SUPPORTING INFORMATION

γ-CYCLODEXTRIN MODULATES CHEMICAL REACTIVITY BY MULTIPLE COMPLEXATION

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I. UV-Vis spectra of MBSC hydrolysis as a function of time.

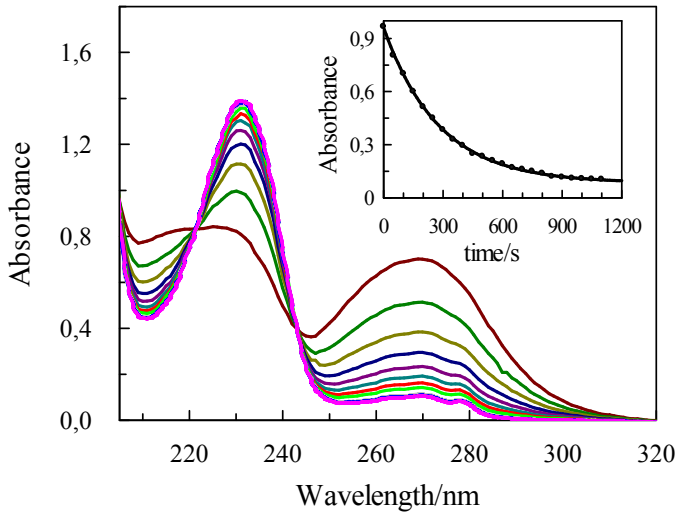


Figure S-1: Spectra of the MBSC hydrolysis, [MBSC] = 1 x 10^{-4} M and example of first order fit (inset), [MBSC] = 1 x 10^{-4} M and [C_{10}TAB] = 1 x 10^{-3} M.

II. Model of self-diffusion coefficients for the 1:1 complex

The model used is based on the assumption that a 1:1 complex is formed between the CD and the guest (G).

$$\mathrm{CD} + \mathrm{G} \underset{}{\overset{K_{1:1}}{\rightleftharpoons}} \mathrm{CD{:}G}$$

Scheme S- 1

The stability of the inclusion complex can be described as an association constant, $K_{1:1}$

$$K_{1:1} = \frac{[CD{:}G]}{[CD]_f[G]_f} \qquad \textbf{S-1}$$

where $[CD]_f$ and $[G]_f$ represent the concentration of noncomplexed species, CD and guest, respectively, and [CD:G] is the concentration of the 1:1 complex.

The procedure for interpreting concentration *vs* NMR self-diffusion data is based on an *n*-site exchange model, in which the number and nature of the sites are identified and the observed self-diffusion coefficient is expressed as a population-weighted average between the sites. In the present study, two different sites for the guest can be identified: the free guest and the complexed guest. Thus, the experimental guest self-diffusion coefficient $D_{G,obs}$, can be described according to equation S-2.

$$D_{G,obs} = (1 - \chi_{CD:G})D_{G,f} + \chi_{CD:G}D_{CD:G} \qquad \textbf{S-2}$$

where $D_{G,f}$ is the self-diffusion coefficient of the free guest, $D_{CD:G}$ is the self-diffusion of the complex and $\chi_{CD:G}$ is the fraction of complexed guest, which is given by

$$\chi_{CD:G} = \frac{C_G - [G]_f}{C_G} \qquad \textbf{S-3}$$

where C_G is the total concentration of guest and $[G]_f$ is the concentration of free guest.

The CD molecules, on the other hand, can exchange between two different sites, and the observed self-diffusion for CD, $D_{CD,obs}$ is given by

$$D_{CD,obs} = (1 - \chi_{CD:G})D_{CD,f} + \chi_{CD:G}D_{CD:G} \qquad \textbf{S-4}$$

$$\chi_{CD:G} = \frac{C_{CD} + [CD]_f}{C_{CD}} \quad \textbf{S-5}$$

where $D_{\mathrm{CD,f}}$ is the self-diffusion of the free CD. The observed self-diffusion for the guest (equation S-2) previously defined can be expressed in terms of binding constants and total concentrations of CD and guest.

$$D_{G,obs} = \frac{D_{G,f} + K_{1:1} D_{CD:G}[CD]}{1 + K_{1:1}[CD]} \quad \textbf{S-6}$$

