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Nitrosation of 2-Acetylcyclohexanone. 2. Reaction in Water in the Absence and Presence of Cyclodextrins

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The kinetic study of the nitrosation of the enol of 2-acetylcyclohexanone (ACHE) has been performed in aqueous acid media in the absence and presence of α- and β-cyclodextrin. The reaction is first-order with respect to both reactants concentration: [nitrite] and [ACHE]; but, unexpectly, the dependence of both $[H^+]$ or $[X^-]$ ($X^- = Cl^-$, Br^-, or SCN^-) is not simple first-order. The experimental findings have been explained on the basis of a reaction mechanism that considers the formation of a chelate-nitrosyl complex intermediate in steady-state. Addition of both α-cyclodextrin (α-CD) or β-cyclodextrin (β-CD) diminishs strongly the observed rate constant, k_o, measured either for enol-nitrosation or for enol-ketonization reactions. In the case of β-CD, the inhibition effect is explained through the formation of nonproductive inclusion complexes between the enol (EH) and β-CD of 1:1 stoichiometry. Nevertheless, the quantitative interpretation of k_o-[α-CD] profiles requires the assumption that the inclusion complexes formation of both 1:1 (EH/α-CD) and 1:2 (EH/α-CD_2) stoichiometries. In the case of enol−ketonization, the EH/α-CD complex is nearly as reactive as the uncomplexed enol.

Introduction

It is well-known that ketones, nitro compounds, and nitriles are among those substrates containing strongly electron-withdrawing groups that undergo electrophilic reactions at carbon.[1] In the case of the nitrosation reaction, the primarily formed C-nitroso compound is usually stable as the oxime tautomer. The reaction occurs by electrophilic addition of the NO^+ to the >C=X function (X = C in ketones,[2] or X = N in nitrocompounds[3]) or to the carbanion, in the case of the activated nitriles.[4] This function is obtained in the tautomerization of the carbonyl compound to the enol/enolate, nitronic acid/nitronate, or carbanion structures, respectively, to the parent compound. Either the tautomerization to these functions or its subsequent nitrosation reaction can be the rate-controlling step, depending upon the reaction conditions or on the carbonyl compound structure. In the former situation, the rate equation is independent of the nitrosating agent concentration, whereas in the latter, the reaction is first order on nitrosation agent concentration. For example, in strong acid medium the nitrosation of ethyl methyl ketone shows zero order on [nitrite] if $[Cl^-] > 0.5$ M, but it shows first-order on [nitrite] if $[Cl^-] < 0.05$ M.[2] In the nitrosation of these ketones of low enol content, it is possible to arrange the experimental conditions such that either the enolization or the nitrosation of the enol is the rate-controlling step.

For ketones with high enol content, the case of most 1,3-diketones, the nitrosation follows the same pattern as that observed in many other ketone reactions, including halogenation, racemization, all in acid media, eq 1.[2,5]

$$\text{rate} = k_1[\text{ketone}][H^+][\text{nitrite}] \qquad (1)$$

In the presence of X^- ($X^- = Cl^-$, Br^-, SCN^-, ...) the rate equation now contains two terms, the first independent of X^- and the second first-order in $[X^-]$, which accounts for the nitrosation by XNO (ClNO, BrNO, SCNNO) whose concentration is much higher than that of NO^+ under the same acid conditions, even though the reactivity of XNO is lower than that of NO^+, eq 2.

$$\text{rate} = (k_1 + k_2[X^-])[\text{ketone}][H^+][\text{nitrite}] \qquad (2)$$

The nitrosation of the nitronic acids derived from aliphatic nitro compounds is also an electrophilic addition to the >C=N− function; nevertheless, the kinetics show a first-order dependence upon the [nitronic acid], curved acidity dependence, and also curved catalysis on $[Cl^-]$ and $[Br^-]$. These experimental findings suggested the formation of reversible O-nitroso intermediates that undergo an internal O- to C-nitroso group rearrangement.[3]

Unexpectedly, the same pattern of behavior has been found in the nitrosation of 2-acetylcyclopentantone, ACPE. Under experimental conditions of [nitrite] >

(1) Touster, O. *Organic Reactions*; Adams, R., Ed.; Wiley: New York, 1953; Vol. 7, Chapter 6.
(2) Leis, J. R.; Peña, M. E.; Williams, D. L. H.; Mawson, S. D. *J. Chem. Soc., Perkin Trans. 2* **1988**, 157.
(3) Iglesias, E.; Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1035.
(4) Iglesias, E.; Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1989**, 343.
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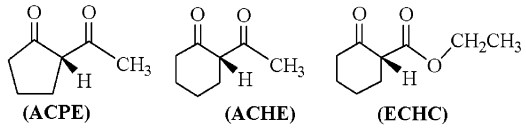
SCHEME 1. Structures of Three Related Diketones



[ACPE], the pseudo-first-order rate constant showed a curved dependence on either $[H^+]$ or $[X^-]$. The kinetic observations were satisfactorily explained assuming the formation of a chelate−nitrosyl complex intermediate in the initial nitrosation step, which is in a steady state and rearranges slowly to the C-nitroso compound.[6]

Herein, we report results obtained from the kinetic study of the nitrosation of 2-acetylcyclohexanone (ACHE) in aqueous acid medium in the absence and presence of cyclodextrins. This diketone is more than 40% enolized in water and the ketonization or enolization are slow processes, in contrast to the case of ACPE, which is less than 30% enolized in water but the keto−enol interconversion is fast. However, if the kinetic pattern of the nitrosation of ACHE resembles that of ACPE, it is different from that observed in the nitrosation of ethyl-2-cyclohexanone carboxylate, ECHC.[7] That is, we present here the case of three compounds of quite similar structure but showing notable differences in reactivity, Scheme 1. Therefore, we could say that the close structure not always determines the pattern of behavior.

In the preceding study, we showed that, in dried dioxane solvent, 2-acetylcyclohexanone exists predominantly in the enol form, while a mixture of both keto and enol tautomers is present in water: the keto−enol equilibrium constant has been measured in water as $K_E = 0.72$; however, the keto−enol tautomerization of ACHE is slow enough to follow the reaction by conventional methods. The reaction exhibits moderate catalysis by strong mineral acids, although the observed reaction rate of spontaneous tautomerization is comparable to the acid-catalyzed pathway at moderate acid concentrations (e.g., 0.2 M); the reaction rate is strongly retarded in D_2O and increases with either the increase in temperature of in the presence of aqueous buffered solutions showing strong general base catalysis. The isotopic effect, along with the Brönsted exponent, point to a mechanism in which the H^+-transfer occurs in the rate-determining step.

