26.4 (d, ^2J(P,C) = 2.4 Hz; *trans*(*syn*)-PC(CH_3)$_2$), 21.7 (d, ^2J(P,C) = 8.6 Hz; *cis*(*syn*)-PC(CH_3)$_2$), 20.0 (d, ^2J(P,C) = 2.7 Hz; *trans*(*anti*)-PC(CH_3)$_2$); ^{1}H NMR ($CDCl_3$): δ = 7.2 – 7.4 (m, 10H, Ph), 1.72 (d, ^3J(H,P) = 17.45 Hz, 3H; *cis*(*syn*)-PC(CH_3)$_2$), 1.66 (d, ^3J(H,P) = 19.23 Hz, 3H; *cis*(*anti*)-PC(CH_3)$_2$), 1.64 (d, ^3J(H,P) = 10.65 Hz, 3H; *trans*(*anti*)-PC(CH_3)$_2$), 1.39 (m, 2H; PCH), 1.27 (d, ^3J(H,P) = 12.01 Hz, 3H; *trans*(*syn*)-PC(CH_3)$_2$). **6b** (*syn*,*syn* isomer): m.p. 179 – 180 °C (decomp); ^{31}P NMR: ($CDCl_3$): δ = – 126.1 (^1J(P,W) = 217.2 Hz); ^{13}C NMR: δ = 197.1 (m, $^{(2+5)}J$ = 29.6 Hz; *trans*-CO), 195.6 (m, $^{(2+5)}J$(P,C) = 7.6 Hz; *cis*-CO), 134.9 (m, $^{(1+4)}J$ = 27.7 Hz; *ipso*-Ph), 131.8 (m, $^{(3+6)}J$ = 11.6 Hz; *m*-Ph), 130.2 (s, *p*-Ph), 128.8 (m, $^{(2+5)}J$ = 9.4 Hz; *o*-Ph), 34.5 (m, $^{(1+2)}J$ = 13.2 Hz; PCH), 29.2 (m, $^{(1+3)}J$ = 14.0 Hz; P*C*(CH_3)$_2$), 25.5 (s, *trans*-PC(CH_3)$_2$), 21.5 (m, $^{(2+4)}J$ = 8.4 Hz; *cis*-PC(CH_3)$_2$); ^{1}H NMR ($CDCl_3$): δ = 7.2 – 7.4 (m, 10H, Ph), 1.78 (s, 2H, CHP), 1.69 (m, ^3J(H,P) = 17.50 Hz, 6H; *cis*-CH_3), (m, ^3J(H,P) = 12.15 Hz, 6H; *trans*-CH_3); HR-MS: calcd for $C_{30}H_{24}O_{10}P_2W_2$ (%): 973.98645; found: 973.98637; IR (KBr): $\tilde{\nu}$ = 2073, 1950 cm^{-1} (CO).

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[13] Crystal structure determination of $C_{30}H_{24}O_{10}P_2W_2$, M_r = 974.11, colorless, space group $P\bar{1}$ (no. 2), a = 8.9501(7), b = 12.4181(6), c = 15.7582(10) Å, α = 88.342(4), β = 83.656(6), γ = 71.097(5)°, V = 1646.8(2) Å^3, Z = 2, ρ = 1.964 g cm^{-3}, μ(Mo$_{K\alpha}$) = 7.13 mm^{-1}. A total of 10787 reflections were measured at 150 K on a CAD4T/rotating anode diffractometer (λ = 0.71073 Å) and averaged in a unique set of 7569 reflections (R_{av} = 0.036). The structure was solved by Patterson methods (DIRDIF-96) and refined on F^2 (SHELXL97) to a final $R1$ = 0.0312 (6350 reflections with $I > 2\sigma(I)$; $wR2$ = 0.072; S = 1.045). The data ware corrected for absorption using PLATON/DELABS. Hydrogen atoms were taken into account at calculated positions. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-138219. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Micellization versus Cyclodextrin – Surfactant Complexation**

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Upon addition of cyclodextrin (CD) to a surfactant solution, a considerable change in the physicochemical properties can be observed, that is, the surface tension of the surfactant solution usually increases.[1] When a concentration of cyclodextrin well in excess of the surfactant concentration is reached, the surface tension approaches that of pure water, indicating that neither surfactant – cyclodextrin complexes nor cyclodextrins themselves are surface active. Other properties such as cloud point, molar conductance, sodium ion activity, ultrasonic properties, spectral behavior, and hydrophobicity are modified by the addition of CD's. It has traditionally been assumed that the cyclodextrin molecules complex the monomers of the surfactant in such a way that the process of micellization will only begin once the surfactant monomers have saturated the cyclodextrin capacity for complexation. The strength of CD – hydrocarbon chain interactions increases for the common water-soluble ionic surfactants as the length of the alkyl chains increases.[2] The large diameter of β-cyclodextrin allows the hydrocarbon chain to coil inside the cavity.[3]

