Effects of β-Cyclodextrin on the Keto−Enol Equilibrium of Benzoylacetone and on Enol Reactivity

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Both β-cyclodextrin and sodium dodecyl sulfate micelles shift the benzoylacetone keto−enol equilibrium to the enol tautomer by preferentially binding the enol form. The UV−vis spectroscopic method was used to quantify the temperature and solvent effects on the keto−enol equilibrium of benzoylacetone in aqueous acid medium. The comparison between the thermodynamic parameters resulting from the binding of the benzoylacetone enol to sodium dodecyl sulfate micelles and from the inclusion of both keto and enol tautomers into the β-cyclodextrin cavity allows us to draw a picture of the possible complex formed in each case. ^{1}H NMR results suggest that benzoylacetone−enol protrudes deeper inside the β-cyclodextrin cavity, whereas the keto tautomer could only have the phenyl ring enclosed in the β-cyclodextrin cavity interior. Nitrosation in acid medium of benzoylacetone in the presence of β-cyclodextrin is reduced below that of free benzoylacetone, indicating that the cyclodextrin complex protects the benzoylacetone enol tautomer, which is in perfect accordance with our picture of the enol·β-cyclodextrin complex.

Introduction

Cyclodextrins, doughnut-shaped molecules, are typical host compounds made up of six to eight glucose units linked together covalently by oxygen atoms and held in shape by means of hydrogen bonding between the secondary hydroxy groups on adjacent units at the wider rim of the cavity.[1−5] An array of properties seems to make cyclodextrin a reasonable choice for an enzyme model,[6,7] including its water solubility, the fact that the guest is bounded reversibly in the cavity, and the fact that a number of equilibrium[8] or chemical[9,10] reactions may be modified by the addition of cyclodextrins.

In previous works, we have shown that the study of the influence of micellar solutions on the absorption spectrum of β-dicarbonyl compounds, like benzoylacetone, can provide a new method for determining keto−enol equilibrium constants of β-dicarbonyl compounds in water.[11,12] As a consequence of the perturbation of the keto−enol equilibrium of benzoylacetone (BZA) brought on by the presence of micelles, the nitrosation reaction of BZA in aqueous acid micellar solutions is greatly modified.[13] In the present study, we investigate the effects of β-cyclodextrin (β-CD) on the keto−enol equilibrium of BZA and dibenzoylmethane (DBM) and on the nitrosation reaction of the enol of BZA, DBM, and acetylacetone (AcAc) in aqueous acid medium. To arrive at a quantitative explanation of the results, we first studied the influence of temperature and solvents on the keto−enol equilibrium of BZA. For that, the absorption spectra of BZA were recorded as a function of the surfactant sodium dodecyl sulfate (SDS) concentration at different temperatures and at two fixed percentages of dioxane in the aqueous surfactant solutions. Thermodynamic parameters corresponding to the association process of the enol of BZA to the SDS micelles were obtained and compared with those found in studying the influence of temperature on the complexation processes between both keto and enol tautomers of BZA and β-CD.

Experimental Section

Materials. Ketones and β-cyclodextrin, Aldrich products of maximum purity, sodium dodecyl sulfate, a Sigma product, and D_2O (Solvents, Documentation, Synthèses Laboratories) were used without further purification. All other reagents were supplied by Merck and were used as received. Solutions were prepared with doubly distilled water obtained from a permanganate solution.

Methods. BZA, DBM, and AcAc were dissolved in dioxane (spectrophotometric grade). From this stock solution, the

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working aqueous solution was prepared daily by diluting 0.2−0.4 mL to 25 mL final volume. All other solutions were prepared in water by directly dissolving the appropriate weight of the desired product in the required water volume.

UV−vis absorption spectra and kinetic measurements were recorded with a Kontron-Uvikon (model 942) double-beam spectrophotometer provided with a thermostated multiple cell holder. The procedure used for obtaining the UV−vis spectra of BZA in the presence of SDS, to determine the keto−enol equilibrium constant in water K_E and the association constant K_s^E of the BZA−enol to SDS micelles, has previously been reported.[11,12] The absorption spectra in the presence of β-CD were recorded following the same procedure, and equal β-CD concentrations were placed in both the cell sample and reference.

^{1}H NMR spectra were obtained with a 200 MHz spectrometer (Bruker AC200F). Chemical shifts were measured with respect to the residual water signal at $\delta = 4.60$ ppm. For these experiments, solutions containing 0.8 mM of BZA were prepared in D_2O. A small amount of the BZA methanolic stock solution was placed in a volumetric flask, and methanol was evaporated with a gentle stream of Ar followed by the addition of D_2O and/or the desired volume of a β-CD solution in D_2O. All solutions were stirred overnight.

Kinetic studies were performed under pseudo-first-order conditions, with [nitrite] at least 20 times greater than [ketone]. All reactions were observed by recording the decrease in absorbance due to enol consumption at $\lambda = 312$ nm for BZA, at 345 nm for DBM, and at 245 nm for AcAc.[12] Every kinetic experiment was started by adding, to the rest of the reaction mixture, 0.10−0.20 mL of $NaNO_2$ aqueous solution, previously thermostated at the required temperature. In every case the integrated method was followed, fitting the experimental absorbance−time data to the first-order integrated equation. Satisfactory correlation coefficients (>0.999) and residuals were attained in every case. All kinetic experiments were carried out at 25 °C.

Results and Discussion

(i) Temperature and Solvent Effects on Keto−Enol Equilibrium. The BZA keto−enol equilibrium was studied in water−dioxane mixtures (an homogeneous solvent whose physical properties change with the mixture composition), in aqueous micellar solutions of SDS (i.e., in a microheterogeneous medium, in which the existence of two main regions of quite different properties, such as the bulk water pseudophase and the micellar pseudophase, may be remarked), and in aqueous β-cyclodextrin solutions.

Figure 1 displays the effect of water−dioxane ($\epsilon = 2.2$)[14] mixtures and SDS aqueous micellar solutions on the UV spectrum of benzoylacetone. The amount of the enol tautomer increases as either the dioxane percentage (Figure 1a) or the surfactant SDS concentration (Figure 1b) is increased. In dioxane, poorly defined isosbestic points are obtained and the maximum wavelength absorption due to the enol tautomer ($\lambda \approx 312$ nm) shifts to lower wavelength as the solvent polarity decreases (a common observation in $\pi \rightarrow \pi^*$ transitions).[15] By contrast, in the presence of SDS micellar solutions, if we assume that the keto form resides in the bulk water phase and the enol form is solubilized in the Stern layer of the SDS micelles (a very hydrated region of dielectric constant—or relative permittivity[16]—estimated between 46 and 56),