Experimental Section

2-Acetylcyclohexanone was commercially available and used without further purification. Cyclodextrins, Aldrich products of maximum purity, were used without further purification. All other reagents were also used as received. Solutions were prepared with doubly distilled water obtained from a permanganate solution.

UV−vis absorption spectra and kinetic measurements were recorded with a double-beam spectrophotometer provided with a thermostated cell holder.

Kinetic data were obtained by observing the rate of decrease in absorbance at 291 nm. The reactions were initiated by injecting 10 μL of a stock solution of ACHE in dioxane (0.018 M) to a 1.0 cm quartz cuvette containing 3.0 mL of aqueous solutions of the rest of reagents that had been previously equilibrated in the instrument cell holder for 15 min. The rate constants are derived from fits of the A_{291} versus time profiles to the first-order integrated equation, eq 3, with A_t, A_0, and A_∞ being the absorbance readings at t, zero, and infinite times, respectively, and with k_o being the observed rate constant measured in s^{-1}. The reactions were followed up to more than five-half-times and in all cases exhibited clean first-order kinetics.

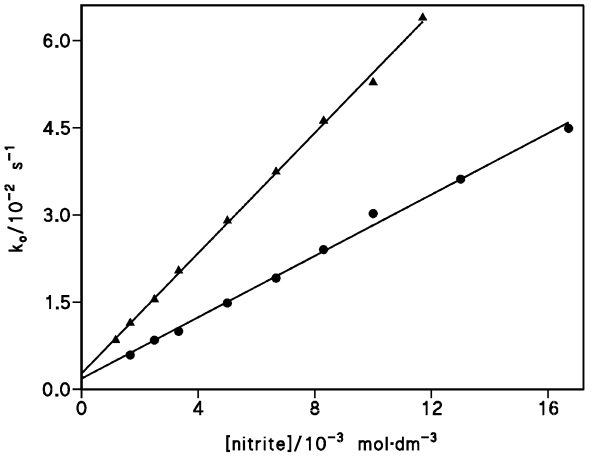


FIGURE 1. Influence of [nitrite] on the pseudo-first-order rate constant k_o, for the nitrosation of ACHE at (●) $[H^+] = 0.020$ M, $I = 0.15$ M ($NaClO_4$), and at (▲) $[H^+] = 0.040$ M, $I = 0.25$ M ($NaClO_4$).

$$A_t = A_\infty + (A_0 - A_\infty)e^{-k_o t} \quad (3)$$

Results and Discussion

Nitrosation in Water. Kinetic data for nitrosation of ACHE were deduced from studies carried out in water with a large excess of nitrite and acid ($HClO_4$ or HCl) by following the decrease of enol concentration. The initial ACHE concentration was always very low ($\sim 6 \times 10^{-5}$ M). Under these conditions, we measured the observed rate constant, k_o, as a function of [nitrite]. Figure 1 shows the results obtained at $[H^+] = 0.020$ or 0.040 M and constant ionic strength of 0.15 and 0.25 M, respectively. Least-squares treatment of the data for k_o [nitrite] yields a small but nonnegligible intercept. Table 1 displays the obtained values.

The k_o values extrapolated at [nitrite] = 0 are not obviously due to the nitrosation reaction and they can be attributed to a reversible nitrosation reaction (decomposition of the C-nitroso compound) or/and to the enol ketonization. By looking at Figure 3 of the preceding paper,[16] one can see that the k_o values extrapolated at [nitrite] = 0 must also include the observed rate constant for enol ketonization, a reaction which is about 10-fold slower than the enol nitrosation under the present conditions of acidity. Then, eq 4 applies, where k refers to the sum of the first-order rate constants for keto−enol tautomerization and for the C-nitroso compound decomposition.

$$k_o = k + \alpha[\text{nitrite}] \quad (4)$$

The influence of $[H^+]$ on the nitrosation reaction was investigated at constant nitrite concentration and ionic strength and variable $HClO_4$ or HCl concentration. The

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TABLE 1. Experimental Conditions and Parameters Obtained in the Nitrosation of ACHE in Aqueous Acid Medium[a]

[nitrite]/M	$[H^+]$/M	I/M	$k/10^{-3}$ s^{-1}	α/M^{-1} s^{-1}	β/M^{-1} s^{-1}	δ/M^{-1}
variable	0.020 ($HClO_4$)	0.15	1.53 ± 0.39	2.69 ± 0.04		
variable	0.040 ($HClO_4$)	0.25	3.25 ± 0.45	4.89 ± 0.07		
1.7×10^{-3}	variable ($HClO_4$)	0.25	1.35 ± 0.25		0.247 ± 0.032	1.35 ± 0.03
1.7×10^{-3}	variable (HCl)	0.25	2.55 ± 0.12		0.311 ± 0.004	1.67 ± 0.25
2.5×10^{-3}	variable ($HClO_4$)	0.25	2.62 ± 0.24		0.307 ± 0.003	1.38 ± 0.15

[a] k_o vs [nitrite] (or $[H^+]$) profiles fitted to eqs 4 (and 5), respectively.

