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Controlled keto-enol tautomerism of coumarin containing β-ketodithioester by its encapsulation in cucurbit[7]uril.

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Abstract: Conventional spectroscopy techniques (UV-Vis, fluorescence and NMR), mass spectrometry and molecular modeling studies were used to assess the inclusion of cucurbit[7]uril (CB7) with coumarin 7-*N*,*N*-diethylamino-2*H*-chromen-2-one derivatives bearing ethyl acetoacetate (**CAM1**) and methyl β-ketodithioester **(CAM2**) moieties. For the first time, it has been demonstrated that the macrocycle CB7 is able to stabilize the keto tautomeric form of both coumarin derivatives. More interestingly, it was also seen that for **CAM2,** the macrocycle CB7 shifts the keto-enol equilibrium from its enol form to the keto tautomer after its inclusion, establishing important differences with the inclusion in β-CD, while for **CAM1,** the macrocycle CB7 maintains the original keto form.

Introduction

Keto-enol equilibrium plays an important role in many fields of biochemistry and chemistry.[1] This phenomenon has attracted significant attention because the quantitative shift of such equilibria toward one or another tautomeric form can be assessed by modulating environmental properties.[1e-g,2] Researches have evidenced the use of supramolecular host-guest systems for the selective interaction of the corresponding keto or enol forms, and this has acquired greater relevance.[1f,3-6] Among the diverse macrocyclic hosts proposed for this purpose, cyclodextrins[3,6,7] have been the most studied; and recently, some research involving cucurbiturils[4,5] has been reported. Regarding the guests tested, the keto-enol tautomerism of monocarbonyl[4,5] and β-dicarbonyl compounds[3,6] has been addressed in the literature. Iglesias *et al*.[3] demonstrated that the presence of either β-cyclodextrin (β-CD) or sodium dodecyl sulfate micelles shifts the benzoylacetone keto-enol equilibrium to the enol tautomer, due to the preferential binding of such tautomeric forms. In addition, the same authors demonstrated that β-CD increases the percentage of the enol of the substrates 2-acetyl-1-tetralone and 2-acetyl-cyclohexanone via the formation of inclusion complexes between the enol tautomer of the substrates and β-CD.[7]

Other authors have studied the inclusion of a monocarbonyl compound, like the cardiotonic drug milrinone (MIR), and the host cucurbit[7]uril (CB7). They found that the keto form of MIR, which is the dominant species in water, is converted into other cationic forms in the presence of CB7.[4] More recently, a study conducted by Saleh *et al*. (2016)[5] reported that when other monocarbonyl species like oxyluciferin dye were assessed, the macrocycle CB7 was able to shift the equilibrium toward the keto form. Nevertheless, for dicarbonyl compounds in the presence of the CB7 host, there has been no reporting on the stability of some specific tautomeric forms. It is important to note that this issue is of significant relevance considering the difference of reactivity of dicarbonyl compounds in comparison with monocarbonyl compounds. Here, our interest is on coumarin derivatives containing systems with dicarbonyl moieties bound at position 3 of the coumarin scaffold. We have recently demonstrated that the host β-CD forms an inclusion complex with the enol tautomer of a dicarbonyl compound like ethyl acetoacetate bearing 7-hydroxy coumarin.[6] On the other hand, our exploratory study found that neither the above mentioned 7-hydroxy coumarin nor benzoylacetone are able to form inclusion complexes with CB7. Taking this into account, here we report new supramolecular systems containing the coumarin (7-*N*,*N*-diethylamino-2*H*-chromen-2-one) derivatives bearing ethyl acetoacetate (**CAM1**) and methyl β-ketodithioester (**CAM2**) moieties as guests, and CB7 as a host; see structures in the Scheme 1. It was expected that the 7-*N*,*N*-diethylamino group bearing coumarin derivatives would interact mainly with CB7, based

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† Footnotes relating to the title and/or authors should appear here.
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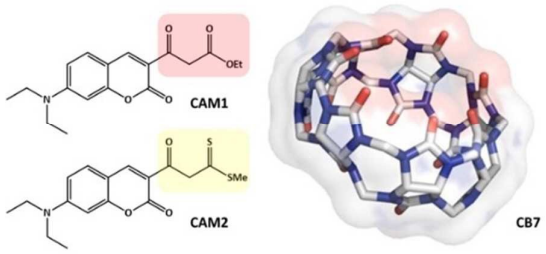
on analogy with similar compounds that contains diethylamino group.[8-10]