The complexation binding constant of guest by CD are expressed as:

$$K_{1:1} = \frac{[CD{:}G]}{[CD][G]} \quad \textbf{S-7}$$

The mass balance for the total concentrations of CD and guest are given by

$$[CD]_T = [CD]_f + [CD{:}G] \quad \textbf{S-8}$$

$$[G]_T = [G] + [CD{:}G] \quad \textbf{S-9}$$

The combination of these equations with the binding constants, gives a second order equation for the concentration of uncomplexed CD (equation S-10):

$$a[CD]_f^2 + b[CD]_f + c = 0 \quad \textbf{S-10}$$

where

$$a = K_{1:1} \quad \textbf{S-11}$$

$$b = 1 + K_{1:1}([G]_T - [CD]_T) \quad \textbf{S-12}$$

$$e = -[CD]_T \quad \textbf{S-13}$$

III. Model of self-diffusion coefficients for the 1:1 and 1:2 complex

On the assumption that higher order complexes than 1:1 are formed, a second equilibrium is established.

$$\mathrm{CD} + \mathrm{G} \overset{K_{1:1}}{\rightleftharpoons} \mathrm{CD{:}G}$$

$$\mathrm{G} + \mathrm{CD{:}G} \overset{K_{1:2}}{\rightleftharpoons} \mathrm{CD{:}G_2}$$

Scheme S- 2

Following the previous procedure, the observed self-diffusion values can be obtained for the guest and CD

$$D_{G,obs} = \chi_{G,f} D_{G,f} + \chi_{CD:G} D_{CD:G} + 2\chi_{CD:G_2} D_{CD:G_2} \quad \textbf{S-14}$$

$$D_{CD,obs} = \chi_{CD,f} D_{CD,f} + \chi_{CD:G} D_{CD:G} + \chi_{CD:G_2} D_{CD:G_2} \quad \textbf{S-15}$$

where $D_{G,f}$, $D_{CD,f}$, $D_{CD:G}$ and $D_{CD:G2}$ are the diffusion coefficients for surfactant, CD, 1:1 complex and 1:2 complex, respectively.

Molar fractions for the different species are referred to the total concentrations of guest as:

$$\chi_{G,f} = \frac{[G]_f}{C_G} \quad \chi_{CD:S} = \frac{[CD:G]}{C_G} \quad \chi_{CD:G_2} = \frac{[CD:G_2]}{C_G} \quad \textbf{S-16}$$

or the total concentration of CD:

$$\chi_{CD,f} = \frac{[G]_f}{C_{CD}} \quad \chi_{CD:G} = \frac{[CD:G]}{C_{CD}} \quad \chi_{CD:G_2} = \frac{[CD:G_2]}{C_{CD}} \quad \textbf{S-17}$$

The complexation binding constants of guest by CD are expressed as:

$$K_{1:1} = \frac{[CD:G]}{[CD][G]} \quad K_{1:2} = \frac{[CD:G_2]}{[CD:G][G]} \quad \textbf{S-18}$$

The mass balance for the total concentrations of CD and guest are given by

$$[CD]_T = [CD]_f + [CD{:}G] + \left[CD{:}G_2\right] \quad \textbf{S-19}$$

$$[G]_T = [G]_f + [CD{:}G] + 2\left[CD{:}G_2\right] \quad \textbf{S-20}$$

The combination of these equations with the binding constants, gives a third order equation for the concentration of uncomplexed guest (equation S-21):

$$a[G]_f^3 + b[G]_f^2 + c[G]_f + c = 0 \quad \textbf{S-21}$$

where

$$a = K_{1:1}K_{1:2} \quad \textbf{S-22}$$

$$b = K_{1:1} + K_{1:1}K_{1:2}(2[CD]_T - [G]_T) \quad \textbf{S-23}$$

$$c = 1 + K_{1:1}([CD]_T - [G]_T) \quad \textbf{S-24}$$

$$e = -[G]_T \quad \textbf{S-25}$$

IV. DOSY experiments for complexation of NPA by γ-CD.

Considering that in complexation process between CD and NPA is established a 1:1 and 1:2 inclusion complexes in a cooperative way, as observed in the case of C_{10}TAB, the experimental data was fitted to a model that takes into account the formation of 1:1 and 1:2 inclusion complexes, using the values of the binding constants ($K^{C10TAB}_{1:1} = 25_{M^{-1}}$ and $K^{C10TAB}_{1:2} = 350_{M^{-1}}$) obtained for the C_{10}TAB, as initial approach.