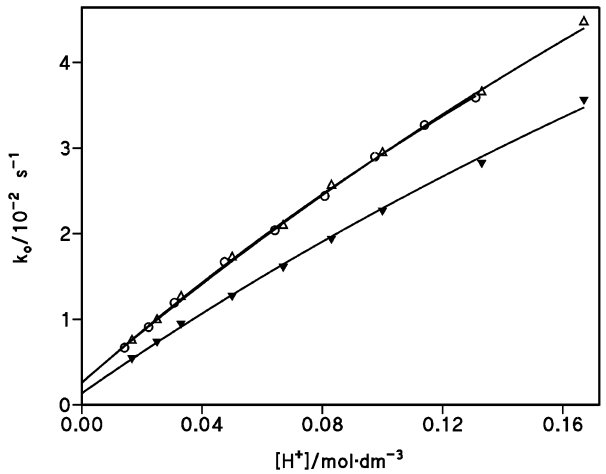


FIGURE 2. Variation of k_o as a function of $[H^+]$ for the nitrosation of ACHE at ionic strength 0.25 M and (▼) [nitrite] = 1.7×10^{-3} M, $HClO_4$; (△) [nitrite] = 2.5×10^{-3} M, $HClO_4$; (○) [nitrite] = 1.7×10^{-3} M, HCl.

obtained data are depicted in Figure 2. Again, at $[H^+] \rightarrow 0$ the overall reaction rate constant is not zero; moreover, the extrapolated k_o values at $[H^+] = 0$ increase with [nitrite] and are also higher when HCl is used instead of $HClO_4$. These findings are explained if the overall reaction is reversible: EH + XNO ⇌ C-nitroso + X^- + H^+, since XNO is in great excess over the ACHE−enol concentration, and k_o, the pseudo-first-order rate constant, includes the concentration of the nonlimiting reagents. The nonlinear regression treatment of k_o−$[H^+]$ profiles with eq 5 affords the results compiled in Table 1.

$$k_o = k + \frac{\beta[H^+]}{1 + \delta[H^+]} \qquad (5)$$

The influence of Cl^-, Br^-, and SCN^- (in general X^-) concentration on the nitrosation reaction of ACHE was analyzed under several experimental conditions of [nitrite], $[H^+]$, and ionic strength. Representative results are plotted in Figure 3, from which we may observe that k_o increases with $[X^-]$ describing curved-down profiles that can be summarized in every case from eq 6, where k_o^w represents the observed rate constant measured in the absence of X^- and its values account for the rate constant due to enol−ketonization, plus the rate constant component of the C-nitroso compound decomposition, and also the rate constant due to nitrosation by NO^+. The latter component is responsible of the high values of k_o obtained at $[X^-] = 0$, in comparison with the intercept values observed, for example, in Figures 1 and 2.

Nonlinear regression analysis of k_o−$[X^-]$ profiles to eq 6 yields the data listed in Table 2. One may note that γ values increase with $[H^+]$ for a given X^-, and also at the same $[H^+]$ this parameter increases on going from Cl^-, Br^- to SCN^-; the same trend of variation may be observed with η-values, even though the effect is more notable.

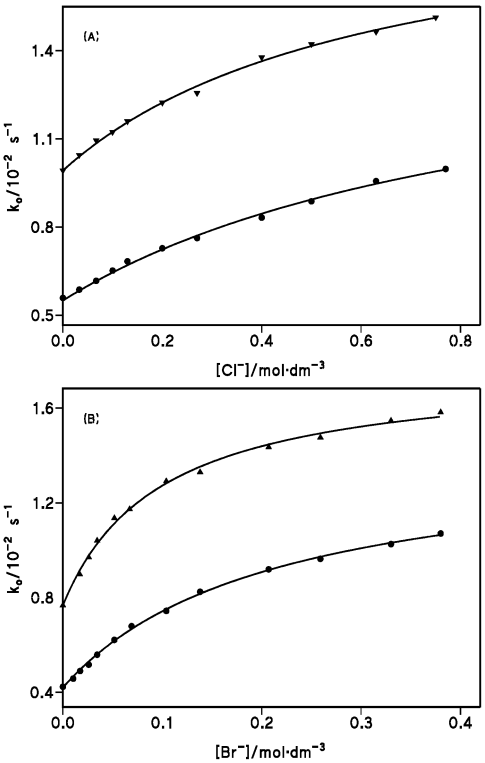


FIGURE 3. Influence of (a) $[Cl^-]$ and of (b) $[Br^-]$ on k_o for the nitrosation of ACHE at [nitrite] = 1.7×10^{-3} M and (●) $[H^+]$ = 0.010 M, (▼, ▲) $[H^+]$ = 0.025 M.

$$k_o = \frac{k_o^w + \gamma[X^-]}{1 + \eta[X^-]} \qquad (6)$$

Mechanism of Nitrosation. The comparison of the previous kinetic findings with those found in the nitrosation of ECHC reveals strong differences in the behavior of 2-acetylcyclohexanone and its ethyl ester. Thus, in the nitrosation of ECHC the experimental variation of either k_o vs [nitrite] or k_o vs $[H^+]$ were good straight lines showing negligible intercept at the origin. The observed reaction in the ECHC system in the absence of nitrite is the hydrolysis of the ester, i.e., an irreversible process and much slower than the nitrosation. In addition, k_o vs $[X^-]$ profiles are good straight lines in concordance with the "normally" found behavior in enol−nitrosation of monoketones[2] or even with some 1,3-diketones.[2,5]

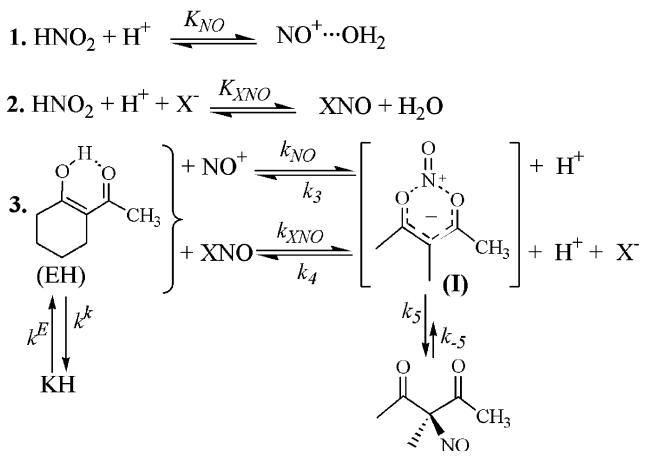
By contrast, the kinetic observations for the nitrosation of ACHE resembles to those found in the case of the

TABLE 2. Experimental Conditions and Parameters Obtained in the Nitrosation of ACHE in Aqueous Acid Medium at [Nitrite] = 1.7 × 10^{-3} M in the Presence of X^{-a}

