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Enol Nitrosation Revisited: Determining Reactivity of Ambident Nucleophiles

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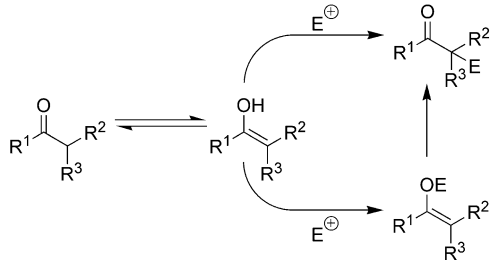
Enols are one of the most important types of ambident nucleophiles being widely used as reagents in organic chemistry. The relevance of enols has led to considerable interest in developing methods to determine the reactivity of their nucleophilic centers. In this sense, the mainstream literature works on this topic make use of a combination of overall rate constants together with the analysis of the reaction products. By knowing the product ratio it is possible to determine the ratio between the reaction rates on each site. Thus, the reactivity for each nucleophilic position can be obtained. This is a reliable approach as long as the isolation or in situ characterization of the reaction products can be carried out. In the case of unstable and/or interconvertible products where the use of identification techniques is not possible, an alternative methodology must be found. For that reason, our research group has developed a model that allows us to study and quantify separately the reaction rates of enol nucleophilic centers even if only one final reaction product is obtained. This model is based on the fact that nitrosation of enols shows well-differentiated behavior depending on whether the reaction proceeds through the carbon or the oxygen atom. The present study provides insights into the ambident nature of enols as well as a methodology for determining the chemical reactivity of their nucleophilic centers.

Introduction

Enols and enolate ions form the most important type of ambident nucleophiles. The term "ambident" is applied to describe all chemical species whose molecular entities possess two alternative and strongly interacting distinguishable reactive centers, to either of which a bond may be made in a reaction. In this sense, it is traditionally accepted that in order to determine the reactivity of each site, these reactive centers must be connected in such a way that the reaction at either site stops or greatly retards subsequent attack at the second site. That would allow either the isolation or in situ characterization of the final products and, therefore, the discrimination between the reactivity of each position. In other words, by knowing the product ratio it is possible to determine the ratio between the reaction rates on each site. However, in enol chemistry there are cases in which this discrimination cannot be carried out by means of identification techniques. This is due to the fact that the subsequent attack at the second site occurs on a time scale faster than that of the detection of the species involved in the reaction (Scheme 1).



Scheme 1.

In such cases, because a single final product is obtained, only the overall reaction rate can be calculated, but not the ratio between the rates on each site. For that reason, our research group has developed a kinetic model that allows us to study and quantify separately the reaction rates of enol nucleophilic centers even if only one final product is obtained. This model is based on the fact that nitrosation of enols shows a well-differentiated behavior depending on whether the reaction proceeds through the carbon or the oxygen atom.

With this aim we have investigated the nitrosation reaction of barbituric acid (HB) in water. However, as preliminary work we re-examined nitrosation of acetylacetone (AcAc).[1] The reason for this choice is that AcAc is a less-complex reactive system and the conclusions drawn from its kinetic analysis will help in elucidating the mechanism

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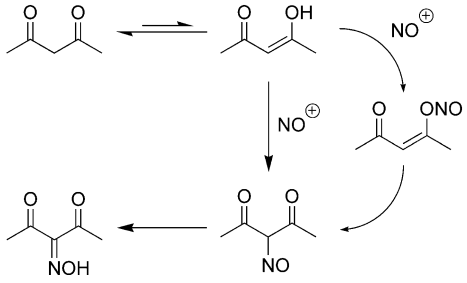
of HB nitrosation and, therefore, in building up a kinetic model to describe quantitatively the ambident nature of enols. AcAc nitrosation shows a simultaneous nucleophilic and general-base catalysis. The observed nucleophilic catalysis points out to a *C*-nitrosation mechanism, where the rate-limiting step consists of electrophilic attack at the olefinic carbon atom of the AcAc enol form. In fact, catalysis by nucleophiles is a distinctive feature of alkene nitrosation. In contrast, the general-base catalysis observed in the presence of buffers points to an *O*-nitrosation mechanism involving a rate-limiting proton transfer. Such experimental behavior is compatible with the one observed in the literature for other alcohol nitrosation reactions. This simultaneous catalysis constitutes the confirmation of two independent reactions on the carbon and oxygen atom of an enol (Scheme 2).



Scheme 2.

In contrast, the much higher acidity of HB compared to AcAc (pK_a^{AcAc} = 8.79[2] and pK_a^{HB} = 4.04[3]) will give rise to a more complex reaction scheme, as the nitrosation of the carbanion enolate ion will constitute an additional reaction pathway. This additional operating mechanism will remarkably affect the kinetic behavior of the overall process, which is proposed to involve both enol and carbanion enolate forms of HB.

Results

Under all experimental conditions used in this study, the reaction rate for HB nitrosation showed a first-order dependence on [HNO_2]. This behavior completely rules out a rate-limiting enolization, as a zero-order dependence on [HNO_2] should be found in such a case. In addition, the pseudo-first-order rate constant for HB nitrosation showed in all cases a linear dependence on [HB] (Figure 1). As shown in this plot, the slopes of the linear fits increase as [H^+] rises ([$HClO_4$] = 0.10–1.00 M).

Figure 2 shows the influence of acid concentration ($HClO_4$) on k_{obs} for HB nitrosation. The obtained results display two well-differentiated dependences on [H^+]. Thus, at [H^+] < 0.10 M a nonlinear dependence of k_{obs} on acid concentration is found, whereas the rate constant exhibits a linear dependence at [H^+] > 0.10 M. This dual behavior points out to the involvement of different and simultaneous operating mechanisms in the nitrosation reaction. Thus, at low acidity a reaction through the carbanion enolate ion would constitute the predominating reaction, whereas at high acidity a mechanism through the neutral form of the enol would prevail.

