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Ester Hydrolysis and Enol Nitrosation Reactions of Ethyl Cyclohexanone-2-carboxylate Inhibited by β-Cyclodextrin

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Both the ester hydrolysis and the nitrosation reactions of the enol tautomer of ethyl cyclohexanone-2-carboxylate (ECHC) are investigated in the absence and presence of β-cyclodextrin (β-CD). The ester hydrolysis reaction is studied in dilute H_2O and D_2O solutions of hydrochloric acid and in aqueous buffered solutions of carboxylic acids (acetic acid and its chloro derivatives). The pseudo-first-order rate constant increases with both the $[H^+]$ and the total buffer concentration, indicating that the hydrolysis is subject to acid and general base catalysis. Substantial solvent isotope effects in the normal direction ($k_H/k_D > 1$) for the acid-catalyzed hydrolysis was observed. Addition of β-CD strongly slows the hydrolysis reaction. The variation of the observed rate constant (k_o) with [β-CD] exhibits saturation behavior, consistent with 1:1 binding between the enol of ECHC and β-CD. The binding is quite strong, and bound ECHC-enol is unreactive. The nitrosation reaction of ECHC in aqueous acid medium, using sodium nitrite in great excess over the concentration of ECHC, yields perfect first-order kinetics, indicating that the slow step is the nitrosation of the enol tautomer. This finding suggests that a great percentage of the total ECHC concentration must exist in the enol form. The nitrosation reaction is of first order in [nitrite] and is catalyzed by the presence of Cl^-, Br^-, or SCN^- ions, which indicates that the attack of the nitrosating agent is the slow step. The nitrosation reaction is also strongly inhibited by the presence of β-CD because of the formation of unreactive inclusion complexes between the host, β-CD, and the guest, the enol of ECHC. In alkaline medium, the formation of the enolate ion is observed, which absorbs at higher wavelengths ($\lambda_{max} = 256$ nm in acid medium shifts to $\lambda_{max} = 288$ nm in alkaline medium). This anion also undergoes ester hydrolysis spontaneously, but shows neither specific basic catalysis nor appreciable effect by the presence of β-CD. From kinetic and spectroscopic measurements the pK_a of the enol of ECHC has been determined as 12.35.

Introduction

Cyclodextrins (CDs) are α-1,4-linked cyclo oligomers of D-glucopyranose, soluble in water, which possess the remarkable property of forming inclusion complexes with a variety of compounds.[1−3] Some of the primary consequences of the complexation process are as follows. The selective inclusion of a species present in an equilibrium (as in keto−enol tautomerism)[4] shifts the position of the equilibrium. The chemical reactivity of the included molecule is modified. (This occurs in the cleavage of nitrophenylesters in basic media[5−7] or in the hydrolysis and aminolysis of alkyl nitrites[8,9]). The solubility of molecules of interest, e.g. pharmaceuticals,[10] is improved.

The vast majority of studies of the influence of CDs on the reactions of organic guests have been carried out in neutral or basic aqueous solutions, and many of these studies are concerned with the hydrolysis of esters in basic medium. Under such conditions, the rate of the cleavage of phenyl acetates increases in the presence of CDs because the phenyl acetate in the CD-cavity transfers the acyl group to an ionized secondary hydroxyl group of CD more efficiently than does the free phenyl acetate to an OH^- (or other base). However, the effect of CDs on the acid-catalyzed hydrolysis of esters has been ignored. This work will attempt to shed light on this issue.

Investigations of the keto−enol equilibria of β-diketones and β-keto-esters have been carried out in several organic solvents.[11−13] Recently, we studied this equilibrium in aqueous micellar solutions[14−16] and in aqueous β-CD solutions.[4] A common observation throughout these studies is that either micellar solutions or β-CD will

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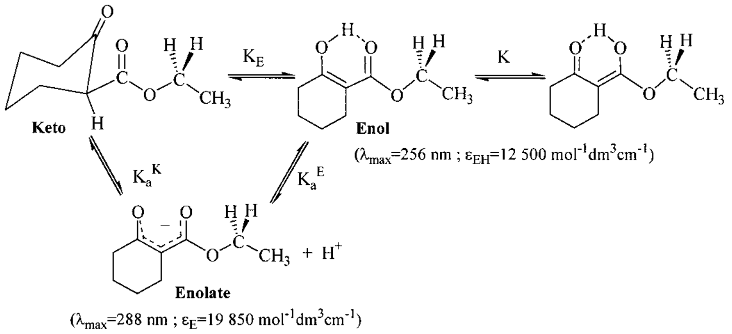
Scheme 1



increase the enol content of β-diketones or β-keto-esters. Few literature references are devoted to the keto–enol tautomerism of ECHC. Ethyl cyclohexanone-2-carboxylate is 63% enolized in methanol,[17] and 88% enolized in the gas phase at 25 °C.[18] By contrast, ethyl cyclopentanone-2-carboxylate contains 0.4% of enol in water, which increases to 2.5% in methanol,[19] and to 27.5% in the gas phase.[18] In unsymmetrical β-keto-esters, the enol function may reside in the ester or ketone groups, but NMR results reveal the highest content of the dicarbonyl compound with the OH group on the cycloalkane[20] ($K < 1$ in Scheme 1). It appears, however, that the enolization equilibria of alkyl ketocycloalkane-2-carboxylates exhibit an interesting variation depending on the ring size, with the enolization equilibrium constant K_E being maxima for the 6, 8, and 10-membered rings, whereas in the benzoylcycloalkanone series the five membered compounds show the highest enolic content.[11,21]

In this work we report the results of the influence of β-CD on two important reactions of ECHC that occur in aqueous acid medium: the ester hydrolysis and the nitrosation of the enol. The presence of β-CD does not modify the keto–enol equilibrium of ECHC in water because this β-keto ester is practically 100% enolized, but the addition of β-CD strongly inhibits both the ester hydrolysis reaction (either acid or general base catalyzed) and the nitrosation of the enol tautomer by several nitrosating agents.

Experimental Section

ECHC, Merck product of the maximum purity, was used as supplied. β-CD was purchased from Aldrich and was used without further purification. D_2O (Solvents, Documentation, Synthèses Laboratories) was >99.9% isotope enrichment and $d = 1.11$. All other reagents were supplied by Merck and were used as received. Solutions were prepared with doubly distilled water (first distilled over potassium permanganate solution and then redistilled).

Pure ECHC was dissolved in dry dioxane (spectrophotometric grade). The hydrolysis (or the nitrosation) reaction of ECHC was initiated with the addition of 10 or 15 μL of a solution of ECHC in dioxane to the reaction mixture to reach a final reaction volume of 3.0 mL.

UV–vis absorption spectra and kinetic measurements were recorded with a Kontron-Uvikon (model 942) double-beam spectrophotometer, provided with multiple cell carriers thermostated by circulating water. The pH was measured with a Crison pH-meter equipped with a Combined glass electrode (GK2401C). In the cases of dicloro- and trichloroacetic acid-trichloroacetate ion buffers, it was necessary to adjust the pH in order to keep it constant as the buffer concentration was allowed to vary. All experiments were performed at 25 °C.

Kinetic experiments were carried out under pseudo-first order conditions, with the acid (the base, or the nitrosating agent) concentration greatly exceeding (more than 25-times) the ethyl cyclohexanone-2-carboxylate concentration ([ECHC] $\approx$ (8 to 4) $\times 10^{-5}$ M). In each kinetic experiment the integrated method was applied, with decreasing absorbance followed during the course of the reaction, fitting the experimental data (absorbance, A-time, t) to the first order integrated equation expressed in eq 1, with A_o, A_t, and A_∞ being the absorbance readings at zero, t, and infinite times, respectively, and with k_o being the observed rate constant measured in s^{-1}.

$$A_t = A_\infty + (A_o - A_\infty)e^{-k_ot} \qquad (1)$$

Results and Discussion

1. Acid Medium. The Ester Hydrolysis Reaction. Spectroscopic Studies. Figure 1a shows the UV-absorption spectra of 6.3 $\times 10^{-5}$ M of ECHC in an aqueous hydrochloric acid solution of $[H^+] = 0.050$ M with water only in the reference cell. The absorption band centered at $\lambda = 256$ nm decreases with time. The spectra of 6.3 $\times 10^{-5}$ M of ECHC dissolved in dioxane displays the same absorption band (dashed line), but the absorbance intensity remains precisely unchanged with regard to time if the solvent was previously dried (the reference cell contains dioxane). Figure 1b shows the UV-absorption spectra of 6.3 $\times 10^{-5}$ M of ECHC in an aqueous solution of acetic acid-acetate buffer of pH 5.50 and [buffer] = 0.10 M. The spectrum resembles that recorded in aqueous hydrochloric acid, except for the band owing to buffer that appears at wavelengths lower than approximately 220 nm and where, it may be noted, reaction is much faster. In fact, to be able to draw scans of the reaction it was necessary to record the reaction spectra in the presence of 4.1 $\times 10^{-3}$ M of β-CD because β-CD strongly decreases the rate of hydrolysis (vide infra).