X^-	$[H^+]$/M	I/M	$k_o^w/10^{-3}$ s^{-1}	γ/mol^{-1} dm^3 s^{-1}	η/mol^{-1} dm^3	r
Cl^-	0.010	0.80	5.6	0.0146 ± 0.0009	0.89 ± 0.09	0.999
Cl^-	0.015	0.40	5.7	0.020 ± 0.002	1.3 ± 0.3	0.999_7
Cl^-	0.025	0.80	9.9	0.031 ± 0.002	1.6 ± 0.2	0.99_8
Br^-	0.010	0.40	4.2	0.066 ± 0.002	4.6 ± 0.2	0.999_4
Br^-	0.015	0.20	5.0	0.103 ± 0.005	7.2 ± 0.5	0.999
Br^-	0.023	0.40	7.7	0.180 ± 0.008	10.15 ± 0.60	0.998
SCN^-	0.010	0.25	3.8	0.81 ± 0.05	59 ± 7	0.999_8
SCN^-	0.015	0.20	4.8	1.32 ± 0.06	92 ± 7	0.999
SCN^-	0.020	0.25	6.2	1.95 ± 0.01	134 ±12	0.999_8

[a] k_o vs $[X^-]$ profiles were analyzed from eq 6.

SCHEME 2. Proposed Reaction Mechanism for the Nitrosation of ACHE in Aqueous Acid Media



nitrosation of aliphatic nitro compounds and also with that observed very recently in the nitrosation of 2-acetylcyclopentanone. Nevertheless, although the keto−enol tautomerization in the ACPE system is fast and the overall nitrosation reaction is irreversible, both k_o vs [nitrite] or k_o vs $[H^+]$ graphs show negliglible intercepts at the origin.[6]

The experimental observations for the nitrosation of ACHE may be mechanistically interpreted as follows. In aqueous strong mineral acid solutions, the effective nitrosating agents are those derived from protonation of nitrous acid: $HNO_2 + H^+ \rightleftharpoons NO^+ + H_2O$, with $K_{NO} = 3 \times 10^{-7}$ mol^{-1} dm^3 being the corresponding equilibrium constant.[8] In the presence of nonbasic nucleophiles (X^-), such as Cl^-, Br^-, or SCN^-, equilibrium formation of nitrosyl compounds, namely XNO, also occurs: $X^- + HNO_2 + H^+ \rightleftharpoons XNO + H_2O$, with K_{XNO} being the corresponding equilibrium constant, which at 25 °C takes on values of 1.14×10^{-3} when $X^- = Cl^-$; 5.1×10^{-2} when $X^- = Br^-$, or 30 mol^{-2} dm^6 when X^- represents SCN^-.[9] Nitrosyl compounds act as nitrosating species and, despite their lower reactivity with regard to that of NO^+, catalysis by X^- is generally observed, due to the greater concentration of the nitrosyl compounds resulting from the high value of K_{XNO} in comparison to K_{NO}. Then, the kinetic features observed here may be explained by means of the reaction mechanism of Scheme 2, in which the enol undergoes nitrosation to give the chelate-nitrosyl complex intermediate in steady-state, and subsequently rearranges to the C-nitroso compound; moreover, the enol-ketonization step is also included, whose rate constant is comparable to that of nitrosation at low $[H^+]$.

From Scheme 2, in which the enol form of ACHE is the nitrosatable species either by NO^+ or by XNO (in the presence of X^-), by taking into account the mass balance equation, $[ACHE]_t = [EH]$, that $[NO^+] = K_{NO}[nitrite][H^+]$; $[XNO] = K_{XNO}[nitrite][H^+][X^-]$, and by assuming a steady-state for the intermediate, eq 7 can be derived, where $k_1 = k_{NO}K_{NO}$ and $k_2 = k_{XNO}K_{XNO}$.

$$k_o = k + \left[\frac{k_1 + k_2[X^-]}{1 + \frac{k_3}{k_5}[H^+] + \frac{k_4}{k_5}[H^+][X^-]}\right][H^+][\text{nitrite}] \quad (7)$$

The comparison of this eq with eq 4 indicates that in aqueous perchloric acid, the α-parameter that increases with $[H^+]$ (see Table 1) equals the expression of $k_1[H^+]$, whereas the comparison with eq 5 shows that the β-parameter (which increases with [nitrite]) is equal to k_1[nitrite]. The corresponding values of both parameters obtained under several experimental conditions which are listed in Table 1 afford an average value of $k_1 = 131$ mol^{-2} dm^6 s^{-1} (or $k_{NO} = 3.7 \times 10^8$ mol^{-1} dm^3 s^{-1}), see Table 3.

The influence of $[X^-]$ was studied at low $[H^+]$ (see Table 2). Since $k_3/k_5 \approx 1.4$ mol^{-1} dm^3, the second term in the denominator of eq 7 is negligible; therefore, the η-parameter in eq 6 is equal to $(k_4/k_5)[H^+]$. The corresponding values listed in Table 2 give the average values of k_4/k_5 shown in Table 3. These values increase with the nucleophilic character of X^- in a relative proportion of 1:6:80, in agreement with the nature of the k_4 process. However, this effect is more pronounced in the case of 2-acetylcyclopentanone, which indicates that the nitrosyl-chelate complex is more stable. On the other hand, the values of γ reported in Table 2 allow the determination of the bimolecular rate constants for the nitrosation carried out by the nitrosyl salts ClNO, BrNO, or SCNNO, which are collected in Table 3, along with values of the same rate constants obtained in the nitrosation of other 1,3-dicarbonyl compounds previously studied. In every case, the reactivity order found as $NO^+ > ClNO > BrNO > SCNNO$ is that expected if one remembers that it is an electrophilic attack, then the most polar the bond

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TABLE 3. Rate Constants Obtained in the Nitrosation of ACHE in Aqueous Acid Medium at 25 °C (See Scheme 2 for Their Meaning)[a]

	ACHE[b] (this work)		ACPE[b] (ref 6)	ECHC[b] (ref 7)	AcAc[b] (ref 5)
X-NO	k_{XNO}/mol^{-1} dm^3 s^{-1}	k_4/k_5/mol^{-2} dm^6	k_{XNO}/mol^{-1} dm^3 s^{-1}	k_{XNO}/mol^{-1} dm^3 s^{-1}	k_{XNO}/mol^{-1} dm^3 s^{-1}
NO^+ ($X = H_2O$)	3.7×10^8	1.4[a]	7.3×10^8	6.1×10^8	4.4×10^7
ClNO	6.9×10^5	80	4.2×10^6	1.7×10^6	7.2×10^4
BrNO	8.1×10^4	460	1.2×10^6	2.2×10^5	7.1×10^3
SCNNO	1.7×10^3	6230	6.5×10^4	3.6×10^3	7.3×10^2

[a] The bimolecular rate constants, k_{XNO}, obtained in the nitrosation of other 1,3-diketones are also reported. [b] ACHE, 2-acetylcyclohexanone; ACPE, 2-acetylcyclopentanone; ECHE, ethyl 2-cyclohexanone carboxylate; AcAc, acetylacetone.

