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First Kinetic Discrimination Between Carbon and Oxygen Reactivity of Enols

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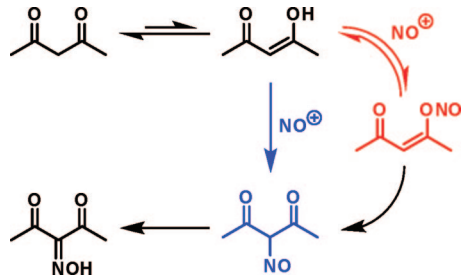

Nitrosation of enols shows a well-differentiated behavior depending on whether the reaction proceeds through the carbon (nucleophilic catalysis is observed) or the oxygen atom (general acid−base catalysis is observed). This is due to the different operating mechanisms for C- and O-nitrosation. Nitrosation of acetylacetone (AcAc) shows a simultaneous nucleophilic and acid−base catalysis. This simultaneous catalysis constitutes the first kinetic evidence of two independent reactions on the carbon and oxygen atom of an enol. The following kinetic study allows us to determine the rate constants for both reaction pathways. A similar reactivity of the nucleophilic centers with the nitrosonium ion is observed.

Introduction

Enols and enolate ions form the most important class of ambident nucleophiles. It may be said without exaggeration that enolate ions are probably the most widely used reagents in organic chemistry. Given the task of creating a new carbon−carbon bond, organic chemists often turn to a large set of reactions (alkylation, acylation, aldol and ester condensation, and Dieckmann and Michael condensation) with alkali enolates as intermediates.[1] The effect of factors determining the position of the attack on an ambident nucleophile may be considered only for kinetically controlled reactions, where the product ratio is determined by the ratio between the reaction rates on each site. Of course, such a limitation narrows considerably the range of reactions to be examined. For ambident anions, the inherent complexity of determining the nucleophilicity of each site is further complicated by the fact that, in most cases, sites are not independent but rather connected in a single mesomeric system which can undergo charge redistribution under the action of an electrophilic agent.[2] Even if it is possible to estimate the charge delocalization in a static system, it is not possible to estimate the contribution of the mesomerism in the reacting system since this contribution depends on both the system itself and the attacking agent. All this makes each ambident system distinctly individual, requiring special and systematic studies. Even though it is obvious from these considerations that ambident reactivity (defined by the ratio of the reactive site nucleophilicities) depends on many factors which are in turn "interconnected", under specific conditions one factor can become dominant and determine the direction of the attack by the electrophilic agent. Among such factors are the natures of the nucleophile, electrophile, and solvent.

From a synthetic point of view,[3] it is known that ketones as well as other carbonyl compounds react with regular nitrosating agents (NO^+, N_2O_3, NOX, and alkyl nitrites) to give nitroso-ketones or keto-oximes, depending on whether the substituted group is a primary or secondary structure. The reaction is quite general, not only for simple ketones but also for other carbonyl-

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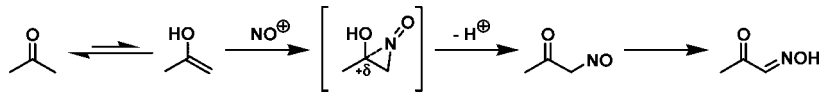
SCHEME 1



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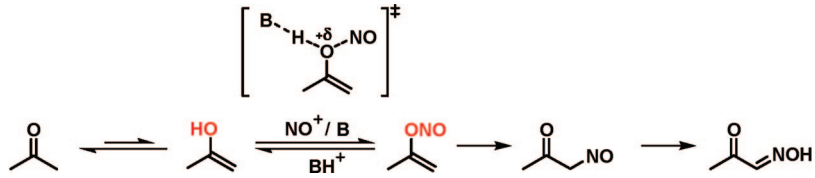

containing compounds such as β-keto acids, β-keto esters, malonic acids, β-dicarbonyl compounds, arylacetic acids, and esters. Detailed studies of the mechanism of this reaction in water have been carried out by Williams and co-workers, as well as other authors, showing that the reaction proceeds through the enol form.[4−11]

In this work, we report that nitrosation of enols shows a well-differentiated behavior depending on the reactive center. On the one hand, C-nitrosation proceeds through a rate-limiting electrophilic attack at the olefinic carbon. This reaction shows catalytic effects due to nitrosyl halide formation as a result of halide addition.[12] On the other hand, O-nitrosation behaves as an equilibrium process where the electrophilic attack at the oxygen atom and the proton transfer proceed through a concerted mechanism.[13] Such a mechanism is consistent with a noncatalytic effect of halide addition and a general-buffer catalysis.

Results and Discussion

As preliminary work, our group has reexamined nitrosation of acetone in water.[4] As known, in the presence of a fairly high concentration of Cl^-, Br^-, or SCN^-, this reaction shows a first-order dependence on [ketone] and $[H^+]$ and zero-order dependence on $[HNO_2]$, $[Cl^-]$, $[Br^-]$, and $[SCN^-]$. Such kinetic behavior indicates clearly that under these conditions nitrosation occurs via the acetone enol form and that enolization is rate limiting. On the other hand, at lower concentrations of added nucleophile, the rate equation includes first-order terms in $[HNO_2]$ and also in $[Cl^-]$ or $[Br^-]$, showing that the reaction of the enol with the nitrosating agent is now rate-limiting. This

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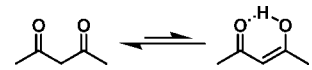

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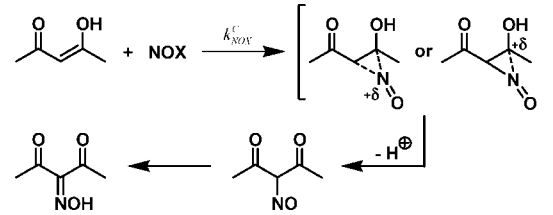

kinetic behavior is compatible with the one observed for alkene nitrosation.[12] In view of this evidence, a reaction pathway where enol nitrosation proceeds directly through the carbon atom can be proposed (Scheme 1).