The enol tautomer of 1,3-dicarbonyl compounds is stabilized by intramolecular hydrogen bonds (Scheme 1); therefore, the enol content increases in aprotic and/or apolar solvents, when intermolecular hydrogen bonding with the solvent does not compete. Here, we attribute the band centered at 256 nm to the enol form of ECHC, and finding the intensity of this absorption band practically the same in both water and pure dioxane solvents

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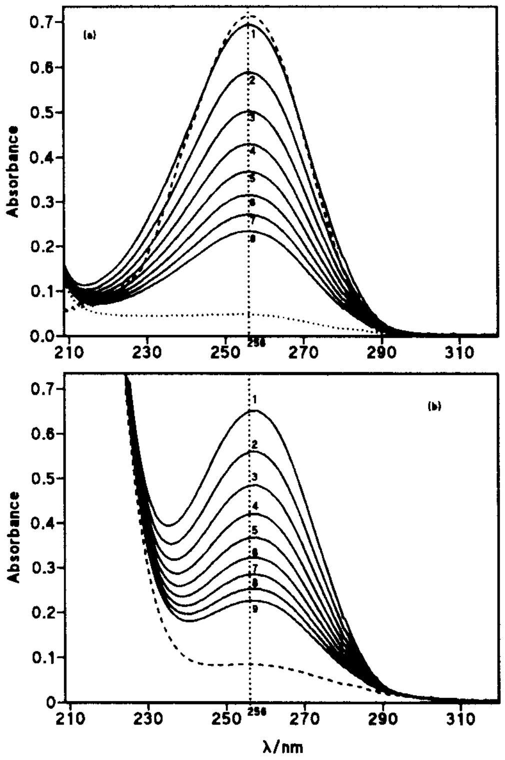

Figure 1. (a) Repeat scans (1–8) every 2 min showing the decreasing absorbance at 256 nm due to the ester hydrolysis of the ester of ECHC-enol (6.3×10^{-5} M) at $[H^+] = 0.050$ M (HCl); (···) the reaction spectra at infinite time; (- - -) the spectra in dry dioxane taken by placing the same solvent in the reference cell; (b) repeat scans every 30 s showing the decreasing absorbance at 256 nm due to general base-catalyzed hydrolysis of the ester of ECHC (6.3×10^{-5} M) in acetic acid-acetate buffer of pH 5.50 and $[\text{buffer}]_t = 0.10$ M in the presence of [β-CD] = 4.1 mM: (- - -) scan at the end of the reaction, approximately.

Table 1. Values of the Observed Rate Constant, k_o, Obtained in the Acid Hydrolysis of Ethyl Cyclohexanone-2-carboxylate as a Function of the Ionic Strength (I = [HCl] + [NaCl]) at $[H^+] = 0.050$ M

I/M	k_o/s^{-1}
0.055	1.38×10^{-3}
0.083	1.39×10^{-3}
0.117	1.29×10^{-3}
0.183	1.34×10^{-3}
0.283	1.40×10^{-3}
0.383	1.49×10^{-3}
0.555	1.40×10^{-3}

indicates that the ECHC is nearly 100% enolized in aqueous acid medium ($K_E \gg 1$).

As obtained from kinetic experiments, the absorbance readings at 256 nm extrapolated at $t = 0$, along with the stoichiometric concentration value of ECHC, result in an estimated $\epsilon_{EH} = 12\,500$ mol^{-1} dm^3 cm^{-1} for the extinction coefficient of the enol tautomer of ECHC (Table 2 contains representative results, vide infra). This is, of course, an approximate value; due to ester hydrolysis it is not possible to prepare aqueous solutions of ECHC. This limitation involves the addition of a very small volume (10–15 μL) of a stock dioxane solution of ECHC to the rest of the reaction mixture (total volume 3 mL), to be able to conduct the study in water with the least possible amount of dioxane solvent. Nevertheless, the extinction coefficient estimated in this way, as the average value of several kinetic and spectral measurements, concurs quite well with the extinction coefficient corresponding to the enol tautomer of other 1,3-dicarbonyl compounds measured at the maximum wavelength absorption and determined from application of the Beer–Lambert law to aqueous solutions of the dicarbonyl compound.[14,22] There is no doubt that the decrease in absorbance at 256 nm is a consequence of the hydrolysis, an acid–base-catalyzed reaction, yielding ethanol and cyclohexanone-2-carboxylic acid.

Table 2. Variation of the Pseudo-first Order Rate Constant Obtained in the Base-Calatyzed Hydrolysis of ECHC ([ECHC] = 8.4×10^{-5} M) as a Function of the Total Acetic Acid–Acetate Buffer Concentration at pH 4.15

[buffer]/M	k_o/s^{-1}	$A_o - A_\infty$[a]	ϵ_{EH}/mol^{-1} dm^3 cm^{-1}
0.0167	1.87×10^{-3}	1.063	12 655
0.025	2.28×10^{-3}	1.184	14 095
0.033	2.66×10^{-3}	1.213	14 440
0.050	3.55×10^{-3}	1.098	13 067
0.066	4.38×10^{-3}	1.101	13 107
0.100	5.98×10^{-3}	1.048	12 476
0.133	7.54×10^{-3}	1.062	12 643
0.167	9.23×10^{-3}	1.018	12 131

[a] Total absorbance decrease at 256 nm.

Kinetic Studies. Acid Catalysis. Reaction kinetics in acid medium were followed by recording the decrease in absorbance at 256 nm. The reaction spectrum was clean in every case, the total decrease in absorbance being of the order of 0.8 units at [ECHC] ≈ 6×10^{-5} M. The fit of the experimental $A - t$ data to eq 1 was excellent in all cases (correlation coefficients were better than 0.9999). Rates of ester hydrolysis were measured in dilute H_2O and D_2O solutions of hydrochloric acid and in H_2O solutions of carboxylic acid buffers. At $[H^+] = 0.050$ M (HCl) we looked at the influence of ionic strength (controlled with NaCl). The observed rate constant, reported in Table 1, reveals no influence of the ionic strength. Specific acid-catalyzed rate constants at I = 0.20 M (controlled with NaCl) were evaluated. Figure 2a displays the corresponding experimental data. The resulting plot implies eq 2.

$$k_o = k_o^w + k_H[H^+] \tag{2}$$

The intercept at the origin of the straight line corresponds to the uncatalyzed reaction, i.e., to spontaneous ester decomposition, where $k_o^w = k_{H_2O}[H_2O] = (0.987 \pm 0.006) \times 10^{-3}$ s^{-1}; whereas the slope gives the rate constant for the specific-acid-catalyzed reaction $k_H = (8.98 \pm 0.08) \times 10^{-3}$ mol^{-1} dm^3 s^{-1}. The noninfluence of ionic strength can be easily accounted for, because the reactive species, the enol form of ECHC, is an uncharged reagent. The study of the influence of the acidity in D_2O also gives a linear relationship between k_o and $[D^+]$ (inset of Figure 2a). One can note the much slower reaction rate in D_2O than in H_2O. Least-squares fitting of the data to the rate law that applies under these conditions, eq 2, gives: $k_o^D = k_{D_2O}[D_2O] = (0.124 \pm 0.005) \times 10^{-3}$ s^{-1} and $k_D = (2.92 \pm 0.04) \times 10^{-3}$ mol^{-1} dm^3 s^{-1}. The combination of the data obtained in H_2O and D_2O gives large kinetic hydrogen isotope effects: $k_{H_2O}/k_{D_2O} = 7.96$ and $k_H/k_D = 3.07$. The former value is the consequence of the kinetic isotope effect of a process in which an O–H (or O–D)

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Table 3. The Intercept (k_o^{buf}) and the Slope (δ) Values Corresponding to k_o versus $[Buffer]_t$ Plots Obtained in the Acid Hydrolysis of ECHC as a Function of the pH of the Reaction Medium

pH	range [buffer]/M	pK_a	$k_o^{buf}/10^{-3}$ s^{-1}	δ/mol^{-1} dm^3 s^{-1}	k_B/mol^{-1} dm^3 s^{-1}
		Acetic Acid−Acetate Buffer			
5.50	(0.016−0.14)	4.77 (4.76[24])	0.976	0.224	**0.258**[a]
5.12	(0.016−0.16)	4.77 (4.76[25])	1.17	0.176	
4.92	(0.02−0.20)	4.77	1.17	0.147	
4.60	(0.02−0.20)	4.77	1.33	0.103	
4.30	(0.02−0.20)	4.77	1.24	0.063	
4.15	(0.02−0.20)	4.77	1.17	0.047	
		Chloroacetic Acid−Chloroacetate Buffer			
3.20	(0.05−0.48)	2.78 (2.86[24])	1.15	0.0153	**0.0210**[a]
2.98	(0.04−0.40)	2.78	1.12	0.0128	
2.74	(0.04−0.40)	2.78	1.10	0.00987	
2.51	(0.04−0.40)	2.78	1.12	0.0073	
		Dichloroacetic Acid−Dichloroacetate Buffer:			
1.35	(0.05−0.5)	1.35[24]	1.39	0.00205	**0.0041**[a]
1.47	(0.06−0.6)	1.35	1.30	0.00235	
		Trichoroacetic Acid−Trichloroacetate Buffer			
0.70	(0.1−0.98)	0.66[25]	2.60	0.00105	**0.0019**[a]

(a) Obtained from eq 4; $k_{of}^{buf} = k_o^w + k_H[H^+]$; $\delta = k_B K_a/(K_a + [H^+])$.