X−NO the most positive charge support the N-atom, which means higher reactivity. The polarity of the X−NO bond increases with the electronegativity of X. On the other hand, whatever the nitrosating agent, the cyclic diketones, ACPE, ACHE, or ECHC, are more reactive than the aliphatic diketone acetylacetone (AcAc), and 2-acetylcyclopentanone is the most reactive substrate as a consequence of the higher stability of the chelate nitrosyl complex intermediate.

Aqueous Cyclodextrin Solutions. Cyclodextrins are attractive components of artificial enzymes: the apolar cavity is a specific, discriminating, and orientating site.[10,11] In aqueous solution, the slightly apolar cyclodextrin cavity is occupied by water molecules (polar−apolar interactions energetically unfavored) and can be readily substituted by appropriate guest molecules of a substrate less polar than water. The driving force of a hydrophobic substrate to bind the interior cavity of a cyclodextrin is the substitution of the high-enthalpy water molecules by stronger substrate-cyclodextrin interactions. This interaction can be established either by a covalent bond or by some noncovalent bond (e.g., H-bonding, van der Waals forces, specific steric disposition, etc).

In the covalent interaction, the reaction usually proceeds according to the Michaelis−Menten type and a catalysis by cyclodextrins is observed, which reveals some characteristics of enzyme-catalyzed reactions, such as saturation limit, competitive inhibition, ...[12,13]

In the noncovalent interaction, the hydrophobic cavity of the CD gives the substrate access to a new reaction environment, in which the reactivity changes. In most cases, the reactivity decreases, i.e. the encapsulated substrate is effectively protected against the other reactant in a bimolecular reaction. In this case, it is often to say that cyclodextrin mediates the reaction.

The effect of cyclodextrin addition on both nitrosation and enol−ketonization reactions of ACHE in aqueous medium is an example of the latter situation. The enol tautomer of ACHE forms inclusion complexes with CD, a fact that gives rise to two observations; on one hand, the keto−enol equilibrium in water is displaced to the enol side (due to enol encapsulation), and second, the included enol is protected against transformations that involved hydrophilic reagents, such as the nitrosating agent, XNO, in nitrosation or the H^+/H_2O in enol ketonization. Next, we describe the work performed on the effect, of β-cyclodextrin (β-CD) on this two reactions undergone by the enol of ACHE in aqueous acid medium, and then we will comment the effect of α-cyclodextrin (α-CD) on the same two reactions.

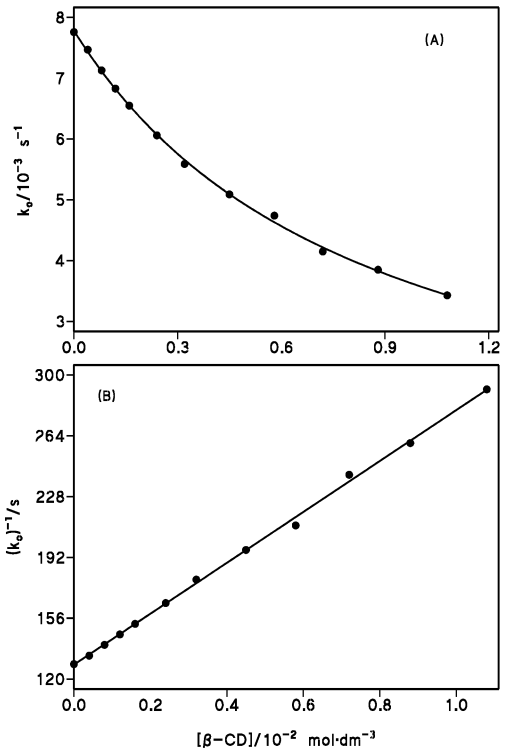

FIGURE 4. (a) Influence of β-CD concentration on the pseudo-first-order rate constant for the nitrosation of the enol of ACHE ([nitrite] = 1.7×10^{-3} M; [H^+] = 0.033 M, HCl); (b) reciprocal plot of k_o as a function of [β-CD].

1. β-Cyclodextrin. (a) Nitrosation Reaction. The influence of β-CD concentration on the nitrosation in acid medium of ACHE has been performed at [nitrite] = 1.7×10^{-3} M and [H^+] = 0.033 M (HCl) by following the absorbance decrease at 291 nm due to enol absorption ($A_0 - A_\infty > 0.85$ absorbance units). Under these experimental conditions, the pseudo-first-order rate constant varies proportional to both [nitrite] and [H^+]. The variation of k_o as a function of [β-CD] is displayed in Figure 4, along with the reciprocal plot of k_o against [β-CD]. The latter graph is a good straight line, which indicates that the inhibition of β-CD is due to the formation of 1:1 unproductive complexes between the enol tautomer (the reactive form in nitrosation) of ACHE and β-CD, according to the proposed reaction mechanism of Scheme 3.

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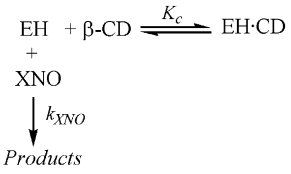
SCHEME 3. Reaction Mechanism for the Nitrosation of ACHE in the Presence of β-CD



Since the [β-CD] is always much higher than the total [ACHE] (= 6.5×10^{-5} M) in eq 8, derived from Scheme 3, the term [β-CD] refers to the stoichiometric concentration.

$$k_o = \frac{k_w}{1 + K_c[\beta - CD]} \quad (8)$$

The solid line in Figure 4a corresponds to the calculated points from eq 8 with $k_w = (7.78 \pm 0.03) \times 10^{-3}$ s^{-1} and $K_c = 117 \pm 2$ $mol^{-1}dm^3$ ($r = 0.999_5$); quite close results of k_w and K_c are determined from the intercept (=128.5 ± 0.9 s) and slope (=15 100 ± 300 mol dm^{-3} s) values of the linear correlation shown in Figure 4b.