However, although this is a well-known mechanism, we have further investigated acetone nitrosation with reference to a possible acid−base catalysis. Thus, in the presence of buffer solutions, we have found new catalytic effects (Figure 1) which show that proton transfer at the acetone enol oxygen is also rate-limiting. These results suggest the existence of a novel pathway for this reaction.

As shown in Figure 1, there is an enhancement of the catalytic efficacy of the buffer as acidity decreases, that is, as the concentration of the base form of the buffer is increased. Such experimental behavior is indicative of general-base catalysis as well as compatible with the one observed for alcohol nitrosation,[13] for which base catalysis is a distinctive feature. In this sense, a mechanism involving an equilibrium process where nitrosation proceeds through the oxygen atom should be considered (Scheme 2).

This insight into nitrosation of ketones leads to a new approach to these reactions. However, regular ketones such as acetone (Ac) react toward the NO^+ at very slow rates. This is due to the low extent of enol formation of this ketone ($K_E^{Ac} = 6.0 \times 10^{-9}$ in aqueous solution at 25 °C).[14] As a result, under mild acidic conditions (pH > 3), a kinetic follow-up of Ac nitrosation becomes difficult or virtually impossible (even if initial-rate methods are used). This lack of reactivity limits considerably the experimental conditions to be used in our study. Likewise, the slow rates may give rise to complications arising from hydrolysis of the oxime product, a reaction which also yields hydroxylamine and hence consumes nitrous acid.

To avoid the problems described above, we have proposed β-diketones as more suitable substrates for the study of

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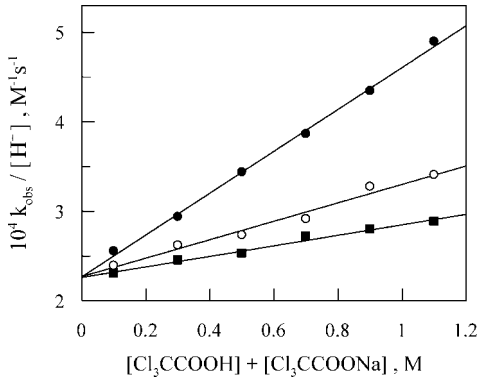

FIGURE 1. Influence of total buffer concentration, Cl_3CCOOH/$Cl_3CCOONa$, on k_{obs} for acetone nitrosation in acidic media. Ionic strength 1.00 M ($NaClO_4$); [Acetone] = 2.5 M; T = 25.0 °C. (■) $[H^+]$ = 0.35 M; Intercept = $(2.26 \pm 0.02) \times 10^{-4}$ M^{-1} s^{-1}; Slope = $(5.87 \pm 0.36) \times 10^{-5}$ M^{-2} s^{-1}; (○) $[H^+]$ = 0.23 M; Intercept = $(2.27 \pm 0.05) \times 10^{-4}$ M^{-1} s^{-1}; Slope = $(1.03 \pm 0.08) \times 10^{-4}$ M^{-2} s^{-1}; (●) $[H^+]$ = 0.14 M; Intercept = $(2.27 \pm 0.04) \times 10^{-4}$ M^{-1} s^{-1}; Slope = $(2.34 \pm 0.06) \times 10^{-4}$ M^{-2} s^{-1}.

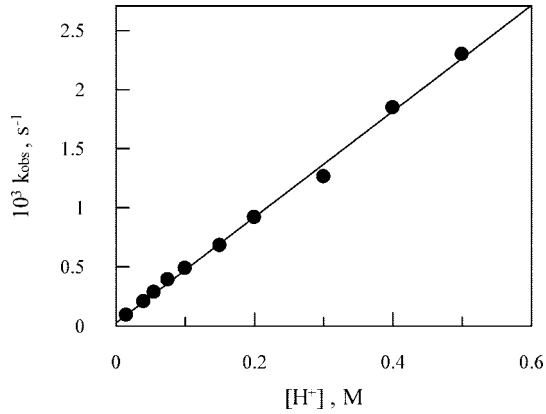

FIGURE 2. Influence of H^+ concentration ($HClO_4$) on k_{obs} for AcAc nitrosation in acidic media. Ionic strength 1.00 M ($NaClO_4$); [AcAc] = 5.3×10^{-4} M; T = 25.0 °C; Intercept = $(2.52 \pm 2.10) \times 10^{-5}$ s^{-1}; Slope = $(4.48 \pm 0.09) \times 10^{-3}$ M^{-1} s^{-1}.

nitrosation reactions of enolizable compounds. With this purpose, we have revisited the nitrosation of acetylacetone (AcAc) in acidic media. Even though the intrinsic reactivity of this compound is lower than that of acetone, its higher enolic content (K_E^{AcAc} = 0.21 in aqueous solution at 25 °C)[15] makes nitrosation occur at a much faster rate. The remarkable extent of AcAc enol formation is due to stabilization of this tautomer through a strong intramolecular hydrogen bond (Scheme 3).

Taking into account these considerations, AcAc appears to be a perfect choice to perform a comprehensive kinetic study with the aim of verifying if C- and O-nitrosation mechanisms are compatible with ambident nucleophiles.

In our mechanistic revision, the pseudofirst-order rate constant for AcAc nitrosation, k_{obs}, shows a linear dependence on both acid ($[HClO_4]$ = 0.015−0.50 M) and acetylacetone concentration ([AcAc] = 5.00×10^{-4}−5.00×10^{-3} M). See Figures 2 and 3, respectively.

