Inclusion Complexes of $\beta$-Cyclodextrin with Keto/Enol Tautomers of 2-Acetyl-1-tetralone. A Comparative Study

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Abstract
The keto–enol interconversion of 2-acetyl-1-tetralone (ATLO) and of 2-acetyl-cyclohexanone (ACHE) occurs at measurable rates in aqueous acid or neutral medium. This finding allowed us to determine the keto–enol equilibrium constants, $K_E$, by following two distinct methods. Both methodologies afford results in complete agreement. The first one is a test of the Beer-Lambert law under two different experimental conditions that contain the substrate only in the enol form or in a mixture of both tautomers in equilibrium. The second method analyses the UV-absorption spectrum of each substrate under keto–enol equilibrium in aqueous $\beta$-cyclodextrin ($\beta$-CD) solutions of variable concentration: the presence of $\beta$-CD increases the percentage of the enol due to the formation of 1:1 inclusion complexes between this tautomer and $\beta$-CD. Rates of keto–enol tautomerization, in neutral and acid medium, and of nitrosation in acid medium under non equilibrium conditions have also been measured. Throughout the study, the presentation of the results is done by comparing the different behaviour observed between ATLO and ACHE. While the enol of ACHE included into the $\beta$-CD cavity shows to be unreactive either in tautomerization or in nitrosation, in the case of ATLO it is observed tautomerization through the complexed enol. In addition, with ACHE only the enol tautomer forms inclusion complexes with $\beta$-CD, whereas with ATLO the keto tautomer entries also to the $\beta$-CD cavity, however the stability constant with the enol is near 3-fold that of the keto isomer. These main differences can be rationalized on the basis of the molecular structure of these diketones.

Introduction
1,3-Diketones, such as 2-acetyl-1-tetralone (ATLO) or 2-acetyl-cyclohexanone (ACHE) have one ionisable proton and three possible tautomeric forms (keto, enol, and enolate), whose equilibrium ratios may be severely affected by changes in the media in which they are dissolved. The keto (KH) and enol (EH) forms are both present in aqueous acid or neutral solutions in measurable proportions. But the enol amount increases in apolar and/or aprotic (non-hydrogen bond donor or acceptor) solvents, being in some cases the predominant species. In aqueous alkaline medium, the enolate is rapidly generated, which in some situations is the only existing species [1].

The formulation of many reaction mechanisms can be aided by data on the effect of solvents on the rates of the reaction [2, 3]. For a given solvent, or any homogeneous solution, the dielectric constant is an important parameter; however, its properties are due to a combination of many interactions including dipole–dipole, charge–dipole, charge–charge, hydrogen bonding, etc [4, 5]. For a micro-heterogeneous solution, such as aqueous surfactant or cyclodextrin solutions, hydrophobic interactions play also a decisive role [6–10].

There have been a large number of studies into the tautomeric equilibria in general [11–13] and of 1,3-dicarbonyl compounds in particular [14, 15] using a great variety of techniques, and carrying out in water, in organic solvents, and recently in aqueous solutions of surfactants forming micelles [16] and of cyclodextrins [17]. We have measured the keto–enol tautomerization constants [18] and the keto–enol equilibrium constants of several 1,3-dicarbonyl compounds in microheterogeneous media by UV–vis spectroscopy and potentiometry [19]. The electronic spectroscopy appears to us as the most reliable method for these compounds because it only requires low concentrations of the substance to afford large changes of the optical density of the solution, thus conducting to accurate data on avoiding the use of drastic experimental conditions.

In this paper, we provide a comparative and systematic study of the keto–enol tautomerization of ATLO and ACHE in water in the absence and presence of...
\( \beta \)-cyclodextrin. Different methods and experimental conditions have been used to design two distinct forms to measure the keto–enol equilibrium constants, \( K_E \), as well as the tautomeric microscopic constants, with excellent agreement between them.

**Experimental**

2-Acetyl-1-tetralone (Aldrich) was used without any additional purification. Dioxane (spectrophotometric grade) was dried with molecular sieves. All other reagents (Aldrich or Merck) were used as received. Stock solutions of ATLO were prepared in dried dioxane. Aqueous solutions of the rest of reagents were prepared with double distilled water obtained from a permanganate solution.