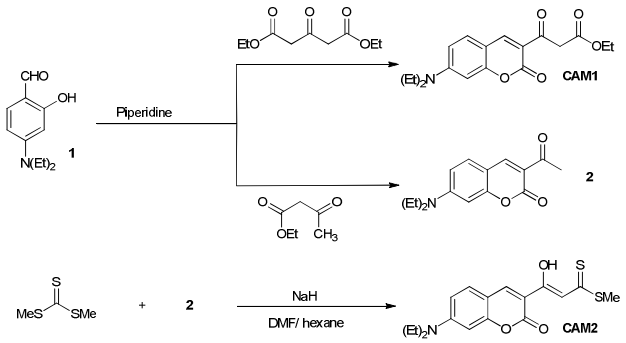


Scheme 1. Structures of compounds used in this study: coumarin guests (**CAM1** and **CAM2**) and the host molecule (CB7).

Thus, considering all the aforementioned studies, we hypothesize that the dicarbonyl free chain bearing coumarin would continue to interact with the portals of CB7. This could lead to the establishment of differences in the modulation of the keto-enol equilibrium of these derivatives in the presence of CB7. Moreover, our purpose was to assess a sulfur-containing analogue of methyl acetoacetate compound for the first time.

Results and discussion

First, **CAM1** and **CAM2** dyes were synthesized using 4-(diethylamino)salicylaldehyde (1) as starting material, by the conventional methodology to obtain coumarin.[11] In particular, the aldehyde was condensed either by a Knoevenagel reaction with diethyl 3-oxopentanedioate to obtain **CAM1**, or with ethyl 3-oxobutanoate to obtain coumarin intermediate 2.[6] The latter was reacted with dimethyl carbonotrithioate in basic media to obtain **CAM2**, see Scheme 2.



Scheme 2. Synthetic route to obtain **CAM1** and **CAM2** guests.

CAM1 and the new coumarin **CAM2** were synthesized in yields of 70% and 15%, respectively. The structures of the dyes were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopies, as well as by high-resolution mass spectra (HRMS-ESI); see Supporting Information (Figures S1-S10).

Second, in order to know which tautomeric form is predominant, the effect of the media polarity on the UV-Vis spectra of both dyes was evaluated.

As shown in Figures S11A and S11B, in all tested solvents, both coumarin derivatives exhibited a characteristic absorption band in the region of 350-500 nm. At this point, it is important to mention that another one of our recent studies[6] pointed to ethyl acetoacetate bearing 7-hydroxy coumarin, which exhibited two UV-Vis absorption bands in aqueous solutions, assigned to the presence of two tautomeric forms, *i.e*. keto (KH) and enol (EH) tautomers. Interestingly, and as previously mentioned, the substitution of 7-hydroxy by a 7-*N*,*N*-diethylamino group as is described here, results in a single band, not only in an aqueous solution, but also in most of the tested solvents (Figure S11). This result could be attributed to the predominance of the tautomeric form (KH) which is helped by the greater electron releasing effect of diethylamino[1g] (σ_p = -0.72) vs hydroxyl group (σ_p = -0.37) existent in coumarin.

With the aim of deepening such spectrophotometric characterization, mainly in terms of the predominance of a specific tautomeric form by **CAM1** and **CAM2**, experiments using ^{1}H NMR were done. Figure S1A shows the spectrum when **CAM1** alone was assessed in DMSO-d_6 as a solvent. In this spectrum, the ^{1}H NMR signals that might play an important role in the tautomeric equilibrium of **CAM1** are those assigned to –CH_2– at 3.94 ppm, for its KH form, and that of –C=CH-C at 6.38 ppm, associated with its EH form. Furthermore, considering the integration of both signals, it was estimated that the percentages are ~90% (KH form) and ~10% (EH), in DMSO-d_6, while in the presence of acetonitrile (Figure S1B) and mixtures of it solvent with water, we only observe the contribution of the KH form. In view of this, we suggested that the absorption band described in Figure S11A, centered at 453 nm, is mainly attributable to the KH form being the predominant tautomer for **CAM1**. Moreover, it is noteworthy that according to the signals obtained in the ^{1}H NMR spectrum of **CAM1**, in the presence of CB7, (Figures S12 and S13), this guest forms an inclusion complex with CB7, keeping its keto tautomeric form (100%). In addition, it is relevant to mention that the main shifts were observed in the protons in the diethylamino group, similar behavior was observed when the intermediate 2 (Scheme 2) was also assessed in the presence of CB7 (Figure S14). Details of the characterization of these inclusion complexes are presented in the Supporting Information, Figures S12-S18.