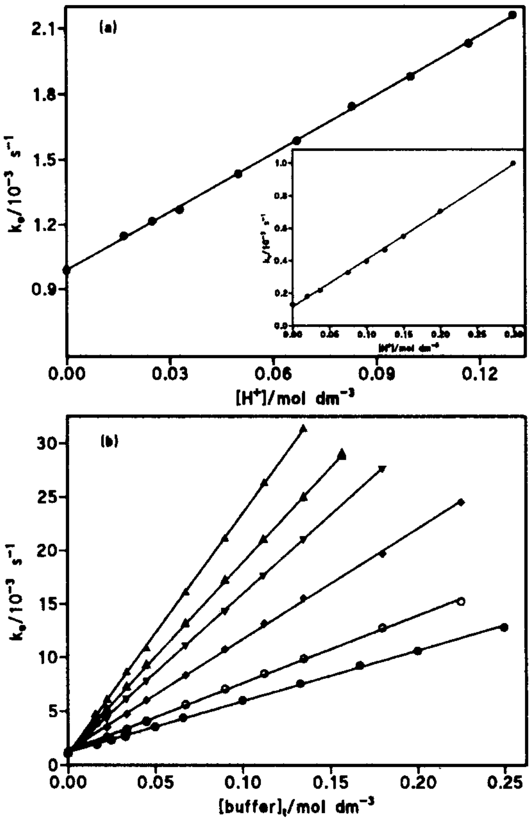

Figure 2. Variation of the pseudo-first-order rate constant, k_o, (a) for the acid-catalyzed hydrolysis of ECHC as a function of [H$^+$] (HCl) at an ionic strength of 0.20 M; (inset) reaction in D_2O, and (b) for the base-catalyzed hydrolysis of ECHC as a function of [buffer] (acetic acid−acetate ion) and of pH: (▲) 5.50; (△) 5.0; (▼) 4.80; (◆) 4.50; (○) 4.30, and (●) 4.15.

bond is broken in the symmetrical transition state of the reaction. In this situation the ratio k_{H_2O}/k_{D_2O} is determined by the zero-point energy difference in the initial state. The symmetric vibrational frequency of an O−H bond (ν = 3300 cm^{-1}) gives at 25 °C a maximum kinetic isotope effect of 8.[23] The ratio of k_H/k_D is classic evidence for the generally accepted mechanism for acid-catalyzed hydrolysis of esters: a rapid equilibrium step involving protonation of the ester on the carbonyl group and subsequent hydration of the cation species thus formed to yield the corresponding alcohol and carboxylic acid. (The analysis of solvent isotope effect based on the fractionation factor theory determines a direct solvent isotope effect of 3.)[24]

General Base Catalysis. We then studied the hydrolysis reaction in aqueous solutions of acetic acid-acetate buffer. Figure 2b shows the observed rate constant obtained as a function of both the buffer concentration and the pH of the solution (Table 2 lists representative results). As one can see, k_o increases with both the pH of the reaction medium and the buffer concentration. These features are typical characteristics of a general base-catalyzed reaction: in aqueous solutions of acetic acid−acetate buffer a new reaction step occurs through the acetate form (Ac$^-$). At constant pH, k_o increases linearly with total buffer concentration according to eq 3, in which K_a is the acidity constant of the acetic acid (pK_a = 4.76).[24,25]

$$k_o = k_o^{\,buf} + k_B[Ac^-] = k_o^{\,buf} + \frac{k_B K_a}{K_a + [H^+]}[buffer]_t \tag{3}$$

The values of k_o^{buf} and δ [$= k_B K_a/(K_a + [H^+])$], corresponding to the intercept and the slope of k_o vs $[buffer]_t$ plots, repectively, are collected in Table 3. It can be noted that k_o^{buf} ($= k_o^w + k_H[H^+]$) is pH-independent, within the experimental error. This finding is a consequence of the value of k_H, which at $[H^+] < 10^{-3}$ M, the term corresponding to the specific-acid catalysis is negligible. On the other hand, δ-values increase with pH, indicating that it is the basic form (the acetate) of the buffer that catalyzes the reaction, as we have assumed in eq 3. In this sense the reciprocal plot of δ-values should increase linearly with [H$^+$], eq 4.

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$$\frac{1}{\delta} = \frac{1}{k_B} + \frac{1}{k_B K_a}[H^+] \qquad (4)$$

The experimental data are plotted in Figure 3a, and from the intercept of the corresponding straight line we obtain: k_B = 0.258 mol^{-1} dm^3 s^{-1} as the catalytic coefficient of the acetate base, and from the ratio of (intercept/slope) = K_a = 1.70 × 10^{-5} mol·dm^{-3} (i.e., pK_a = 4.77) for the acidity constant of acetic acid, which agrees quite well with published values.

General base catalysis is likewise affected by monochloroacetic acid buffers: a series of experiments (not shown) at four different pH values also reveals a linear relationship between k_o and [buffer] at constant pH. The intercept of the corresponding straight lines (k_o^{buf}) is practically pH-independent (into the range 2.5 to 3.2), while the slope increases with pH. As with acetic acid, the reciprocal plot of the slope depends linearly on the [H$^+$] (see insert of Figure 3a), and the plot of the data according to eq 4 yields a value of 0.021 mol^{-1} dm^3 s^{-1} for k_B and a pK_a of 2.78 for monochloroacetic acid, again in good agreement with published values.[25] The catalytic coefficients for the basic catalysis by dichloroacetate and trichloroacetate ions were estimated from studies of the hydrolysis reaction in aqueous buffer solutions at only two pH values, in the former case, and at one pH value in the latter, because of the lower catalysis observed and because of the strong absorption of the buffer in this region (in fact, reaction kinetics with trichloroacetic were monitored at 270 nm). The values of k_o^{buf} and of δ obtained from the linear plot of k_o against [buffer] are reported in Table 3. From δ-values, along with published pK_a values for these two weak acids, we estimated the values of 4.15 × 10^{-3} and 1.89 × 10^{-3} mol^{-1} dm^3 s^{-1} for k_B, the catalytic coefficients by dichloroacetate and trichloroacetate ions, respectively. The rate constants k_B for the basic form of the buffer led to a perfect linear Brönsted plot (see Figure 3b) with β = 0.496 ± 0.009 (r = 0.9995), suggesting that the attack of the basic form of the buffer is involved in the rate-controlling step of the reaction, that is, ester hydrolysis goes through tetrahedral intermediates (see Chart 1). (Notice that we do not use statistical corrections for the equivalent sites of proton attachment in the acetate ion and in Cl-acetate derivatives, because in all cases $q = 2$, $p = 1$. The slope (i.e., the β-value) of the Brönsted plot is then independent of statistical corrections. The rate constant corresponding to the reaction by H_2O is not included in the correlation, because H_2O acts as a nucleophile).

The Effect of β-Cyclodextrin. The influence of β-CD on the ester hydrolysis reaction of ECHC was investigated under several experimental conditions. Figure 4 shows typical results of the variation of the pseudo-first-order rate constant corresponding to the acid-catalyzed hydrolysis, both in H_2O and in D_2O, as a function of β-CD concentration, while Figure 5 shows typical results of the influence of [β-CD] on k_o for the general base-catalyzed ester hydrolysis obtained in 0.20 M of acetic acid and in a buffer of acetic acid-acetate of pH 5.50 and [buffer]$_t$ = 0.10 M. In every case a strong inhibition by the addition of increasing amounts of β-CD is observed, but the hydrolysis reaction is not suppressed even at high [β-CD]; that is, a limiting inhibition level is obtained. The same plots shown that the reciprocal plot of k_o against [β-CD] gives perfectly straight lines. These findings indicate the formation of 1:1 inclusion complexes between ECHC-enol and β-CD, which should be unreactive. One may note the formation of inclusion complexes by comparing the reaction spectrum of Figures 1a and 1b. The small red shift of λ_{max} in the presence of β-CD is indicative of a change in the microenvironment of the enol of ECHC; i.e. the polarity of β-CD cavity is lower (methanol like)[26] than that of water. In addition, the linear relationship observed between the reciprocal plot of k_o and [β-CD] (vide infra) is a consequence of the unreactive complex formation. Thus, Scheme 2 can be proposed toward a quantitative interpretation of the experimental results.

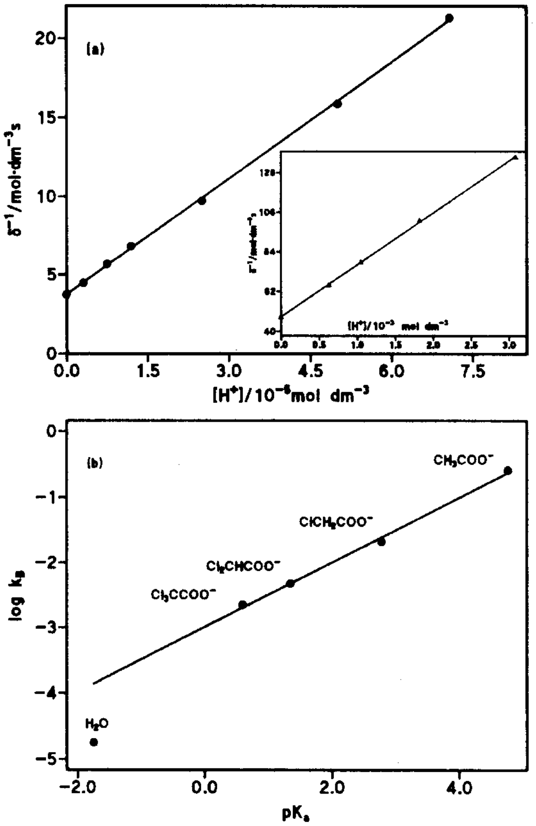

Figure 3. (a) Linear relationship between the reciprocal plot of the slopes of k_o versus [buffer], and [H$^+$], i.e., between δ^{-1} and [H$^+$], for the case of acetic acid−acetate ion; the inset shows the same plot obtained in the case of monochloroacetic acid−monochloroacetate ion; (b) Brönsted plot corresponding to the base catalyzed hydrolysis of the ester of ECHC enol by acetate ion and its Cl-derivatives; the catalytic coefficient corresponding to H_2O is also shown. (No statistical corrections have been applied.)