Figure 4 shows the catalytic effect on k_{obs} for AcAc nitrosation due to halide addition. This well-reported behavior is a consequence of the formation of the corresponding nitrosyl

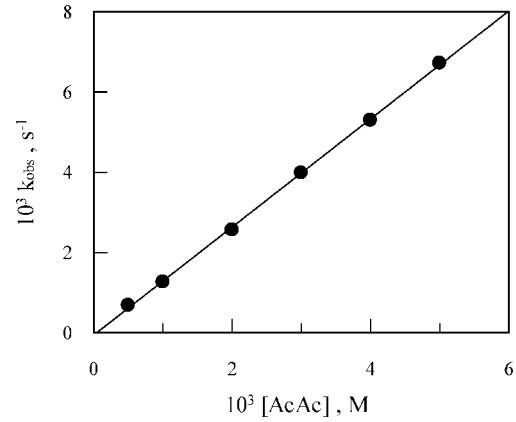

FIGURE 3. Influence of AcAc concentration on k_{obs} for AcAc nitrosation in acidic media. Ionic strength 1.00 M ($NaClO_4$); $[H^+]$ = 0.13 M; T = 25.0 °C; Intercept = $(-6.26 \pm 4.55) \times 10^{-5}$ s^{-1}; Slope = 1.35 ± 0.01 M^{-1} s^{-1}.

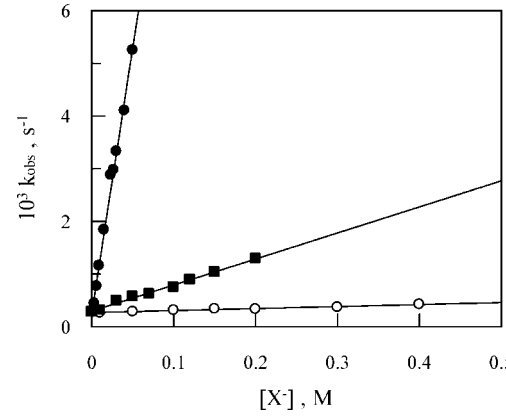

FIGURE 4. Influence of halide concentration on k_{obs} for nitrosation of AcAc in acidic media. Ionic strength 1.00 M ($NaClO_4$); [AcAc] = 5.3×10^{-4} M; $[HClO_4]$ = 0.052 M; T = 25.0 °C. (○) Cl^-; Intercept = $(2.70 \pm 0.07) \times 10^{-4}$ s^{-1}; Slope = $(3.81 \pm 0.31) \times 10^{-4}$ M^{-1} s^{-1}; (■) Br^-; Intercept = $(2.98 \pm 0.17) \times 10^{-4}$ s^{-1}; Slope = $(4.94 \pm 0.16) \times 10^{-3}$ M^{-1} s^{-1}; (●) SCN^-; Intercept = $(2.63 \pm 0.26) \times 10^{-4}$ s^{-1}; Slope = $(1.00 \pm 0.03) \times 10^{-1}$ M^{-1} s^{-1}.

halide. The high catalytic efficacy of these agents is due to the value of their formation equilibrium constant (K_{NOCl} = 1.14×10^{-3} M^{-1}; K_{NOBr} = 5.10×10^{-2} M^{-1} and K_{NOSCN} = 32 M^{-1}).[16−18]

This experimental behavior is consistent with a reaction path where AcAc enol nitrosation proceeds directly through the carbon atom (Scheme 4). Alkene nitrosation shows halide catalysis, which is compatible with the attack of the NO^+ at the carbon atom as a rate-limiting step.[12]

A two-stage process through a nitroso carbocation intermediate can take place. The stereochemistry is explained by a cyclic onium structure[11d,19] involving either a fully bonded three-membered ring or an electrostatic interaction between the nitrogen atom and the developing positive charge on carbon.

There is a simple way to rule out the possibility that the reaction can proceed, at least partially, via a small concentration of the enolate−carbanion form. For this approach, based on the magnitude of the observed rate constants, the rate law r =

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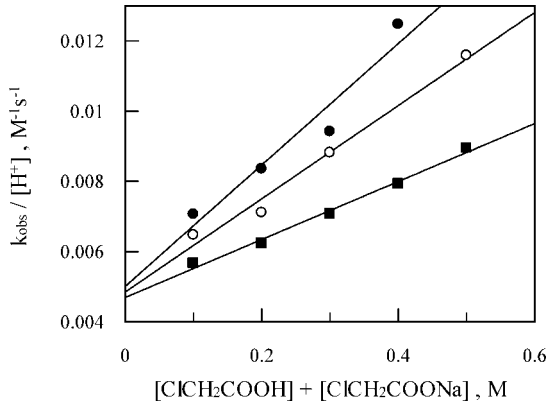


FIGURE 5. Influence of total buffer concentration, $ClCH_2COOH$/$ClCH_2COONa$, on k_{obs} for AcAc nitrosation in acidic media. Ionic strength 1.00 M ($NaClO_4$); [AcAc] = 5.3×10^{-4} M; $T = 25.0$ °C. (■) pH = 2.23; Intercept = $(4.69 \pm 0.15) \times 10^{-3}$ M^{-1} s^{-1}; Slope = $(8.26 \pm 0.46) \times 10^{-3}$ M^{-2} s^{-1}; (○) pH = 2.69; Intercept = $(4.84 \pm 0.37) \times 10^{-3}$ M^{-1} s^{-1}; Slope = $(1.33 \pm 0.12) \times 10^{-2}$ M^{-2} s^{-1}; (●) pH = 3.15; Intercept = $(5.00 \pm 0.41) \times 10^{-3}$ M^{-1} s^{-1}; Slope = $(1.73 \pm 0.18) \times 10^{-2}$ M^{-2} s^{-1}.