At $[H^+] = 0.015$ M, [nitrite] $= 1.7 \times 10^{-3}$ M, and [β-CD] $= 5.2 \times 10^{-3}$ M, we studied the influence of $[Br^-]$ on the nitrosation of the enol of ACHE. The results of k_o vs $[Br^-]$ profiles (data not shown) fit perfectly eq 6 when $k_o^{w'} = 2.4 \times 10^{-3}$ s^{-1}, $\gamma' = 0.057 \pm 0.003$ mol^{-1} dm^3 s^{-1}, and $\eta = 6.4 \pm 0.5$ mol^{-1} dm^3. These values are in good agreement with the calculated ones if one assumes that the nitrosation occurs in aqueous medium; i.e., the complexed enol is unreactive, which implies that $k_o^{w'} = k_o^w/(1 + K_c[\beta\text{-CD}])$ and $\gamma' = \gamma/(1 + K_c[\beta\text{-CD}])$.

(b) Tautomerization Reaction. We study also the influence of [β-CD] on the enol−ketonization of ACHE in water and in aqueous hydrochloric acid 0.033 and 0.066 M. The k_o vs [β-CD] profiles, shown in Figure 5a, resemble those observed in nitrosation. The effect of β-CD is an inhibition of the tautomerization reaction which is catalyzed by H^+, as it can be observed in the absence of β-CD (see the preceding paper in this issue[16]). The observed inhibition can be due to the formation of unproductive complexes (like in the case of nitrosation) or due to the formation of productive complexes less reactive than the free enol. In the former situation eq 8 works also here for the quantitative treatment of k_o vs [β-CD] profiles. Solid lines in Figure 5a correspond to the calculated points from eq 8 by using the k_w and K_c values reported in Table 4; the Figure C shows the reciprocal plot of k_o against [β-CD]; in every case, good straight lines are drawn, as expected from eq 8.[14]

Moreover, in studying the tautomerization reaction, the absorbance readings at infinite time (A_∞) increase with the [β-CD]. This is an expected result if the enol is the only tautomer forming inclusion complexes with the β-CD host. As the enol forms intramolecular H-bonds, the included guest is protected from the competition with water molecules in H-bonding formation, which would stabilize the enol isomer. Then, once the keto−enol equilibrium is reached ($t = \infty$) the Scheme 4 should apply, and from which it can be defined an apparent keto−enol equilibrium constant according to eq 9.

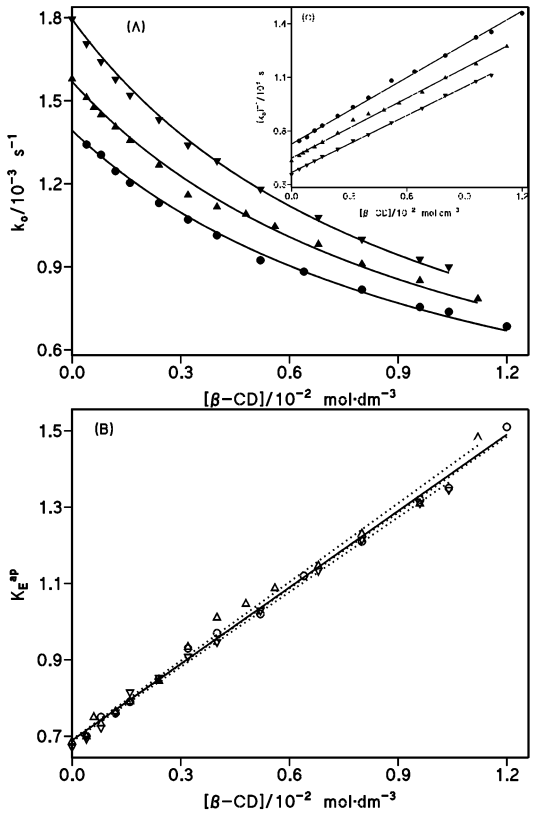
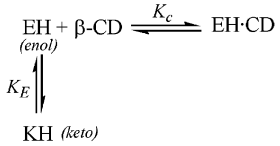


FIGURE 5. (a) Influence of β-CD concentration on the pseudo-first-order rate constant for the enol-ketonization at $[H^+]$ equal to (●) 0, (▲) 0.033, and (▼) 0.066 M, HCl. The inset shows the reciprocal plot of k_o. The calculated lines were generated from eq 8 with the fitted constants in Table 4. (b) Variation of K_E^{app} as a function of [β-CD].

SCHEME 4. Keto-Enol Equilibrium Steps in the Presence of β-CD



$$K_E^{app} = \frac{[EH]_t}{[KH]} = \frac{[EH]_w + [EH{\cdot}CD]}{[KH]_w} = K_E(1 + K_c[\beta{-}CD]) \quad (9)$$

On the other hand, the experimental values of K_E^{app} can be determined for each [β-CD] as $A_\infty/(A_o - A_\infty)$, where A_o and A_∞ are the absorbance values at zero and infinite time, respectively, and both were obtained in the fit of eq 1 to the experimental pairs *A*-time. Figure 5b shows the variation of K_E^{app} determined in this way as a function of [β-CD]. According to eq 9, a straight line is obtained and least-squares treatment of all points, i.e., obtained in the experiments carried out in water or either at 0.033 and 0.066 M of HCl, gives $K_E = 0.689 \pm 0.005$

(14) Data in Figure 5 can also be fitted if one assumes the formation of reactive EH·CD complexes. In that case, K_c increases a little (up to 122−128 mol^{-1} dm^3); however, the rate constant for the tautomerization of the complexed enol is of the order of $(2.1-2.4) \times 10^{-4}$ s^{-1}, i.e., near 10-fold lower than the rate constant measured in water and since the highest [β-CD] < 0.01 M, the term $k_c K_c[\beta\text{-CD}]$ is negligible in comparison with k_w.