On the other hand, in the case of **CAM2**, the ^{1}H NMR signals (DMSO-d_6; Figure S4A) attributed to –CH_2– of its KH form do not appear, while a signal at 7.67 ppm, associated with the proton present in –C(OH)=CH-C(S)-SMe of EH form does appear. Therefore, these results indicate that the EH tautomeric form is the main one for **CAM2**. Considering this relevant NMR information, it is proposed that the absorption band shown in the UV-vis spectra of **CAM2** (Figure S11B) practically corresponds to the EH form. The latter would be a consequence of a strong intramolecular interaction,

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hydrogen-bond type, induced by the sulfur atom present in the β-ketodithioester moiety of the dye.[12]

Nevertheless, in the case of a solution containing **CAM2** and CB7, Figure 1 illustrates important changes in the ^{1}H NMR spectrum of **CAM2** alone (A) in comparison with that obtained after the addition of CB7 (B). In fact, surprisingly, it was observed that in the latter spectrum, Figure 1(B), a new signal appears at 8.35 ppm, which is associated with the H_b aromatic proton of its KH form. This is a consequence of the stabilization of this tautomeric form when the macrocycle CB7 is present.

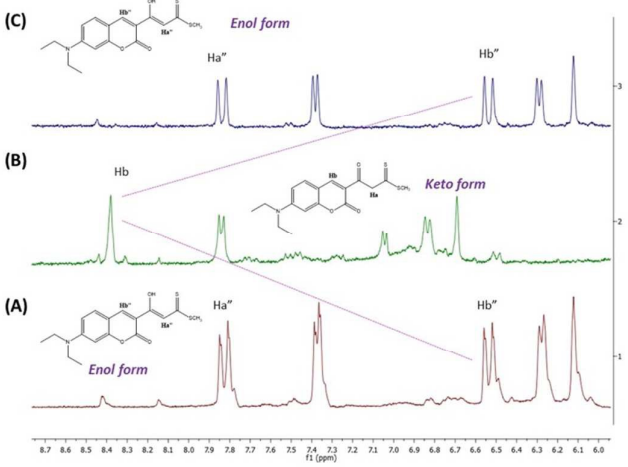

Figure 1. Partial comparison of ^{1}H NMR spectra (400 MHz) for: (A) **CAM2** alone, (B) **CAM2** plus CB7 (3 eq.) and (C) **CAM2** plus β-CD (3 eq.) in CD_3CN/D_2O.

Furthermore, it is known that the EH form for dicarbonyl compounds, such as ethyl acetoacetate[6] and benzoylacetylacetone[3], are the predominant forms, either in low-polarity aprotic solvents or β-CD. Thus, arise the relevance to asses what happens with **CAM2** when β-CD is employed instead of CB7. With regard to this, Figures 1C and S19 show that the signals associated to the EH tautomeric form of **CAM2** are maintained in the presence of β-CD. Therefore, the most interesting fact that has been evidenced is that CB7 shifts the tautomeric equilibrium of the **CAM2** dye alone, from its EH (predominant tautomer) to the KH form, stabilizing it, whereas β-CD maintains the EH form of **CAM2**.

In addition, the changes in the characteristic absorption bands (Figure S11) and the emission spectra of **CAM2** and **CAM1** when CB7 is present (Figure 2 and S20, respectively) confirms the formation of an inclusion complex between them. Indeed, we also observed that the slightly fluorescent coumarin dyes **CAM1** (quatum yield Φ_f of 0.011) and **CAM2** ($\Phi_f \approx 0.0014$) were converted into species with higher quantum yields ($\Phi_f \approx 0.035$ and 0.0055, respectively) in aqueous solutions containing CB7. This is in accordance with other studies reported for different coumarin-CB7 complexes.[8-10]

In relation to the determination of the stoichiometry of both inclusion complexes, and based on Job plot (Figure S17) and ESI-mass spectrometry analysis (Figure S15), it was established that 1:1 host/guest complexes are formed. Once the stoichiometry was established, we determined the association constants, K_1. These constants, between dyes (**CAM1** and **CAM2**) and CB7, were obtained by fluorescence titration experiments. As an example, in the case of **CAM2,** its concentration remained constant and the concentration of CB7 increased between 0 and 150 μM.