$k_{NO}^{O^-}$[enolate][NO^+] will be considered. From this expression, after the corresponding mass balances, the following equation is obtained

$$k_{obs} = k_{NO}^{O^-} K_a^{AcAc} K_{NO} \frac{[H^+]^2}{(K_a^{AcAc} + [H^+])(K_a^{HNO_2} + [H^+])} [AcAc]_T \quad (1)$$

where $k_{NO}^{O^-}$ is the nitrosation rate constant through the enolate form; K_{NO} is the equilibrium constant for NO^+ formation ($K_{NO} = 3.5 \times 10^{-7}$ M^{-1}); and $K_a^{HNO_2}$ and K_a^{AcAc} are the acidity constant for nitrous acid and AcAc, respectively ($K_a^{HNO_2} = 3.80 \times 10^{-4}$ M and $K_a^{AcAc} = 1.62 \times 10^{-9}$ M).

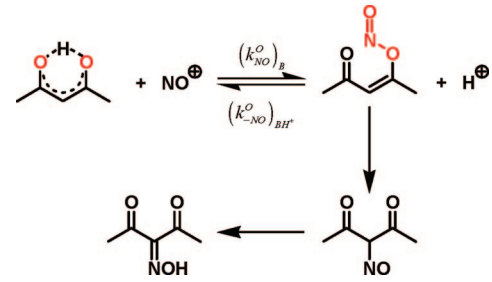
Assuming diffusion-controlled kinetics for nitrosation through the enolate form ($k_{NO}^{O^-} \sim 10^{10}$ M^{-1} s^{-1}), it is possible to estimate a value for the observed rate constant as a function of pH and AcAc concentration. Thus, at pH = 1 and [AcAc] = 5.3×10^{-4} M, $k_{obs} = 2.58 \times 10^{-9}$ s^{-1} is obtained. On the other hand, the experimental k_{obs} under the same conditions (see Figure 2) is found to be 2×10^5 times larger than the previously calculated one, which completely confirms that nitrosation reaction of AcAc proceeds entirely through the enol form.

To investigate a simultaneous O-nitrosation mechanism, experiments were conducted in $ClCH_2COOH$, $Cl_2CHCOOH$, and Cl_3CCOOH buffer solutions. Figure 5 shows the observed catalytic effect.

As in the case of acetone, the catalytic efficacy of the buffer increases with the pH, which is indicative of a general base catalysis. The observed buffer catalysis is compatible with the kinetic behavior found in O-nitrosation reactions.[13] Therefore, a mechanism through an equilibrium process where proton transfer is rate limiting can be proposed (Scheme 5). This mechanism and the nature of the electrophilic attack will be discussed in detail.

Intermolecular transfer of the nitroso group is the basis of the widely studied transnitrosation reactions. *O*-Nitroso compounds (alkyl nitrites[20]), *N*-nitroso compounds (*N*-nitrososulfonamides[21]), and *S*-nitroso compounds (thionitrites[22]) are well-known among the potential nitroso group donors. Likewise, 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,[23] amino acids[24] in acidic media, and hydroxylamines;[25] the *C*-NO→*N*-NO migrations found in the nitrosation of indoles[26] in acidic media, and the *N*-NO→*C*-NO migrations observed in the Fischer-Hepp[27] rearrangement. Also, *S*-NO→*N*-NO migrations are common when studying nitrosation of cysteine in acidic[28] and basic or neutral[29] media, thioureas,[30] and thioproline or thiomorpholine.[31]

SCHEME 5



SCHEME 6

Taking into account the keto−enol isomerization of acetylacetone, there are different pathways which can be considered as an explanation for a base-catalyzed nitrosation (Scheme 6).

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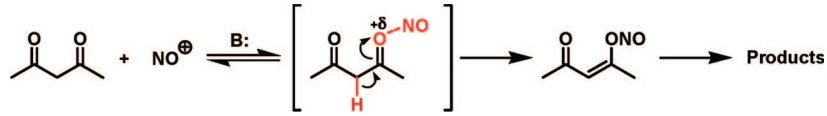
SCHEME 7



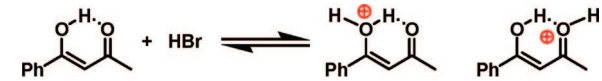
1. Nitrosation through the AcAc Keto Form. A reaction mechanism through the AcAc keto form would involve an attack at the carbonyl oxygen assisted by a proton transfer at C3 to give the corresponding alkyl nitrite as shown in Scheme 7.

However, it is important to note several factors regarding the mechanism shown in Scheme 7. Thus, the formation of such a carbanion ($pK_a^K = 8.71$)[15] would be thermodynamically disfavored against the proton transfer at the alcohol oxygen of the enol tautomer ($pK_a^E = 8.03$).[15] The lower acidity of the AcAc keto form compared to the enol form rules out the involvement of the keto tautomer in the reaction. Likewise, kinetically speaking, a reaction through a carbon acid would also be less favored than that of a reaction through an oxygen acid. This means that from a kinetic point of view the participation of the keto form can also be excluded. In addition, AcAc nitrosation shows nucleophilic catalysis which is a distinctive feature of nitrosation of alkenes. The observed catalysis implies the existence of a double bond and hence the involvement of the AcAc enol form in the reaction. Another evidence for this statement is the behavior found for the nitrosation of several ketones where enolization is rate limiting.[4] Such behavior indicates that the formation of the enol tautomer is critical in order that the reaction takes place. Therefore, all the experimental evidences point toward a base-catalyzed nitrosation through the AcAc enol form.