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Association constants for interaction between surfactants and CDs have been determined using various techniques such as conductance, conductance stopped-flow, speed of sound, fluorescence, surfactant-selective electrode, and surface tension. However, the data in the literature show an amazingly large scattering in the values of the association constants as well as the association mode. For example, the constant K_1 for 1:1 complex formation between sodium dodecyl sulfate (SDS) and β-CD has been reported to be 300, 356, 1380 – 7230, 3630, 6600, 8360, 21 000, and 25 600 M^{-1}.[4] For the interaction between SDS and α-CD, some researchers determined only the 1:1 complex formation constants (K_1) while others determined 1:1 and 1:2 complex formation constants (K_1 and K_2) or their product (K_1K_2). A similar situation has been observed in the case of cationic surfactants.

Recently, we developed a kinetic model based on the micellar pseudophase formalism to study the effect of β-CD in micellar systems. The model was successfully applied to reactions that are catalyzed by β-CD[5, 6] and those that are not.[7] In both cases we observed a significant quantity of uncomplexed β-CD in equilibrium with the micellar system and the absence of interactions between β-CD and the micelles once these have been formed. Here we present the results of a study on the basic hydrolysis of *m*-nitrophenylacetate (*m*-NPA) in micelle – β-CD mixed systems of dodecyltrimethylammonium bromide (LTABr), trimetyltetradecylammonium bromide (TTABr), and trimethyloctadecylammonium chloride (OTACl). Contrary to expectations[8] the concentration of the uncomplexed β-CD in equilibrium with the micellar system increases with the length of the hydrocarbon chain of the surfactant. The main implications of this result are of crucial importance for using CDs as transfer agents for hydrophobic substances[1] and for determining the stoichiometry of the surfactant – CD complexes.

The experimental procedure for the preparation of *m*-NPA and for the study of its basic hydrolysis in mixed micelle – β-CD systems has recently been described.[5] Figure 1 shows the variation of the pseudo-first-order rate constant k_{obs} for the basic hydrolysis of *m*-NPA with the surfactant concentration. The experiments were carried out under conditions which allowed the influence of the surfactant concentration on k_{obs} to be studied, while ensuring that the total concentration of β-CD remained constant. The surfactant concentration at the minimum of the curve obtained by plotting k_{obs} versus this concentration is taken as the onset of micellization and equal to the critical micellar concentration (cmc_{app}).[9] The inhibitory effect of added surfactant below the concentration where micellization starts is attributed to complexation of the surfactant monomers by β-CD and release of *m*-NPA into the bulk aqueous medium. This decreases k_{obs} by reducing the concentration of the *m*-NPA – β-CD complexes. The observed behavior of k_{obs} after micellization is typical of micellar catalyzed reactions.[10]

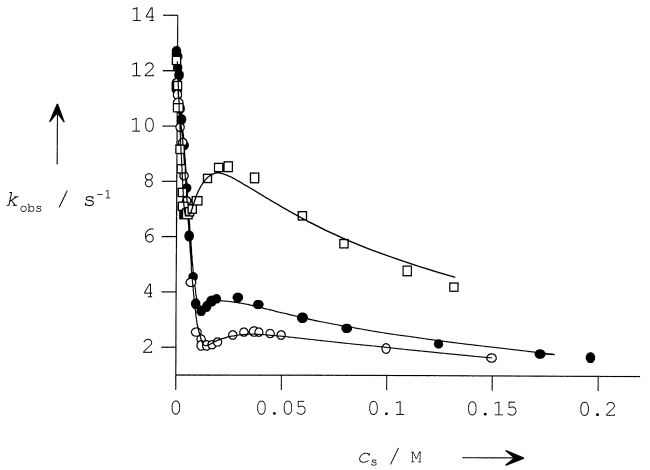

Figure 1. The influence of surfactant concentration c_S on k_{obs} for the alkaline hydrolysis of *m*-NPA in the presence of β-CD ($c_{CD} = 1.00 \times 10^{-2}$ M). ○ LTABr – β-CD systems, ● TTABr – β-CD systems, □ OTACl – β-CD systems. $c_{OH^-} = 0.175$ M, $T = 25\,^{\circ}C$. Curves were obtained by fitting Equation (1) to the experimental results (see Table 1).