TABLE 4. Rate and Equilibrium Constants Obtained in the Study of the Nitrosation or Enol−Ketonization Reactions of the Enol of ACHE in the Presence of *β*-Cyclodextrin and α-Cyclodextrin

β-Cyclodextrin (eq 8, Scheme 3)

reaction	$[H^+]$/M	$k_w/10^{-3}$ s^{-1}	K_c/mol^{-1} dm^3
nitrosation	0.033	7.78 ± 0.03	117 ± 0.02
enol−ketonization	0.00	1.393 ± 0.008	95 ± 2
enol−ketonization	0.033	1.57 ± 0.01	94 ± 1
enol−ketonization	0.066	1.770 ± 0.006	95.8 ± 1.5

α-Cyclodextrin (eqs 10 and 11, Schemes 5 and 6)

reaction	$[H^+]$/M	$k_w/10^{-3}$ s^{-1}	K_{11}/mol^{-1} dm^3	K_{12}/mol^{-2} dm^6	$k_c/10^{-3}$ s^{-1}
nitrosation	0.033	8.05 ± 0.06	20 ± 1	247 ± 25	
enol−ketonization	0.0	1.41	18 ± 4	236 ± 61	1.19 ± 0.09
enol−ketonization	0.033	1.60	18 ± 3	270 ± 41	1.05 ± 0.13

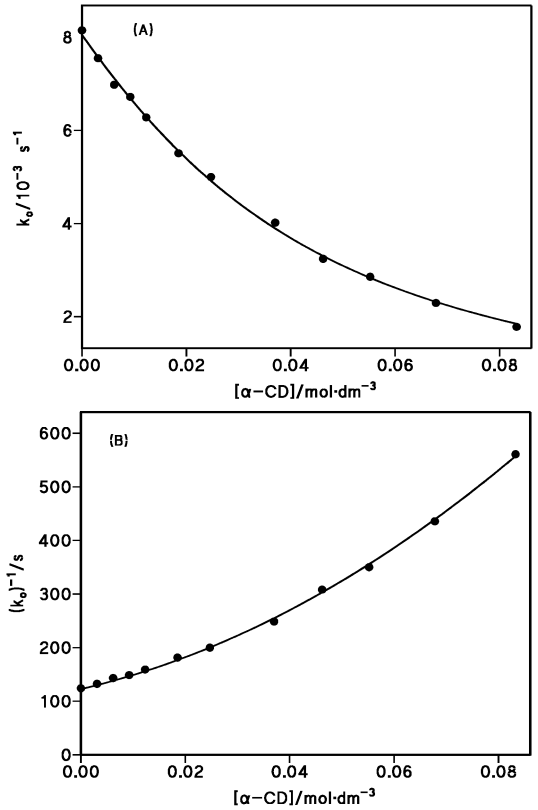
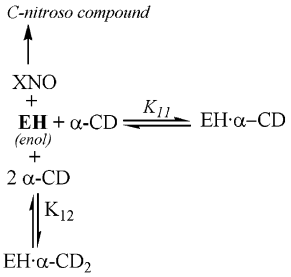


FIGURE 6. (a) Plot of k_o vs [α-CD] for the nitrosation of the enol of ACHE at [nitrite] = 1.7×10^{-3} M, $[H^+]$ = 0.033 M, HCl; (b) reciprocal plot of k_o vs [α-CD].

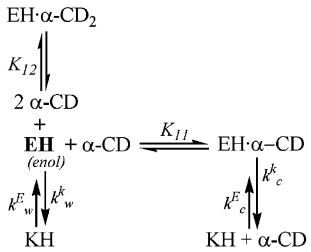
and $K_c = 97 \pm 2$ mol^{-1} dm^3. The former value is in good agreement with that determined in water (see the preceding paper in this issue[16]), whereas the latter is also in concordance with that determined either from nitrosation or tautomerization kinetic studies.

2. α-Cyclodextrin. (a) Nitrosation Reaction. The influence of α-CD on the nitrosation of the enol of ACHE in aqueous acid medium (HCl, 0.033 M) has been analyzed at constant [nitrite] (= 1.7×10^{-3} M), acidity, and [ACHE] (= 6.2×10^{-5} M) much lower than [α-CD]. Under these experimental conditions, the absorbance versus time profiles fit perfectly the integrated first-order equation, where $A_o - A_\infty \approx 0.85$ and $A_\infty \approx 0.075$ absorbance units. The results of k_o obtained as a function of [α-CD] are shown in Figure 6a. A decrease of k_o by more than 4.5-fold at the highest [α-CD] with respect to the value obtained in the absence of α-CD can be observed; moreover, the reciprocal plot of k_o does not increase linearly with the [α-CD]; see Figure 6b. This fact suggest the formation of nonproductive inclusion complexes other than of 1:1 stoichiometry. We postulated the formation of 1:1 and 1:2 inclusion complexes between the enol of ACHE and α-CD according to Scheme 5.

SCHEME 5. Proposed Reaction Scheme for the Nitrosation of ACHE in the Presence of α-CD



SCHEME 6. Postulated Rate and Equilibrium Steps for the Enol−Ketonization in Water in the Presence of α-CD



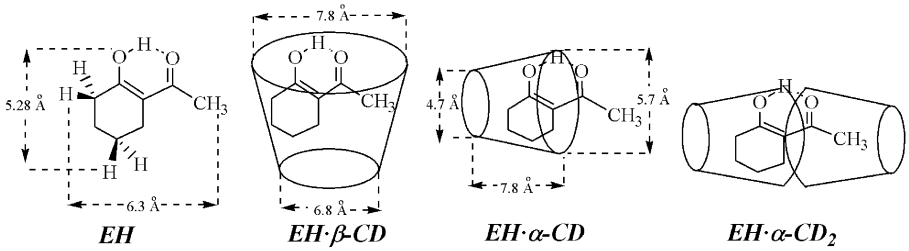
The resulting expression of k_o by starting from this scheme is that of eq 10, where k_w refers to the rate constant of nitrosation in the absence of α-CD.

$$k_o = \frac{k_w}{1 + K_{11}[\alpha\text{-CD}] + K_{12}[\alpha\text{-CD}]^2} \qquad (10)$$

Solid line in Figure 6 correspond to the fit of this eq to the experimental points when $k_w = (8.05 \pm 0.06) \times 10^{-3}$ s^{-1}; $K_{11} = 20 \pm 1$ mol^{-1} dm^3, and $K_{12} = 247 \pm 25$ mol^{-2} dm^6 ($r = 0.999_6$). If eq 10 applies, the graph of $(1/k_o)$ against [α-CD] should not be a straight line; the resulting plot can be seen in Figure 6b. The nonlinear analysis in the form of $(k_o)^{-1}$ versus [α-CD] gives quite similar values for the unknown parameters to that determined above.

