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The role of water release from the cyclodextrin cavity in the complexation of benzoyl chlorides by dimethyl-β-cyclodextrin

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ABSTRACT

The influence of temperature on the solvolysis of substituted benzoyl chlorides in the presence of dimethyl-β-cyclodextrin (DM-β-CD) was studied. Based on the influence of the DM-β-CD concentration on chemical reactivity in this process, the cyclodextrin has a catalytic effect on the solvolysis of 4-nitrobenzoyl chloride (4-NO_2) but an inhibitory effect on that of 4-methoxy-(4-MeO), 3-chloro-(3-Cl) and 3-trifluoromethyl-(3-CF_3) benzoyl chlorides. These disparate effects are related to a difference in reaction mechanism; thus, DM-β-CD catalyses associative solvolysis and inhibits dissociative solvolysis. Examining the influence of temperature on the solvolytic process allowed the stoichiometry of the host–guest complexes formed to be established. The formation constants for the complexes of *meta*-substituted benzoyl chlorides increased with increasing temperature. On the other hand, the equilibrium formation constants for the 1:1 host–guest complexes of *para*-substituted benzoyl chlorides exhibited the opposite trend. The equilibrium formation constant for 2:1 host–guest complexes for the *para*-substituted benzoyl chlorides increased with increasing temperature. These differences are ascribed to the release of water from the DM-β-CD cavity during the formation of the host–guest complex.

1. Introduction

Cyclodextrins (CDs) are the most important host molecules in supramolecular chemistry.[1–4] In fact, the cyclodextrin molecule is often described as a torus, but is more realistically pictured as a shallow truncated cone, the primary hydroxyl rim of the cavity opening having a somewhat reduced diameter relative to the secondary hydroxyl rim. It is the position of this cavity that makes CDs attractive subjects for study.[5]

In aqueous solutions, the non-polar cyclodextrin cavity is occupied by water molecules, which can be readily substituted by appropriate guest molecules (G) with a lower polarity than water. [6–10] Most CD–G complexes have a 1:1 and 2:1 stoichiometry but complexes of 1:2 and 2:2 stoichiometries have also occasionally been reported.[11–21] The driving forces leading to the inclusion complexation of cyclodextrin were thought to include electrostatic, van der Waals, hydrophobic, charge-transfer and hydrogen-bonding interactions.[22] Additional factors are penetration of the hydrophobic part of the G molecule into the CD cavity and dehydration of the organic G,[7,23,24] conformational changes, [3,6,25–27], and the release of water molecules from the CD. [24,28–30] Thermodynamic studies of the inclusion of different guests in cyclodextrins were carried out in the last years[31–36] Recently Valente et al. evaluated the thermodynamic factors of the CD–G association between bolaform surfactants and cyclodextrins.[37] It was found that the association is stronger between G and α-CD than that found for the same bolaform surfactant and β-CD. The complex formation was exothermic, more so for α-CD than for β-CD and the process has a negative entropy change for the former and a positive for the latter. The different thermodynamic behaviour observed between α- and β-CD was explained based on the curvature of the cavity of the CD, the properties of the included water and interactions between surfactant and water with the interior of the cavity.

The primary aim of this work was to acquire a deeper knowledge of the factors governing the formation of host–guest complexes between cyclodextrins and hydrophobic organic compounds. Solvent effects on the kinetics of the inclusion of the G (ruthenium complex) in β-CD were described as a consequence of the competition of the cosolvent for the β-CD cavity.[38] In our laboratory we have studied hydrolysis reactions and how the presence of dioxane, acetonitrile or DMSO decrease the inhibitory effect of β-CD on increasing the proportion of organic cosolvent as a result of a competitive reaction involving the formation of an inclusion complex between β-CD and the cosolvent.[39] We used a kinetic method in order to determine the solvolysis rate in the presence of cyclodextrin at variable temperatures. The reaction used as probe

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was the solvolysis of benzoyl chlorides, the size and hydrophobic nature of which make them highly suitable guests for inclusion in the DM-β-CD cavity (the host). The mechanism behind the solvolysis of benzoyl chlorides (BzCl) in water and various other solvents is well known.[40–42]