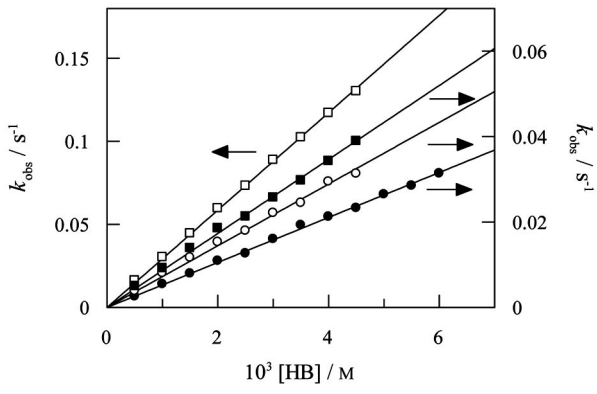


Figure 1. Influence of HB concentration on k_{obs} for HB nitrosation in acidic media. Ionic strength 1.00 M ($NaClO_4$); T = 25.0 °C. (●) [H^+] = 0.10 M; (○) [H^+] = 0.20 M; (■) [H^+] = 0.30 M; (□) [H^+] = 1.00 M.

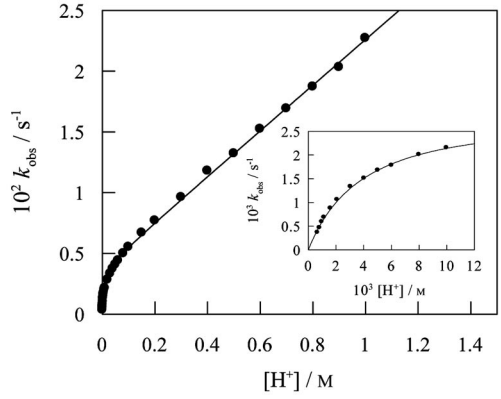


Figure 2. Influence of H^+ concentration ($HClO_4$) on k_{obs} for HB nitrosation. Ionic strength 1.00 M ($NaClO_4$); [HB] = 1.0×10^{-3} M; T = 25.0 °C.

In the presence of nucleophiles such as Cl^-, Br^-, or SCN^-, HB nitrosation undergoes a remarkable catalytic effect (Figure 3). This well-reported behavior[4–7] is a consequence of the formation of the corresponding nitrosating agents (NOCl, NOBr, and NOSCN), whose catalytic efficacy lie in the value of their equilibrium constant of formation (K_{NOCl} = 1.14×10^{-3} M^{-1};[8] K_{NOBr} = 5.10×10^{-2} M^{-1},[9] and K_{NOSCN} = 32 M^{-1}[10]).

The observed nucleophilic catalysis can be attributed to a reaction pathway where nitrosation takes place through the carbanion enolate form. Given the absence of a transferable proton in the conjugate base, the only possible rate-limiting step will be the attack of NO^+ either at the carbon or the oxygen atom of the deprotonated form of HB. Likewise, this experimental behavior can be also ascribed to a simultaneous reaction pathway where HB nitrosation proceeds through the carbon atom of the neutral enol form (Scheme 3). This claim is supported by studies on alkene nitrosation[11] where this catalysis is a distinctive feature.

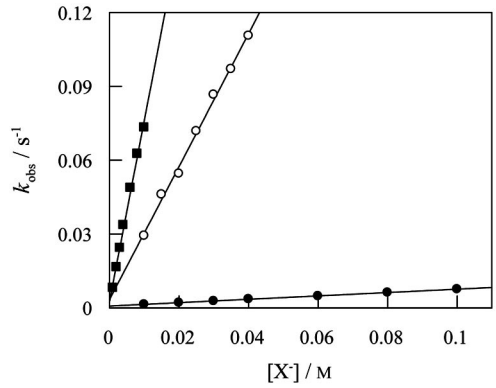
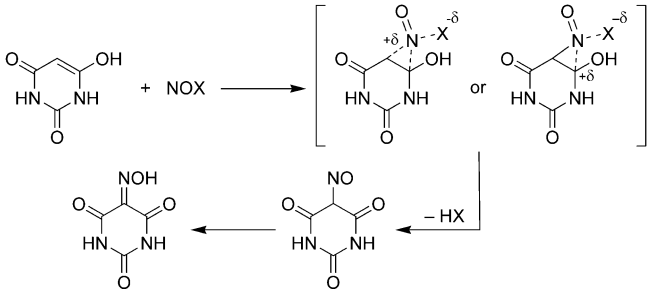


Figure 3. Influence of nucleophile concentration on k_{obs} for HB nitrosation. Ionic strength 1.00 M ($NaClO_4$); [HB] = 1.0×10^{-3} M; [H^+] = 1.0×10^{-3} M; T = 25.0 °C. (●) Cl^-; (○) Br^-; (■) SCN^-.



Scheme 3.

In Scheme 3 a two-stage process through a nitroso carbocation intermediate is proposed. This intermediate is explained by a cyclic onium structure[6,12] involving either a fully bonded three-membered ring or an electrostatic interaction between the nitrogen atom and the developing positive charge on carbon.

Accordingly, the presence of Cl^-, Br^-, and SCN^- in the reaction medium catalyzes the nitrosation of both HB carbanion enolate and enol forms. In this sense, our experiments on the influence of proton concentration on the reaction rate in the presence of nucleophiles provide evidence for the coexistence of these reaction pathways. Thus, as shown in Figure 4a, there is an enhancement in the catalytic effect of Br^- as acidity is increased. Because the amount of carbanion enolate form is decreasing, this effect must be due to the catalysis of the enol nitrosation pathway (see also Figures S1 and S2 in the Supporting Information).