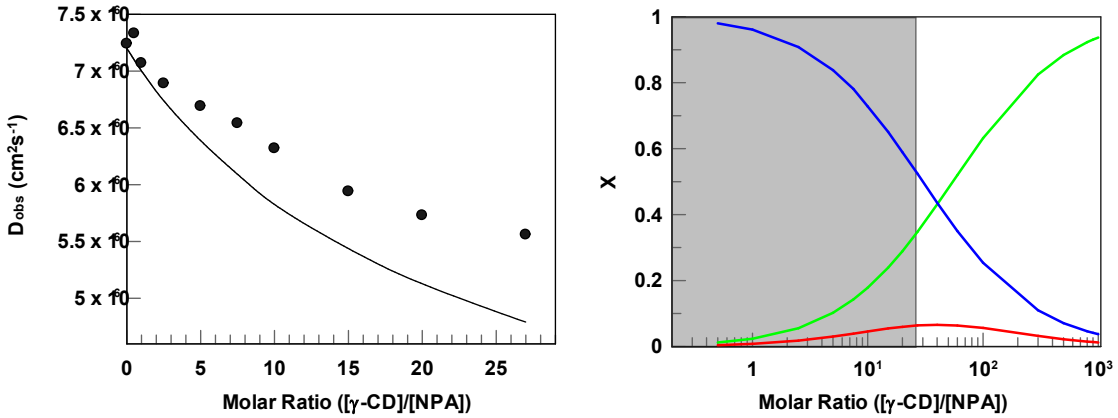


Figure S- 2: (Left) Self-diffusion coefficients of [NPA] = 1 mM for varying γ-CD concentrations. Black line shows the fit to the model with a 1:1 and 1:2 host:guest complexes, using $K_{1:1}$=25 M^{-1} and $K_{1:2}$=350 M^{-1}. (Right) Respective mole fraction (X) distribution of free NPA (blue line), 1:1 complex (green line) and 1:2 complex (red line).

As can be seen from Figure S-2, it is evident that these binding constants fail to reproduce the experimental behavior. In order to fit the experimental data to eq S-14 and determine the binding constants of the established complexes of CD with NPA, this equation was solved for different values of $K^{NPA}_{1:1}$ and $K^{NPA}_{1:2}$. The values of $K^{NPA}_{1:1}$ and $K^{NPA}_{1:2}$, for which we obtain the best root-mean-square deviation (χ^2) values in the fitting of eq S-14 to the experimental results, were taken as optimal (Figure S-3).

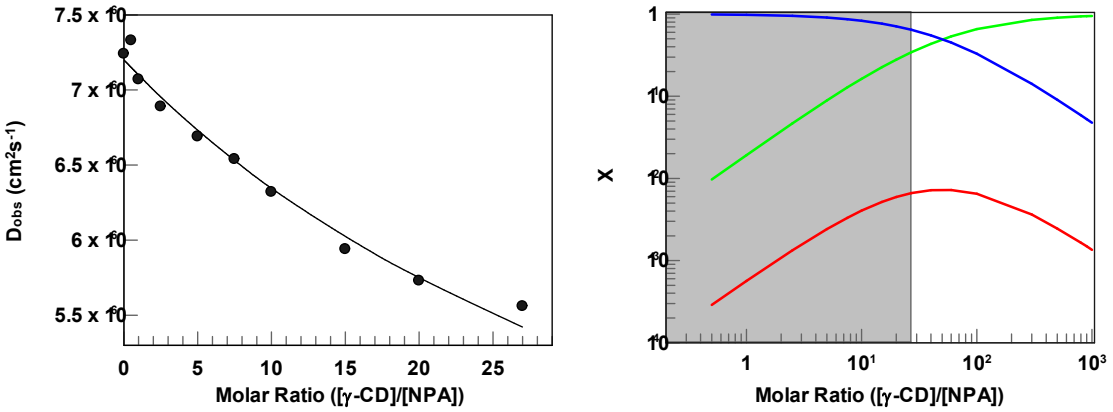


Figure S- 3: (Left) Self-diffusion coefficients of [NPA] = 1 mM for varying γ-CD concentrations. Black line shows the fit to the model with a 1:1 and 1:2 host:guest complexes. (Right) Respective mole fraction (X) distribution of free NPA (blue line), 1:1 complex (green line) and 1:2 complex (red line).