Previous studies in our laboratory have shown the influence of α-, β- and γ-cyclodextrins on the solvolysis of substituted benzoyl chlorides.[43] We found that the presence of α- and γ-CD causes alterations in behaviour, which are related to the stability of the CD–G complexes, the stoichiometry of the complexes (causing the formation of complexes α-CD–BzCl with 1:1 stoichiometries for those which are substituted in the *meta* position and 2:1 for those substituted in the *para* position) and the displacement of water in the interior of the cavity causing the solvolysis reaction to be detected in the interior of the cavity of γ-CD when *meta*-substituted BzCl are used. In more recent work, we determined the stoichiometry of CD–BzCl complexes and the electrophilicity or nucleophilicity of the cyclodextrin involved.[44] With a given BzCl, the mechanism can be associative or dissociative depending on whether the solvolytic reaction takes place in the bulk water or within the CD hydrophobic cavity. Based on our results, the formation of the CD–BzCl complex additionally involves the substitution of water molecules in the DM-β-CD cavity. Clearly, inclusion of a benzoyl chloride in a CD cavity cannot lead to the displacement of all water molecules present in it. The more closely the guest can be fitted in the cyclodextrin cavity, the greater will be the number of water molecules released from the cavity. The combination of these two effects (viz. inclusion of the benzoyl chloride and displacement of water molecules) affects the equilibrium formation constants for CD–G complexes in various ways.

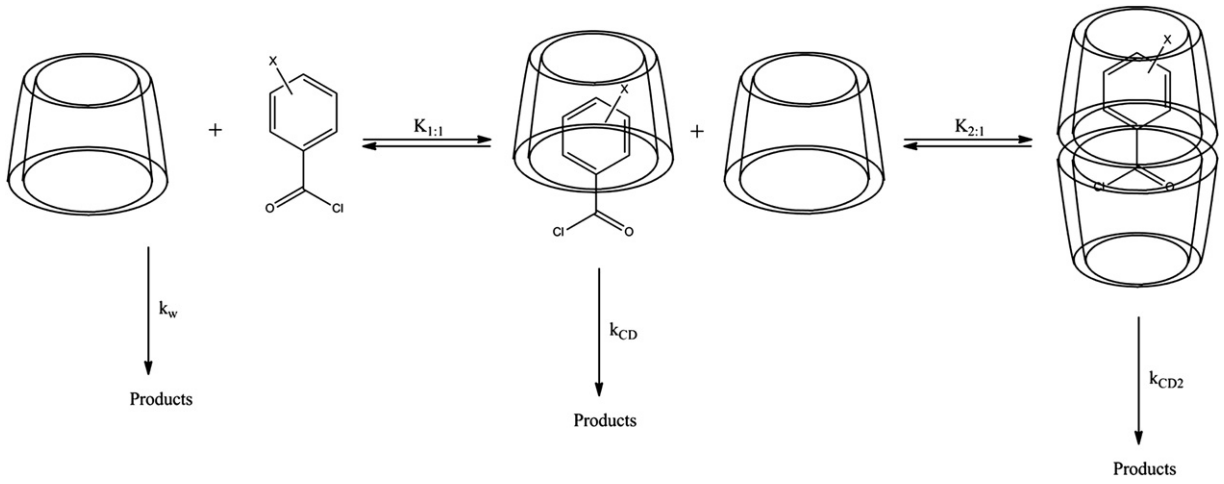
2. Results

Examining the influence of the DM-β-CD concentration on the solvolysis rate constants for various benzoyl chlorides (BzCl) at 25 °C revealed three different types of experimental effects (viz. inhibition, catalysis and a combination of both) depending on the particular halide.[44] The influence of the temperature precluded an unambiguous interpretation of the results; thus, the stoichiometry of some CD–BzCl complexes was found to change with this variable. We will first discuss the two reaction schemes used to study the solvolysis of benzoyl halides in the presence of DM-β-CD and then examine the ensuing rate laws against experimental evidence.

2.1. Complexation models

Benzoyl halides can form 1:1 and 2:1 CD–BzX complexes. Whichever the stoichiometry, the reaction develops in the bulk water or the complexed halide reacts with the CD cavity. If both mechanisms occur, then the rate constant will be the combination of the solvolysis rate of BzX in water and that of the CD-complexed benzoyl halide. Under these conditions, experimental evidence can be examined in the light of various reactions schemes depending on the stoichiometry of the particular complex.

2.1.1. 1:1 CD–G complexes. Simplification of Scheme 1 provides the simplest way of interpreting the experimental results obtained in the solvolysis of benzoyl halides in the presence of CDs leading to the formation of a 1:1 complex.



Scheme 1.

This kinetic scheme conforms to the following rate law:

$$k_{obs} = \frac{k_w + k_{CD}K_{1:1}[DM-\beta-CD]}{1+K_{1:1}[DM-\beta-CD]} \quad (1)$$

where k_w and k_{CD} are the solvolysis rate constants for the benzoyl halides in water and their inclusion complexes with cyclodextrin; and $K_{1:1}$ is the equilibrium formation constant for the CD–BzCl complex. If the extent of reaction within the CD cavity is negligible relative to the aqueous medium (i.e., $k_w \gg k_{CD}K_{1:1}$[DM-β-CD]), then Eq. 1 reduces to a linear relation between $1/k_{obs}$ and [DM-β-CD].