In other words, if the carbanion enolate pathway was the only nucleophile-catalyzed route of HB nitrosation for a reaction series where there is a set amount of added Br^- and a variable amount of H^+, a leveling off in the k_{obs} vs. [H^+] plot should be obtained. As seen in Figure 4b, not even at high proton concentrations can a plateau be reached. On the contrary, the rate constant keeps increasing with acid concentration (as it happens in Figure 2). This observation points to a simultaneous nucleophile-catalyzed enol pathway.

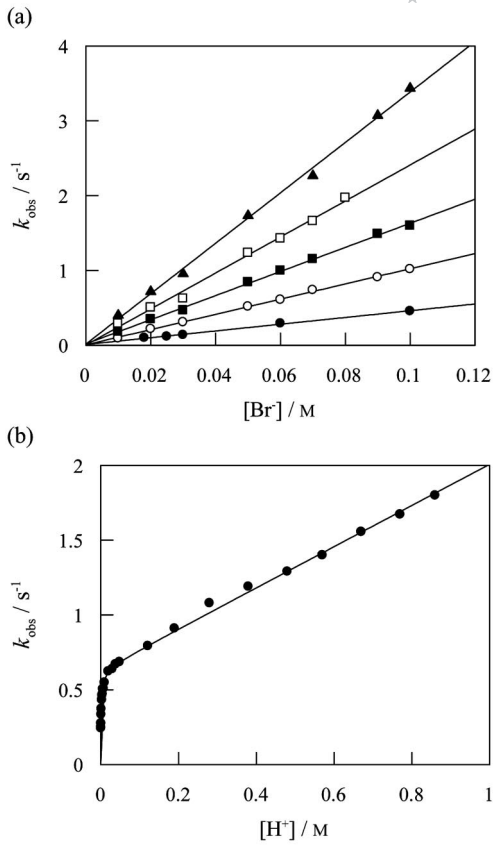


Figure 4. (a) Influence of Br^- concentration on k_{obs} for HB nitrosation. Ionic strength 1.00 M ($NaClO_4$); [HB] = 1.0×10^{-3} M; T = 25.0 °C. (●) [H^+] = 1.0×10^{-3} M; (○) [H^+] = 5.0×10^{-3} M; (■) [H^+] = 5.0×10^{-2} M; (□) [H^+] = 4.0×10^{-1} M; (▲) [H^+] = 8.0×10^{-1} M (some data omitted for clarity). (b) Influence of H^+ concentration on k_{obs} for HB nitrosation. Ionic strength 1.00 M ($NaClO_4$); [HB] = 1.0×10^{-3} M; [Br^-] = 5.0×10^{-2} M; T = 25.0 °C.

Figure 5 shows that HB nitrosation is also a buffer-catalyzed reaction (see also Figures S3 and S4, Supporting Information). This is compatible with the effects observed for alcohol nitrosation in the presence of buffers,[13] for which general acid–base catalysis is a distinctive feature.

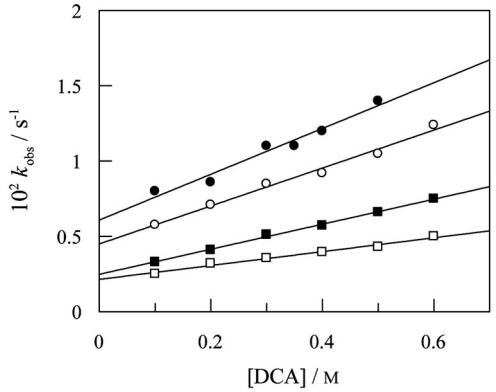


Figure 5. Influence of dichloroacetic acid buffers on k_{obs} for HB nitrosation. Ionic strength 1.00 M ($NaClO_4$); [HB] = 1.0×10^{-3} M; T = 25.0 °C. (●) pH = 0.77; (○) pH = 1.16; (■) pH = 1.52; (□) pH = 2.09 (some data omitted for clarity).

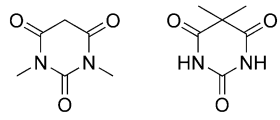
Nevertheless, in contrast to alcohols, HB *O*-nitrosation can be described by an irreversible base-catalyzed process. This claim is supported by the results obtained from ^{13}C NMR and DEPT spectral analyses, where the oxime is detected as the only final product of the reaction between HB and NO^+. In this sense, it is well known that the identification of the products of a reaction helps to define the reaction course, as the proposed mechanism must account for their formation.

On the basis of the identification of the final product, we can deduce that alkenyl nitrite formation is followed by two consecutive fast steps: the internal rearrangement of the *O*-nitroso species to give the *C*-nitroso compound, and the subsequent tautomerization to the more stable oxime (Scheme 4). As a result, even though alcohol nitrosation is a reversible process, we will consider the reaction between the oxygen atom of the HB enol form with NO^+ as a virtually irreversible process. In addition, and regarding the nature of the *O*-nitrosation step, it must be noted that the enol forms of β-diketones such as HB show two different oxygen atoms as potential nucleophilic centers: the carbonyl oxygen atom and the alcohol oxygen atom. As a result, two different reaction pathways may be suggested (Scheme 4). Such pathways are kinetically indistinguishable and have been deeply discussed in previous work.[1]

With regard to the internal rearrangement shown in Scheme 4, it must be said that *O*-nitroso compounds are well known among the potential NO group donors in nitrosation chemistry. Thus, many reactions described in the literature involve intramolecular transfer of the nitroso group. Typical examples are the O–NO→N–NO migrations observed in the nitrosation of amides and ureas,[14] amino acids[15] in acidic media, and hydroxylamines;[16] the C–NO→N–NO migrations found in the nitrosation of indoles[17] in acidic media; and the N–NO→C–NO migrations observed in the Fischer–Hepp rearrangement.[18] Also, S–NO→N–NO migrations are common when studying nitrosation of cysteine in acidic[19] and basic or neutral[20] media, thioureas[21] and thioproline or thiomorpholine.[22]