We can go forward from this scheme, taking into account that all the stoichiometric [β-CD] is free (the concentration of ECHC is much smaller than that of β-CD), and easily arrive at eq 5, where k_o^w is the observed rate constant corresponding to uncomplexed ECHC-enol, and with K_c being the equilibrium constant for complex formation.

$$k_o = \frac{k_o^w}{1 + K_c[\beta\text{-CD}]} \qquad (5)$$

The experimental points were adapted to this model and solid curves in Figures 4 and 5 show the excellent

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[26] Madrid, J. M.; Mendicuti, F.; Matticie, W. L. *J. Phys. Chem. B* **1998**, *102*, 2037; Street, K. W., Jr.; Acreer, W. E., Jr. *Appl. Spectrosc.* **1988**, *43*, 1315.

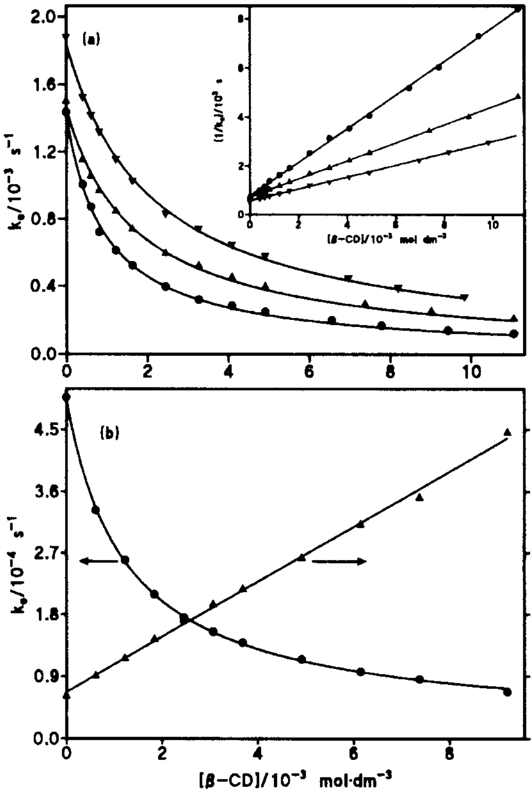
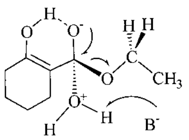


Figure 4. Influence of β-CD concentration on (a) the acid-catalyzed hydrolysis of ECHC at [H^+] equal to (●) 0.050 M, HCl; (▲) 0.050 M, $HClO_4$, and (▼) 0.10 M, $HClO_4$; (inset) reciprocal plot of k_o as a function of [β-CD]. Solid lines fit to eq 5; for parameters see Table 4. (b) Variation of k_o (●) and $1/k_o$ (▲) as a function of [β-CD] for the acid-catalyzed hydrolysis of the ECHC ester in D_2O at [H^+] = 0.125 M.

Chart 1



fit of the data obtained to the model. In the same figures we also see the reciprocal plot of k_o against [β-CD], exhibiting in all cases a perfect linear relationship, which corroborates the validity of eq 5 and provides evidence for the formation of unreactive inclusion complexes under the several experimental conditions used. The insert of Figure 4a shows clearly that the slopes of the straight lines, which according to eq 5 are equal to K_c/k_o^w, depends strongly on the acid being used. The decreasing slope on going from HCl to $HClO_4$ and on increasing the concentration of the latter suggest that the ClO_4^- ion must affect K_c values.

Table 4 contains the fitted parameters used to generate the curves (solid lines) in Figures 4 and 5. Three points should be noted. First, calculated k_o^w values agree perfectly with experimental k_o^w, which substantiates the formation of unreactive complexes. Second, values of K_c depend on the experimental conditions. On this point, the literature[10,27,28] reports the formation of inclusion complexes between β-CD and anions, such as ClO_4^-, I^-, and Br^-. The presence of these anions would act as a *potential inhibitor* even though, in the present study, the catalytic effect is due to the competition between these anions and the enol of ECHC for the β-CD cavity, which decreases the complexed substrate concentration with the concomitant increase in the rate of hydrolysis. In such a situation a new equilibrium step must be included into Scheme 2: $\beta\text{-CD} + I \rightleftharpoons \beta\text{-CD}\cdot I$, K_I (with I representing a potential inhibitor) and, consequently, the expression of K_c becomes that of $K_c^{ap} = K_c/(1 + K_I[I])$.

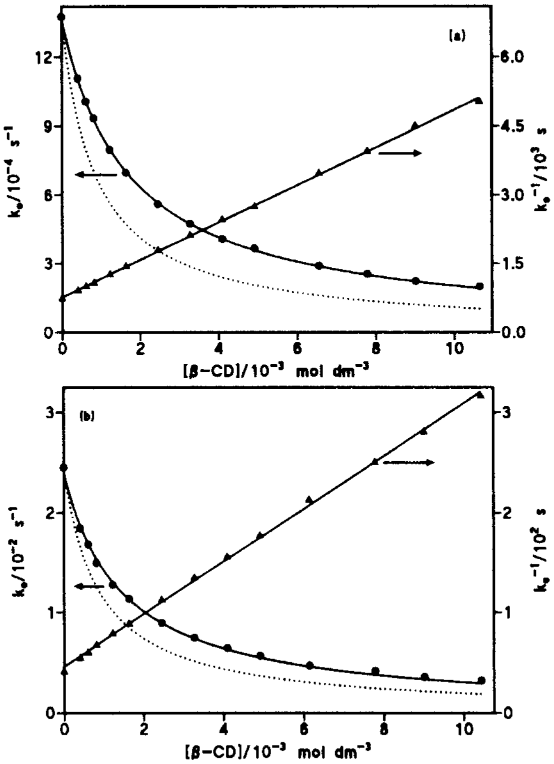
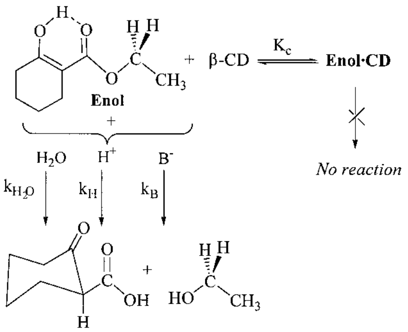


Figure 5. (●) Variation of k_o as a function of [β-CD] for the ester hydrolysis reaction of ECHC performed in (a) 0.20 M of acetic acid and (b) in a buffer solution of acetic acid–acetate of pH 5.50 and [buffer]$_t$ = 0.10 M. Solid lines fit eq 5; for parameters, see Table 4; (▲) reciprocal plot of k_o against [β-CD]; (···) calculated k_o values from eq 5 using K_c = 1156 mol^{-1} dm^3.

Scheme 2



When the reaction is performed in pure water, K_c = 860 mol^{-1} dm^3, i.e., 20% lower than the value attained when the reaction is acid catalyzed by HCl (0.05 M). The nature of the reaction should not affect the substrate inclusion. The literature[27] establishes a value of 2.56 mol^{-1} dm^3 for the binding constant of Cl^- to β-CD; then the presence of 0.050 M of Cl^- is not sufficient to present competition effects. In fact, the K_c value (=1156 mol^{-1}

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[27] Rohrbach, R. P.; Rodríguez, L. J.; Eyring, E. M. *J. Phys. Chem.* **1977**, *81*, 944.

[28] Tee, O. S.; Bozzi, M.; Hoeven, J. J.; Gadosy, T. A. *J. Am. Chem. Soc.* **1993**, *115*, 8990.

Table 4. Experimental Conditions and Parameters Determined in the Fitting Process of Eq 5 to the Experimental Data Obtained in the Kinetic Study of the Influence of β-CD in the Hydrolysis of ECHC under Several Experimental Conditions

aqueous medium	hydrolysis reaction	k_o^w/s^{-1} [d]	k_o^w/s^{-1} [e]	K_c/M^{-1}	cc	K_I/ M^{-1}	K_I/M^{-1} [f]
HCl; 0.050 M	acid catalyzed	$(1.384 \pm 0.02) \times 10^{-3}$	$(1.43 \pm 0.015) \times 10^{-3}$	1156 ± 30	0.999_3		2.56[27]
D_2O; HCl, 0.125 M	acid catalyzed	$(0.487 \pm 0.005) \times 10^{-3}$	$(0.496 \pm 0.001) \times 10^{-3}$	804 ± 16	0.9999		
$HClO_4$; 0.050 M	acid catalyzed	$(1.434 \pm 0.004) \times 10^{-3}$	$(1.46 \pm 0.02) \times 10^{-3}$	619 ± 14	0.999_3	19	20[10]; 27[27];
$HClO_4$; 0.10 M	acid catalyzed	$(1.881 \pm 0.005) \times 10^{-3}$	$(1.795 \pm 0.015) \times 10^{-3}$	471 ± 11	0.999_6	22	13.7[28]
water only	spontaneous	$(1.017 \pm 0.003) \times 10^{-3}$	$(1.15 \pm 0.04) \times 10^{-3}$	860 ± 33	0.9999		
AcH; 0.20 M[a]	acid catalyzed	$(1.374 \pm 0.007) \times 10^{-3}$	$(1.352 \pm 0.004) \times 10^{-3}$	578 ± 5	0.9999	5.0	
AcH/Ac$^-$;0.17 M; pH 4.15[b]	acid−base catalyzed	$(4.381 \pm 0.002) \times 10^{-3}$	$(4.382 \pm 0.005) \times 10^{-3}$	617 ± 4	0.9999	5.1	
AcH/Ac$^-$; 0.10 M; pH 5.50[c]	base catalyzed	$(24.53 \pm 0.06) \times 10^{-3}$	$(24.1 \pm 0.2) \times 10^{-3}$	694 ± 18	0.999_4	6.7	