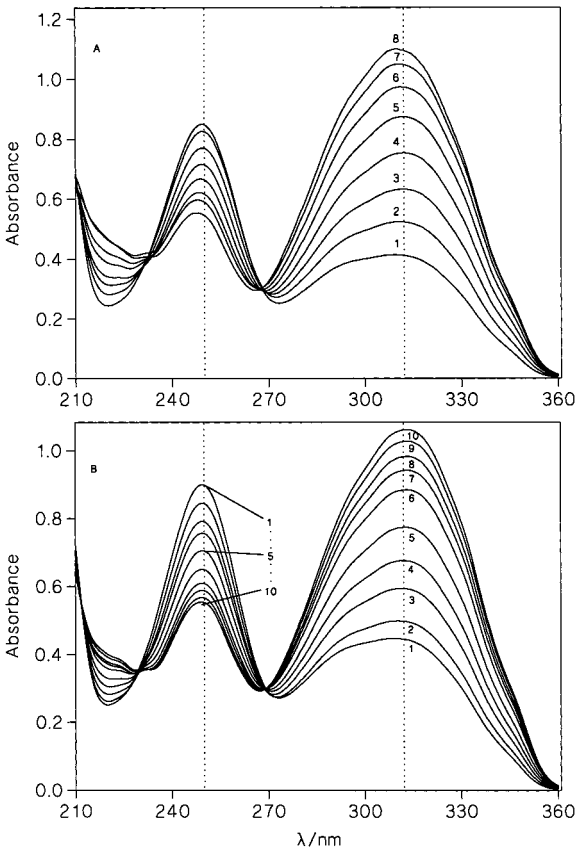

Figure 1. Absorption spectra of BZA obtained (a) in water−dioxane mixtures of (1) 0.2%, (2) 10%, (3) 20%, (4) 30%, (5) 40%, (6) 50%, (7) 60%, (8) 70% v/v of dioxane ([BZA] = 7.0×10^{-5} mol dm^{-3}) and (b) absorption spectra of BZA (8.0×10^{-5} mol dm^{-3}) obtained in the presence of [HCl] = 0.033 mol dm^{-3} as a function of SDS concentration at (1) 0.0, (2) 8.8×10^{-3}, (3) 1.1×10^{-2}, (4) 1.32×10^{-2}, (5) 1.76×10^{-2}, (6) 2.8×10^{-2}, (7) 4.4×10^{-2}, (8) 6.6×10^{-2}, (9) 0.132, (10) 0.28 mol dm^{-3}.

no change in the microenvironment of both absorbing species will occur on increasing the surfactant concentration. Consequently, two well-defined isosbestic points are drawn on varying the [SDS], which also means that the enolization constant, K_E = [enol]/[keto], remains independent of the parameter being varied.[17]

The influence of [SDS] on the BZA spectrum was studied at several temperatures and in the presence of two constant percentages of dioxane in the aqueous SDS micellar solutions. We followed the recently proposed method[11,12] to analyze the experimental results. Hence, the variation of the absorbance of the solution at 312 nm or at 250 nm, the two maximum absorption bands, is related to the micellized surfactant concentration ($[SDS]_m = [SDS]_t -$ cmc, with cmc being the critical micelle concentration calculated from the same experiment[18]) to obtain the unknown parameters K_E and K_s^E; the corresponding equilibrium processes are included in Scheme 1 for comparison purposes with the case of β-cyclodextrin. Both K_E and K_s^E can be determined by nonlinear (or linear) regression analysis of the experimental data $A_\lambda - [SDS]_m$ (or to the linearized equation resulting from the dependence of A_{312} with $[SDS]_m$). The obtained

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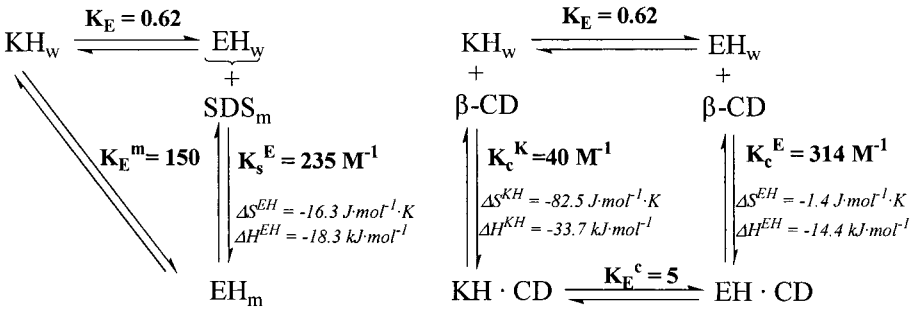
Scheme 1



a) *Enolization in SDS micelles* **b)** *Enolization in β-cyclodextrin*

Table 1. Experimental Conditions and Thermodynamic Parameters Obtained by Studying the Influence of [SDS] on the Absorption Spectra of BZA

data of $A_{312} - [SDS]_m$ fitted to $A_{312} = [A°_{312}(1 + K_s^E[SDS]_m)]/[1 + ((K_E K_s^E)/(1 + K_E))[SDS]_m]$							
medium[a]	t/°C	cmc/mol dm^{-3}	$A°_{312}$	K_s^E/mol^{-1} dm^3	$K_E/(1 + K_E)$	K_E	cc
SDS	16.9	2.5×10^{-3}	0.4001	284 ± 8	0.422 ± 0.002	0.73	0.9992
SDS	25.0	2.5×10^{-3}	0.362	235 ± 7	0.390 ± 0.001	0.64	0.9997
SDS	32.0	2.0×10^{-3}	0.3568	191 ± 6	0.389 ± 0.002	0.63	0.9994
SDS	41.2	2.1×10^{-3}	0.3339	161 ± 5	0.383 ± 0.002	0.62	0.9994
SDS/10%[b]	25.0	4.0×10^{-3}	0.4762	85.5 ± 2.5	0.481 ± 0.002	0.93	0.9994
SDS/20%[b]	25.0	5.0×10^{-3}	0.5670	40 ± 2	0.562 ± 0.004	1.28	0.9994
SDS/2%[c]	25.0	1.0×10^{-3}	0.100[d]	1100	0.39	0.68	0.99
Data of $A_{250} - [SDS]_m$ fitted to $A_{250} = [A°_{250} + (A^{\infty}_{250} K_E K_s^E/(1 + K_E))[SDS]_m]/[1 + ((K_E K_s^E)/(1 + K_E))[SDS]_m]$							
medium[a]	t/°C	cmc	$A°_{250}$	A^{∞}_{250}	$K_s^E K_E/(1 + K_E)$	K_E	cc
SDS	16.9	2.5×10^{-3}	0.7443	0.440 ± 0.002	110 ± 3	0.63	0.9993
SDS	25.0	2.5×10^{-3}	0.7340	0.451 ± 0.002	99 ± 3	0.73	0.9995
SDS	32.0	2.0×10^{-3}	0.7709	0.473 ± 0.002	74.5 ± 3	0.64	0.9991
SDS	41.2	3.0×10^{-3}	0.7638	0.485 ± 0.002	62 ±2	0.63	0.9994
SDS/10%[b]	25.0	3.5×10^{-3}	0.7085	0.448 ± 0.003	43 ±2	1.01	0.999
SDS/20%[b]	25.0	5.0×10^{-3}	0.6638	0.440 ± 0.005	23 ±1	1.33	0.999
SDS/2%[c]	25.0	1.0×10^{-3}	0.238[e]	0.077[e]	475	0.75	0.99

[a] Aqueous solutions of SDS in the presence of [HCl] = 0.033 mol·dm^{-3}. [b] Refers to the percentage of dioxane in the aqueous SDS solutions. [c] Dibenzoylmethane at 1.2×10^{-5} mol·dm^{-3}. [d] At 345 nm. [e] At 254 nm.

parameters are independent of the analysis procedure used and are listed in Table 1.

The K_E values do not appear to be temperature dependent (at least, in the range studied), which is indicative of the small value of the enthalpy ($\Delta H°$) corresponding to the enolization equilibrium in water.[19] Also, one can see that a decrease in the dielectric constant makes the enol content greater; e.g., values of K_E are 0.63 in water, 0.95 in 10% v/v dioxane−water, and 1.3 in 20% v/v dioxane−water. Most studies[20] concerning the determination of $\Delta H°$ and $\Delta S°$ for β-dicarbonyl compound enolization refer to acetylacetone, ethylacetoacetate, and dimethylacetoamide. Almost all studies have been carried out in apolar solvents and have employed the NMR method. Inspection of the data reveal important conclusions: the enol formation is always favored enthalpically and disfavored entropically and $\Delta G°$ differences between apolar solvents and water are mainly due to the more negative $\Delta S°$ values in the latter.