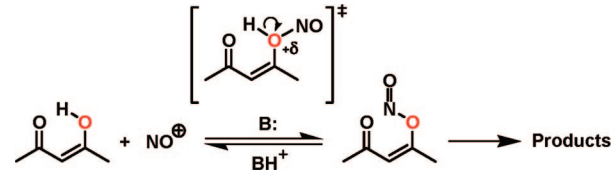
2. Nitrosation through the AcAc Enol Form. The AcAc enol form shows two potential nucleophilic centers: the carbonyl oxygen atom and the alcohol oxygen atom. Take the behavior of AcAc in acidic media as a criterion may suggest that protonation at the carbonyl oxygen of the AcAc enol form is favored over protonation of the alcohol group. Hence, the carbonyl oxygen would be more basic than the alcohol oxygen and therefore a better nucleophile.

Using as reaction media H_2SO_4, Brouwer[32,33] dealt with the idea of a protonation at the carbonyl oxygen of acyclic β-dicarbonyl compounds where the terminal groups were alkyl or aryl. In stronger acid systems such as $HF-SbF_5$, SbF_5-HFSO_3, or neat $HFSO_3$, and depending on the reaction conditions, a mono- or dication structure was proposed.[32−36] Later works of Clark et al.[37] studied the intramolecular hydrogen bonds in β-diketones. For that, and in contrast with earlier works, they focused their attention on the tautomeric nature of these compounds. Thus, these authors analyzed by NMR spectroscopic techniques the protonation of the keto and enol forms of several diketones in CBr_2F_2. In this sense, the behavior of benzoylacetone is noteworthy. A solution of this compound in CBr_2F_2 gave an NMR spectrum consistent with the enol tautomer. Peaks due to the keto form were not detected. There are two possible isomeric enol forms for this diketone, but evidence in favor of the structure shown in Scheme 8 was obtained. Therefore,

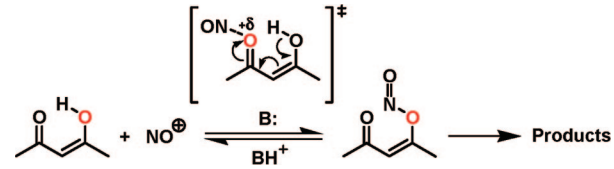
SCHEME 8



SCHEME 9



SCHEME 10



benzoylacetone constitutes a perfect example for the study of protonation of enolized β-diketones given the absence of the keto form. In light of the spectral changes observed by the authors, the structures shown in Scheme 8 for the protonated benzoylacetone were proposed.

The observation of two distinct hydroxy signals in the spectrum of protonated benzoylacetone contrasted with the results previously found[32] for the same substrate in 96% H_2SO_4 and $HF-SbF_5$ where mono- and diprotonated species were generated, respectively. This is clear evidence of the influence of the reaction media on the final products of the protonation reaction. In this sense, it must be noted that all the studies described above have been performed in nonaqueous media, so drawing conclusions from such works regarding oxygen nucleophilicity of β-diketones in aqueous solution should be done carefully. Most importantly, the observed final product of the protonation is the thermodynamically stable species. Regarding this matter, and since the reaction is not subject to kinetic control, the remarkable influence of the intramolecular hydrogen bond on the stability should be a factor to take into account.

Under all these considerations, we can propose two possible mechanisms to explain a base-catalyzed O-nitrosation of the AcAc enol form:

2.A. Reaction through the Alcohol Oxygen. By analogy with the kinetic behavior observed for acetone nitrosation (Scheme 2), we might consider a concerted mechanism involving an electrophilic attack and a proton transfer at the alcohol oxygen of the enol form (Scheme 9).

2.B. Reaction through the Carbonyl Oxygen. Another feasible explanation would be a mechanism involving an electrophilic attack at the carbonyl oxygen assisted by a proton transfer at the alcohol oxygen (Scheme 10).

The impossibility to discriminate between a nitrosation mechanism through the alcohol or carbonyl oxygen of acetylacetone (Schemes 9 and 10, respectively) is inherent to the intrinsic nature of β-diketones. Therefore, given that these

(32) Brouwer, D. M. *J. Chem. Soc., Chem. Commun.* **1967**, 515–516.
(33) Brouwer, D. M. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 225–237.
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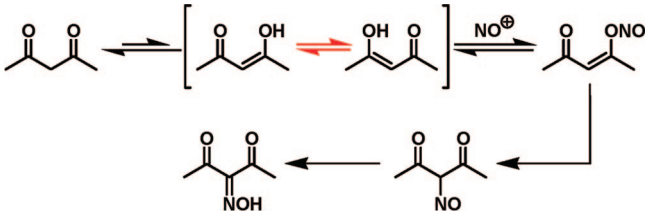
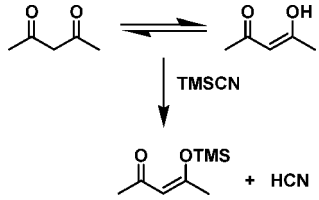
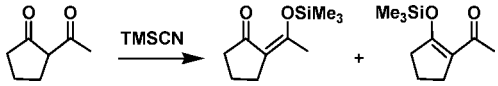
SCHEME 11



SCHEME 12



SCHEME 13



mechanisms are kinetically indistinguishable, we should no further consider a reaction through the carbonyl or alcohol oxygen of the AcAc enol form but just a reaction through the oxygen atom. As known, the two equivalent Kekule structures depicted in Scheme 11 do not adequately represent the electronic distribution within the AcAc molecule. Thus, the true structure, the so-called resonance hybrid, would lie somewhere between these extremes. That means that both AcAc oxygens present an identical charge distribution and therefore the same nucleophilicity.

A silylation reaction constitutes also a good example of these kinetically indistinguishable mechanisms. Thus, Foley[38] reinvestigating Gostevskii works[39,40] monitored the AcAc silylation by NMR demonstrating that in the absence of solvent the first product formed when AcAc is allowed to react with Me_3SiCN is a trimethylsilyl enol ether (Scheme 12).

