $\delta\Delta H$ values and Hammett σ constants (Fig. 3). This feature could be understood by thinking that the EDG (electron donating group) 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 (electron withdrawing group) on the ΔH_{het} and ΔH_{homo} is just opposite).

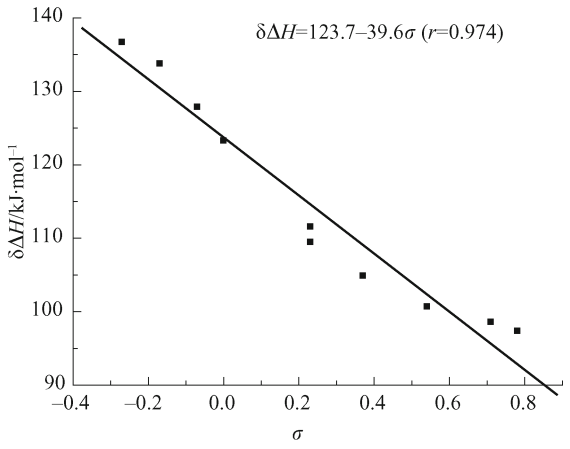


Fig. 3 Correlation of $\delta\Delta H$s of benzyl nitrites with Hammett σ constants

Further inspection of the ΔH_{het}(O–NO)s in Table 1 shows that these bond energies are much larger than our previously studied ΔH_{het}(O–NO)s of *O*-nitrosoyl carboxylate compounds [5] (107.4 ~ 146.7 kJ/mol). This phenomenon is mainly attributed to the stability effect of the adjoining carbonyl group on the oxoanion relative to the adjoining methylene of benzyl nitrite. The difference in the stability between these two types of oxoanions can also be verified by their corresponding oxidation potentials.

In summary, heterolytic and homolytic bond dissociation energies of the O–NO bonds in ten substituted benzyl nitrites were obtained in acetonitrile with direct calorimetry measurements combined with electrochemical methods. We believe that the structural and energetic information disclosed in this work should be useful in understanding chemical and biological functions of organic nitrites.

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