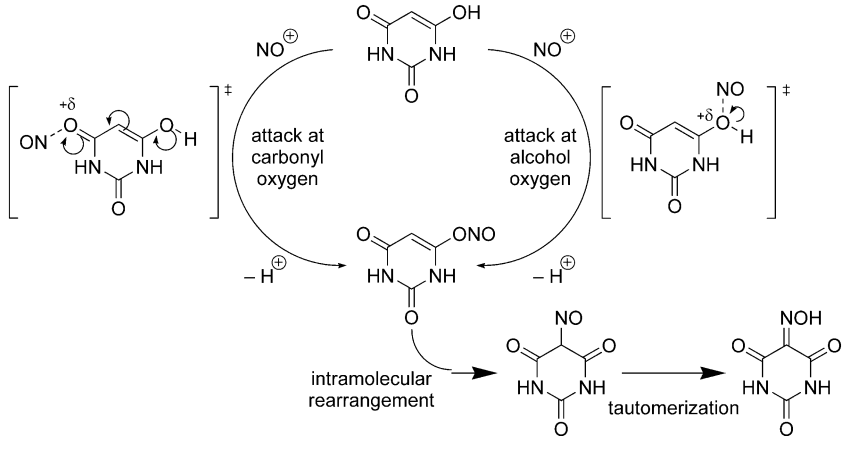
It may be suggested that the catalytic effects observed in the presence of buffers might be ascribed to a nucleophilic catalysis instead of an *O*-nitrosation mechanism. Thus, the buffer base would act as a nucleophilic catalyst towards *C*-nitrosation, in a fashion analogous to Cl^-, Br^-, or SCN^-, through formation of an acyl nitrite as the ultimate nitrosating agent. As a consequence, the catalysis found in the presence of buffers would be due to an increase in the nitrosating agent concentration as buffer concentration is increased. Although this may seem like a reasonable assumption, the results obtained in this study confirm without a doubt the nature of the *O*-nitrosation step, ruling out the idea of buffer-catalyzed *C*-nitrosation (for a comprehensive discussion see Supporting Information, Section 3).

Additional experiments with HB derivatives have been carried out in order to elucidate entirely the mechanism of HB nitrosation. Thus, nitrosation of 1,3-dimethylbarbituric acid (13HB) and 5,5-dimethylbarbituric acid (55HB) has been studied (Scheme 5).

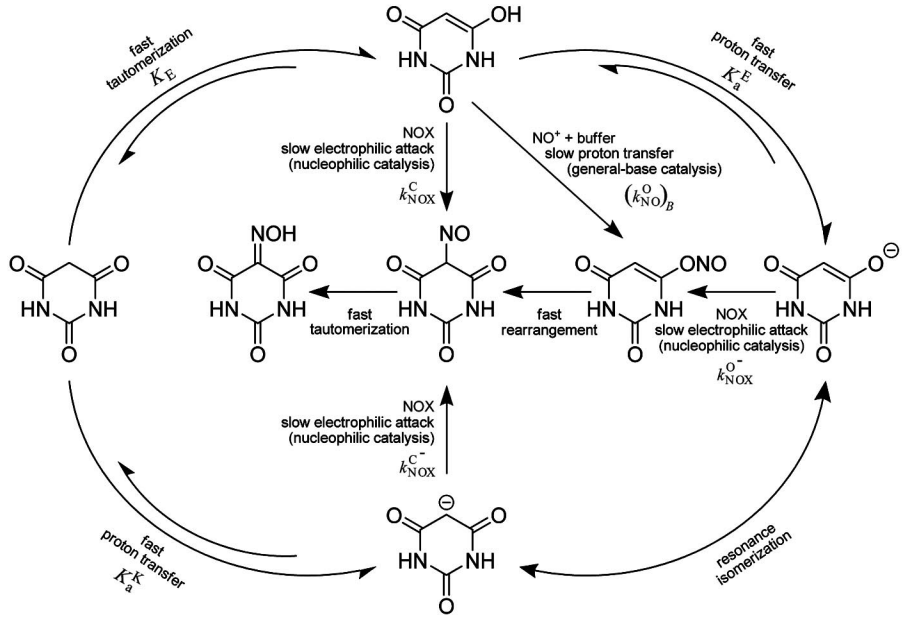


Scheme 5.

13HB nitrosation presents a similar kinetic behavior to the one observed for HB, that is, first-order dependence on $[HNO_2]$ and [13HB], dual dependence on $[H^+]$, as well as both nucleophilic and general-base catalyses (see Supporting Information, Section 4). The only difference found is a lower reactivity, presumably due to the lower acidity of 13HB ($pK_a^{13HB} = 4.68$[3]). In contrast, 55HB gives rise to no reaction under any of the experimental conditions used. This lack of reactivity confirms the enol formation as a requisite for nitrosation to take place. Furthermore, the absence of any reaction allows us to rule out an unlikely *N*-nitrosation mechanism at the ureic moiety of HB.



Scheme 4.



Scheme 6.