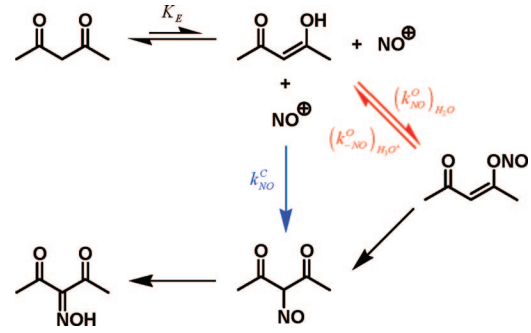
These results are the confirmation of a reaction occurring via the enol form. However, an attack at either the carbonyl or alcohol oxygen would be valid to explain the mechanism of the reaction. Another good example of these indistinguishable mechanisms is the silylation of 2-acetylcyclopentanone in $CDCl_3$[41] (Scheme 13) where a ca. 1:1 ratio mixture of the two possible trimethylsilyl enol ethers is obtained in quantitative yield.

In this sense, Leffler et al.[42] determined by ^{17}O and ^{13}C NMR the equilibrium constant between the two enol tautomers of this β-diketone as a function of temperature. However, the obtained results (equilibrium constants close to 1 in every case) are not conclusive to draw conclusions regarding the nature of the electrophilic attack.

In any case, this issue is not the central aim of this work. The main question addressed in this paper is the evidence for a novel nitrosation mechanism in β-diketones which leads us to the discrimination between the carbon and oxygen reactivity of an enol tautomer.

In the absence of buffers, AcAc enol nitrosation on the oxygen atom will show base catalysis by water and acid catalysis by H_3O^+. The proposed mechanism is shown in Scheme 14.

SCHEME 14



Given this reaction scheme, the following rate equation is obtained

$$k_{obs} = \{k^C_{NO} + (k^O_{NO})_{H_2O} + (k^O_{-NO})_{H_3O^+}K_{ONO}\} \times \frac{K_E}{1+K_E} K_{NO} \frac{[H^+]^2}{K_a^{HNO_2} + [H^+]} [AcAc]_T \quad (2)$$

where k^C_{NO} and $(k^O_{NO})_{H_2O}$ are the rate constants for enol nitrosation on the carbon and oxygen atom, respectively. The rate constant $(k^O_{-NO})_{H_3O^+}$ is the denitrosation rate constant of the alkyl nitrite (formed from the reaction between the NO^+ and the oxygen atom of the enol form), and K_{ONO} is the equilibrium constant for the formation of the alkyl nitrite. In the absence of any other acids, rate constants for O-nitrosation and denitrosation show base catalysis by H_2O and acid catalysis by H_3O^+, respectively. Equilibrium constants K_E, K_{NO}, and $K_a^{HNO_2}$ correspond to AcAc keto−enol equilibrium ($K_E = 0.21$),[15] formation equilibrium of NO^+ from HNO_2, and acidity constant of nitrous acid, respectively. Considering that under the experimental conditions $K_a^{HNO_2} \ll [H^+]$, eq 2 can be simplified as

$$k_{obs} = \{k^C_{NO} + (k^O_{NO})_{H_2O} + (k^O_{-NO})_{H_3O^+}K_{ONO}\} \times \frac{K_E K_{NO}}{1+K_E} [H^+][AcAc]_T \quad (3)$$

Equation 3 predicts a linear dependence of k_{obs} on both acid and AcAc concentrations. However, from these plots, it is not possible to estimate the values of the two different reaction pathways. From the acid concentration influence on k_{obs}, it is possible to obtain $\{k^C_{NO} + (k^O_{NO})_{H_2O} + (k^O_{-NO})_{H_3O^+}K_{ONO}\} = (1.41 \pm 0.14) \times 10^8\ M^{-1}\ s^{-1}$. Likewise, from the AcAc concentration influence, a value of $\{k^C_{NO} + (k^O_{NO})_{H_2O} + (k^O_{-NO})_{H_3O^+}K_{ONO}\} = (1.71 \pm 0.17) \times 10^8\ M^{-1}\ s^{-1}$ is obtained. Both values are in good agreement, being smaller than the expected for a diffusion-controlled reaction.

In the presence of halides and considering that only the nitrosation pathway through the carbon atom of the enol form shows halide catalysis, it is possible to obtain the following rate equation

$$k_{obs} = \{K_{NO}(k^C_{NO} + (k^O_{NO})_{H_2O} + (k^O_{-NO})_{H_3O^+}K_{ONO}) + K_{NOX}k^C_{NOX}[X^-]\} \frac{K_E}{1+K_E} [H^+][AcAc]_T \quad (4)$$

where K_{NOX} is the equilibrium constant for formation of the corresponding nitrosyl halide[19] from NO^+ and k^C_{NOX} is the rate constant for the reaction between the carbon atom of the enol form and the NOX. From the slopes shown in Figure 4, it is possible to obtain values for $k^C_{NOX}:k^C_{NOCl} = (7.0 \pm 0.4) \times 10^4$

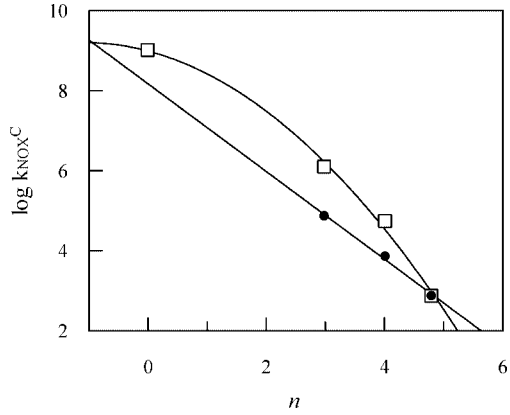


FIGURE 6. Correlation between the NOX nitrosation rate constants and the Swain nucleophilicity index (H_2O) for H_2O-NO^+, (Cl^-) for Cl−NO, (Br^-) for Br−NO, and (SCN^-) for NCS−NO for nitrosation of cysteine (□) and AcAc (●). Intercept = 8.2 ± 0.3; Slope = −1.09 ± 0.08.