In regard to the values of K_s^E, the addition of dioxane to water reduces the solvent organization, which simplifies the solubility of hydrophobic molecules, like BZA−enol, and consequently K_s^E decreases strongly (from 235 mol^{-1} dm^3 in water, to 40 mol^{-1} dm^3 in 20% v/v dioxane−water). In the same sense, as the structure of water is more ordered at low temperatures (reaching maximum at 4 °C), then K_s^E values diminish on increasing temperature (e.g., from 284 mol^{-1} dm^3 at 17 °C to 161 mol^{-1} dm^3 at 42 °C).

The van't Hoff plot corresponding to K_s^E draws a good straight line, yielding the values of $\Delta S° = -16.3$ J·mol^{-1} K^{-1} and $\Delta H° = -18.3$ kJ·mol^{-1}. van der Waals interactions between the enol and the hydrocarbon chains of the surfactant monomers in the micelle account for the favorable enthalpic contribution, which is also due, in a great part, to the gain in the number of intramolecular hydrogen bonds with the enol tautomer in the micellar phase. Because of resonance with the phenyl ring, these intramolecular interactions can be of types O···H−O or $^-$O···H−O, whose energy ranges between (50−150) kJ mol^{-1}.[21] Despite the increase in entropy accompanying the enol departure of the water phase, a greater loss is associated with enol solubilization in the micelle; however, the unfavorable entropic factor is less significant than the enthalpic one, which causes the association process to be energetically favorable.

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(20) For example, in the case of enolization of acetylacetone in water $\Delta H° = -11.29$ kJ/mol and $\Delta S° = -51.8$ J/mol·K, and then K_E varies from 0.21 to 0.16 in the temperature range of 15−40 °C. (Spencer, J. N.; Holmboe, E. S.; Kirshenbaum, M. R.; Firth, D. W.; Pinto, P. *Can. J. Chem.* **1982**, *60*, 1178.

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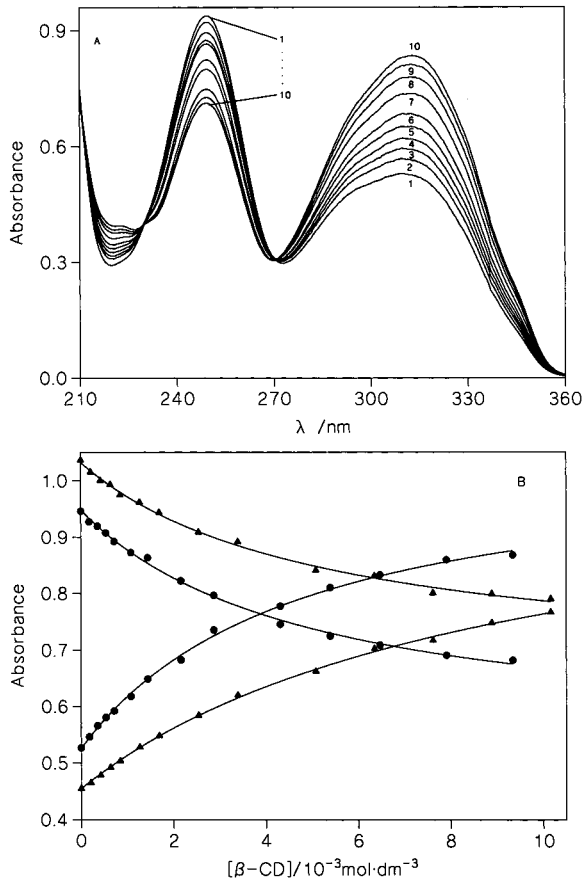

Figure 2. (a) Absorption spectra of BZA (7.0×10^{-5} mol dm^{-3}) in the presence of [HCl] = 0.033 mol dm^{-3} as a function of β-CD concentration at (1) 0.0, (2) 0.36, (3) 0.72, (4) 1.08, (5) 1.44, (6) 2.16, (7) 2.89, (8) 4.31, (9) 5.39, (10) 6.47 mmol dm^{-3}; (b) influence of β-CD concentration on the absorbance readings at (●) 10 °C and at (▲) 36 °C; lines fit eqs 1 (ascending curve) and 2 (descending curve).

Figure 2 exhibits the effect of β-CD concentration on the absorption spectra of BZA. As in the case of SDS aqueous micellar solutions, addition of cyclodextrin shifts the benzoylacetone keto−enol equilibrium to the enol tautomer. Nevertheless, unlike with SDS, the isosbestic points are not very well-defined, as occurring in the case of water−dioxane mixtures. Remembering that the enol tautomer is stabilized by intramolecular hydrogen bonding, the increases in absorbance at 312 nm with [β-CD] may be the consequence of the formation of an inclusion compound between the enol and β-CD of 1:1 stoichiometry. Since, in aqueous solutions, intramolecular hydrogen bonding is widely replaced by intermolecular interactions with the solvent, the BZA−enol is more extensively stabilized in the hydrophobic cavity interior of CD. But on first sight the keto tautomer could also form inclusion complexes with β-CD (vide infra), as stated in Scheme 1b, where KH, EH, KH·CD, and EH·CD stand for the keto molecules, enol, keto·β-CD complex, and the enol·β-CD complex, respectively.

Following the same procedure as for that of micellar solutions,[11] starting from Scheme 1b and taking into account that BZA concentration (= 7.0×10^{-5} mol·dm^{-3}) is much smaller than [β-CD] (i.e., [β-CD]$_t$ = [KH·CD] + [EH·CD] + [β-CD] ≃ [β-CD]) one can easily arrive to eqs 1 and 2 to relate the absorbance variation at two maximum absorption bands with [β-CD].

$$A_{312} = \frac{A^\circ_{312}(1 + K_c^E[\beta\text{-}CD])}{1 + Z[\beta\text{-}CD]} \quad \text{with } Z = \frac{K_c^K + K_c^E K_E}{1 + K_E} \tag{1}$$

$$A_{250} = \frac{A^\circ_{250} + A^\infty_{250} Z[\beta\text{-}CD]}{1 + Z[\beta\text{-}CD]} \quad \text{with} \quad Z = \frac{K_c^K + K_c^E K_E}{1 + K_E} \tag{2}$$

Fitting the experimental data of A_λ − [β-CD] to eqs 1 or 2, the parameters reported in Table 2 were obtained. The results obtained in the study of the influence of β-CD on the absorption spectrum of dibenzoylmethane are also included. The UV-absorption spectrum of acetylacetone does not show appreciable changes by the presence of β-CD.

If one assumes that the inclusion complexation of the keto form with β-CD is negligible (in which case $Z = K_c^E K_E/(1 + K_E)$, as in the case of SDS micellar solutions), the model also fits quite well to the experimental data, but the resulting K_E values (≈ 0.9) are much higher than those expected (K_E = 0.62) and reported in Table 1 or determined with other methods.[22] As one cannot accept that the presence of β-CD could modify the value of K_E, because the properties of the bulk water solvent remain unchanged by the presence of β-CD, this apparent discrepancy can be solved by considering as well as the formation of an inclusion complex between the keto tautomer and CD: KH·CD, with K_c^K being the stability constant (Scheme 1b). Such an alternative could also explain the appearance of two poorly defined isosbestic points in the BZA spectra as a function of [β-CD]; thus, the microenvironments of both absorbing species are changing.