[a] Aqueous solution of acetic-acid 0.20 M. [b] Aqueous buffered solution of acetic acid−acetate of pH 4.15 at [buffer] = 0.17 M. [c] Aqueous buffered solution of acetic acid−acetate of pH 5.50 at [buffer] = 0.10 M. [d] Experimental value. [e] Determined value. [f] Literature value.

dm^3) obtained in the presence of this concentration of Cl$^-$ ions is even higher than that obtained in pure water. We attribute this result to a *salting out* effect due to the presence of ions in water. In the presence of electrolytes, the polarity of water solutions increases and, consequently, hydrophobic substrates, such as ECHC-enol, are *salting out* from water solvent. Therefore, we take the value of $K_c = 1156$ mol^{-1}dm^3, found in the presence of HCl, as the true value for the binding constant of ECHC enol to β-CD when the aqueous solution contains electrolytes. On this basis, using the values of K_c^{ap} $(=K_c/(1 + K_I[I])$ reported in Table 4, along with the value of K_c and the concentration of the corresponding inhibitor (generally represented by I), we determine the values of K_I as reported in the same table. As shown, these values are in close agreement with the literature values, also included in the table when possible. Dotted lines in Figure 5 correspond to the calculated k_o values from eq 5 by using $K_c = 1156$ mol^{-1} dm^3.

A third point to note is the stronger binding (by more than three times) of ECHC enol to β-CD than the enol of benzoylacetone (or 1-phenylbutane-1,3-dione, BZA). BZA forms inclusion complexes with β-CD, the corresponding equilibrium constant is $K_c = 300$ mol^{-1} dm^3 at 25 °C.[4] Possible reasons to this fact could be the formation of H-bonds between the secondary OH groups of the host and the O-atom of the ester function of ECHC; this results in a stronger host−guest interaction, one that is not possible in the case of BZA as the guest. In addition, the size and shape of ECHC, in comparison to those of BZA, must be determinative. The structure of ECHE, along with this special host−guest interaction, leaves the reaction center (the carbonyl group of the ECHC enol) deeper inside the β-CD cavity and thus protected from the other reagent (H$^+$, H_2O, acetate ion), which would explain the nonreaction through the complexed enol. (Due to the ester hydrolysis in water, or in D_2O, that ocurs during the sample preparation, e.g., to obtaine NMR spectra, it was not possible to get further insigths on the complex structure).

1. Acid Medium. The Enol Nitrosation Reaction. Nitrosation of enols is a well-known reaction.[29,30] For ketones with high enol content, the rate-controlling step is, generally, the reaction between the enol and the nitrosating agent. Therefore, the rate equation is first-order on ketone and nitrosating agent concentrations. In contrast, when the percentage of enol is low, the enolization path becomes rate determining, and the reaction is independent of the nitrosating agent concentration.[31]

In aqueous mineral acid solutions of sodium nitrite, nitrosation is promoted by the nitrosating agents derived from nitrous acid (pK_a = 3.15):[32] $HNO_2 + H^+ \rightleftharpoons NO^+$ ($H_2NO_2^+$, nitrosonium ion) with $K_{NO} = 3.5 \times 10^{-7}$ mol^{-1} dm^3; or if Cl$^-$, Br$^-$, and SCN$^-$ (in general X$^-$ ions) are present, new nitrosating agents are formed: $HNO_2 + H^+ + X^- \rightleftharpoons XNO$, with K_{XNO} being the corresponding equilibrium constant, with K_{XNO} values varying from 1.14×10^{-3} (Cl$^-$), 0.051 (Br$^-$), or 30 mol^{-2} dm^6 (SCN$^-$).[33,34]

Results in the preceding section indicate that practically the entire amount of ECHC exists in water as enol tautomer, i.e., the reactive form toward nitrosation. To be able to record scans of the nitrosation spectrum, Figure 6a shows the decrease absorbance at 256 nm due to the nitrosation of the enol in the presence of 4.1 mM of β-CD at [HCl] = 0.050 M and [nitrite] = 1.67×10^{-3} M. The scans were recorded every 30 s. One should note that the spectra scans in Figure 1, corresponding to hydrolysis of the ester at the same acid concentration but without β-CD, were recorded after 2 min intervals. On the other hand, the decrease in absorbance is due to the disappearance of the enol, since stabilization of the C-nitroso compound is impossible through intramolecular H-bonding. The C-atom bearing the −NO group changes from sp^2 (planar) to sp^3 (nonplanar), see Chart 2.

The nitrosation reaction was carried out with a large excess of sodium nitrite over the ECHC concentration. Figure 6b shows the influence of [nitrite] on the pseudo-first-order rate constant when the reaction is done in both aqueous hydrochloric and perchloric acids. The linear relationship between both parameters indicates that the reaction is first-order in [nitrite]. The intercept, i.e., the value of k_o for the hydrolysis reaction, results negligible. (The calculated value from the previous section is 1.1×10^{-3} s^{-1}.) The corresponding slopes are (6.83 ± 0.05) and (3.58 ± 0.08) mol^{-1}dm^{3}s^{-1} respectively for the nitrosation in aqueous hydrochloric or perchloric acid.

In Figure 7b one can see the variation of k_o as a function of acidity (controlled with $HClO_4$) at [nitrite] = 1.7×10^{-3} M. For comparative purposes, the k_o corre-

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(29) Touster, O. *Organic Reactions*; Wiley: New York, 1953; Vol. 7, Chapter 6.

(30) Williams, D. L. H. In *Organic Reactivity: Physical and Biological Aspects*; Golding, B. T., Griffin, R. J., Maskill, K., Eds.; The Royal Society of Chemistry: Cambridge, 1995; p 320. Leis, J. R.; Peña, M. E.; Williams, D. L. H., Mawson, S. D. *J. Chem. Soc., Perkin Trans. 2* **1988**, 197.

(31) Williams, D. L. H.; Graham, A. *Tetrahedron* **1992**, *48*, 7973.

(32) Tummavuori, J.; Lumme, P. *Acta Chem. Scand.* **1968**, *22*, 2003.

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(34) Stedman, G.; Whincup, P. A. E. *J. Chem. Soc.* **1963**, 5796.

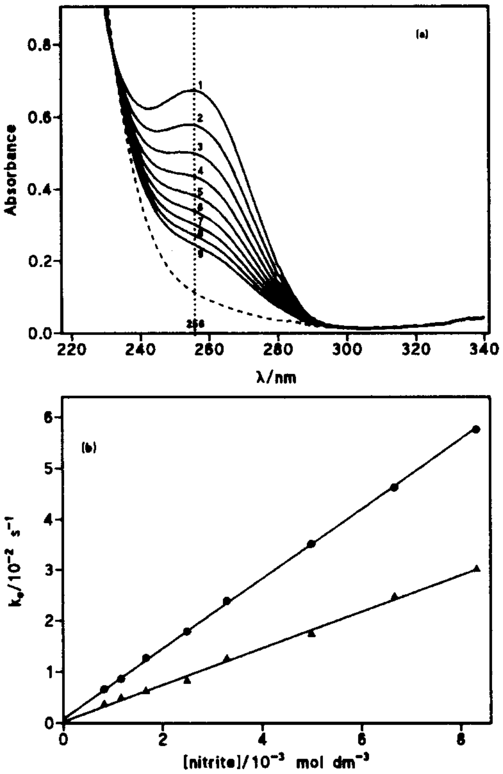
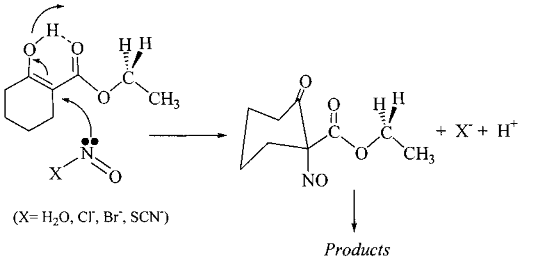


Figure 6. (a) Repeat scans (1−9) every 30 s showing the decreasing absorbance at 256 nm due to the nitrosation ($[\text{nitrite}]_o = 1.67 \times 10^{-3}$ M) of the enol of ECHC ($[\text{ECHC}]_o = 6.3 \times 10^{-5}$ M) in aqueous acidic ($[H^+] = 0.050$ M, HCl) solutions of [β-CD] = 4.1 mM; (- - -) scan taken at infinite time; (b) first-order dependence of the observed rate constant k_o upon [nitrite] fot the nitrosation of the enol of ECHC in aqueous mineral acid: (●) HCl, 0.025 M, and (▲) $HClO_4$, 0.017 M.