From this method we obtain as optimal values, $K_{1:1}^{NPA} = 20\ M^{-1}$ and $K_{1:2}^{NPA} = 30\ M^{-1}$. Fitting the experimental data (Figure S- 3) to eq S-14, we also obtain the values of the diffusion coefficients of $D_f^{NPA} = 7.2 \times 10^{-6}$ cm^2s^{-1}, $D_{1:1}^{NPA} = 2.2 \times 10^{-6}$ cm^2s^{-1} (1:1 complex), and $D_{1:2}^{NPA} = 2.0 \times 10^{-6}$ cm^2s^{-1} (1:2 complex). These results are compatible with the increment of the molecular weight due to the formation of the host:guest complexes.

V. Solvolysis of MBSC in the presence of cationic micelles.

The influence of the surfactant concentration on the solvolytic rate constant was over a wide range of surfactant concentrations that included the region before the cmc, where the molecules of the surfactants are like monomers dispersed in the solution, and the region after the cmc, where the surfactant molecules are associated to form micelles. The effect of the surfactant concentration on the pseudo-first-order rate constant, k_{obs}, for the hydrolysis of MBSC is shown in Figure S-4. As can be seen, the observed rate constant remains practically unchanged on increasing the surfactant concentration up to the cmc. At concentrations above the cmc a clear decrease in k_{obs} can be observed. At this point the surfactant forms micellar aggregates and the substrate is incorporated into the micelles, where the rate of the solvolytic reaction is smaller than in bulk water due to its lower polarity.

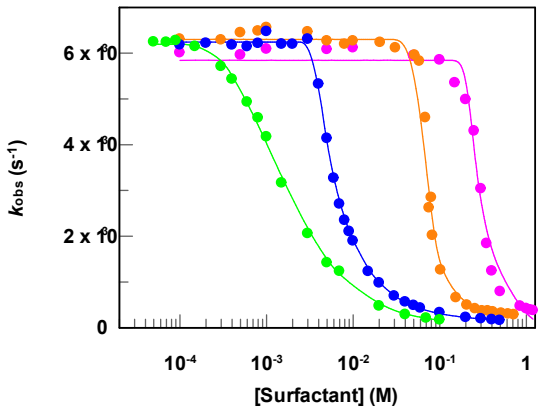
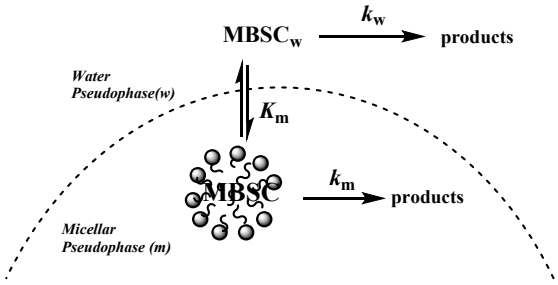


Figure S- 4: Influence of the surfactant concentration on the observed rate constant for the hydrolysis of MBSC at 25.0°C. (●) C_8TAB, (●) C_{10}TAB, (●) C_{14}TAB and (●) C_{18}TAC.

The micellar pseudophase formalism was applied to obtain a quantitative interpretation of the experimental results for the solvolysis of MBSC. Two well-differentiated environments were considered: water and a micellar pseudophase between which the MBSC is distributed (Scheme S-3).



Scheme S- 3

By considering that the solvolysis can simultaneously take place in water, k_w, and at the micellar pseudofase, k_m, it is possible to derive the following rate equation, which relates the observed rate constant with the surfactant concentration.

$$k_{obs} = \frac{k_w + k_m K_m [Dn]}{1 + K_m [Dn]} \qquad \textbf{S-26}$$

Where K_m is the distribution constant of MBSC between the water and the micellar pseudophases, $[D_n]$ is the concentration of micellized surfactant, $[D_n] = [\text{surfactant}]_T$ - cmc and k_m is the rate constant in the micellar pseudophase. The critical micelle concentration values are required to fit the experimental results to eq S-26 and these values can be obtained kinetically as the minimal surfactant concentration necessary to observe an appreciable change in k_{obs}. Fitting the experimental results to eq S-26 allowed us to obtain the parameters listed in Table S-1.