Values of K_c^K were determined from Z {=$(K_c^K + K_c^E K_E)/(1 + K_E)$} by using known values of K_c^E and K_E. The latter was obtained from data in Table 1 (and results already published[11]) as the average value of K_E = 0.62, not temperature dependent.

The results reported in Table 2 indicate that BZA−enol forms an inclusion complex more stable than that of the keto tautomer. Taking into account that $\Delta G = -RT\cdot\ln K = \Delta H - T\Delta S$, the study of the influence of temperature on K_c^E and K_c^K allows us to obtain the thermodynamic parameters of the corresponding equilibrium processes. The plots of ln K_c^E (or ln K_c^K) against $1/T$ are good straight lines, and from the intercept and slope values the following thermodynamic parameters can be obtained: (i) for enol inclusion $\Delta S^{EH} = -1.4$ J/mol·K and $\Delta H^{EH} = -14.7$ kJ/mol; (ii) for keto inclusion $\Delta S^{KH} = -82.5$ J/mol·K; $\Delta H^{KH} = -33.7$ kJ/mol.

The geometries of both tautomers of BZA were optimized,[23] and while the enol is a planar molecule, the keto form is not. The vertical distance between H_{14} and H_{16} is 4.35 Å, whereas the horizontal distances between H_{15} and O_{11}, in the enol, and between H_{15} and C_{10}, in the keto, are 8.30 and 8.65 Å, respectively. Considering the shape and dimensions of β-CD[1,24,25] (Scheme 2), the only way

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(25) Li, S.; Purdy, W. C. *Chem. Rev.* **1992**, *92*, 1457.

Table 2. Thermodynamic Parameters Obtained in Water by Studying the Influence of β-Cyclodextrin Concentration on the Absorption Spectra of BZA at 6.7 × 10^{-5} mol·dm^{-3} and in the Presence of [HCl] = 0.033 mol·dm^{-3}

data of A_{312} − [β-CD] fitted to eq 1						
t/°C	$A°_{312}$	K_c^E/mol^{-1} dm^3	*Z*/mol^{-1} dm^3	K_E[b]	K_E	K_c^K/mol^{-1} dm^3
10.0	0.5252	431 ± 17	215 ± 11	0.995	0.62	81.1
15.3	0.4915	387 ± 16	186 ± 10	0.889	0.62	61.4
20.3	0.5111	348 ± 10	162 ± 6	0.889	0.62	46.7
25.0[a]	0.3865	314 ± 9	145 ± 6	0.896	0.62−0.72[22]	40.2
31.1	0.4658	283 ± 16	126 ± 6	0.802	0.62	28.7
36.0	0.4550	254 ± 8	112 ± 5	0.776	0.62	24.0
25.0[c]	0.273[d]	445 ± 26	274 ± 19	1.60	0.65	163

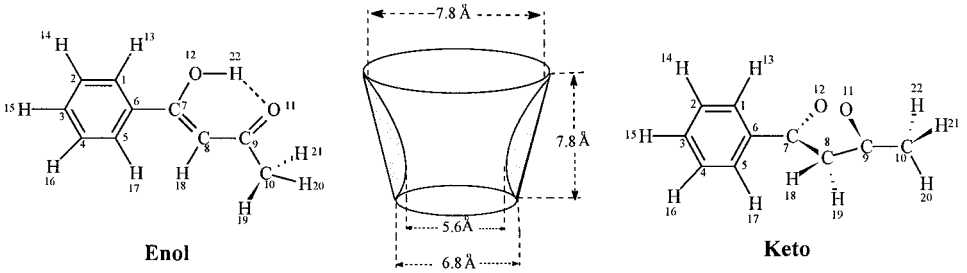
$\ln(K_c^E) = A + B(1/T)$; $A = (-0.185 \pm 0.096)$; $B = (1.77 \pm 0.03) \times 10^3$; $r = 0.9995$

data of A_{250} − [β-CD] fitted to eq 2						
t/°C	$A°_{250}$	A^{∞}_{250}	*Z*/mol^{-1} dm^3	K_E[b]	K_E	K_c^K/mol^{-1} dm^3
10.0	0.9498	0.538 ± 0.012	214 ± 13	0.986	0.62	79.5
15.3	0.9343	0.536 ± 0.003	186 ± 12	0.935	0.62	53.0
20.3	1.0176	0.588 ± 0.005	164 ± 10	0.851	0.62	48.3
25.0[a]	0.7593	0.421 ± 0.003	144 ± 8	0.847	0.62	38.6
31.1	1.0134	0.579 ± 0.006	126 ± 14	0.802	0.62	28.7
36.0	1.0260	0.533 ± 0.008	113 ± 13	0.801	0.62	25.5

$\ln(K_c^K) = A + B(1/T)$; $A = (-8.4 \pm 0.3)$; $B = (4.05 \pm 0.10) \times 10^3$; $r = 0.999$

[a] At [BZA] = 5.0 × 10^{-5} mol dm^{-3}. [b] Calculated values by assuming $Z = K_c^E K_E/(1 + K_E)$. [c] Dibenzoylmethane 2.3 × 10^{-5} mol dm^{-3} in 2% dioxane. [d] At 345 nm.

Scheme 2



both keto and enol tautomers can enter the β-CD cavity is lengthwise, and in no circumstances could both BZA tautomers be encapsulated completely in the β-CD cavity.

In light of thermodynamic results and molecular modeling calculations, one could say that the enol form is a molecule capable of deeply protruding into the CD cavity. The enol adopts a cyclic form stabilized by intramolecular hydrogen bonds.Then, the interactions between the enol and CD are van der Waals forces. The practically insignificant entropic factor in the enol inclusion can be accounted for in the following way.

The β-CD cavity is filled with water molecules,[2,26] and then their release from the β-CD interior, together with the desolvation of the guest in the inclusion process, leads to an increase in entropy. This gain in entropy seems almost entirely compensated for by the entropy reduction when the two species, enol and CD, combine to form one species: this complexation process results in the loss of a translational degree of freedom. On the other hand, the enthalpic factor, which approximates the ΔH obtained in the solubilization process of the enol in the SDS micellar interphase, is due to the host−guest van der Waals interactions and to interactions between the expelled water molecules and the others in the bulk water phase.

The keto tautomer is not a planar molecule: the phenyl ring is in a different plane from that of the carbonyl groups. Consequently, the degree of penetration of the keto tautomer in the CD cavity is expected to be less than that of the enol tautomer. In addition, the carbonyl groups need to be stabilized by hydrogen-bond interactions by means of either secondary hydroxyl groups of β-CD or water molecules. At this point, one reasonable possibility is the formation of a complex in which only the phenyl ring was inside the β-CD cavity with the carbonyl group close to the phenyl ring forming hydrogen bonds with the OH groups located on the wider rim and with the other carbonyl group outside the β-CD cavity solvated by water molecules. This should mean that the keto form could penetrate the β-CD interior as for as about half the total deepness of the cavity. Such a picture should explain, first, that the important decrease in the entropic factor (a lower degree of penetration means that the included water molecules may not be entirely expelled in the complexation process) and, second, that the higher value of ΔH^{KH}, which is more than two times the value obtained in the case of the enol tautomer, may be attributed to the hydrogen-bonding formation between the β-CD host and keto guest. Molecular docking between the keto tautomer and β-CD was performed by molecular modeling techniques.[23] Docking was performed starting from the minimum β-CD geometries (energy = 26.29 *k*cal/mol) and keto tautomer (energy = 13.28 *k*cal/mol). The energy for the calculated minimum conformation, where