A more detailed analysis showed that the surfactant concentration at the point of micellization (cmc_{app})[9] shifts to lower values when the length of the hydrocarbon chain increases (Figure 1): $cmc_{app} = 1.25 \times 10^{-2}$, 1.00×10^{-2}, and 4.50×10^{-3} M for LTABr, TTABr, and OTACl respectively in the presence of a constant concentration of β-CD (see Table 1). This decrease in cmc_{app} and in particular the fact that these values are lower than $c_{\beta\text{-CD,tot}}$ has normally been attributed to the existence of surfactant – CD complexes with stoichiometry 1:2.

Micellization in mixed surfactant – CD systems has traditionally been believed to occur only after the complexation capacity of the cyclodextrins has been saturated. Therefore, the concentration of surfactant at cmc_{app} will be $cmc_{app} = c_{CD,tot} + c_{surfactant\ monomers}$. For surfactants with a long hydrocarbon chain the concentration of surfactant monomers in equilibrium with the micellar system is very small. Thus, when experiments are carried out with a high $c_{CD,tot}$ it can be observed that $cmc_{app} = c_{CD,tot}$. At the same time, the supposition that the complexation capacity of the CD must be saturated before micellization begins would indicate that $c_{CD,tot} \approx c_{surfactant\text{–}CD}$. Therefore the quotient $c_{CD,tot}/cmc_{app}$ will provide us with the stoichiometry of the surfactant – CD complex. As we will show, this traditional notion should be rejected. Likewise, the minimum value of the curve obtained by plotting k_{obs} versus c_S shifts to give greater values of k_{obs} as the length of the hydrocarbon chain of the surfactant increases.

To explain the experimental behavior we applied our kinetic model based on the micellar pseudophase formalism (Scheme 1). Three simultaneous pathways were included: reaction of the free substrate with OH^- in aqueous medium, catalyzed reaction of the CD-complexed substrate, and reaction of the substrate with OH^- at the Stern layer of the micelles.

The rate equation (1) for k_{obs} was derived based on Scheme 1, where k_w, k_{CD}, and k_m are the rate constants for the reaction of the substrate in water, in the substrate – CD

$$k_{obs} = \frac{k_w c_{OH^-} + (k_m K_s^m - k_w) m_{OH} c_{D_n} + k_{CD} K_s^{CD} c_{\beta\text{-CD,f}}}{1 + K_s^m c_{D_n} + K_s^{CD} c_{\beta\text{-CD,f}}} \quad (1)$$

complex, and at the Stern layer of the micelles, respectively; K_s^m and K_s^{CD} are the binding constants of the substrate to the

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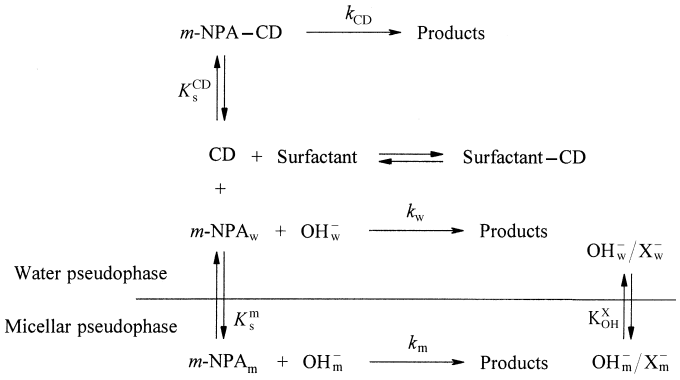

Scheme 1. The micellar pseudophase formalism used in the kinetic model.

micelles and cyclodextrin, and m_{OH} and c_{D_n} are the interfacial concentration of OH^- and the concentration of micellized surfactant. Details on the calculation of c_{D_n} and m_{OH} have recently been described for β-CD–micelle mixed systems.[5, 6]

For the application of Equation (1) it is necessary to determine the concentration of uncomplexed β-CD ($c_{\beta\text{-CD,f}}$) for each surfactant concentration. It is difficult to evaluate $c_{\beta\text{-CD,f}}$ due to the great disparity of the equilibrium constants for complexation between different surfactants and β-CD. In previous studies we have obtained $c_{\beta\text{-CD,f}}$ by means of simulation, supposing that the complex formed between the surfactant and β-CD presents a stoichiometric ratio of 1:1. The cmc_{app} values presented earlier seem to indicate the existence of complexes with ratios of 1:1 and 1:2, which would suggest that the simulation needs to take two complexation constants into account, the values of which should be closely linked. Hence, we calculated $c_{\beta\text{-CD,f}}$ on the basis of k_{obs} values for surfactant concentrations smaller than cmc_{app}. The experimental values of k_{obs}, obtained from a study of the influence of the β-CD concentration on k_{obs} in the basic hydrolysis of *m*-NPA in the absence of surfactants, lead to a kinetic behavior of saturation [Eq. (2)]. Equation (2) can be rearranged [Eq. (3)] to obtain values for $c_{\beta\text{-CD,f}}$ from experiments carried out in the presence of surfactants through the use of $k_w = (9.0 \pm 0.1)\,M^{-1}s^{-1}$, $k_{CD} = (31 \pm 2)\,s^{-1}$, and $K_s^{CD} = (54 \pm 5)\,M^{-1}$ determined previously.[5]