(b) Tautomerization Reaction. The influence of α-CD on the tautomerization reaction has been studied

SCHEME 7. Assumed Conformation of the Inclusion Complexes Formed between the Enol of ACHE and β- or α-Cyclodextrin



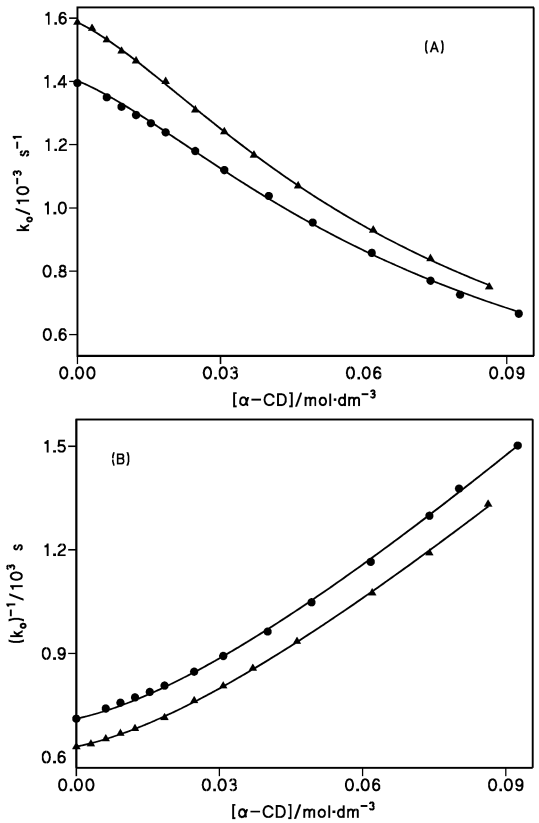


FIGURE 7. (a) Plot of k_o vs [α-CD] for the enol−ketonization reaction of ACHE at [H^+] equal to (●) 0 and (▲) 0.033 M, HCl. The calculated curves were generated from eq 11 with the fitted constants in Table 4; (b) reciprocal plot of k_o against [α-CD].

in water and in aqueous hydrochloric acid (0.033 M). The results are displayed in Figure 7.

It can be observed that α-CD inhibits also the enol ketonization reaction; however, the comparison between Figures 6 and 7 indicates that while in nitrosation k_o decreases more than 4.5-fold at the highest [α-CD] used, the reduction effect in enol−ketonization is approximately half, i.e., $k_w/k_o \approx 2.1$ with k_o being the observed rate constant measured in the presence of 0.095 M of α-CD. One can also note that the reduction effect is slower at low [α-CD] than at the higher [α-CD]. In addition, the reciprocal plot of k_o against [α-CD] is not a straight line, which suggests again the formation of both inclusion complexes of 1:1 and 1:2 stoichiometries between the enol of ACHE and α-CD. Such an unusual behavior of α-CD has already been observed in the cleavage of 2-nitrophenyl propanoate in aqueous phosphate buffer.[15] These experimental findings lead to the proposal of the reaction mechanism of Scheme 6, in which we are assuming the formation of 1:1 reactive complexes as well as nonproductive complexes of stoichiometry 1:2.

From this scheme eq 11 may be derived, in which k_c is the first-order rate constant of the tautomerization of the included enol: EH·α-CD.

$$k_o = \frac{k_w + K_{11}k_c[\alpha\text{-CD}]}{1 + K_{11}[\alpha\text{-CD}] + K_{12}[\alpha\text{-CD}]^2} \qquad (11)$$

The solid lines in Figure 7 were drawn from the above equation with the values of k_w, K_{11}, K_{12}, and k_c reported in Table 4. The reactivity of the complexed enol, k_c, is quite similar to the rate constant measured in water, k_w. This means that the reaction center in the ACHE molecule should not be very far inside the α-CD cavity to allow the access of H_2O molecules. Therefore, taking into account the dimensions of both the α-CD host and the enol (EH) guest of the optimized structures for the gas phase, we could postulate the structures shown in Scheme 7 for the most probable conformations adopted for the different inclusion complexes. From this picture, we can understand the nonreactivity of the complexed enol with β-CD, neither in nitrosation nor in tautomerization; by contrast, due to the dimensions of α-CD in comparison with that of EH, the latter is not deeper encapsulated by one α-CD molecule which allows the presence of solvent molecules surrounding the complex, consequently the 1:1 complexed enol can be reactive as experimentally has been observed. However, in nitrosation the reaction is not possible due to, first, the concentration of the nitrosating agent, XNO, is too small, and second, the XNO are very hydrophilic species.

Conclusions

The nitrosation of ACHE in aqueous strong acid media goes through the enol tautomer and is catalyzed by the nonbasic nucleophiles, Cl^-, Br^-, or SCN^-, due to the appearance of new nitrosation reaction paths involving the nitrosyl salts: XNO. The reactivity of these nitrosating agents decreases with the electronegativity and/or polarizability of X. By contrast, the observed trend of the nucleophilic character, evaluated from the ratio k_4/k_5, increases in the order $Cl^- < Br^- < SCN^-$, in accordance with the higher hydration degree of the anion which reduces its nucleophilicity. The presence of β-CD decreases the rate of the reaction for both enol-nitrosation

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and enol-ketonization. The inhibition is due to the protection of the enol tautomer included into the cyclodextrin cavity. Addition of α-CD reduces also the reaction rate for both enol−nitrosation and enol−ketonization, however the effect is smaller in the latter reaction as a consequence of, whereas in the tautomerization reaction the enol encapsulated by only one molecule of α-CD reacts with the H_2O molecules, the reaction is not possible with any nitrosating agent (XNO is highly hidrophilic species present at very small concentrations). Therefore, the inhibition effect is higher in nitrosation than in tautomerization. Moreover, in the presence of α-CD, the formation of inclusion complexes of stoichiometry 1:2 is kinetically detected.

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