Nitrosation, Thiols, and Hemoglobin: Energetics and Kinetics
Willem H. Koppenol*  
Institute of Inorganic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zurich, 8093 Zurich, Switzerland

ABSTRACT: Nitrosothiols are powerful vasodilators. Although the mechanism of their formation near neutral pH is an area of intense research, neither the energetics nor the kinetics of this reaction or of subsequent reactions have been addressed. The following considerations may help to guide experiments. (1) The standard Gibbs energy for the homolysis reaction RSNO → RS* + NO*(aq) is +110 ± 5 kJ mol⁻¹. (2) The electrode potential of the RSNO, H⁺/RSH, NO*(aq) couple is −0.20 ± 0.06 V at pH 7. (3) Thiol nitrosation by NO²⁻ is favorable by 37 ± 5 kJ mol⁻¹ at pH 7. (4) N₂O₃ is not involved in in vivo nitrosation mechanisms for thermodynamic — its formation from NO₃⁻ costs 59 kJ mol⁻¹ — or kinetic — the reaction being second-order in NO₂⁻ — reasons. (5) Hemoglobin (Hb) cannot catalyze formation of N₂O₃, be it via the intermediacy of the reaction of Hb[FeNO²⁺] with NO or reaction of Hb[FeNO] with NO₂⁻ (+88 kJ mol⁻¹). (6) Energetically and kinetically viable are nitrosations that involve HNO₂ or NO⁺ in the presence of an electron acceptor with an electrode potential higher than −0.20 V. These considerations are derived from existing thermochemical and kinetics data.

INTRODUCTION
How nitrogen monoxide can escape from blood to contribute to relaxation of blood vessels is an unsolved mystery. NO⁺ in blood is rapidly consumed by binding to deoxyhemoglobin¹,² and reaction with oxyhemoglobin.³⁻⁵ Nitrosation of a thiol or formation of dinitrosoiron complexes may be a way to preserve NO⁺, although reduction by one electron is necessary to set NO⁺ free from a nitrosothiol. The energetics of these reactions have not been addressed. I show here that standard Gibbs energies and electrode potentials and the rate constants derived from these are easily calculated. The results allow one to eliminate reaction mechanisms and thereby to focus on possible pathways.

NITROSATION BY NO₂⁻
Standard Gibbs Bond Dissociation Energy of RS–NO. The energetics of nitrosation of thiols require knowledge of the Gibbs energy of reaction 1, in which RSNO represents a nitrosated cysteine as in S-nitrosoglutathione.

RSNO(aq) → RS⁺(aq) + NO⁺(aq)  
(1)

For CH₃CH₂SNO, Bartberger et al. calculated a bond dissociation energy of 134 kJ mol⁻¹ and a Gibbs dissociation energy of 89.5 kJ mol⁻¹ in the gas phase.⁶ With the same ab initio technique, Baciu and Gauld reproduced this value and calculated a slightly higher bond dissociation energy of 139 kJ mol⁻¹ for nitrosocysteine.⁷ Assuming that the −TΔS terms for both nitroso compounds are the same, −44.5 kJ mol⁻¹, one arrives at a gas-phase Gibbs bond dissociation energy of nitrosocysteine of 94.5 kJ mol⁻¹. To derive a Gibbs bond dissociation energy that is valid in water, we must dissolve nitrosocysteine, cysteine, and NO⁺. To a first approximation, the hydration energies of cysteine and nitrosocysteine are assumed to be the same. Additionally, NO⁺ needs to be dissolved, which costs 15 kJ mol⁻¹ (Table 1). Thus, in water, ΔΒ⁰G°₁ = +110 kJ mol⁻¹ with an estimated error of 5 kJ mol⁻¹, which reflects the uncertainty in the ab initio calculations and the fact the hydration energies do not fully cancel because R⁺ is more polar than R−SH.⁸,⁹

How easily is RSNO reduced by one electron to liberate NO⁺? The electrode potential of the RSNO, H⁺/RSH, NO⁺(aq) couple, reaction 2, follows from addition of reactions 1 and 3 (Table 1) and is −0.20 ± 0.06 V at pH 7 vs the normal hydrogen electrode.