Inset to Figure 2 shows the variation of the fluorescence intensity of **CAM2** with the concentration of CB7. Fitting this data to a 1:1 binding model[9], an apparent equilibrium constant $K_{CAM2CB7}$ value of (1.3±0.4) ×10^5 M^{-1} was determined (in aqueous solution). In the case of **CAM1,** a binding constant value of (3.9±0.2)×10^3 M^{-1} was calculated (Figure S20).

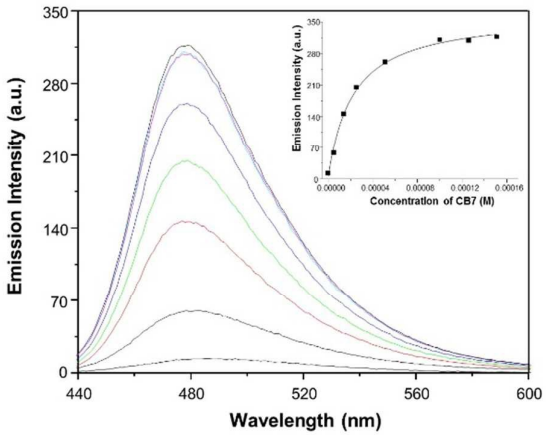

Figure 2. Fluorescence spectra of the coumarin-derivative **CAM2** (10 μM) with increasing concentrations of CB7 (0-150 μM). Inset shows the Fluorescence titration of 10 μM **CAM2** with CB7 in aqueous solution. The effective binding constant was determined as $K_{CAM2CB7}$ = (1.3 ± 0.4) × 10^5 M^{-1} fluorescence titration curves for the respective dye with CB7 (in aqueous solutions). Excitation and emission slits of 5 (nm) were used.

Given that for the **CAM2** dye it is possible to control its tautomerism by CB7, studies of its interactions using docking[13] and molecular dynamic simulations were also done.[14] As mentioned above, experimental data indicates that **CAM2** dye in the presence of CB7 is mainly in its KH form. Thus, in order to evaluate the binding energy of this complex, molecular docking methodology was used to generate it, taking into account its KH tautomeric form.

The results show that the **CAM2**-CB7 complex has a binding energy of -2.1 kcal/mol, which is approximately 1 kcal/mol more stable than that of the **CAM1**-CB7 complex. This result is in accordance with the larger apparent binding constant value experimentally determined for **CAM2**-CB7 ($K_{CAM2CB7}$ = 1.3× 10^5 M^{-1}) in comparison with the **CAM1**-CB7 complex ($K_{CAM1CB7}$ = 3.9 × 10^3 M^{-1}).

Alternatively, the pair (**CAM2**-CB7) was solvated and submitted to a molecular dynamic simulation for 10 ns. Figure 3A shows the molecular dynamic simulation of the

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inclusion complex **CAM2**-CB7, in the absence and presence of water, at times 0 and 10 ns. It was observed that in the beginning, the thioester group of **CAM2** was located inside the CB7 macrocycle, and it remain there during whole simulation. On the other hand, the lateral chain was extended during the simulation (5.1 Å), as shown in Figure 3B. Nevertheless, the thioester group interacted with water molecules generating hydrogen bonds during the whole simulation (Figure 3C). It is important to mention that similar results were obtained when times higher than 10 ns (until 55 ns) of molecular dynamics simulations were performed (not shown).

An additional study involving the pair (**CAM1**-CB7) was conducted for comparison purposes. As shown in Figure 4A, the molecular dynamic simulation of the inclusion complex **CAM1-CB7**, in the absence and presence of water, can be observed at times 0 and 10 ns. Figure 4B displays the change of the initial position (obtained from docking) in the host-guest complex of **CAM1**-CB7 at top left and bottom left. According to these results, it can be observed that the ketoester chain of the guest **CAM1** moves around 9 Å from the border of CB7 (Figure 4B).