M^{-1} s^{-1}, $k_{NOBr}^{C} = (2.03 \pm 0.06) \times 10^4$ M^{-1} s^{-1}, and $k_{NOSCN}^{C} = (6.6 \pm 0.2) \times 10^2$ M^{-1} s^{-1}. These values are compatible with the ones reported in the literature.[43] As expected, it can be observed that reactivity decreases in the order NO^+ > NOCl > NOBr > NOSCN. This behavior is justified on the basis of the polarity of the X−NO bond. An increase of 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 the reactivity. The origin of the large catalytic effect of NOSCN in Figure 4 lies only in the magnitude of the equilibrium constant K_{NOSCN} for nitrosyl thiocyanate formation. This effect is well-documented in the literature.[4,7,19,43]

Figure 6 shows a good correlation between the k_{NOX}^{C} rate constants of AcAc and the Swain nucleophilicity index (n) of the halide.[44] On the other hand, results for nitrosation of cysteine[19] in Figure 6 show a nonlinear behavior of the NO^+ value. This deviation from linearity is due to an approach to a diffusion-controlled reaction. From the linear correlation of AcAc, it is possible to estimate a value for $k_{NO}^{C} = (1.26 \pm 0.05) \times 10^8$ M^{-1} s^{-1}. This value is compatible with the value for the sum previously obtained, $\{k_{NO}^{C} + (k_{NO}^{O})_{H_2O} + (k_{-NO}^{O})_{H_3O^+}K_{ONO}\} = (1.55 \pm 0.11) \times 10^8$ M^{-1} s^{-1}.

In the presence of buffer solutions, eq 3 must be redefined taking into account the reaction pathways through the oxygen atom of the enol form, which show general acid−base catalysis

$$k_{obs} = \left\{ (k_{NO}^{C} + (k_{NO}^{O})_{H_2O} + (k_{-NO}^{O})_{H_3O^+}K_{ONO}) + \frac{((k_{NO}^{O})_{B^-}K_a^{BH} + (k_{-NO}^{O})_{BH}K_{ONO}[H^+])}{K_a^{BH} + [H^+]}[Buffer] \right\} \times \frac{K_E K_{NO}}{1 + K_E}[H^+][AcAc]_T \quad (5)$$

where $(k_{NO}^{O})_{B^-}$ and $(k_{-NO}^{O})_{BH}$ are the nitrosation and denitrosation rate constants of the enol form catalyzed by bases and acid,

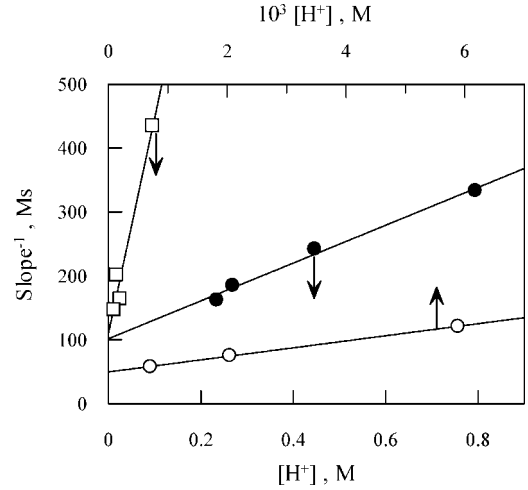


FIGURE 7. Influence of [H^+] on 1/Slope for the buffer catalysis of AcAc nitrosation in acidic media. Ionic strength 1.00 M ($NaClO_4$); [AcAc] = 5.3 × 10^{-4}M; T = 25.0 °C. (○) $ClCH_2COOH/ClCH_2COONa$; Intercept = 49.7 ± 0.8Ms; Slope = (1.21 ± 0.02) × 10^4 s; (□) $Cl_2CHCOOH/Cl_2CHCOONa$; Intercept = 110 ± 13 Ms; Slope = (3.37 ± 0.27) × 10^3 s; (•) $Cl_3CCOOH/Cl_3CCOONa$; Intercept = 102 ± 10 Ms; Slope = (2.96 ± 0.21) × 10^2 s.

TABLE 1. $(k_{NO}^{O})_{B^-}$ Values for AcAc Nitrosation through the Oxygen Atom of the Enol Form for Different Bases

catalyst	$(k_{NO}^{O})_{B^-}$, M^{-1} s^{-1}
$ClCH_2COO^-$	(6.2 ± 0.1) × 10^8
Cl_2CHCOO^-	(3.8 ± 0.3) × 10^8
Cl_3CCOO^-	(3.0 ± 0.2) × 10^8

respectively, and K_a^{BH} is the acidity constant of the buffer compound. As shown in Figure 5, eq 5 predicts a linear dependence between k_{obs} and total buffer concentration. Slopes of Figure 5 and the corresponding to $Cl_2CHCOOH$ and Cl_3CCOOH satisfy eq 6.

$$\text{Slope} = \frac{(k_{NO}^{O})_{B^-}K_a^{BH} + (k_{-NO}^{O})_{BH}K_{ONO}[H^+]}{K_a^{BH} + [H^+]} \frac{K_E K_{NO}}{1 + K_E}[AcAc]_T \quad (6)$$