$$k_{obs} = \frac{k_w c_{OH^-} + k_{CD} K_s^{CD} c_{\beta\text{-CD,f}}}{1 + K_s^{CD} c_{\beta\text{-CD,f}}} \quad (2)$$

$$c_{\beta\text{-CD,f}} = \frac{k_w c_{OH^-} - k_{obs}}{k_{obs} K_s^{CD} - k_{CD} K_s^{CD}} \quad (3)$$

As opposed to other methods used in the past, this method of calculating $c_{\beta\text{-CD,f}}$ has the advantage of not presupposing any stoichiometry for the surfactant–CD complex. The kinetic model which has been developed considers that $c_{\beta\text{-CD,f}}$ remains constant once micelles have been formed and that there is no interaction of any kind between the β-CD and the micellar system once the latter has formed.[5, 6] The curves described in Figure 1 correspond with the fit of Equation (1) to the experimental k_{obs} values. Table 1 shows the values obtained for k_m and K_s^m in simple micellar systems and in mixed micelle–β-CD systems. Likewise the values of the $c_{\beta\text{-CD,f}}$ obtained at the point of micellization are shown.

The concentration $c_{\beta\text{-CD,f}}$ at the point of micellization increases with the length of the hydrocarbon chain of the surfactant. This increase in $c_{\beta\text{-CD,f}}$ is the reason why the values of k_{obs} at the minimum of the k_{obs} versus c_S curves increase with the length of the hydrocarbon chain. It would be reasonable to suppose that the concentration of uncomplexed β-CD in equilibrium with the micellar system would decrease when the length of the hydrocarbon chain of the surfactant increases, due to the enhanced hydrophobicity. However, it is necessary to consider the mixed micelle–CD as a system in which the surfactant monomers display a competition between autoassociation, micellization, and complexation with the CD. This therefore contradicts the traditional notion which suggests that the complexation capacity of the CD must be saturated before the micellization process can begin. An increase in the hydrophobicity of the surfactant gives rise to an increase in its affinity for complexation with the CD, but at the same time implies an increase in its tendency to micellize. The critical micellar concentration of a surfactant can be considered as a measure of its tendency towards autoassociation. Usually the more surface active the amphiphilic monomer,[11] the higher the tendency for micellization and, hence, the lower the critical micellar concentration. Accordingly, the longer the total carbon chain length of the monomeric surfactant, the lower the critical micellar concentration.

Table 1. Results obtained by fitting Equation (1) to the experimental data for the alkaline hydrolysis of *m*-NPA in micelle–β-CD mixed systems.[a]

Surfactant	$c_{\beta\text{-CD,tot}}$ [M]	cmc_{app} [M]	$c_{\beta\text{-CD,f}}$ [M]	cmc_{real} [M]	K_s^m [M^{-1}]	k_m [s^{-1}]
LTABr	–	–	–	1.00×10^{-2}	25 ± 3	12.9 ± 0.4
	1.00×10^{-2}	1.50×10^{-2}	2.34×10^{-4}	5.23×10^{-3}	29 ± 3	13.6 ± 0.2
TTABr	–	–	–	1.20×10^{-3}	63 ± 4	10.0 ± 0.2
	1.03×10^{-2}	1.00×10^{-2}	1.06×10^{-3}	7.60×10^{-4}	44 ± 4	18.6 ± 0.3
OTACl	–	–	–	5.00×10^{-4}	130 ± 10	16.1 ± 0.5
	1.00×10^{-2}	5.50×10^{-3}	3.35×10^{-3}	–	73 ± 9	25.3 ± 0.5

[a] See text for details. For each entry the first line of data is for the simple micellar systems, while the second line is for the mixed micelle–β-CD systems.

Studies of the literature that deal with the variation of the surfactant–CD complexation constants indicate that this variation increases with the length of the hydrocarbon chain of the surfactant. Beyond a certain length, which depends on the type of surfactant used, deviations are produced from this linear relationship, indicating that the association constants of surfactant–CD complexes reach a limiting value.[12] The balance between micellization and CD complexation causes $c_{\beta\text{-CD,f}}$ to increase with the length of the hydrocarbon chain in the sequence LTABr < TTABr < OTACl.