Chart 2



sponding to the hydrolysis reaction at the same acidities is also plotted. Again, there is a linear relationship between k_o and $[H^+]$. The hydrolysis reaction is only important at low $[H^+]$ (it represents 30% of the k_o value); in fact the slope of the straight line changes from (0.366 ± 0.004) mol^{-1}dm^{3}s^{-1} to (0.355 ± 0.005) mol^{-1} dm^3 s^{-1} when correction owing to hydrolysis reaction is taken into account (i.e. $k_o^{cor} = k_o - k_h$, with k_h being the first-order rate constant obtained for the hydrolysis reaction at the same $[H^+]$ as k_o).

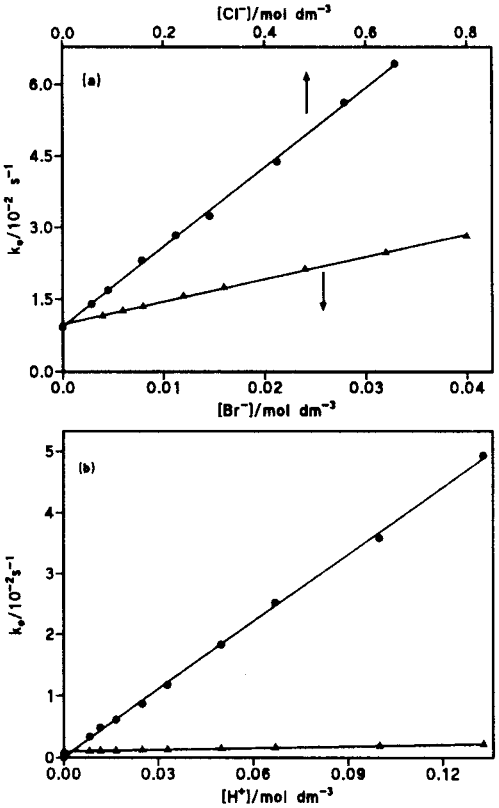


Figure 7. (a) Influence of (●) Cl^- and (▲) Br^- concentration on the pseudo-first-order rate constant of the nitrosation of the enol of ECHC at $[H^+] = 0.025$ M (by using HCl in the case of Cl^- and $HClO_4$ in the case of Br^-) and [nitrite] = 1.67×10^{-3} M; (b) influence of the acidity (controlled with $HClO_4$) on the pseudo-first-order constant for the nitrosation reaction ([nitrite] = 1.67×10^{-3} M) of the enol of ECHC in water.

The presence of Cl^-, Br^-, or SCN^- brings about the formation of a new nitrosating agent in the reaction medium: the nitrosyl halides (XNO), which are less reactive than NO^+, but whose concentrations are higher, with consequent effects on reactivity. Usually, when nitrosation is the rate-determining step, the presence of X^- accelerates the reaction. This effect can be understood by looking at the results in Figure 7a, which shows the variation of k_o as a function of $[Cl^-]$ and $[Br^-]$. It is noteworthy that nearly 5-times as much $[Cl^-]$ as $[Br^-]$ is required to observe the same reaction rate, keeping the rest of the reaction conditions constant. This experimental finding reflects the relative concentrations of ClNO and BrNO in the reaction medium, even when BrNO is less reactive than ClNO. The intercept of the straight lines resulting from the plots of k_o versus $[X^-]$ corresponds to the nitrosation reaction by NO^+, and the values obtained are (9.2 ± 0.3) × 10^{-3} and (9.7 ± 0.1) × 10^{-3} s^{-1} for the influence here of $[Cl^-]$ and $[Br^-]$, respectively, at equivalent experimental conditions. Nevertheless, the slopes are quite different: (1.67 ± 0.2) and (0.468 ± 0.007) mol^{-1} dm^3 s^{-1}, for Cl^- and Br^-, respectively. These experimental outcomes can be summarized in eq 6.

$$k_o = (k_1 + k_2[X^-])[\text{nitrite}][H^+] \qquad (6)$$

Values of k_1 and k_2 are collected in Table 5, along with the experimental conditions used in each case. Values of k_1 are independent of the presence of X^-, because this rate constant represents the reaction via NO^+ and the ECHC enol, then $k_1 = k_{NO}K_{NO}K_E/(1 + K_E)$, in which k_{NO} is the bimolecular rate constant of the mechanistic step $NO^+ + \text{enol} \rightarrow \text{products}$; K_{NO} is the equilibrium constant for NO^+ formation in aqueous acid mineral solutions of sodium nitrite ($[NO^+] = K_{NO}[\text{nitrite}]\,[H^+]$), and K_E is the keto−enol equilibrium constant. The latter constant must be higher than 1; for example, 90% enolization means $K_E = 9$, but the results in the previous section are consistent with nearly 100% enolization. As a conse-

Table 5. Experimental Conditions and Parameters Obtained in the Nitrosation of the Enol of Ethyl Cyclohexanone-2-carboxylate ([ECHC] = 6.3×10^{-5} M) in Acid Medium

[nitrite]/M	$[H^+]$/M	$[X^-]$/M	$k_1/M^{-2}s^{-1}$	$k_2/10^4\ M^{-3}s^{-1}$	$K_{NO/or\ XNO}$[a]	$k_{XNO}/M^{-1}s^{-1}$[b]
variable	0.017 ($HClO_4$)		211 ± 5		3.5×10^{-7}	6.0×10^8
variable	0.025 (HCl)	0.025 (Cl^-)	6.83 ± 0.05 (c)			
1.67×10^{-3}	variable($HClO_4$)		219 ± 2		3.5×10^{-7}	6.3×10^8
1.67×10^{-3}	0.025 (HCl)	variable (Cl^-)	220 ± 8	$(1.99 \pm 0.03) \times 10^3$	1.14×10^{-3}	1.75×10^6
1.67×10^{-3}	0.025 ($HClO_4$)	variable (Br^-)	232 ± 3	$(1.12 \pm 0.01) \times 10^4$	0.051	2.2×10^5
1.67×10^{-3}	0.010 ($HClO_4$)	variable(SCN^-)	226 ± 6	$(1.08 \pm 0.02) \times 10^5$	30	3.6×10^3

[a] Literature[33,34] values for the equilibrium constants of NO^+ formation (K_{NO}) and XNO formation (K_{XNO}). [b] bimolecular rate constants for the nitrosation attack by NO^+ or XNO (X = Cl^-; Br^-, SCN^-).

quence, $k_1 = k_{NO}K_{NO}$, the calculated average value being 220 $mol^{-2}\ dm^6\ s^{-1}$, which leads to $k_{NO} = 6.3 \times 10^8\ mol^{-1}\ dm^3\ s^{-1}$, very close to the accepted value for a diffusion controlled process.

Proceding in the same way, we find that k_2 is the experimental rate constant accounting for the nitrosation of the enol of ECHC by nitrosyl halides. Then, $k_2 = k_{XNO}K_{XNO}K_E/(1 + K_E)$, with k_{XNO} being the bimolecular rate constant of the mechanistic step: XNO + enol → products. Obviously, its value depends on the nature of X: the most reactive XNO would produce the highest value. As above, taking into account the value of K_E, one arrives at $k_2 = k_{XNO}K_{XNO}$. From the corresponding values of K_{XNO}, we determine the bimolecular rate constant for the reaction between the ECHC enol and XNO as 1.75×10^6, 2.20×10^5, and $3.60 \times 10^3\ mol^{-1}\ dm^3\ s^{-1}$ for $X^- = Cl^-$, Br^-, and SCN^-, respectively. Reactivity decreases in the series NO^+ > ClNO > BrNO > SCNNO, as is usually found in nitrosation reactions performed in water.

At this point we must address the higher reactivity of the enol of ECHC in comparison with the enols of benzoylacetone or acetylacetone (two β-diketones) or of ethyl aceto-acetate or ethyl benzoyl acetate (two β-keto esters).[15] The ECHC enol proves to be more than 10-times (the case of NO^+) or nearly 100-times (the case of BrNO) more reactive than the aforementioned enols of the 1,3-dicarbonyl compounds. The higher difference observed with BrNO than with NO^+ is a clear consequence of the *reactivity−selectivity principle*.[35] On the other hand, the higher reactivity shown by the enol of ECHC can be explained taking into account the basicity values; for example, the pK_a of ECHC is 10.94[36] while that of benzoylacetone is 8.70.[14]

Table 6. Values of the Observed Rate Constant, k_o, Obtained in the Nitrosation of the Enol of Ethyl Cyclohexanone-2-carboxylate at [Nitrite] = 1.67×10^{-3} M and $[H^+]$ = 0.025 M ($HClO_4$) as a Function of the Ionic Strength ($I = [HClO_4] + [NaClO_4]$)

I/M	k_o/s^{-1}
0.025	0.866×10^{-2}
0.058	0.969×10^{-2}
0.092	0.992×10^{-2}
0.158	1.141×10^{-2}
0.225	1.255×10^{-2}
0.292	1.360×10^{-2}
0.425	1.638×10^{-2}
0.658	2.237×10^{-2}
0.792	2.510×10^{-2}

Table 6 reports the values of k_o obtained as a function of ionic strength (controlled with $NaClO_4$) on k_o. In contrast to the hydrolysis reaction, the pseudo-first-order rate constant for the nitrosation reaction increases with the ionic strength of the medium. Taking into account that the rate-determining step of the nitrosation is the reaction between the enol (a neutral species) and the nitrosating agent NO^+ or XNO (see Chart 2), we should not expect to see any effect of the ionic strength on the rate of this process. However, we have to take into account the equilibrium processes that occur prior to the rate-determining step, i.e., to generate the nitrosating agents, and the effect of ionic strength on the activity coefficient of H^+, which in a rigorous treatment of the effect of ionic strength should be included in eq 6. But this is not an important effect because $\gamma_\pm$ for $HClO_4$ varies from 0.803 at 0.1*m*, to 0.785 at 0.7*m*.[37] The main effect of ionic strength, which accounts for the increase of k_o by more than a factor of 2.5 on going from $I = 0.06$ to 0.8 M, is the increase of the $[NO^+]$; in other words, the equilibrium constant K_{NO} depends on ionic strength.