Conductimetric cmc values have been obtained under our experimental conditions and are compatible with those kinetically obtained. As an example, the cmc value for C_{10}TAB obtained by conductimetric method (Figure S-5), cmc=(6.00±0.02) x 10^{-2} M, is equivalent to that reported in Table S-1 and kinetically obtained.

Table S-1 reports the binding constants of MBSC to the micelles, K_m, and the rate constants for the solvolysis, k_m, inside the micellar aggregate. The association constants values, K_m, increase with the number of carbon atoms in the surfactant alkyl chain. This behavior is well documented in the literature as a consequence of the increase in the surfactant's hydrophobicity, as the length of the hydrocarbon chain increases. The values of k_m do not present any clear variation, which is probably due to the uncertainty

of their determination, as a consequence of the small percentage of solvolysis that takes place in the micellar aggregates.

Table S- 1: Critical micelle concentration, MBSC binding constants to cationic micelles and solvolytic rate constants in bulk water and in the cationic aggregates obtained by fitting eq S-26 to the experimental data.

Surfactant	cmc/M	K_m/M^{-1}	$10^3\ k_w/s^{-1}$	$10^4\ k_m/s^{-1}$
C_8TAB	0.20	15±2	5.9±0.1	0.6±0.1
C_{10}TAB	6.00×10^{-2}	106±10	6.3±0.1	1.7±0.4
C_{14}TAB	3.50×10^{-3}	379±9	6.24±0.02	1.4±0.1
C_{18}TAC	2.25×10^{-4}	705±31	6.19±0.04	0.8±0.5

The same behavior is expected in the case of NPA in the presence of cationic micelles due to its suitable polarity for bind cationic micelles.

VI. Conductimetric determination of critical micelle concentration in the presence and absence of γ-CD.

Electrical conductivity of aqueous surfactant solutions shows an inflection point on increasing the surfactant concentration. This result is a consequence of the surfactant monomers being fully dissociated and the micelle only partially dissociated (as a general estimation more than 50% of counterions are bounded to the micelle in order to screen the electrostatic repulsions between the surfactant head groups). From the inflection point the critical micelle concentration can be obtained. As a recent example see: Marcolong, J. P.; Mirenda, M. *J. Chem. Ed.* **2011**, *88*, 629-633.
Following plots show the critical micelle concentration of C10TAB both in the absence and presence of γ-CD, [γ-CD] = 2.0×10^{-2} M.

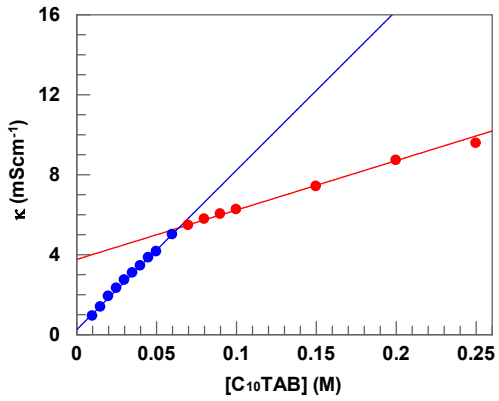


Figure S- 5: Determination of cmc for C_{10}TAB. Plot of specific conductivity *vs* [C_{10}TAB].

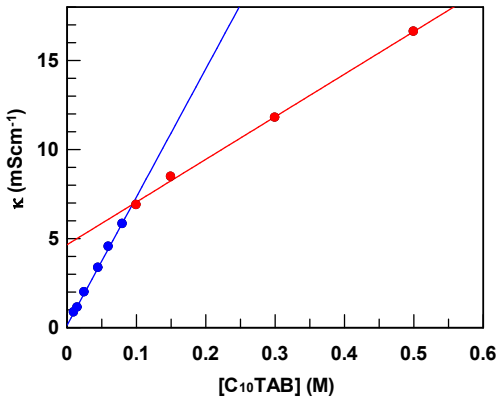


Figure S- 6: Determination of cmc for MBSC solvolysis in the presence of C_{10}TAB/ γ-CD mixed systems. Plot of specific conductivity vs [C_{10}TAB]. [γ-CD] = 2.0×10^{-2} M.