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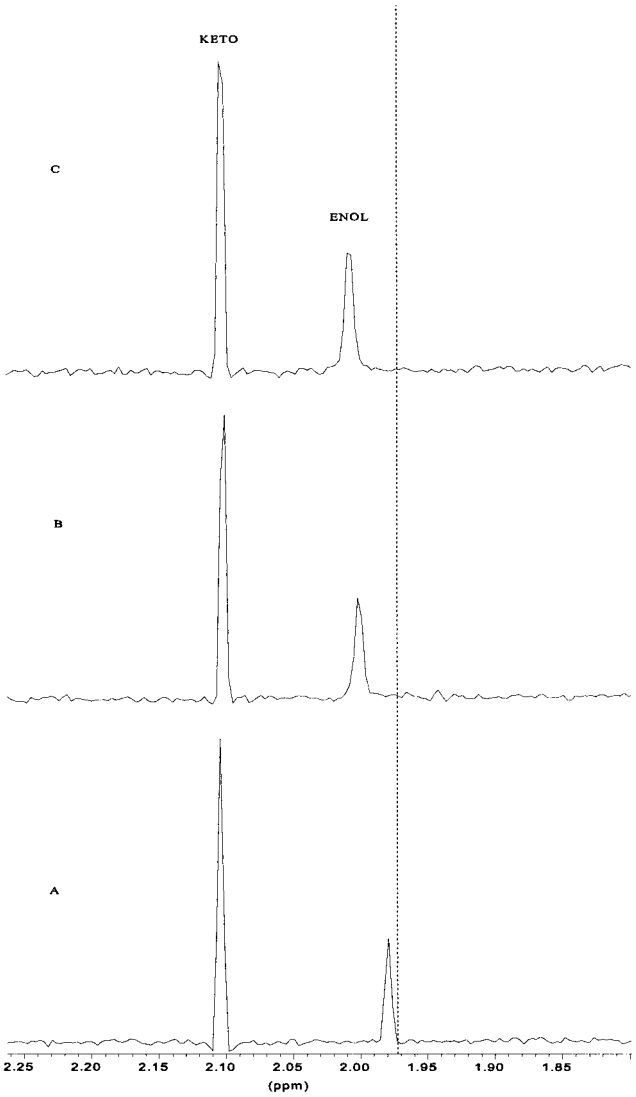

Figure 3. ^{1}H NMR for the methyl signal of keto and enol tautomers of benzoylacetone (8.0×10^{-4} mol·dm^{-3}) in D_2O in the absence (A) and in the presence of 0.89×10^{-3} (B) and 1.20×10^{-3} mol·dm^{-3} (C) of β-cyclodextrin.

the keto tautomer is included in the β-CD cavity with the carbonyl group close to the phenyl ring forming H-bonds with secondary OH groups of β-CD, was 20.67 *k*cal/mol. Even though it is a rough simulation of what can occur in the water solution, the energy of the complex decreases considerably.

Further arguments in favor of the proposed complex structure are obtained from NMR measurements. Figure 3 shows the effect of β-CD on the ^{1}H NMR for the methyl signals corresponding to both keto and enol tautomers. The position for the chemical shift is determined by the average environment sensed by the probe taking into account the fraction bound and free. It can be seen that no shift is observed for the methyl signal corresponding to the keto tautomer; this observation is in complete agreement with our picture of the β-CD·keto complex. By contrast, the methyl signal of the enol tautomer shifts when the complex is formed; shift values are collected in Table 3 as a function of β-CD concentration. Following the work of Bohne et al.,[27] we used these shift values to estimate the equilibrium association constant of BZA−enol to β-CD; the resulting K_c^E value is 352 mol^{-1} dm^3, which is in perfect agreement with the value reported in Table 2 obtained at the same temperature (~20 °C) from UV−vis spectrophotometry. We can also note from Figure 3 that the relative intensity of the peaks (keto−enol) decreases as [β-CD] increases, again in accordance with the spectrophotometric measurements, which evidence a displacement of benzoylacetone keto−enol equilibrium toward the enol tautomer on increasing [β-CD]. The relative areas of both peaks (calculated only in an approximate way) yield the percentages of both tautomers reported in Table 3. Finally, analysis of the shifts corresponding to the protons of β-CD[1,27,28] can be related to the location of the guest in the cyclodextrin cavity. The glucose H_3 and H_5 protons are located within the cavity, whereas protons H_6 are located at the narrower entrances and protons H_2 and H_4 at the wider entrance. In the presence of benzoylacetone, the H_3, H_5, and H_6 β-CD signals shift by 0.02, 0.08, and 0.02 ppm, respectively, whereas a much smaller shift (<0.006 ppm) is observed for H_4 and H_2. This observation suggests that since enol and keto tautomers of BZA penetrate into the β-CD cavity lengthwise and the enol tautomer protudes deeper inside than the keto tautomer does the methyl group of the latter should be outside the cavity.

Even though DBM is a greater molecule than BZA, the results agree with the formation of a 1:1 complex. The existence of isosbestic points near λ = 380 and 270 nm, even if not well-defined, indicates this. A plausible explanation may be that DBM yields only one indistinguishable enolic form, since it is symmetrically substituted. Methyl orange anion of the structure (two phenyl rings attached at both ends of −N=N−) close to DBM also yields an inclusion complex with β-CD of 1:1 stoichiometry.[5]

Further evidence for the formation of this complex-type can be obtained from the kinetic results of the nitrosation reaction of the enol form. The reactive species is the enol; i.e., the nitrosation occurs by an electrophilic attack of the nitrosating agent (X−NO, X = Cl, Br, SCN, ...) on the double bond of the enol (−(OH)C=CH−). Therefore, we might expect a reduction in the reactivity of the complex EH·CD because of the lower polarity of the CD interior and of the restricted access of the nitrosating agent to the reaction center.

(ii) Kinetic Results. In aqueous acidic solutions of sodium nitrite at low concentrations, the equilibria put forward in Scheme 3 can be stablished to account for the formation of the possible nitrosating agents: NO^+, and also nitrosyl halides (XNO) when X^- (= Cl^-, Br^-, SCN^-, ...) is present in the medium.[29]

Scheme 3

$$HNO_2 + H^+ \overset{K_{NO}}{\rightleftharpoons} NO^+ \quad (\text{or } NO_2H_2^+\text{: hydrated } NO^+)$$

$$HNO_2 + H^+ + X^- \overset{K_{XNO}}{\rightleftharpoons} XNO \quad (X^- = Cl^-, Br^-, SCN^-, ...)$$

(27) Barros, T. C.; Stefaniak, K.; Holzwarth, J. F.; Bohne, C. *J. Phys. Chem. A* **1998**, *102*, 5639.

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Table 3. ^{1}H NMR Chemical Shifts, δ (ppm), of $-CH_3$ Protons of Both Keto and Enol Tautomers and of CH Protons of β-Cyclodextrin in D_2O Measured with Respect to the Residual Water Signal at $\delta = 4.60$ ppm

[β-CD]/M	[BZA]/M	$\delta_{Me}{}^K$ (area)	$\delta_{Me}{}^E$ (area)	$\Delta\delta$	% enol	% keto
0.00×10^{-3}	0.80×10^{-3}	2.154 (1.00)	2.029 (0.465)		32	68
0.89×10^{-3}	0.80×10^{-3}	2.148 (1.00)	2.047 (0.640)	0.018	39	61
1.18×10^{-3}	0.80×10^{-3}	2.151 (1.00)	2.053 (0.695)	0.024	41	69
2.36×10^{-3}	0.80×10^{-3}	2.148 (−)	2.063 (−)	0.034		

CH protons of β-CD[a]		δ (H_3)	δ (H_5)	δ (H_6)	δ (H_2)	δ (H_4)
9.0×10^{-3}	0.0	3.753	3.628	3.670	3.469	3.418
0.89×10^{-3}	0.80×10^{-3}	3.734	3.545	3.648	3.465	3.414
1.20×10^{-3}	0.80×10^{-3}	3.734	3.545	3.651	3.465	3.414

[a] Assignment of the ^{1}H NMR signals of β-CD as in refs 27 and 28.