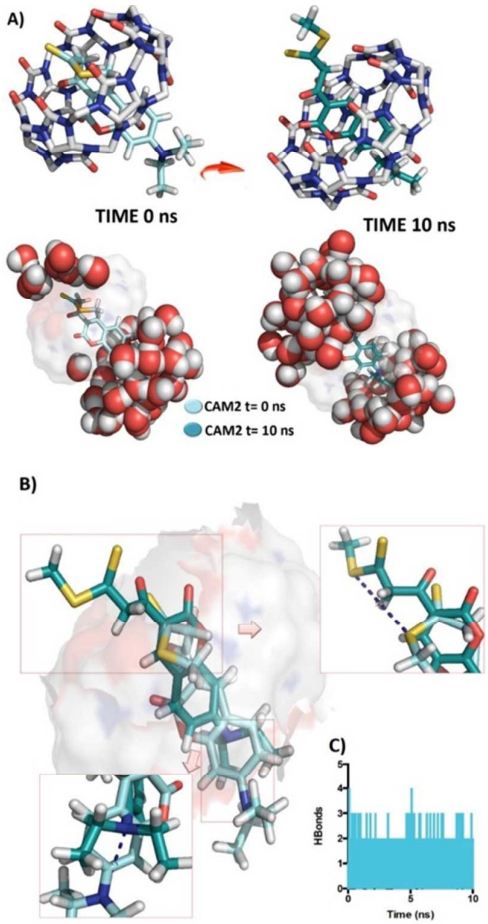

Figure 3. A) Molecular dynamic simulation of inclusion complex of **CAM2**-CB7 at 0 and 10 ns. The upper and bottom pictures show the system without solvent and the solvated system, respectively. B) Changes in the position of **CAM2** during the simulation. A close view shows the conformation of the lateral chain of **CAM2**. C) Hydrogen bonds between the host-guest complex and water during the simulation. The light and dark cyan colors represent the carbon atoms for **CAM2**, while the white color represents the carbon atoms of CB7.

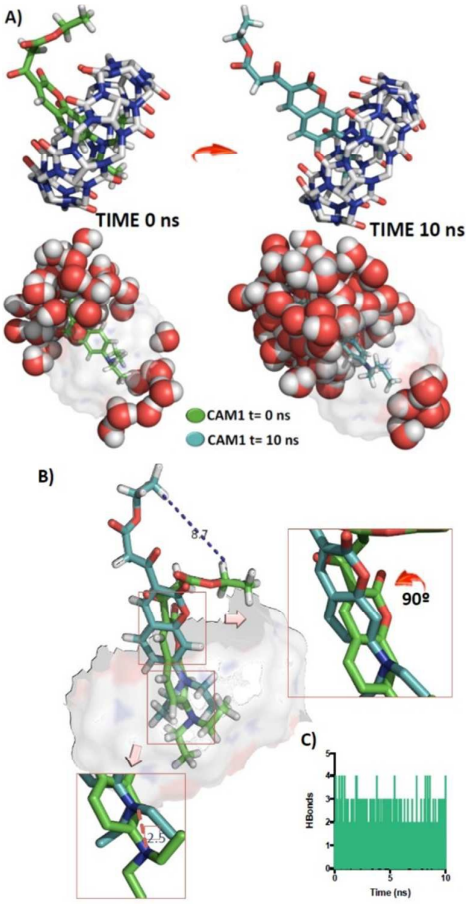

Figure 4. A) Molecular dynamic simulation of inclusion complex of CAM1-CB7 at 0 and 10 ns. The upper and bottom pictures show the system without solvent and the system solvated, respectively). B) Changes in the position of CAM1 during the simulation. A close view shows the conformation of the lateral chain of CAM1. C) Hydrogen bonds between the host-guest complex and water during the simulation. The green and cyan colors represent the carbon atoms for CAM1, while the white color represents the carbon atoms of CB7.

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Furthermore, the reorganization of **CAM1** causes the aromatic center to change by 90º and at the same time the *N,N*-diethylamino group shifts the original position in 2.5 Å, interacting more and better with water molecules, which is reflected in a hydrogen bond network (Figure 4C).