The implications of this concentration $c_{\beta\text{-CD,f}}$ in the investigation of the mixed micelle–β-CD systems are very important, particularly for studying the stoichiometry of the surfactant–β-CD complexes as the existence of a significant concentration of uncomplexed CD clearly questions the

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traditional methodology. In fact, the results shown in Table 1 indicate that the surfactant–β-CD complexes fundamentally display a stoichiometric ratio of 1:1. From data in Table 1 we can derive the concentration of complexed β-CD in the presence of OTACl as $c_{\text{surfactant}-\beta\text{-CD}} = 6.65 \times 10^{-3}$M ($c_{\beta\text{-CD,tot}} = c_{\beta\text{-CD,f}} + c_{\text{surfactant}-\beta\text{-CD}}$). Because cmc_{app} is smaller than $c_{\text{surfactant}-\beta\text{-CD}}$ we can suggest that there are OTACl–β-CD complexes with stoichiometries of both 1:1 and 1:2. Therefore one of the main conclusions to be drawn from this study is the necessity to revise the stoichiometries of the existing surfactant–CD complexes referred to in the library, derived from the values of cmc_{app}.

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[8] If the length of the hydrocarbon chain of the surfactant is increased, the hydrophobicity and consequently the equilibrium constant of the surfactant–CD complex would also increase. This increase in the complexation equilibrium constant would imply a reduction in the concentration of free cyclodextrin in equilibrium with the micellar system once the latter had formed.
[9] In mixed surfactant–CD systems the critical micellar concentration can be defined as: $\text{cmc}_{\text{app}} = c_{\text{surfactant-CD}} + c_{\text{surfactant monomer}} = c_{\text{surfactant-CD}} + \text{cmc}_{\text{real}}$, where cmc_{real} represents the concentration of free surfactant monomers in equilibrium with the micellar system and $c_{\text{surfactant-CD}}$ is the concentration of surfactant monomers complexed with the CD.
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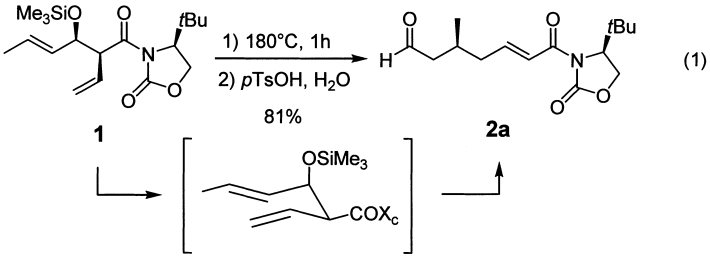
Domino Michael Aldol and Domino Michael Mannich Reactions: Highly Stereoselective Synthesis of Functionalized Cyclohexanes**

Christoph Schneider* and Oliver Reese

Efficiency and elegance are valued characteristics of domino transformations.[1] Even more appealing are those domino processes which form carbon–carbon bonds and thereby generate new chiral centers stereoselectively. We report here on domino Michael aldol and domino Michael Mannich reactions which in a single step give rise to highly substituted and functionalized cyclohexanes with very high stereocontrol.[2] The 7-oxo-2-enimides **2** used as substrates for the domino reactions were easily obtained in good yields and stereoselectivity by a thermal [3.3]-sigmatropic rearrangement of silylated *syn*-aldols **1** [Eq. (1)].[3] Compounds **2** have been sucessfully employed by us in syntheses of enantiopure tetrahydropyrans,[4] piperidines,[5] terpenols,[6] and polyol structures.[7]



(1)

We have already been able to show that chemoselective nucleophilic additions to the aldehyde moiety in **2a** are feasible and lead to oxygen and nitrogen heterocycles by intramolecular hetero Michael additions.[4, 5] We have now found that this sequence can be reversed when organocopper and -aluminum reagents are employed. Thus, the Lewis acid assisted addition of monoorganocuprates (Yamamoto cuprates)[8] to **2a** gave rise to the cyclohexanol **3a**[9] in moderate yield but complete stereocontrol (Table 1). The reaction is assumed to proceed by an initial, highly stereoselective Michael addition[10] of the cuprate reagent to the aluminum chelate complex **A**[11] and then formation of an imide enolate which is trapped intramolecularly by the aldehyde. The homogenous *syn*-stereochemistry of the aldol reaction results from the intramolecular transposition of the metal ion from the enolate oxygen atom to the aldehyde oxygen atom in the presumed transition structure **B**. As principal side product we

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