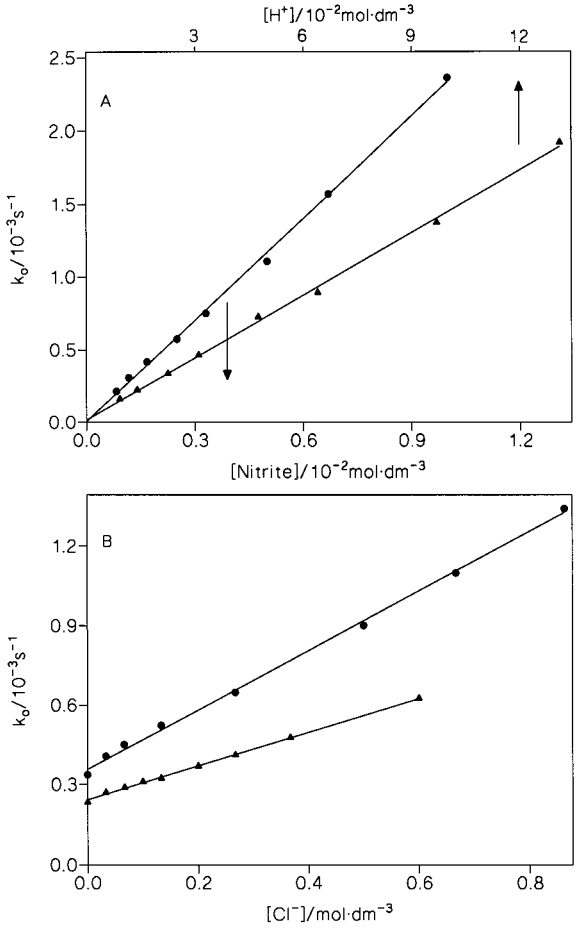

Figure 4. (a) Influence of (●) [nitrite] at $[H^+] = 0.040$ mol dm^{-3} and (▲) $[H^+]$ at [nitrite] $= 2.5 \times 10^{-3}$ mol dm^{-3} in the nitrosation of dibenzoylmethane in water at [DBM] $= 2.5 \times 10^{-5}$ mol dm^{-3}; (b) influence of Cl^- concentration in the nitrosation of BZA at [nitrite] $= 1.67 \times 10^{-3}$ and $[H^+] = 0.031$ mol dm^{-3} (●) in the absence of β-CD and (▲) in the presece of [β-CD] $= 4.6 \times 10^{-3}$ mol dm^{-3}.

The nitrosation reaction of BZA, and other β-dicarbonyl compounds, has been studied in water.[12] The reaction is first order in both [ketone] and $[H^+]$ and is also first order with respect to total nitrite concentration (see Figure 4a for the case of DBM). Therefore, eq 3 can be formulated in which k_1 is the rate constant for the reaction via NO^+ and k_2 refers to the rate constant for the reaction via XNO.

$$\text{rate} = (k_1 + k_2[X^-])[\text{ketone}]_t[H^+][\text{nitrite}] \quad (3)$$

To test possible mechanistic changes induced by the presence of β-CD, we first examined the influence of $[Cl^-]$ on the nitrosation of BZA at $[H^+] = 0.030$ mol·dm^{-3} and [nitrite] $= 1.67 \times 10^{-3}$ mol·dm^{-3} in the absence and presence of 4.6×10^{-3} mol·dm^{-3} of β-CD. In both situations, the observed rate constant varies linearly with $[Cl^-]$ (see Figure 4b), whose slope and intercept values are statistically different from zero in both cases. The intercept values were $(3.6 \pm 0.1) \times 10^{-4}$ and $(2.42 \pm 0.03) \times 10^{-4}$ s^{-1}, in the absence and presence of β-CD, respectively; and the slope values were $(11.2 \pm 0.2) \times 10^{-4}$ and $(6.4 \pm 0.1) \times 10^{-4}$ mol^{-1} dm^3 s^{-1}, in the absence and presence of β-CD, respectively. These results indicate that β-CD inhibits the nitrosation reaction of BZA−enol either in the nitrosation by NO^+ (intercept term) or by ClNO (slope term).

We then studied the influence of β-CD concentration under different experimental conditions: when only the NO^+ was the nitrosating agent, i.e., by using $HClO_4$ as the source of H^+ (see Figure 5); or in the presence of X^- (= Cl^-, Br^-, or SCN^-), i.e., when nitrosation by nitrosyl halides, XNO, also takes place (see Figure 6). In both situations k_o decreases as [β-CD] increases.

The results obtained in the previous section point out that the enol of BZA froms a 1:1 inclusion complex with β-CD. On the other hand, in electrophilic substitutions, as appropiate to nitrosation reactions, the enol is the reactive form. Then the mechanistic hypothesis shown in Scheme 4 for the case of benzoylacetone, with the rate-controlling steps being the nitrosation of the enol, is assumed. The values reported for the equilibrium constants have been obtained in the previous section and refer to 25 °C, except for the equilibrium constant between the two enol forms,[30] which are kinetically indistinguishable because the reaction center (=CH−) is the same in both isomers.

The reaction rate will be the sum of the rates of the reaction via free and complexed enol, and by NO^+ or XNO as stated in eq 4.

$$\text{rate} = (k_{NO}[NO^+] + k_{XNO}[XNO])[EH] + (k_{NO}{}^c[NO^+] + k_{XNO}{}^c[XNO])[EH{\cdot}CD] \quad (4)$$

The anions ClO_4^-, SCN^-, Br^-, and Cl^- form inclusion complexes with β-CD. The corresponding stability constants, in mol^{-1} dm^3, are reported in the literature[31] as $K(ClO_4^-) = 13.7$, $K(Br^-) = 1.66$, or $K(ClO_4^-) = 26.7$, $K(SCN^-) = 9.9$, $K(Br^-) = 6.5$, and $K(Cl^-) = 2.56$.[32] The

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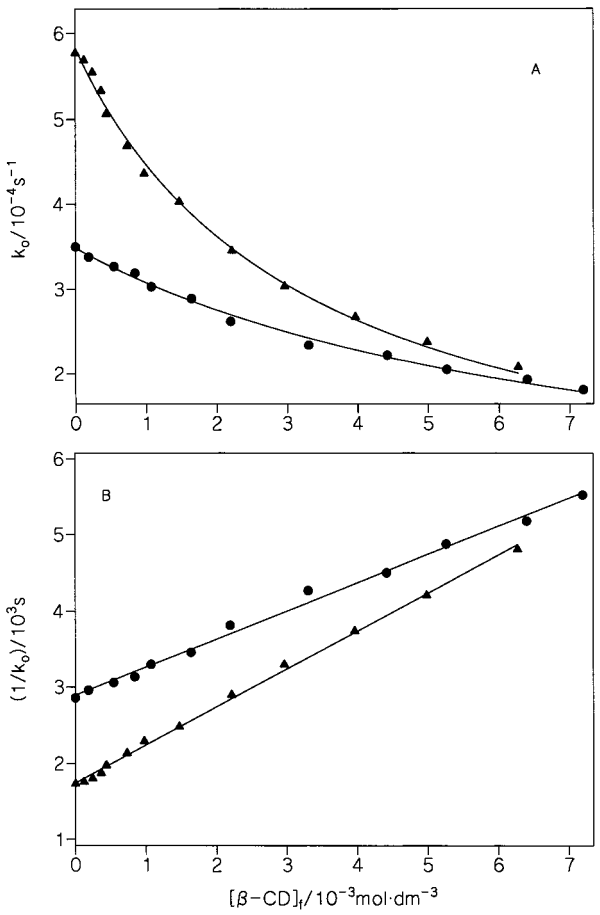

Figure 5. (a) Variation of k_o as a function of free [β-CD] in the nitrosation of (▲) DBM at [nitrite] = 2.5×10^{-3} mol·dm^{-3} and at [H^+] = 0.040 mol·dm^{-3} ($HClO_4$) and of (●) BZA at [nitrite] = 1.67×10^{-3} mol dm^{-3} and at [H^+] = 0.032 mol dm^{-3} ($HClO_4$); solid lines fit to eq 5; for parameters, see Table 4; (b) reciprocal plot of k_o against free [β-CD].