On the basis of the experimental results described in this section we can formulate an initial mechanistic hypothesis for HB nitrosation. Thus, according to the influence of proton concentration on the rate constant (Figure 2), we can assume that HB nitrosation proceeds through both enol and carbanion enolate forms. Besides, it has also been confirmed that HB nitrosation behaves simultaneously as a nucleophile and buffer-catalyzed process. Nucleophilic catalysis (Figure 3) points to a mechanism where the electrophilic attack is rate determining. The nature of this attack will depend on whether the NO^+ reacts with the enol or the carbanion enolate forms of HB. Thus, enol nitrosation will involve direct attack at the carbon atom (*C*-nitrosation), whereas carbanion enolate nitrosation will imply either attack at the carbon or the oxygen atom. Because the conjugate base of HB has no transferable proton, whether the reaction proceeds through the carbanion or the enolate form, the reaction will be nucleophile catalyzed. In contrast, buffer catalysis (Figure 5) points towards irreversible *O*-nitrosation involving a rate-limiting proton transfer. Therefore, in light of all these experimental observations the following mechanism depicted in Scheme 6 can be proposed.

The above mechanism exhibits four different routes for HB nitrosation: two reaction pathways through the enol and two through the HB deprotonated forms. In this sense, while carbon and oxygen reactivity of the enol tautomer can be easily discriminated, a kinetically indistinguishable mechanism will be considered for the nitrosation of the HB conjugate base.

Discussion

HB Nitrosation in the Absence of Added Catalyst

From the mechanism shown in Scheme 6 the rate law given in Equation (1) can be derived (for a complete deduction, see Supporting Information, Section 5), where $k_{NO}^{C^-}$, $k_{NO}^{O^-}$ are the reactivity constants of the carbanion and enolate forms of HB towards NO^+, k_{NO}^{C} and $k_{NOH_2O}^{O}$ are the reactivity constants of the carbon and oxygen atom of the HB enol form, K_E is the HB enolization constant (K_E = 0.05[23]), K_{NO} is the NO^+ formation constant, and K_a^{HB} and $K_a^{HNO_2}$ are the acidity constants for HB and HNO_2, respectively.

$$k_{obs} = \frac{\dfrac{K_a^K K_{NO}[HB]_T\left(k_{NO}^{C^-}+k_{NO}^{O^-}\right)}{2K_a^K + K_a^{HNO_2}(1+K_E)}\left[H^+\right] + \dfrac{K_E K_{NO}[HB]_T\left\{k_{NO}^{C}+\left(k_{NO}^{O}\right)_{H_2O}\right\}}{2K_a^K + K_a^{HNO_2}(1+K_E)}\left[H^+\right]^2}{1+\dfrac{1+K_E}{2K_a^K + K_a^{HNO_2}(1+K_E)}\left[H^+\right]} \quad (1)$$

Equation (1) predicts both linear and nonlinear dependences of the rate constant on proton concentration. As shown in Figure 2, the agreement between the model results and the experimental data is satisfactory. From this nonlinear fit, a value $k_{NO}^{C^-} + k_{NO}^{O^-} = (1.09 \pm 0.09) \times 10^{10}\ M^{-1}\,s^{-1}$ was calculated. As expected, the reaction through the carbanion enolate form is a diffusion-controlled process. The value obtained for the sum of the reactivity constants through the neutral enol form was $k_{NO}^{C} + (k_{NO}^{O})_{H_2O} = (9.19 \pm 1.02) \times 10^7\ M^{-1}\,s^{-1}$. Similar results were found when 13HB nitrosation was studied. Thus, for the *N*,*N*-dimethylated derivative of HB the values $k_{NO}^{C^-} + k_{NO}^{O^-} = (2.21 \pm 0.10) \times 10^{10}\ M^{-1}\,s^{-1}$ and $k_{NO}^{C} + (k_{NO}^{O})_{H_2O} = (1.30 \pm 0.11) \times 10^8$ were obtained.

HB Nitrosation in the Presence of Nucleophiles

As we explained in the previous section, the nitrosation mechanism of HB shows three nucleophile-catalyzed routes, that is, three reaction pathways where the electrophilic at-

tack is rate determining. Such pathways are the nitrosation of the enol and the carbanion enolate forms (Scheme 6).

In the presence of nucleophiles the rate law given in Equation (2) for HB nitrosation can be obtained (for details, see Supporting Information, Section 6), where $k^{C^-}_{NOX}$, $k^{O^-}_{NOX}$ are the reactivity constants of the carbanion and enolate forms of HB towards NOX, k^{C}_{NOX} is the reactivity constant of the carbon atom of the enol form, and K_{NOX} is the equilibrium constant for the formation of the nitrosating agent.

$$k_{obs} = \frac{\frac{K_a^K K_{NO}[HB]_T\left(k_{NO}^{C^-}+k_{NO}^{O^-}\right)}{2K_a^K+K_a^{HNO_2}(1+K_E)}[H^+]+\frac{K_E K_{NO}[HB]_T\left\{k_{NO}^{C}+\left(k_{NO}^{O}\right)_{H_2O}\right\}}{2K_a^K+K_a^{HNO_2}(1+K_E)}[H^+]^2}{1+\frac{1+K_E}{2K_a^K+K_a^{HNO_2}(1+K_E)}[H^+]} + \frac{\frac{K_a^K K_{NOX}[HB]_T\left(k_{NOX}^{C^-}+k_{NOX}^{O^-}\right)}{2K_a^K+K_a^{HNO_2}(1+K_E)}[H^+]+\frac{K_E K_{NOX}[HB]_T k_{NOX}^{C}}{2K_a^K+K_a^{HNO_2}(1+K_E)}[H^+]^2}{1+\frac{1+K_E}{2K_a^K+K_a^{HNO_2}(1+K_E)}[H^+]}[X^-] \quad (2)$$

Equation (2) is a binomial expression where the first term corresponds to the reaction in the absence of added catalyst, and the second one to the nucleophile-catalyzed process. On the one hand, this expression predicts that for a reaction series where there is a set amount of added $HClO_4$ but a variable amount of nucleophile a linear plot of k_{obs} vs. $[X^-]$ will be obtained (as shown in Figure 3). On the other hand, the slopes of such plots [Equation (3)] would rise in a nonlinear fashion as proton concentration is increased.