The Effect of β-Cyclodextrin on the Nitrosation. Finally, we looked at the influence of [β-CD] on the nitrosation reaction under several experimental conditions. Figure 8 includes typical results. In each case, strong inhibition was observed, and the reciprocal plot of k_o against [β-CD] is a perfect straight line. These findings point to the formation of unreactive complexes between β-CD and the enol of ECHC, because the ECHC enol is the only reactive species toward nitrosation. Consequently, the results here provide evidence that the included species is the enol tautomer of ECHC and not the keto form. The experimental results in Figure 8 can be fitted to an eq of type (5), but in this case $k_o^w = (k_1 + k_2[X^-])[\text{nitrite}][H^+]$.

Table 7 contains the fitted parameters used to generate the curves (solid lines) in Figure 8. Three points should be noted. First, calculated values of k_o^w (arrived at by nonlinear regression analysis) conform quite well with those expected, if we take into account the parameters of Table 5 and the experimental conditions of Table 7. Second, the K_c values are also in complete accord with those determined through the study the hydrolysis reaction under the same experimental conditions, except for the presence of 1.67×10^{-3} M of $NaNO_2$, which should not have any effect on the inclusion process, as the experimental results confirm it. This finding evidences that the same molecule, i.e. the enol, forms inclusion complexes with β-CD either in the hydrolysis or in the nitrosation reaction. As in the hydrolysis reactions, perchlorate ions compete with the enol of ECHC for the

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(35) Pross A. *Theoretical and Physical Principles of Organic Reactivity*; John Wiley & Sons: New York, 1995; Chapter 5. Exner, O. *J. Chem. Soc., Perkin Trans. 2*, **1993**, 973.

(36) Bell, R. P.; Vogelsong, D. C. *J. Chem. Soc.* **1958**, 243. The authors measure the pH of partly neutralized aqueous solutions of ECHC; they also point that the pH changes with time, probably because of hydrolysis of the ester.

(37) Robinson, R. A.; Stokes, R. H. *Electrolyte Solutions,* 2nd ed.; Butterworths: London, 1959.

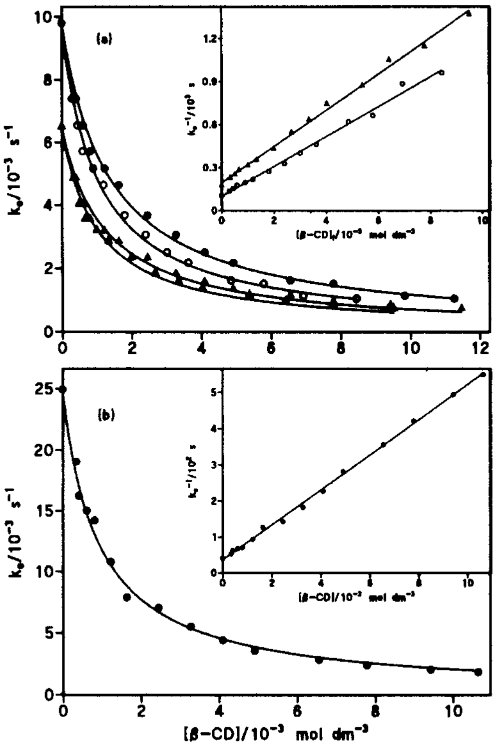


Figure 8. Variation of k_o for the nitrosation of the enol of ECHC in aqueous acid medium at [nitrite] = 1.67 × 10^{-3} M as a function of (a) total [β-CD] (●, ▲) and of free [β-CD] (○, △) at [$HClO_4$] equal to 0.017 M (triangles) and 0.025 M (circles); the inset shows the reciprocal plot of k_o as a function of [β-CD] and at (b) [HCl] = 0.050 M; the inset shows the reciprocal plot of k_o against total [β-CD]. Solid lines fit an eq of type 5; for parameters, see Table 7.

β-CD cavity. At [ClO_4^-] = 0.05 or 0.10 M we can consider these concentrations high enough in comparison with [β-CD] (0.01 M is the highest concentration used) to assume that the uncomplexed [ClO_4^-] (i.e., the [I] in the expression of K_c^{ap}) is constant and equal to the stoichiometric value; in other words we can neglect the concentration of perchlorate ions forming complexes. Then, $K_c^{ap} = K_c/(1 + K_I[I])$. Fitting eq 5 to the experimental points, we determined the K_c^{ap} reported in Table 7. From these values, along with the [ClO_4^-] (i.e., [I]) one obtains the K_I values which are also listed in the table. In the experiments performed at [ClO_4^-] = 0.017 or 0.025 M one cannot consider negligible the amount of perchlorate ion forming complexes. Under these conditions we assumed $K_I = 15$ mol^{-1} dm^3 to determine the free β-CD concentration ([CD]) by solving the equation: $[CD]^2 + [CD][K_I^{-1} + [I]_o - [\beta\text{-CD}]_o] - [\beta\text{-CD}]_oK_I^{-1} = 0$ at each initial [β-CD].[8] By fitting experimental k_o data versus [CD], either by nonlinear regression analysis (eq 5) or by linear regression analysis -reciprocal plot of k_o vs [CD]- (see open points in Figure 8) one obtains the K_c values listed in Table 7. As can be seen, there is a total agreement between these results and those determined in the presence of Cl^- ions, i.e., when no competition effects are possible. Third, the complexed enol is even unreactive toward BrNO, for example, in contrast to benzoylacetone. (The included enol of benzoylacetone is unreactive toward NO^+, but reacts with ClNO or BrNO.[4]) These results corroborate our statements put forward in the hydrolysis reaction section: the ECHC enol must locate deeper inside the β-CD cavity forming H-bonds between the O-ester and the secondary OH groups of the wider β-CD rim.

2. Basic Medium. We also investigated the ester hydrolysis reaction in alkaline conditions. The spectra of ECHC (6.3 × 10^{-5} M) at [OH^-] = 0.1 M are displayed in Figure 9a. One can see that the absorption band centered at 288 nm decreases with time. Figure 9b illustrates the variation of the observed rate constant for the alkaline hydrolysis as a function of [OH^-]. At low [OH^-], k_o increases and then levels off at high [OH^-]. Also included in the same figure are some experimental points performed in the presence of 0.011 M of β-CD. One can see that the effect of [β-CD] depends on the [OH^-]. The insert shows the total decrease absorbance, $\Delta A = A_o - A_\infty$, measured at 288 nm, due to enolate/carbanion disappearance as a function of [OH^-]. Table 8 reports the observed rate constant of the enolate hydrolysis reaction obtained as a function of ionic strength. One can see that k_o is independent of both the nature and concentration of electrolytes.

The pK_a of ECHC enol in water reported in the literature[36] is 10.94. Working at [OH^-] > 10^{-2} M, the stoichiometric concentration of ECHC would be that of the enolate. Delocalization of the negative charge gives rise to three resonant forms (the *two enolates* and the *carbanion* which are a single entity) unfavorable for the attack by OH^-; thus, such a process leads to the formation of a doubly negative-charged transition state. In other words, the enolate hydrolyses spontaneously; in fact, when the entire amount of ECHC is ionized, the rate is not affected by increasing [OH^-]; that is to say, the catalysis by OH^- is negligible. The results of the influence of ionic strength rule out the possibility of a reaction between enolate and OH^-, or a catalysis by the ionic strength would have been observed. These considerations lead us to proposed Scheme 3 to explain the experimental observations.Taking into account that the total ethyl cyclohexanone-2-carboxylate is the sum of the enol and the enolate concentrations, $[ECHC]_t = [EH] + [E^-]$, one easily arrives from Scheme 3 to eq 7, in which k^E_{water} is the uncatalyzed rate constant for the enolate hydrolysis, and K_b^E is the equilibrium constant of the enol basicity, i.e., $K_b^E = K_a^E/K_w$.

$$k_o = \frac{k^E_{water}\,K_b^E[OH^-]}{1 + K_b^E[OH^-]} \qquad (7)$$

The solid lines in Figure 9b correspond to the fit of eq 7 to the experimental points with the following values of the corresponding unknown parameters: $K_b^E = 35.6 \pm 0.7$ mol^{-1}dm^3 and $k^E_{water}\,K_b^E = (7.90 \pm 1.5) \times 10^{-2}$ mol^{-1} dm^3 s^{-1}. These results yield pK_a^E = 12.4 (by taking pK_w = 14) and $k^E_{water} = 2.22 \times 10^{-3}$ s^{-1}. The pK_a^E so determined is higher than the value that has been published; on the other hand, the rate of the ester hydrolysis through the enolate, k^E_{water}, is more than twice the rate constant of the ester hydrolysis in neutral aqueous medium ($k_{water} = 0.987 \times 10^{-3}$ s^{-1}, see section 1). This finding is quite reasonable, thus the enolate must be more reactive than the neutral enol. In addition, the absorbance decrease at 288 nm for a given [OH^-] is related to the enolate concentration according to the following expression: $\Delta A = \epsilon_E l[E^-]$, with ϵ_E being the extinction coefficient of the enolate at this wavelength,