RSNO + H⁺ + e⁻ → RSH + NO⁺  
(2)

Monohydrogenascorbate, with E°(asc⁺⁻, H⁺/Hasc⁻) = +0.28 V,¹⁰ should thus not reduce RSNO, as observed. On the basis of this observation and that dithionite did reduce RSNO, Bohle and co-workers concluded that the electrode potential was less than 0 V,¹¹ in agreement with the present estimate. A value of −0.20 V implies that, in the presence of redox couples with electrode potentials larger than that value, generation of NO⁺(aq) is uphill. On the other hand, redox couples with such potentials would help formation of RSNO from RSH and NO⁺. Indeed, iron is known to help in formation of nitrosothiols.¹²

Energetics of Nitrosation. The energetics of nitrosation by HNO₂ are now calculated by addition of reactions −1, −3, and 4 (Table 1), in which RSH stands for glutathione and represents thiols in general. Here and below frequent use is made of the equalities ΔΒ¹G° = −RT lnK = −nFΔE° in which R is the gas constant, n the number of electrons in the reaction equation, and F the Faraday constant. Nitrosation of RSH by
Nitrosation by the simplest of nitrosothiols, HSNO, is ca. 12 kJ stronger than that of HS−NO−, and between the electrode potentials, $E^{\text{ox}}_{\text{HSNO}} = +0.94 \text{ V}^{15}$ and $E^{\text{ox}}_{\text{HS−NO−}} = +0.92 \text{ V}^{15}$ at pH 7. Given a $pK_a$ of H$_2$S of 7.1, this value also applies to $E^{\text{ox}}_{\text{HS−NO−}}$ at pH 7. Consequently, transnitrosation of RSH by HSNO is downhill by the same amount.

**NITROSATION BY N$_2$O$_3$**

One or Two NO$_2$\(^{-}\)? Given that nitrosation is possible with one or two NO$_2$\(^{-}\), we now ask which reaction is more likely. An interesting observation, published in 2003,$^{17}$ is that a concentration of 2.5 $\mu$M in blood causes some vasodilation with a much larger effect observed at about 200 $\mu$M. How can one produce NO$_2$\(^{-}\) or RSNO, from NO$_2$\(^{-}\) and deliver the former to the endothelial cell from where it can diffuse into the muscle layer surrounding the blood vessel? Basu et al.$^{18}$ followed up on a proposal by Robinson and Lancaster$^{19}$ that deoxyhemoglobin catalyze formation of N$_2$O$_3$ from NO$_2$\(^{-}\) according to reactions 10–12. The advantage of N$_2$O$_3$ is that it does not interact with Fe$^{2+}$ in hemoglobin.

\[
\text{HbFe}^{2+} + \text{NO}_2^{-} + 2\text{H}^{+} \rightarrow \text{HbFe}^{3+} + \text{NO}^\prime(\text{aq}) + \text{H}_2\text{O} \\
\text{HbFe}^{3+} + \text{NO}_2^{-} \rightarrow \text{Hb[FeNO}_2]\text{]^{2+}} 
\]
Hb[FeNO₃]²⁺ + NO⁻(aq) → Hb[FeNO]²⁺ + N₂O₃(aq)  \quad (12)

Addition of Reactions 10–12 results in reaction 6; thus, hemoglobin is thought to act as a catalyst. As shown in Table 1, \( \Delta_{\text{rxn}} G°^\circ = +59 \text{kJ mol}^{-1} \) at pH 7, which, given a plasma concentration of 2.5 \( \mu \text{M} \) N₂O₃, results in an equilibrium concentration of 2.8 \( \times 10^{-22} \text{ M} \) N₂O₃. Given that the rate of hydrolysis, \( k_{\text{hydrolysis}} \), is known (Table 1), \( k_6 \) is 2.4 \( \times 10^{-8} \text{ M}^{-1} \text{s}^{-1} \). Half-lives of Reactions 6 and 6 can now be calculated. The \( t_{1/2} \) of hydrolysis of N₂O₃ (reaction –6) is \( (\ln 2)/k_6 \) or 0.693/530 \( \text{s} \) = 1.3 ms. The \( t_{1/2} \) of reaction 6 is given by \( 1/(k_6[N_2O_3]^-) \) or 1.7 \( \times 10^{13} \text{ s} \) or slightly more than 500,000 years. At a concentration of 200 \( \mu \text{M} \) N₂O₃, these numbers are different but still do not support formation of N₂O₃.

Another reaction that ought to be taken into account is reaction 7, dissociation of N₂O₃. If N₂O₃ were formed, it at that dilute concentration, completely dissociate into NO⁺ and NO₃⁻ before it hydrolyzes: the \( t_{1/2} \) of reaction 7 (Table 1) is 0.693/8.0 \( \times 10^{-3} \text{ s} = 8.7 \mu \text{s} \). Thus, formation of N₂O₃ is thermodynamically and kinetically unlikely.