$$\text{Slope} = \frac{\frac{K_a^K K_{NOX}[HB]_T\left(k_{NOX}^{C^-}+k_{NOX}^{O^-}\right)}{2K_a^K+K_a^{HNO_2}(1+K_E)}[H^+]+\frac{K_E K_{NOX}[HB]_T k_{NOX}^{C}}{2K_a^K+K_a^{HNO_2}(1+K_E)}[H^+]^2}{1+\frac{1+K_E}{2K_a^K+K_a^{HNO_2}(1+K_E)}[H^+]} \quad (3)$$

As shown in Figure 6, in the presence of Br^- the agreement between the model results and the experimental data is satisfactory (see also Figures S10 and S11 for HB nitrosation in the presence Cl^- and SCN^-, respectively).

Hence, by fitting Equation (3) to our experimental data, the reactivity constants of the enol and carbanion enolate forms of HB with NOCl, NOBr, and NOSCN were obtained (Table 1).

As expected, in all cases the carbanion enolate form has a much higher reactivity than the enol tautomer. In addition, taking into account the results obtained in the absence of catalysts, it can be also observed that reactivity decreases following the order $NO^+ > NOCl > NOBr > NOSCN$ (Figure 7).

The behavior shown in Figure 7 is justified on the basis of the polarity of the X–NO bond. An increase in X electronegativity leads to an increase in the positive charge on the nitrogen atom, making the nitroso group a better electrophilic acceptor and, therefore, increasing its reactivity. Thus, the origin of the large catalytic effect of NOSCN

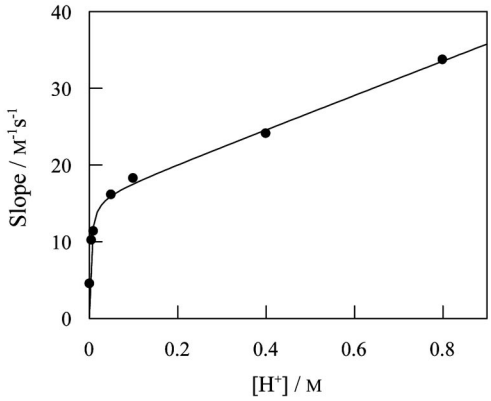


Figure 6. Verification of Equation (3). Influence of H^+ concentration ($HClO_4$) on slope for HB nitrosation in the presence of Br^-. Ionic strength 1.00 M ($NaClO_4$); [HB] = 1.0×10^{-3} M; T = 25.0 °C.

Table 1. Reactivity constants of the enol and carbanion enolate forms of HB with NOCl, NOBr, and NOSCN.

NOX	$k^{C^-}_{NOX} = +k^{O^-}_{NOX}$ / $M^{-1}s^{-1}$	k^{C}_{NOX} / $M^{-1}s^{-1}$
NOCl	$(1.09 \pm 0.15) \times 10^9$	$(1.73 \pm 0.33) \times 10^7$
NOBr	$(7.78 \pm 1.18) \times 10^8$	$(1.99 \pm 0.42) \times 10^6$
NOSCN	$(4.78 \pm 0.61) \times 10^6$	$(3.90 \pm 2.20) \times 10^3$

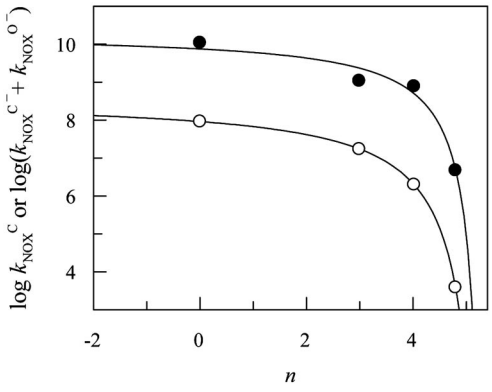


Figure 7. Correlation between the nitrosation rate constants and the Swain nucleophilicity index: $n_{H_2O} = 0$ (for H_2O–NO^+), $n_{Cl^-} = 2.99$ (for Cl–NO), $n_{Br^-} = 4.02$ (for Br–NO) and $n_{SCN^-} = 4.80$ (for NCS–NO). (●) Nitrosation of HB carbanion enolate form; (○) nitrosation of HB enol form.

(Figure 3) would lie in the magnitude of the equilibrium constant K_{NOSCN} for nitrosyl thiocyanate formation. This effect is well documented in the literature.[4–7] The leveling offs shown in Figure 7 correspond to the diffusion-controlled rate limits of HB nitrosation. As expected, the plateau value for the carbanion enolate form (1×10^{10} $M^{-1}s^{-1}$) is higher than that of the corresponding enol (1×10^8 $M^{-1}s^{-1}$). This is a predictable result, as the reactivity of the negatively charged HB towards NO^+ must be greater than that of the neutral enol.

HB Nitrosation in the Presence of Buffers

HB nitrosation is a buffer-catalyzed reaction where the reaction proceeds through the oxygen atom of the enol

form, the proton transfer being the rate-limiting step (Schemes 4 and 6). As we explained in the previous section, this behavior is compatible with the kinetic effects observed for alcohol nitrosation,[13] for which general-base catalysis is a distinctive feature.