Despite the fact that it has been demonstrated that water molecules can be encapsulated inside of CB7[15] in both host-guest complexes, the CB7 host underwent a deformation in order to accommodate the guest (Figure 5A), generating favorable interactions in the absence of water molecules.

Furthermore, a study of the long-range interactions of host-guest complexes was carried out using Particle Mesh Ewald (PME).[16] An upper view of the CB7 macrocycle in its complexes with **CAM1** (Figure 5B) and **CAM2** (Figure 5C) shows that a less negative potential is generated with **CAM2** when compared with **CAM1**, which is reasonable in view of the solvation of the former.

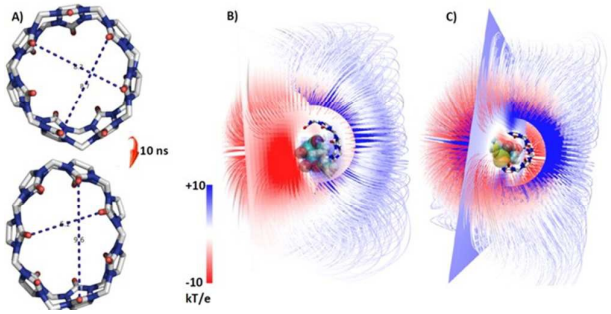

Figure 5. (A) Schematic representation of the change of the diameter of CB7 during the simulation. The long-range electrostatic interactions of host-guest complexes were treated using the Particle Mesh Ewald (PME) method for (B) **CAM1**-CB7 complex and (C) **CAM2**-CB7 complex. Charge distribution on the complexes is represented with blue, white and red color for positive, neutral and negative charge, respectively.

In order to explain the stabilization of different tautomeric forms between **CAM2** and the macrocycles CB7 or β-CD, docking studies were carried out. For this dye different binding modes were observed in β-CD and CB7, where the main modification is related to the solvent exposition of the diethylamino group. In fact, as shown in Figure 6, in the presence of β-CD, **CAM2** exposes its diethylamino group to the solvent and the enol binding to the thioester group remains inside the cavity. However, when **CAM2** forms a complex with CB7, the thioester group remains outside the cavity and interacts with solvent water molecules favoring the KH tautomeric form, and **CAM2**-CB7 is the most stable complex (Table S1). The stabilization of the KH form by CB7 could be attributed to the electrostatic interaction of the protons present in the –C(O)-CH_2-C(S)-SMe moiety of the KH form of **CAM2** with ureido oxygens on the CB7 portals, which would promote the extinction of the EH form.

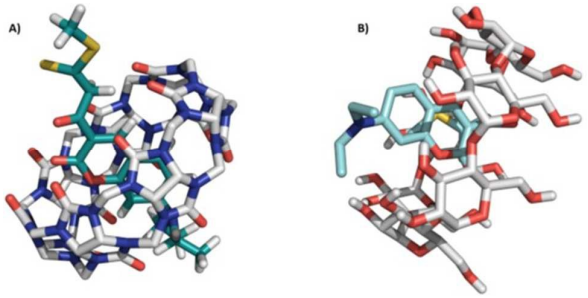

Figure 6. Docking studies of the inclusion complexes of **CAM2**-CB7 (A) and **CAM2**-β-CD (B).

Conclusions

In summary, CB7 is able to form 1:1 host-guest complexes with the KH tautomeric form of coumarin 7-*N*,*N*-diethylamino-2*H*-chromen-2-one derivatives bearing ethyl acetoacetate and methyl β-ketodithioester moieties. Interestingly, for the guest (**CAM2),** the macrocycle CB7 shifts the keto-enol equilibrium from its enol form to the keto tautomer after its inclusion. It establishes important differences of the inclusion of this kind of guest with CB7 and β-CD. It also enables the proposal that the architecture of the dye can be structurally modified by an external stimulus, like the incorporation of the macrocycle CB7. It is proposed that the aforementioned evidence could have a significant impact on the modulation of the reactivity of dicarbonyl compounds using a supramolecular strategy.