**Catalysis by Hemoglobin.** Can hemoglobin act as a catalyst as proposed? Formation of N₂O₃ must be fast or NO⁺ disappears by binding to hemoglobin or reaction with oxyhemoglobin. Thus, given a \( t_{1/2} \) of 1.7 \( \times 10^{13} \text{ s} \), N₂O₃ needs to be produced on the second time scale, ca. 10³ times faster. If that were feasible, it would not help because the rate of hydrolysis would increase by the same factor. Are these results very sensitive to the precise values of the Gibbs energies? The answer is no: to be physiologically relevant, nanomolar concentrations of N₂O₃ need to be produced. To achieve a 1 \( \mu \text{M} \) concentration of N₂O₃ at equilibrium, the Gibbs energy of reaction 6 has to change by 69 kJ/mol to become –10 kJ/mol, which still does not make formation of N₂O₃ thermodynamically reasonable. However, electron transfer from NO₃⁻ to Hb-[FeNO]⁺ is favorable by 29 kJ/mol, which is off by 117 kJ/mol. In spite of the large difference in Gibbs energies for reactions 12 and 14, Hopmann et al. conclude that both reactions are energetically reasonable. However, electron transfer from NO₃⁻ to Hb-[FeNO]⁺ is not exothermic: from the equilibrium between NO⁺ and HbFe²⁺ and NO₃⁻ and HbFe³⁺ one calculates (Table 1) that E°(Hb[FeNO]⁺/Hb[FeNO]²⁺) is +0.47 V for T-state hemoglobin and +0.54 V for R-state hemoglobin. Combined with the electrode potential of the NO₃⁻/NO₂⁻ couple, 1.04 V (Table 1), electron transfer is unfavorable by at least 48 kJ/mol.

It is truly regrettable that these ab initio calculations provide neither consistent nor proper estimates of Gibbs energies because it implies that any proposed intermediates and transition states are similarly compromised. Gibbs energies can be correctly and rapidly calculated per manum. Are reactions 12 and 14 possible if we let N₂O₃ hydrolyze? We deduct the Gibbs energy of reaction 6 and obtain +22 and +29 kJ/mol, respectively. These numbers are small enough to let the reactions proceed if products are removed. The Gibbs energy of +29 kJ/mol also applies to reaction 16:

\[
\text{Hb[FeNO]³⁺} + \text{H₂O} \rightarrow \text{HbFe²⁺} + \text{NO}_2⁻ + 2\text{H}^+ \quad (16)
\]

Reaction 11 results in Hb[FeNO₂]²⁺, in which NO₂⁻ is thought to be partially oxidized by Fe³⁺. Given a binding energy of only 16 kJ/mol (reaction 10) and the difference in electrode potential between the couples HbFe³⁺/HbFe²⁺ and NO₃⁻(aq)/NO₂⁻ of 0.9 V (Table 1), such a partial electron transfer is unlikely, as was recognized by Berto and Lehnert.

The conclusion is that N₂O₃ cannot play a role in the preservation of NO⁺. Furthermore, given the low physiological concentration of NO₂⁻, any mechanism that relies on two NO₂⁻ to occur on a second time scale is kinetically doomed.

**Nitrosation by HNO₂, by NO⁺ and an Electron Acceptor, and by ONOO⁻.** Returning to the original observation, which is that injection of 0.40 mM N₂O₃ into the brachial artery of the upper arm resulted in a final concentration of ca. 2.5 \( \mu \text{M} \) as measured in the ipsilateral antecubital vein, led to noticeable vasodilation and having shown that the N₂O₃ pathway is most unlikely, one can ask whether HNO₂ present under these conditions at a concentration of ca. 0.25 mM, is the agent responsible. Like N₂O₃, HNO₂ is neutral and could penetrate endothelial cells. Nitrosation is thermodynamically possible, but is it fast enough? The rate of nitrosation is given by:

\[
\text{rate} = k[H^⁺][\text{HNO}_2][\text{RSH}] \quad (17)
\]