Figure 7 shows a linear dependence of 1/Slope on [H^+] for different buffers. This dependence implies that $(k_{NO}^{O})_{B^-}K_a^{BH} \gg (k_{-NO}^{O})_{BH}K_{ONO}[H^+]$ so eq 6 can be rewritten as

$$\frac{1}{\text{Slope}} = \frac{(1 + K_E)}{K_E} \frac{1}{K_{NO}} \frac{1}{[AcAc]_T} \times \left\{ \frac{1}{(k_{NO}^{O})_{B^-}} + \frac{1}{(k_{NO}^{O})_{B^-}K_a^{BH}}[H^+] \right\} \quad (7)$$

From eq 7 and Figure 7, a value of the acidity constant of each one of the carboxylic acids can be obtained: $pK_a^{MCA} = 2.39 \pm 0.01$; $pK_a^{DCA} = 1.61 \pm 0.06$; and $pK_a^{TCA} = 0.46 \pm 0.05$. These pK_a values are in good agreement with those found in the literature. Likewise, rate constants for the base-catalyzed nitrosation through the oxygen atom of the enol form can be obtained (see Table 1).

From $(k_{NO}^{O})_{B^-}$ values shown in Table 1, a Brønsted plot was constructed (see Figure 8).

From this plot, a value of $\log(k_{NO}^{O})_{B^-} = (8.39 \pm 0.08) + (0.15 \pm 0.05)pK_a^{BH}$ was obtained. The small value obtained for the Brønsted coefficient indicates that proton transfer lags behind the attack of the nitrosating agent in the transition state, which

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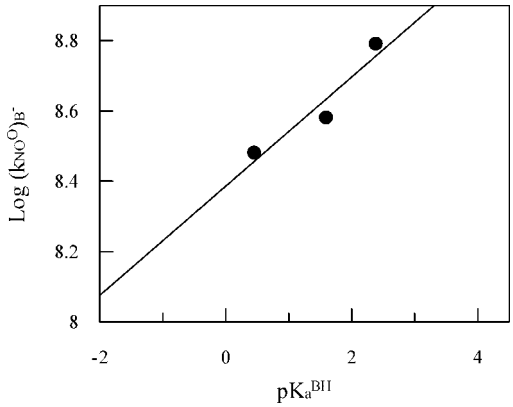

FIGURE 8. Brønsted plot of general base catalysis for AcAc nitrosation in acidic media. Ionic strength 1.00 M ($NaClO_4$); [AcAc] = 5.3×10^{-4}M; $T = 25.0$ °C.

is consistent with the opposite trend observed in the acid hydrolysis of alkyl nitrites.[13] Nonperfect synchronization between different processes is well-documented.[45] The Brønsted correlation allows us to obtain an extrapolated value of $(k^{O}_{NO})_{H_2O} = (1.32 \pm 0.02) \times 10^8$ M^{-1} s^{-1} which is compatible with the one obtained from the sum of the three reaction pathways: $\{k^{C}_{NO} + (k^{O}_{NO})_{H_2O} + (k^{O}_{-NO})_{H_3O^+}K_{ONO}\} = (1.55 \pm 0.11) \times 10^8$ M^{-1} s^{-1}. Extrapolated values for nitrosation by NO^+ at the oxygen atom of the AcAc enol form, $(k^{O}_{NO})_{H_2O} = (1.32 \pm 0.02) \times 10^8$ M^{-1} s^{-1}, and at the carbon atom, $k^{C}_{NO} = (1.26 \pm 0.05) \times 10^8$ M^{-1} s^{-1}, are similar. These values indicate that $\{k^{C}_{NO} + (k^{O}_{NO})_{H_2O}\} \gg (k^{O}_{-NO})_{H_3O^+}K_{ONO}$ which should be a consequence of the small value of the equilibrium constant for formation of the alkyl nitrite derived from the AcAc enol form. The values of these equilibrium constants are close to 1 in ethanol, and they dramatically decrease as the acidity of alcohol is increased.[19]

Conclusions

The first kinetic evidence of ambident reactivity of enols is reported in this paper. Thus, nitrosation of enols shows a well-differentiated behavior depending on whether the reaction proceeds through the carbon or the oxygen atom. This is due to the different operating mechanisms for C- and O-nitrosation. On the one hand, AcAc nitrosation shows nucleophilic catalysis which is a distinctive feature of nitrosation of alkenes. In this case, C-nitrosation proceeds through a rate-limiting electrophilic attack at the olefinic carbon of the AcAc enol form. On the other hand, in the presence of buffers, AcAc nitrosation shows general acid−base catalysis. Such experimental behavior is compatible with the one observed in the literature for O-nitrosation reactions. In this sense, a mechanism involving an equilibrium process where proton transfer is rate-limiting is proposed. This simultaneous catalysis constitutes the confirmation of two independent reactions on the carbon and oxygen atom of the AcAc enol form. This study allows us to determine the rate constants for both reaction pathways. A similar reactivity of the nucleophilic centers with the nitrosonium ion is observed. The main conclusions of this work are supported for the results obtained in the acetone nitrosation reaction.

Experimental Section

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 $\mu = 1.0$ M ($NaClO_4$). All rates were measured in a UV−vis spectrophotometer and monitored at 372 nm for Ac (disappearance of NO^+) and 275 nm for AcAc (formation of the oxime). Typical nitrosating agent concentrations were $[NaNO_2] = (4-5) \times 10^{-5}$ M. Ac, AcAc, acid, halide, and buffer concentrations were always in large excess over the nitrosating agent, ensuring pseudofirst-order conditions. As expected for secondary C-nitroso-compounds,[19] under all the experimental conditions the oxime was the only reaction product observed.

Acknowledgment. This work was supported by Ministerio de Ciencia y Tecnología (Project CTQ2005-04779) and Xunta de Galiza (PGIDIT07-PXIB209041PR and 2007/085).

Supporting Information Available: Deduction of eq 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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