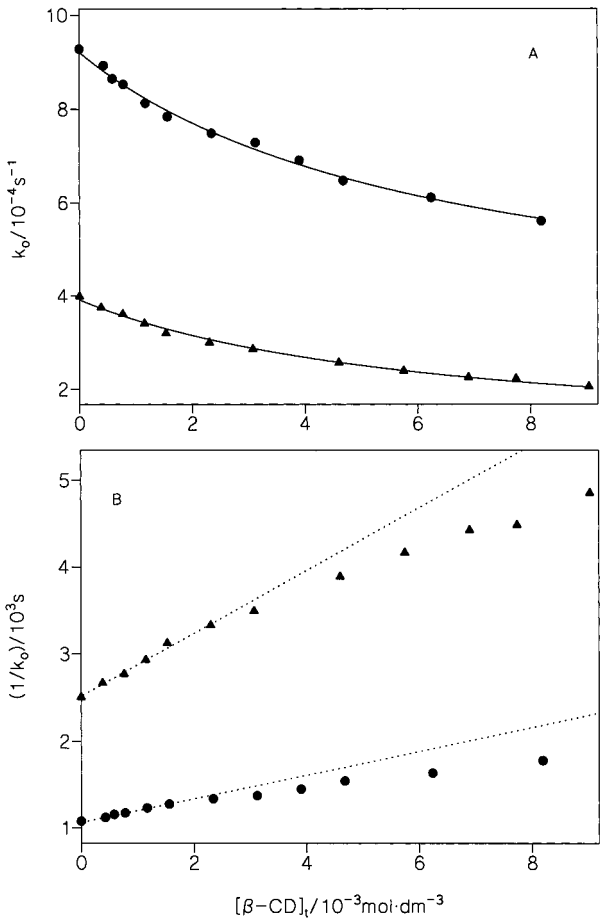

Figure 6. (a) Variation of k_o as a function of total [β-CD] in the nitrosation of BZA at (●) [nitrite] = 3.1×10^{-3} mol dm^{-3}, [H^+] = 0.031 mol dm^{-3}, and [Br^-] = 0.031 mol dm^{-3} and at (▲) [nitrite] = 1.67×10^{-3} mol dm^{-3}, [H^+] = 0.031 mol dm^{-3}, and [Cl^-] = 0.031 mol dm^{-3}; solid lines fit to eq 5; for parameters, see Table 4; (b) reciprocal plot of k_o against total [β-CD].

small values for the stability constants of the complexes formed between β-CD and Cl^- or Br^-, together with the small concentration used of these ions, means that no corrections are necessary to the free [β-CD], which is assumed to be the total [β-CD]. The same applies to the case of SCN^-, which has been used at 8.0×10^{-4} mol·dm^{-3}, but since we have used perchloric acid, it was necessary to do the appropriate corrections due to ClO_4^- ions.

We worked with the values reported in ref 31 in order to get better agreement in the Z values determined in this section and those reported in Table 2. Then, taking into account that $[BZA]_t \ll [\beta\text{-CD}]_t$, we can assume that, when HCl or HBr was used to acidify the reaction medium, the total amount of cyclodextrin concentration is free; but, when ClO_4^- ions are present, we must consider the quantity of β-CD-forming complexes with perchlorate ions. Free cyclodextrin concentration is determined by solving the equation: $[CD]_f^2 + [CD]_f\{K_i^{-1} + [ClO_4^-] - [CD]_t\} - [CD]_t/K_i = 0$ at each β-CD concentration, with K_i being the stability contant formed between ClO_4^- ion and β-CD.

Hence, starting from eq 4 and Scheme 4, one easily arrives at eq 5, which relates the variation of k_o with free [β-CD]. In this equation, $k_1 = k_{NO}K_{NO}K_E/(1 + K_E)$; $k_2 = k_{XNO}K_{XNO}K_E/(1 + K_E)$, i.e., the nitrosation through the free enol, whereas the same expressions for k_1^c and k_2^c refer to the nitrosation through the complexed enol, and finally $Z = (K_c^K + K_c^E K_E)/(1 + K_E)$.

$$k_o = \frac{[\text{nitrite}][H^+][(k_1 + k_2[X^-]) + (k_1^c + k_2^c[X^-])K_c^E[\beta\text{-CD}]]}{1 + Z[\beta\text{-CD}]} \quad (5)$$

A multiple regression analysis of eq 5 using experimental k_o and [β-CD] values, along with K_c^E and Z values determined in the previous section, affords the results listed in Table 4, where experimental conditions are also indicated; values of k_1 and k_2, determined here or taken from published data,[12] are also reported. Curves in Figures 5 and 6 are the theoretical fits of the experimental data to eq 5. Figures 5b and 6b show the reciprocal plot of k_o against [β-CD], and we can note two different behaviors depending on if the reaction is performed in the absence (Figure 5b) or in the presence of X^- (Figure 6b). According to eq 5, a linear plot of $1/k_o$ vs [β-CD] indicates that the complexed enol is unreactive; i.e. the situation found when the nitrosation agent is the NO^+, either with the enol of BZA or DBM. Similar behavior has been observed for reactions between a complexed

Scheme 4

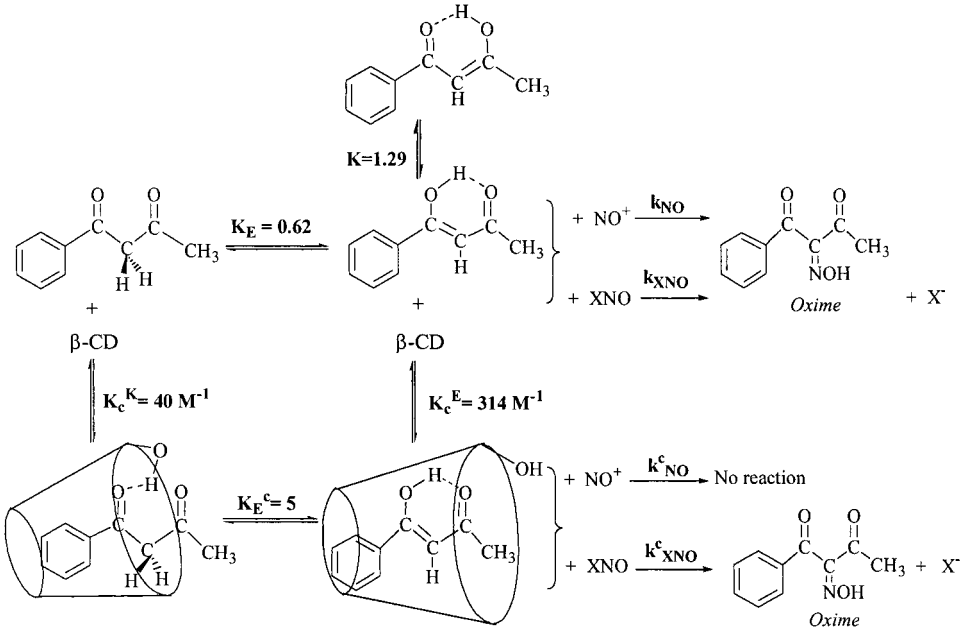

Table 4. Experimental Conditions and Results Obtained in the Nitrosation of BZA and DBM in Aqueous Acid Medium in the Presence of *β*-CD