Experimental

Materials and equipment

All solvents and reagents were purchased from Sigma-Aldrich and used as received. Unless indicated otherwise, all solutions employed in this study were prepared in aqueous solution (pH=5.5). The compounds ethyl 3-(7-(diethylamino)-2-oxo-2H-chromen-3-yl)-3-oxopropanoate (**CAM1**) and methyl 3-(7-(diethylamino)-2-oxo-2*H*-chromen-3-yl)-3-oxopropanedithioate (**CAM2**) were synthesized according to the procedures described in the Supporting Information.

Absorption and steady-state fluorescence spectra were obtained using a HP-8453 diode array spectrophotometer and Cary Eclipse fluorescence spectrophotometer, respectively.

High-resolution mass spectrometry (HRMS-ESI) studies.

High-resolution mass spectra (HRMS-ESI) were obtained from Thermo Fisher Scientific Exactive Plus mass spectrometer. The analysis for the reaction products was performed with the following relevant parameters: heater temperature, 50 °C; sheath gas flow, 5; sweep gas flow rate, 0 and spray voltage, 3.0 kV at negative mode. The accurate

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mass measurements were performed at a resolution of 140.000.

Electrospray ionization mass spectrometry (ESI-MS/MS).

The detection of the inclusion complex **CAM1**-CB7 was undertaken on an AB SCIEX Triple Quad™ 4500 LC/MS/MS Mass Spectrometer equipped with a Turbo Ion Spray (AB Sciex) ion source. Specific compound-dependent MS parameters for each dye were determined by direct infusion into the MS of individual standards dissolved in 10% (vol/vol) acetonitrile (concentration of 25 µM) at a flow rate of 7 µL/min. The 4500 QTRAP system was operated in positive ion mode using the multiple reaction monitoring (MRM) scan type. A declustering potential (DP) of +180, entrance potential (EP) of +10, and collision cell exit potential (CXP) of +25 were used. The ion spray voltage was set at +3500 V, source temperature was set at 300 °C, collision gas (CAD) was set to high, and source gas GS1 and GS2 were set to 10 and 20, respectively. All data were acquired using Analyst 1.6.2 (AB Sciex).

Nuclear magnetic resonance (NMR) studies.

^{1}H NMR spectra were obtained at 25 °C on Bruker Avance 400 MHz spectrometer using TMS as an internal standard. The NMR spectra were processed with MestreNova software v9.0.

Determination of the quantum yield of emission.

Fluorescence quantum yields of dyes were measured using a solution of quinine sulfate in 0.5 mol/L H_2SO_4 as standard (Φs = 0.546). All values were corrected taking into account the solvent refraction index. Quantum yields were calculated using Eq. 1, where the subscripts x and s denote sample and standard, respectively, Φ is the quantum yield, η is the refractive index, and Grad is the gradient from the plot of integrated fluorescence intensity vs. absorbance.

$$\Phi_x = \Phi_s \left(\frac{Grad_x}{Grad_s}\right)\left(\frac{\eta_x^2}{\eta_s^2}\right) \qquad \textbf{(Eq. 1)}$$

Modeling molecular studies

The dyes were constructed using Gaussian03[17] and the partial charges of compounds were corrected using ESP methodology. Topology and parameters for **CAM1** and **CAM2** and CB7 were obtained using the ParamChem server, which uses CHARMM27 force field and a database to organic compounds.

Molecular Docking

In order to obtain information regarding the principal host-guest interactions, the molecular docking of CAM1 and CAM2 in CB7 was carried out using AutoDock 4.0 suite.[18] In general, the grid maps were calculated using the autogrid4 option and were located on the center of β-CD. The volumes for the grid maps were 40 x 40 x 40 points (a grid-point spacing of 0.375 Å). The autotors option was used to define the rotating bonds in the ligand. In the Lamarckian genetic algorithm (LGA) dockings, an initial population of 1500 random individuals with a population size of 100 individuals was employed, a maximum number of 2.5 x 10^6 energy evaluations, a maximum number of 27,000 generations, a mutation rate of 0.02 and a cross-over rate of 0.80. The docked compound complexes were built using the lowest docked-energy binding positions.

Molecular dynamic simulations

Each host-guest complex was solvated with a TIP3 water model and submitted to molecular dynamics (MD) simulations for 10 ns using a NPT ensemble. NAMD 2.6 was used to perform MD calculations.[18,19] Periodic boundary conditions were applied to the system in the three coordinate directions. A pressure of 1 atm and a temperature of 310 K were maintained.