in which \( k = 4.6 \times 10^6 \text{ M}^{-2} \text{s}^{-1} \). It is of course not correct to use eq 17 if the thiol of interest, for instance, hemoglobin β-chain cysteine 93, is not homogeneously distributed. The following considerations, therefore, result in only a rough estimate. Given a concentration inside the red blood cell of 5 mM hemoglobin, and thus of 10 mM β-chain cysteine 93, and of a HNO₂ concentration of 0.25 \( \times 10^{-9} \text{ M} \), then the rate of nitrosothiol formation is \( 1 \times 10^{-13} \text{ M} \text{s}^{-1} \), which would appear to be too slow. However, the concentration of NO₂⁻ at the site of injection was much higher. It may thus be possible that the small extent of vasodilation was caused by HNO₂.
If nitrosation does not involve NO\textsuperscript{−} but NO\textsuperscript{*} then an electron acceptor with an electrode potential larger than −0.20 V (reaction 2) is required. Iron(III) cytochrome c is such an electron acceptor for the nitrosation of glutathione,\textsuperscript{26} and the overall reaction is favorable: Mechanistically, reaction 19
\[
\text{CytFe}^{3+} + e^- \rightarrow \text{CytFe}^{2+} \quad (18)
\]
\[
\text{RSH} + \text{NO}^* \rightarrow \text{RSNO} + \text{H}^+ + e^- \quad (2-2)
\]
\[
\text{CytFe}^{3+} + \text{NO}^* + \text{RSH} \rightarrow \text{CytFe}^{2+} + \text{RSNO} + \text{H}^+ - 44 \text{kJ mol}^{-1} \quad (19)
\]
requires three reactants to be present at the same time in close proximity, which makes it kinetically unlikely. However, this problem is obviated by binding of glutathione to cytochrome c prior to reaction with NO\textsuperscript{*}. A similar mechanism can be written for methemoglobin with an overall Gibbs energy change of −26 kJ mol\textsuperscript{−1}. Dioxgen may also act as an electron acceptor;\textsuperscript{27} given an \( E^0(\text{O}_2/\text{O}_2^+) \) of −0.35 V,\textsuperscript{28} the reaction is uphill but pulled through by the diffusion-controlled reaction of the product, \( \text{O}_2^+ \), with another NO\textsuperscript{*}.\textsuperscript{29} As experimentally observed, this nitrosation reaction is second order in NO\textsuperscript{*}.\textsuperscript{30}

Alternatively, NO\textsuperscript{*} may first bind to iron(III) followed by the nitrosation reaction. In the case of methemoglobin this process is less favorable but still possible: Experimental evidence for this pathway exists.\textsuperscript{30} However, in vivo, this reaction pathway seems unlikely as the concentration of methemoglobin is small and because NO\textsuperscript{*} is more likely to react with oxy- and deoxy-hemoglobin.

A modification that involves NO\textsuperscript{3−} and hemoglobin as a catalyst allows the following kinetically and thermodynamically feasible reactions: The only assumption made is that reaction of Hb[FeNO]\textsuperscript{3+} with RSH takes place before NO\textsuperscript{*} reatcs with oxyhemoglobin. Indeed, if dissociation of NO\textsuperscript{*} from Hb[FeNO]\textsuperscript{3+} takes place then we have reaction 10, which is slow, 1 M\textsuperscript{−1} s\textsuperscript{−1} at pH 7.5.\textsuperscript{31}

\[
\text{Hb[FeNO]}^{3+} \rightarrow \text{HbFe}^{3+} + \text{NO}^* \quad (-13)
\]
\[
\text{HbFe}^{3+} + e^- \rightarrow \text{HbFe}^{2+} \quad (-15)
\]
\[
\text{RSH} \rightarrow \text{RS}^- + \text{H}^+ + e^- \quad (-3)
\]
\[
\text{RS}^- + \text{NO}^* \rightarrow \text{RSNO} \quad (-1)
\]
\[
\text{Hb[FeNO]}^{3+} + \text{RSH} \rightarrow \text{HbFe}^{2+} + \text{RSNO} + \text{H}^+ - 8 \text{kJ mol}^{-1} \quad (20)
\]

The equations and energetics provided here can be used as LEGO blocks to build a reaction mechanism. Once an energetically favorable mechanism has been established, one must ask the question whether the kinetics are fast enough. It is important to keep in mind that the reactions used to calculate a Gibbs energy, such as reactions −1, 3, −13, and −15 above, do not necessarily take place: they serve to produce the Gibbs energy of reaction 20. In particular, given that the RS\textsuperscript{*} radical is in equilibrium with RSH, where R\textsuperscript{*} stands for a carbon-centered radical elsewhere in the molecule,\textsuperscript{36,37} one would do well to avoid RS\textsuperscript{*} in mechanisms of nitrosation.

The approach used here is not new,\textsuperscript{38−40} requires only pencil and paper, and may help in defining the reaction one has an interest in prior to embarking on possibly elaborate, expensive, and technically difficult laboratory experiments or in silico calculations.

**AUTHOR INFORMATION**

**Corresponding Author**

*E-mail: koppenol@inorg.chem.ethz.ch.

**Notes**

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