UV–vis absorption spectra and kinetic measurements were recorded with a double-beam spectrophotometer (Uvikon 942 or XL) provided with a thermostatted cell holder. A matched pair of quartz cells with \( l = 1 \) cm light was used. Kinetic measurements were carried out under pseudo-first order conditions, with the concentration of ATLO, the limiting reagent, being more than 20 times lower than that of the other reactants. Both the enol tautomerization and enol nitrosation reactions have been studied by monitoring the decreasing absorbance at \( \lambda = 343 \) or 291 nm due to the enol form, respectively of ATLO or ACHE. Both reactions were initiated by injecting 10–40 \( \mu L \) of a stock dioxane solution of diketone into 3.0 mL of water containing the rest of the reagents. The experimental data (absorbance-time, \( A-t \)) were fitted to the pseudo-first order integrated equation, Equation (1), by obtaining satisfactory correlation coefficients \( (r > 0.9999) \) and residuals in every experiment.

\[
A = A_\infty + (A_o - A_\infty)e^{-k_o t}
\] (1)

The observed rate constant, \( k_o \), of tautomerization is the sum of the rate constants corresponding to enol-ketonization, \( k_o^k \), and keto-enolization, \( k_o^e \), \( k_o = k_o^k + k_o^e \).

Molecular dimensions were estimated by Hypercube Hyper Chem 7.0 on personal computer.

**Results and discussion**

A diluted solution \( (\sim 8 \times 10^{-5} \text{ M}) \) of ATLO, either in water or organic solvents, shows two absorption bands whose relative intensities change with both the time and the solvent (Figure 1). These two bands, with maxima at 343 nm and 254 nm, were tentatively assigned to the enol (EH) and keto (KH) forms, respectively: the only two tautomeric forms in equilibrium, an assumption that is confirmed by the presence of clearly defined isosbestic points in this region (at 274 and 238 nm).

Nevertheless, the absorbance at 343 nm decreases with time when ATLO dissolved in dioxane is diluted in water (10 \( \mu L \) in 3.0 mL); whereas the contrary is observed if a concentrated aqueous ATLO solution is diluted in e.g., dioxane – or DMSO – (100 \( \mu L \) in 2.9 mL). The reaction being observed is the slow keto–enol tautomerization, i.e., ATLO is fully enolized in aprotic solvents such as dioxane or DMSO, while a mixture of the two tautomers (keto and enol) is present in water, and their interconversion is slow, as we have already found with 2-acetyl-cyclohexanone [18] but in contrast to that observed with 2-acetyl-cyclopentanone [19b] or even with other 1,3-diketones [16]. Therefore, Figure 1 shows the reaction spectra of enol–ketonization as the neat reaction, but the process corresponds to the keto–enol equilibrium approach.

We make use of these experimental features to measure keto–enol equilibrium constants in water by following different methodologies.

1. Beer–Lambert law. Rate constants for enol–ketonization were determined in water at 25 °C for different initial ATLO concentrations. The results reported in Table 1 show that the extrapolated values of the initial absorbance \( (t \to 0) \), \( A_\infty \) at \( \lambda = 343 \text{ nm} \) increase proportional to [ATLO]; the same trend is observed with \( A_o \) values, i.e., the optimised absorbance readings at \( t \to \infty \). At the beginning of the tautomerization reaction, the practical totality of ATLO is in the enol form, then Equation (2) can be used to relate \( A_o \) and [ATLO]; whereas at the end of the reaction, a mixture of both keto and enol tautomers exists in equilibrium, being \( K_E \) the corresponding equilibrium constant: \( KH = EH, K_E \); then, Equation (3) can be obtained to explain the variation of \( A_o \) as a function of [ATLO]. Therefore, \( K_E \) can be determined as the quotient of \( A_o/(A_o-A_\infty) \) at each [ATLO]. The resulting data, shown also in Table 1 (entry four), give \( K_E = 0.95 \).