Keywords: keto-enol equilibrium • β-ketodithioester • cucurbit[7]uril • coumarin • dicarbonyl compounds.

Acknowledgements

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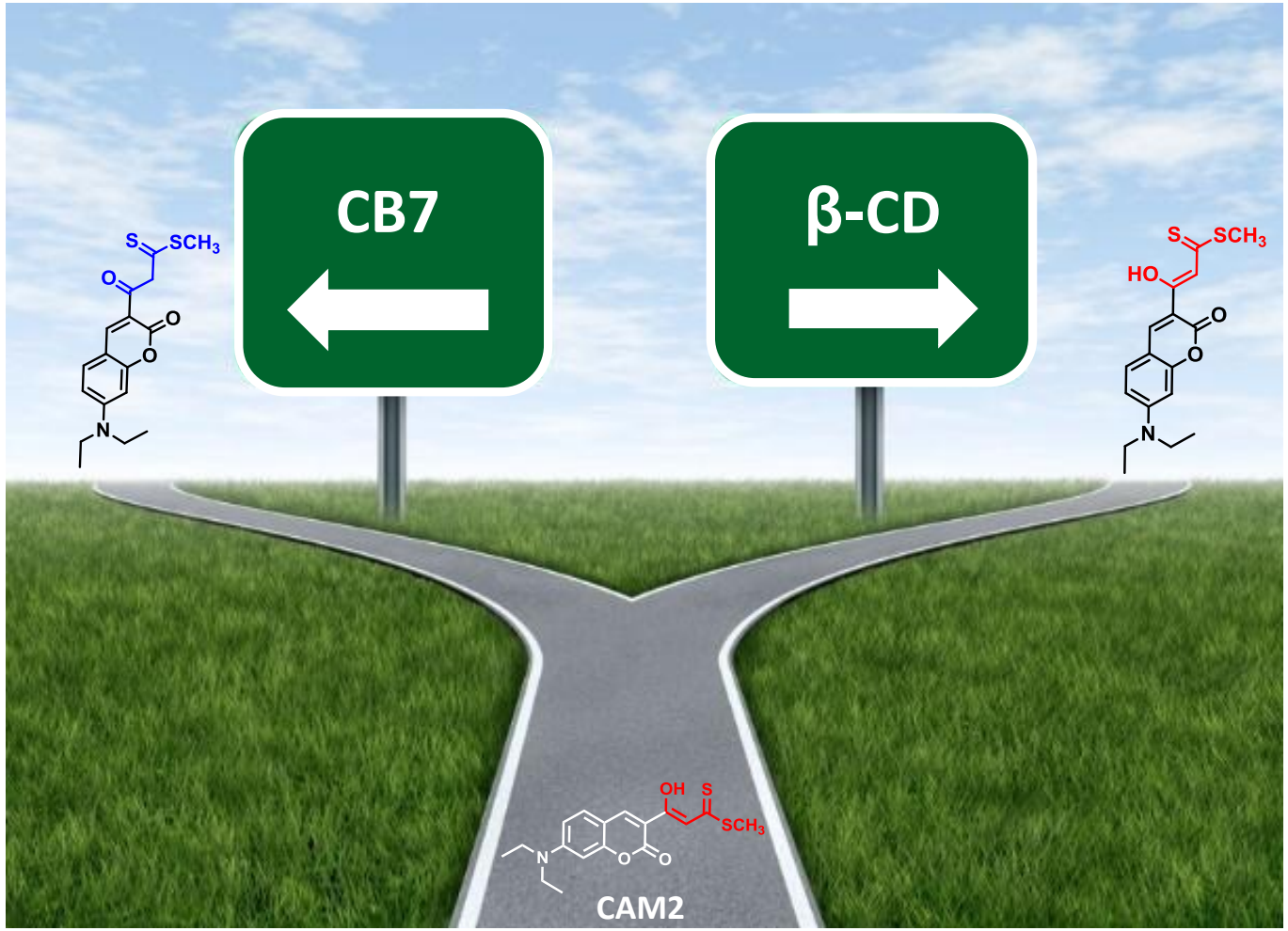

CB7 shifts the tautomeric equilibrium of the **CAM2**, from its enol- to the keto-form, whereas β-CD maintains the enol form.