VII. Solvolysis of MBSC in γ-CD:surfactant mixed systems.

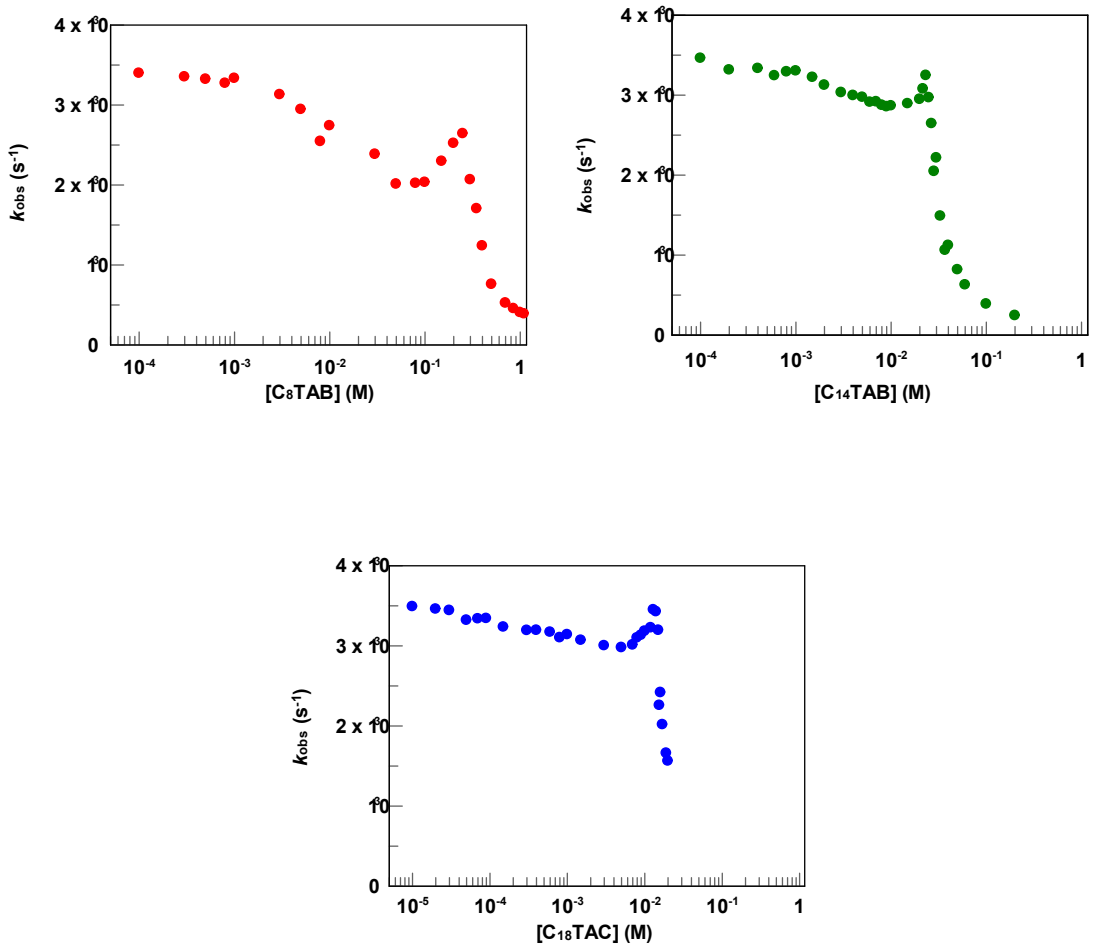
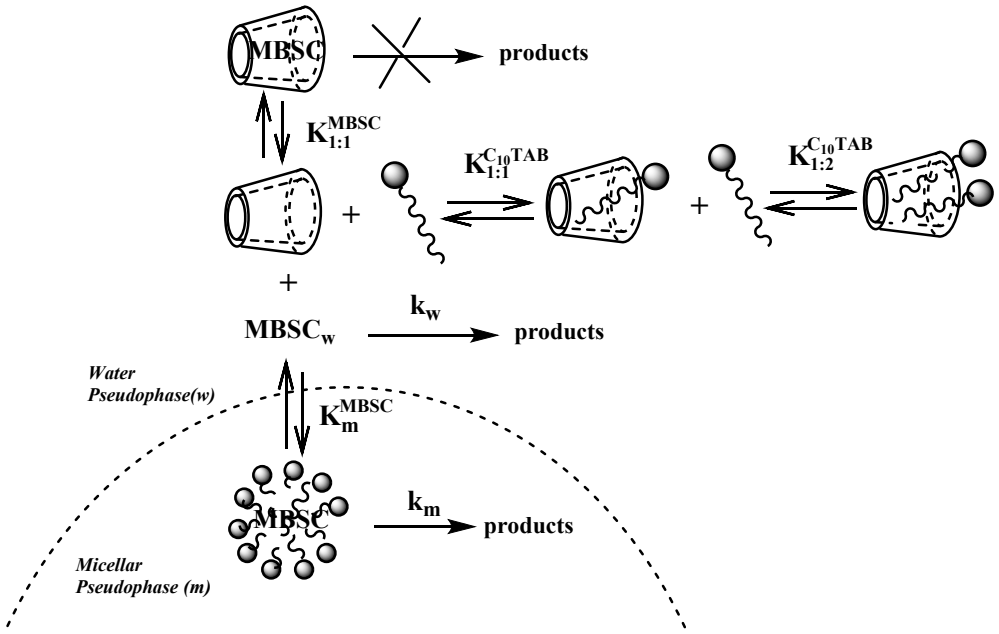