2.1.2. 2:1 CD–G complexes. Scheme 1 shows the reaction mechanism for the formation of 2:1 CD–BzX inclusion complexes. Three potential reaction sites have been considered, namely: the bulk water, the 1:1 complex and the 2:1 complex.

This mechanism conforms to the following rate law:

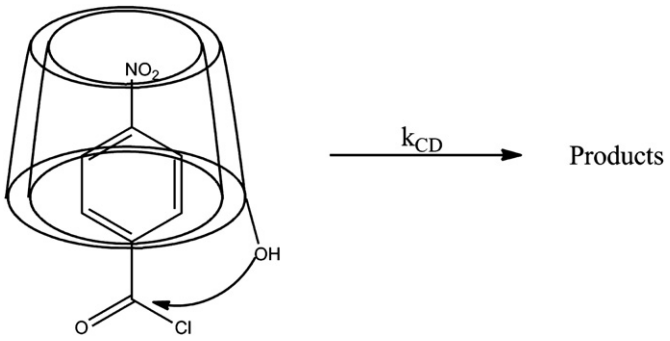
$$k_{obs} = \frac{k_w + k_{CD}K_{1:1}[DM-\beta-CD] + k_{CD2}K_{1:1}K_{2:1}[DM-\beta-CD]^2}{1+K_{1:1}[DM-\beta-CD] + K_{1:1}K_{2:1}[DM-\beta-CD]^2} \quad (2)$$

If the reactivity of the 2:1 complex within the CD cavity is negligible, then $k_{CD} \gg k_{CD2}$[DM-β-CD] and Eq. 2 simplifies to

$$k_{obs} = \frac{k_w + k_{CD} + K_{1:1}[DM-\beta-CD]}{1+K_{1:1}[DM-\beta-CD] + K_{1:1}K_{2:1}[DM-\beta-CD]^2} \quad (3)$$

2.2. Influence of temperature on the solvolysis of 4-NO_2

The solvolysis of 4-NO_2 takes place via an associative mechanism. Figure 1 illustrates the influence of the DM-β-CD concentration on the observed solvolysis rate constant for 4-NO_2 at a variable temperature. In general, k_{obs} increased with increasing temperature. By contrast, the DM-β-CD concentration had two distinct effects. Thus, as can be seen from Figure 1A and 1B, k_{obs} increased with increasing DM-β-CD concentration displaying a levelling off behaviour at 15.0 °C≤T≤30.0 °C. The solid lines in Figure 1and 1B testify to the close fitting of Eq. 1 to the experimental values. This equation corresponds to the formation of a 1:1 CD–G complex. By fitting Eq. 1 to experimental data, we obtained the rate constant for the reaction within the CD cavity (k_{CD}), as well as the overall equilibrium constant ($K_{1:1}$). Table 1 shows the results, which are consistent with the expected solvolytic behaviour for benzoyl chlorides bearing electron-withdrawing substituents by effect of hydroxyl groups in cyclodextrin acting as efficient nucleophiles in an associative reaction mechanism (Scheme 2).[43,44]



Scheme 2.

as the temperature is raised. Thus, above 30 °C, the reactants can form both 1:1 and 2:1 complexes (see Scheme 3). Figure 1C and 1D testify to the close fitting of Eq. 2 to the experimental results. As can be seen, only the 1:1 complex was formed in the presence of low concentra-