Table 7. Experimental Conditions and Parameters Determined by Fitting the Experimental Data Obtained in the Study of the Influence of β-CD on the Nitrosation ([Nitrite] = 1.67 × 10^{-3} M) of the Enol of ECHC in Aqueous Mineral Acid to Eq 5

aqueous medium	$k_o^w/10^{-3}$ s^{-1}	K_c/M^{-1}	K_c^{ap}/M^{-1}	cc	K_I/M
HCl; 0.050 M	24.9 ± 0.5	1117 ± 34		0.999_7	2.56^{27}
$HClO_4$; 0.017 M	6.10 ± 0.01	893 ± 20[a]		0.999_8	15[b]
$HClO_4$; 0.025 M	9.85 ± 0.2	1020 ± 40[a]			15[b]
$HClO_4$; 0.025 + $NaClO_4$; 0.085 M	9.05 ± 0.1		477 ± 16	0.999_5	13.4
	9.35 ± 0.3[c]		501 ± 10[c]	0.999_7	12.3
$HClO_4$; 0.05 M	17.8 ± 0.3		629 ± 26	0.999	15.5
	17.0 ± 0.6[c]		576 ± 30[c]	0.999	18.8
HBr; 0.017 M	19.25 ± 0.15	873 ± 18		0.999_4	5.6^{27}
	19.1[c]	929 ± 16[c]			

[a] Obtained from the regression analysis of k_o versus $[\beta\text{-CD}]_{free}$ that has been calculated by solving the equation $[CD]_f^2 + [CD]_f\{K_I^{-1} + [I]_o\text{-}[\beta\text{-CD}]_o\}\text{-}[\beta\text{-CD}]_o/K_I = 0$. [b] Assumed value of K_I to determine free β-CD concentration. [c] Obtained from linear regression analysis.

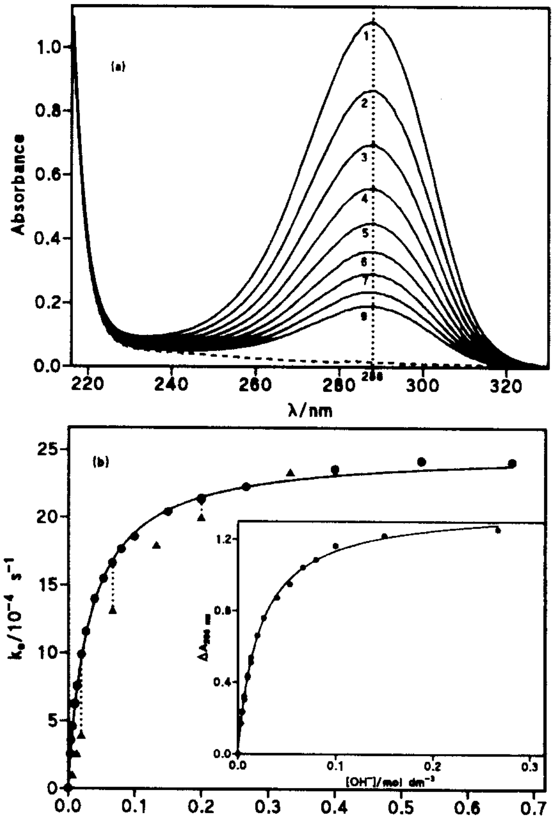
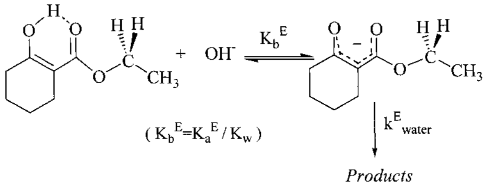


Figure 9. (a) Repeat scans (1−9) every 2 min showing the decreasing absorbance at 288 nm due to alkaline hydrolysis of the enolate/carbanion of ECHC ($[ECHC]_o = 6.3 \times 10^{-5}$ M) in aqueous solutions of [OH⁻] = 0.10 M, (- - -) scan at infinite time; (b) variation of the pseudo-first-order rate constant of the alkaline hydrolysis of the enolate of ECHC as a function of [OH⁻]; solid line fit eq 7, for parameters, see text; (▲) in the presence of 0.011 M of β-CD; (inset) total decrease absorbance readings at 288 nm ($A_o - A_\infty$) as a function of [OH⁻]; solid line fit eq 8, for parameters, see text.

Table 8. Values of the Observed Rate Constant, k_o, Obtained in the Alkaline Hydrolysis of Ethyl Cyclohexanone-2-carboxylate at [OH⁻] = 0.10 M and [ECHC] = 6.3 × 10^{-5} M as a Function of the Ionic Strength

[salt]/M	I/M	k_o/s^{-1}	$\Delta A = A_o - A_\infty$
NaOH; 0.10	0.10	(1.888 ± 0.001) × 10^{-3}	1.2145 ± 0.0003
$NaClO_4$; 0.067	0.17	(1.891 ± 0.0009) × 10^{-3}	1.1770 ± 0.0002
$NaClO_4$; 0.13	0.23	(1.882 ± 0.0008) × 10^{-3}	1.1723 ± 0.0001
$NaClO_4$; 0.27	0.37	(1.861 ± 0.0006) × 10^{-3}	1.1036 ± 0.0002
NaCl; 0.067	0.17	(1.877 ± 0.0009) × 10^{-3}	1.2521 ± 0.0002
NaCl; 0.13	0.23	(1.863 ± 0.0006) × 10^{-3}	1.2613 ± 0.0003
NaCl; 0.27	0.37	(1.840 ± 0.0003) × 10^{-3}	1.2684 ± 0.0006
NaCl; 0.50	0.60	(1.848 ± 0.0005) × 10^{-3}	1.2606 ± 0.0001

Scheme 3



and l = 1 cm the light path. Again, taking into account that $[ECHC]_t = [EH] + [E^-]$, one obtains eq 8 to relate ΔA with the [OH⁻].

$$\Delta A = \frac{\epsilon_E l K_b^E [OH^-][ECHC]_t}{1 + K_b^E [OH^-]} \qquad (8)$$

The solid line in the insert of Figure 9b corresponds to the fit of eq 8 to the experimental points when $K_b^E = 44.5 \pm 1$ mol^{-1} dm^3 and $\epsilon_E l K_b^E [ECHC]_t = 62 \pm 1$ mol^{-1} dm^3. Since $[ECHC]_t = 6.3 \times 10^{-5}$ M, from the these results one determines ϵ_E = 22 065 mol^{-1} dm^3 cm^{-1}, in good agreement with the extinction coefficient determined from absorbance readings at different [ECHC] in alkaline medium, nevertheless, we consider this value more reliable, since the absorbance readings are extrapolated to initial time to avoid the hydrolysis reaction. Again, the calculated K_b^E value gives $pK_a^E = 12.3$, i.e., there is a quite good agreement between kinetic and spectroscopic results.

Finally, the influence of [β-CD] can be qualitatively explained as follows. At [OH⁻] > 0.10 M, approximately, the whole β-CD molecules have ionized a secondary OH group (C-2 or C-3)[38] (i.e., the host is negatively charged: $pK_a = 12.2$),[39] and also the guest, the enolate. Then, with the repulsive electrostatic interactions in mind, it is easy to understand the greater stability of the system with the enolate not included in the ionized β-CD cavity. At lower [OH⁻] the amount of neutral β-CD molecules increases, which can form inclusion complexes with the enolate strongly stabilized by H-bonding, and consequently the effect of β-CD increases. But at low [OH⁻] also increases the enol concentration, which is included into the β-CD cavity. All these processes presents difficulties for the quantitative analysis of the influence of β-CD on alkaline hydrolysis of ECHC at low [OH⁻].

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Conclusions

The present work reports the results of the study of two reactions occurring in ethyl cyclohexanone-2-carboxylate in aqueous solution. The compound is unstable in water because of hydrolysis of the ester. Careful choice of reaction conditions allows the study of both ester hydrolysis and enol nitrosation reactions of ECHC. The hydrolysis reaction is slower in strong mineral acid than in aqueous buffered solutions of carboxylic acids because specific acid-catalyzed reaction is less important than the general base-catalyzed pathway. There is no effect of ionic strength, and a good Brönsted plot for the basic catalysis of acetate ion and its Cl-derivatives was observed, with $\beta = 0.5$ indicating a symmetrical transition state. Addition of β-CD strongly inhibits the reaction because of the strong binding of the ECHC enol to β-CD produces unreactive 1:1 inclusion complexes. Some species, such as ClO_4^-, acetate ion, or acetic acid are also viewed as including into the β-CD, and the kinetic results allow us to attain the equilibrium constant for the inclusion of these species. The nitrosation reaction of the ECHC enol in strong mineral acid is faster than the acid or alkaline hydrolysis of the ester, and is also inhibited by the presence of β-CD, again as a consequence of the formation of unreactive complexes between the enol and β-CD, but the nitrosation is extremely slow in weak acids (pH > 3). The study of the ester hydrolysis in alkaline medium shows that the reaction is not catalyzed by OH^- because of enolate formation under these conditions. Nevertheless, the spontaneous ester hydrolysis in alkaline medium is more than twice as fast as in neutral medium, due to the higher reactivity of the enolate over the enol. Both kinetic and spectroscopic results yields a pK_a^E for the ECHC enol of 12.35. Finally, ester hydrolysis in alkaline medium is unaffected by the presence of β-CD because of repulsive electrostatic interactions, which prevent the formation of inclusion complexes.

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