Figure S- 7: Influence of the surfactant concentration on the k_{obs} for the hydrolysis of MBSC at 25.0 °C in the presence of γ-CD (2.0×10^{-2} M) and (●) C_8TAB, (●) C_{14}TAB, (●) C_{18}TAC.

VIII. Kinetic analysis with a competitive binding mode

The kinetic model considers the absence of interactions between micelles and CD, a competitive binding model for the CD-catalyzed reaction as well as the existence of two simultaneous reaction paths (Scheme S-4): the reaction of the free substrate in the aqueous medium and the reaction of the substrate associated with the micelle.



Scheme S- 4

This mechanistic scheme allows us to derive the following expression for the observed rate constant:

$$k_{obs} = \frac{k_w + k_m K^{MBSC}_m [D_n]}{1 + K^{MBSC}_m [D_n] + K^{MBSC}_{1:1} [CD]_f + K^{C_{10}TAB}_{1:1} [C_{10}TAB][CD]_f} \quad \text{S-27}$$

To solve the previous equation it is necessary know the values of cmc, which were kinetically evaluated as the minimal surfactant concentration where an appreciable change in k_{obs} is observed (Figure S-7) as well as the concentration of the uncomplexed CD for each surfactant concentration. The values of $[CD]_f$ were determined from binding constants. The method of free CD calculation from binding constants takes into account simultaneous substrate complexation by CD, $K^{MBSC}_{1:1}$, surfactant complexation with 1:1, $K^{C_{10}TAB}_{1:1}$, and 1:2 stoichiometry, $K^{C_{10}TAB}_{1:2}$.

$$K_{1:1}^{MBSC} = \frac{[CD{:}MBSC]}{[MBSC]_w[CD]_f} \quad K_{1:1}^{C_{10}TAB} = \frac{[CD{:}C_{10}TAB]}{[CD]_f[C_{10}TAB]} \qquad \text{S-28}$$

$$K_{1:2}^{C_{10}TAB} = \frac{[CD{:}(C_{10}TAB)_2]}{[CD{:}C_{10}TAB][C_{10}TAB]}$$

The mass balances for the total concentrations of CD, surfactant and substrate for surfactant concentrations below the critical micelle concentration are:

$$[CD]_T = [CD]_f + [CD{:}MBSC] + [CD{:}C_{10}TAB] + [CD{:}(C_{10}TAB)_2] \qquad \text{S-29}$$

$$[S]_T = [S]_f + [CD{:}C_{10}TAB] + 2[CD{:}(C_{10}TAB)_2] \qquad \text{S-30}$$

$$[MBSC]_T = [MBSC]_f + [CD{:}MBSC] \qquad \text{S-31}$$

Previously obtained values ($K_{1:1}^{MBSC}$ =38M^{-1}, $K_{1:1}^{C_{10}TAB}$ =25M^{-1}; $K_{1:2}^{C_{10}TAB}$ =350M^{-1}; k_w=5.7×10^{-3}s^{-1}; k_m=1.8×10^{-4}s^{-1}) for equilibrium and rate constants have been used in order to solve equations S-27 to S-31.