medium	$[H^+]^a$	[nitrite]^a	$[X^-]^a$	$k_1{}^b$	$k_2{}^c$	$k_2{}^cK_c{}^E$	Z^d	$k_2{}^c$
system benzoylacetone (BZA)−*β*-cyclodextrin (*β*-CD)								
$H_2O/HClO_4$	0.023	1.67×10^{-3}		7.24			$156 \pm 4 - 152$	
$H_2O/HClO_4$	0.030	1.67×10^{-3}		7.24			$133 \pm 4 - 129$	
H_2O/HCl	0.030	1.67×10^{-3}	0.030 (Cl^-)	7.91^e	22	204 ± 8	155 ± 3	0.65
H_2O/HBr	0.030	3.1×10^{-3}	0.030 (Br^-)	10.6^e	100	427 ± 13	145 ± 6	1.36
$H_2O/HClO_4$	0.030	1.67×10^{-3}	8.0×10^{-4} (SCN^-)	14.65^e	10220	1400 ± 20	160 ± 9	4.46
system dibenzoylmethane (DBM)−water								
$H_2O/HClO_4$	variable	2.5×10^{-3}		5.8				
$H_2O/HClO_4$	0.040	variable		5.3				
$H_2O/HClO_4$	0.030	2.5×10^{-3}	variable/Cl^-	5.6	10.1			
system dibenzoylmethane (DBM)−*β*-CD								
$H_2O/HClO_4$	0.040	2.5×10^{-3}		5.8			$293 \pm 9 - 285$	

^{a} In mol·dm^{-3}. ^{b} mol^{-2} dm^6 s^{-1}. ^{c} mol^{-3} dm^9 s^{-1}. ^{d} Values of $Z = (K_c{}^K + K_c{}^E K_E)/(1 + K_E)$ in mol^{-1} dm^3 obtained by fitting the data of k_o − [*β*-CD] to eq 5, and obtained from the linear plot of $1/k_o$ against [*β*-CD]. ^{e} Corresponding values of $k_1 + k_2[X^-]$.

substrate and H_3O^+, i.e., specific acid hydrolysis,[33] and have been explained as due to the noninclusion of H_3O^+ cation into the *β*-CD cavity. In fact, whereas the binding of anions of many types by CDs has been observed, and it can be quite strong,[31,32,34] the binding of cations has rarely been observed, and only for large organic dyes,[5] long-chain surfactants,[35] and metal ions with organic ligands.[36] In contrast, the binding of simple cations appears to be relatively unfavorable, e.g., piperidinium ions bind only weakly and much less than neutral piperidine.[37] The foregoing considerations along with the small NO^+ concentrations ($K_{NO} \approx 3.5 \times 10^{-7}$ mol^{-1} dm^3)[38] explain the absence of reaction of the complexed enol toward NO^+.

On the contrary, when the nitrosation reaction is promoted by XNO, results in Figure 6b and data in Table 4 indicate that the nitrosation of the complexed enol also occurs. Nevertheless, values of $k_2{}^c$, i.e., the term of the reaction of the complexed enol with nitrosyl halides (or pseudohalides), are smaller than those obtained in water in every case, e.g., more than 30 times when ClNO is the nitrosating agent. This effect can be attributed to the lower polarity of the *β*-CD cavity. The trend of reactivity found in water k_2(ClNO)/k_2(BrNO)/k_2(SCNNO) as 1:4.5:460 is associated with the nucleophilicity order of the anions and is often found in nitrosation studies.[29,39] If the nucleophilicity is still the driving force for catalysis in the nitrosation of the complexed enol, the change in the efficiency detected: $k_2{}^c$(ClNO)/$k_2{}^c$(BrNO)/$k_2{}^c$(SCNNO) as 1:2:7 is probably explained by the inversion of the nucleophilicity order in the cyclodextrin interior. It is hown that the order $Br^- > Cl^- > SCN^-$ is only applicable when the nucleophile is deactivated by hydration, whereas the "natural" order of nucleophilicity $SCN^- > Br^- > Cl^-$ is observed in solvents such as acetonitrile, acetone, etc.[15] A similar reduction in the catalysis efficiency is often found in nitrosation reactions carried out in dioxane−

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water[40] or acetonitrile−water[41] mixtures and also for the nitrosation in the micellar phase.[13]

The kinetic results obtained for the nitrosation of DBM corroborates the BZA outcome, i.e., the formation of a 1:1 inclusion complex between DBM−enol and β-CD that is unreactive toward NO^+. The enol form of DBM is also a planar molecule and is larger than the enol molecule of BZA, but since it is symmetrically substituted, there is only one indistinguishable DBM enol, which explains the formation of only 1:1 complex.

We also examined the influence of [β-CD] on the nitrosation of acetylacetone (AcAc) at [AcAc] = 1.5×10^{-4} mol·dm^{-3}, [nitrite] = 1.67×10^{-3} mol·dm^{-3}, [H^+] = 0.015 mol·dm^{-3}, and [Br^-] = 0.017 mol·dm^{-3}, by observing the decreased absorbance at 245 nm due to enol consumption. The results of the observed rate constant showed to be independent of [β-CD]; in fact, $k_o = 3.23 \times 10^{-4}$ s^{-1} in the absence of β-CD and $k_o = 3.09 \times 10^{-4}$ s^{-1} at [β-CD] = 9.0×10^{-3} mol·dm^{-3}. Because AcAc is quite soluble in water, no inclusion complex appears to form under these experimental conditions. Moreover, the results of AcAc evidence that the presence of β-CD has no effect on nitrosation reactions in acid media; in other words, since β-CD has many alcoholic groups, an inhibition of the nitrosation rate by the presence of β-CD could also be attributed to a reduction of the nitrosating agent through the equilibrium process: β-CD·OH + HNO_2 ⇌ β-CD·ONO + H_2O, which is very common for alcohols[42] and is responsible for the inhibition of alcohols in nitrosation reactions.[43] Therefore, the results attained in the nitrosation of AcAc rule out this possibility, at least for the experimental conditions of this work.

Conclusions

This investigation demonstrates that both keto and enol tautomers of BZA form inclusion compounds with β-cyclodextrin of 1:1 stoichiometry. A detailed description of the complexation was achieved by employing complementary techniques that provide information on different aspects of the complexation process. Values of the thermodynamic functions obtained for the inclusion processes suggest that the enol form protudes deep inside the CD cavity, with "hydrophobic interactions" being the main driving force of the inclusion process; meanwhile, the keto tautomer is about half included in the CD cavity, forming hydrogen bonding with the OH groups located on the wider rim of the CD host. ^{1}H NMR measurements corroborate these complex structures. The particular structure of the complex enol·CD causes this species to be less reactive in nitrosation reactions than the uncomplexed enol, due mainly to the lower polarity of the CD interior and of the restricted access of the nitrosating agent to the reaction center.

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