From this mechanism the rate law given in Equation (4) can be derived (for a complete deduction, see Supporting Information, Section 8), where $k^{O}_{NOB^-}$ is the nitrosation reactivity constant of the oxygen atom of the HB enol form towards NO^+ in the presence of buffers.

$$k_{obs} = \frac{\dfrac{K_a^K K_{NO}[HB]_T\left(k_{NO}^{C^-}+k_{NO}^{O^-}\right)}{2K_a^K + K_a^{HNO_2}(1+K_E)}\left[H^+\right] + \dfrac{K_E K_{NO}[HB]_T\left\{k_{NO}^{C}+\left(k_{NO}^{O}\right)_{H_2O}\right\}}{2K_a^K + K_a^{HNO_2}(1+K_E)}\left[H^+\right]^2}{1+\dfrac{1+K_E}{2K_a^K + K_a^{HNO_2}(1+K_E)}\left[H^+\right]} + \frac{K_E K_{NO} K_a^{BH}\left[H^+\right]^3[HB]_T\left(k_{NO}^{O}\right)_{B^-}}{\left\{2K_a^K+(1+K_E)\left[H^+\right]\right\}\left(K_a^{HNO_2}+\left[H^+\right]\right)\left(K_a^{BH}+\left[H^+\right]\right)}[Buffer]_T \quad (4)$$

Equation (4) is a binomial expression where the first term corresponds to the reaction in the absence of added catalyst, and the second one to the base-catalyzed process. This equation predicts a linear dependence of the observed rate constant on buffer concentration (Figure 4). The slopes of the k_{obs} vs. [Buffer] plots will be given by Equation (5). Equation (5) can be rewritten [Equation (6)].

$$\text{Slope}' = \frac{K_E K_{NO} K_a^{BH}\left[H^+\right]^3[HB]_T\left(k_{NO}^{O}\right)_{B^-}}{\left\{2K_a^K+(1+K_E)\left[H^+\right]\right\}\left(K_a^{HNO_2}+\left[H^+\right]\right)\left(K_a^{BH}+\left[H^+\right]\right)} \quad (5)$$

$$\frac{\text{Slope}'\left\{2K_a^K+(1+K_E)\left[H^+\right]\right\}\left(K_a^{BH}+\left[H^+\right]\right)\left(K_a^{HNO_2}+\left[H^+\right]\right)}{K_E K_a^{BH} K_{NO}\left[H^+\right]^2[HB]_T} = Y = \left(k_{NO}^{O}\right)_{B^-}\left[H^+\right] \quad (6)$$

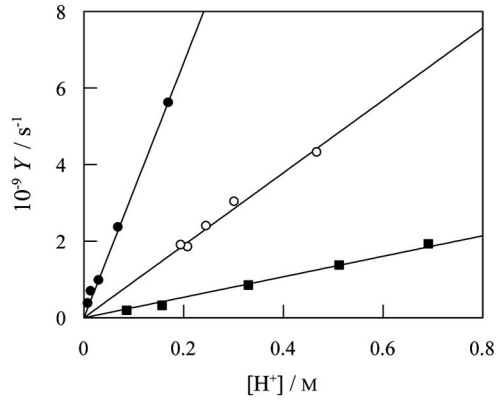


Figure 8. Verification of Equation (6). Influence of H^+ concentration on Y for HB nitrosation in the presence of buffers. Ionic strength 1.00 M ($NaClO_4$); [HB] = 1.0×10^{-3} M; T = 25.0 °C. Nitrosation of HB carbanion enolate form; (●) dichloroacetic acid; (○) tricholoroacetic acid; (■) trifluoroacetic acid.

As shown in Figure 8, the agreement between the model results and the experimental data is satisfactory.

Therefore, by fitting Equation (6) to our experimental results, the nitrosation reactivity constants in the presence of dichloro- (DCA), trichloro- (TCA), and trifluoroacetic acid (TFA) buffers were obtained (Table 2).

Table 2. Nitrosation reactivity constants of HB in the presence of DCA, TCA, and TFA buffers.

Buffer	$k^{O}_{NOB^-}$ / $M^{-1}\,s^{-1}$
DCA	$(3.23 \pm 0.07) \times 10^{10}$
TCA	$(9.19 \pm 0.64) \times 10^{9}$
TFA	$(2.90 \pm 0.07) \times 10^{9}$

The data shown in Table 2 can be used to construct a Brønsted plot in order to determine the value for the reactivity constant of the oxygen atom in the absence of buffers (Figure 9).

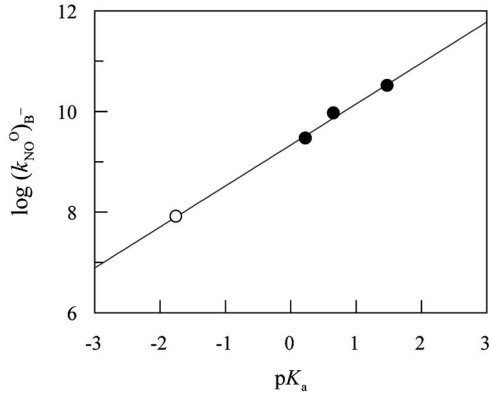


Figure 9. Brønsted plot for general-base catalysis of HB nitrosation by carboxylic acid buffers. Ionic strength 1.00 M ($NaClO_4$); [HB] = 1.0×10^{-3} M; T = 25.0 °C. (○) Extrapolated value for water.

The Brønsted correlation allows us to obtain an extrapolated value of $(k^{O}_{NO})_{H_2O} = (8.12 \pm 1.01) \times 10^7\ M^{-1}\,s^{-1}$, which is compatible with the one obtained previously: $k^{C}_{NO} + (k^{O}_{NO})_{H_2O} = (9.19 \pm 1.02) \times 10^7\ M^{-1}\,s^{-1}$. In addition, the value for the Brønsted coefficient (β = 0.81) points to an electrophilic attack lagging behind the proton transfer in the transition state. Nonperfect synchronization between different processes is well documented.[24]

Interpretation of Results

A comparison between the reactivity constants for AcAc[1] and HB nitrosation is shown in Table 3.

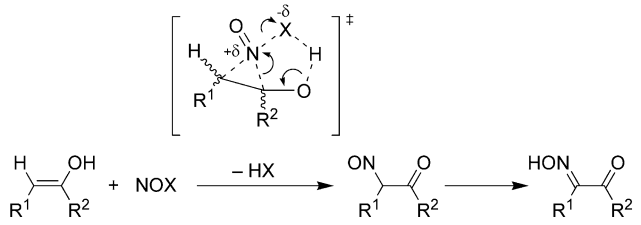
In the absence of added catalyst the HB and AcAc enol forms react at similar rates by both *C*- and *O*-nitrosation mechanisms. Given their different properties (it must be noted that AcAc is a more basic nucleophile) this behavior can be justified on the basis of diffusion-controlled kinetics for both substrates. In addition, as expected for HB, the carbanion enolate ion is more reactive towards NO^+ than its corresponding enol tautomer. Owing to its nature, AcAc does not show reaction through its deprotonated form.

Table 3. Comparison between the reactivity constants for AcAc and HB nitrosation.

	$k/M^{-1}s^{-1}$	AcAc	HB
No added catalyst	k_{NO}^{C}	(1.3±0.1)×10^8	>(9.2±1.0)×10^7
	$(k_{NO}^{O})_{H_2O}$	(1.3±0.2)×10^8	(8.1±1.0)×10^7
	$k_{NO}^{C^-} + k_{NO}^{O^-}$	–	(1.1±0.1)×10^{10}
In the presence of nucleophiles	k_{NOCl}^{C}	(7.0±0.4)×10^4	(1.7±0.3)×10^7
	k_{NOBr}^{C}	(2.0±0.1)×10^4	(2.0±0.4)×10^6
	k_{NOSCN}^{C}	(6.6±0.2)×10^2	(3.9±2.2)×10^3
	$k_{NOCl}^{C^-} + k_{NOCl}^{O^-}$	–	(1.1±0.1)×10^9
	$k_{NOBr}^{C^-} + k_{NOBr}^{O^-}$	–	(7.8±1.2)×10^8
	$k_{NOSCN}^{C^-} + k_{NOSCN}^{O^-}$	–	(4.8±0.6)×10^6
In the presence of buffers	$(k_{NO}^{O})_{ClCH_2COO^-}$	(6.2±0.1)×10^8	
	$(k_{NO}^{O})_{Cl_2CHCOO^-}$	(3.8±0.3)×10^8	(3.2±0.1)×10^{10}
	$(k_{NO}^{O})_{Cl_3CCOO^-}$	(3.0±0.2)×10^8	(9.2±0.6)×10^9
	$(k_{NO}^{O})_{F_3CCOO^-}$		(2.9±0.1)×10^9

The results obtained in the presence of nucleophiles indicate that reactivity decreases following the well-established order $NO^+ > NOCl > NOBr > NOSCN$. As we explained in the discussion section, this behavior is due to the polarity of the X–NO bond. Once again, the carbanion enolate ion displays a higher reactivity towards NOX than the one found for the neutral enol. Both enol and carbanion enolate pathways exhibit chemical-control behavior.

As pointed out above, AcAc is a much more basic nucleophile than HB ($pK_a^{AcAc} = 8.79$[2] and $pK_a^{HB} = 4.04$[3]), which seems to suggest that AcAc should be a more reactive species. However, as shown in Table 3, HB clearly shows a higher reactivity than AcAc towards NOX. A tentative explanation for this marked difference can be given on the assumption of an intramolecular proton-assisted process for *C*-nitrosation (Scheme 7).



Scheme 7.

As shown in Scheme 7, the alcohol proton would solvate the nucleophile leaving group, promoting the opening of the cyclic onium structure and, therefore, leading to the *C*-nitroso compound. According to this hypothesis, the more acidic proton of HB compared to AcAc would facilitate the reaction to take place.

Lastly, the expected results were obtained when the base-catalyzed nitrosation rate constants for AcAc and HB were compared. Taking into account that the proton transfer is rate-determining for *O*-nitrosation, the higher the acidity of the alcohol group of the enol form of the substrate, the faster the reaction will occur.

Conclusions

A methodology for determining chemical reactivity of ambident nucleophiles is reported. This approach is based on the different operating mechanisms for enol nitrosation. Thus, *C*-nitrosation proceeds through a rate-limiting electrophilic attack at the olefinic carbon atom of the enol tautomer, whereas *O*-nitrosation involves a process where proton transfer is rate determining. The observed nucleophilic and general-base catalyses constitute the confirmation of two simultaneous but independent reactions on the carbon and oxygen atoms of the enol. This study allows us to discriminate the reactivity of these strongly interacting nucleophilic centers. The methodology described in this work represents an alternative to the use of identification techniques in order to determine the nucleophilicity of ambident species.

Experimental Section

General: All chemicals were of the highest commercially available purity and were used as supplied. All kinetic experiments were conducted in water at 25 °C and μ = 1.0 M ($NaClO_4$). All rates were measured in a UV/Vis spectrophotometer and monitored at 280 nm (formation of the oxime). Typical nitrosating agent concentrations were $[NaNO_2] = (4–5) \times 10^{-5}$ M. HB, 13HB, 55HB, acid, halide, and buffer concentrations were always in large excess over the nitrosating agent, ensuring pseudo-first-order conditions. As expected for secondary *C*-nitroso compounds,[6] under all the experimental conditions the oxime was the only reaction product observed.

Supporting Information (see footnote on the first page of this article): Influences of substrate, proton, nucleophile, and buffer concentration on k_{obs} for HB and 13HB nitrosation; deduction of Equations (1), (2), and (4) and verification of Equation (3) together with a comprehensive discussion of an alternative mechanism for HB nitrosation.

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