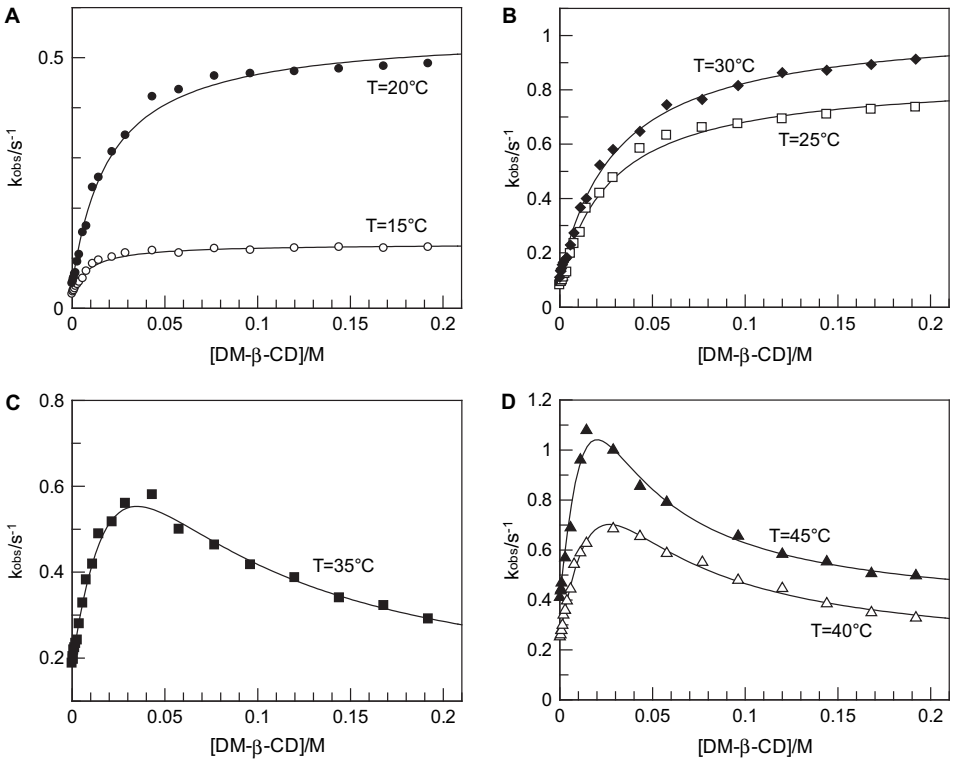


Figure 1. Influence of the DM-β-CD concentration on k_{obs} for the solvolysis of 4-NO_2 at a variable temperature: (○) 15 °C, (●) 20 °C, (□) 25 °C, (◆) 30 °C, (■) 35 °C, (△) 40 °C and (▲) 45 °C. The solid lines were obtained by fitting Eq. 1 and 2 to experimental data.

Table 1
Kinetic parameters obtained by fitting Eqs. 1 and 2 to experimental data for 4-NO_2

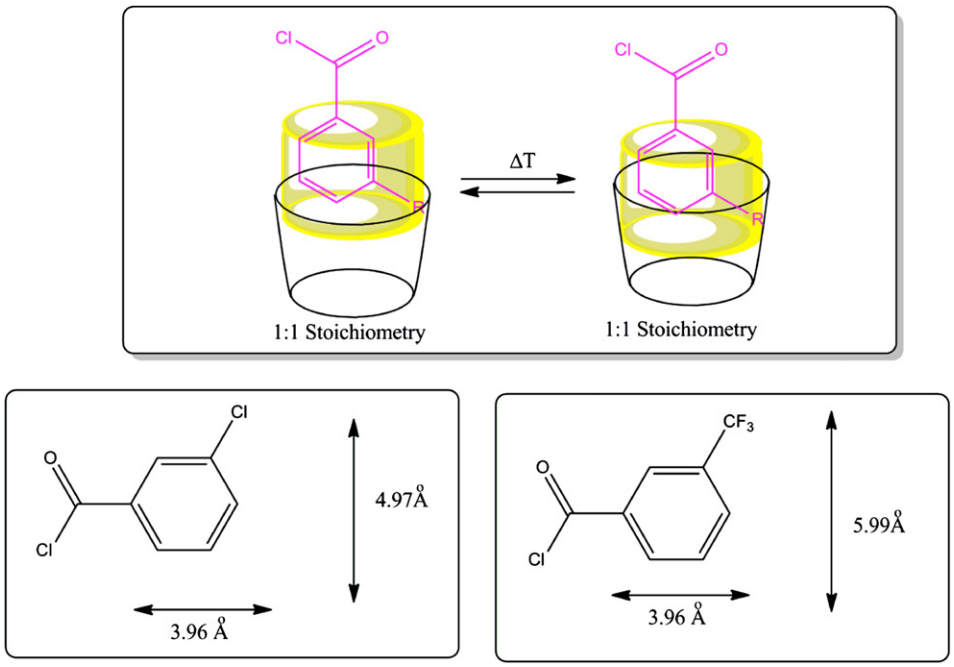
T/°C	k_{cd}/s^{-1}	k_w/s^{-1}	$K_{1:1}/M^{-1}$	$K_{2:1}/M^{-1}$	k_{CD2}/s^{-1}
15	$(1.28\pm0.02)\times10^{-1}$	$(2.8\pm0.1)\times10^{-2}$	110±9		
20	$(5.5\pm0.1)\times10^{-1}$	$(4.9\pm0.2)\times10^{-2}$	49±4		
25	$(8.5\pm0.2)\times10^{-1}$	$(8.2\pm0.4)\times10^{-2}$	36±3		
30	1.04±0.01	$(1.1\pm0.1)\times10^{-1}$	32±2		
35	1.59±0.04	$(1.88\pm0.09)\times10^{-1}$	20±2	32±4	$(8\pm3)\times10^{-2}$
40	3.10±0.07	$(2.5\pm0.1)\times10^{-1}$	14±2	84±7	$(1.7\pm0.2)\times10^{-1}$
45	7.4±0.3	$(4.1\pm0.2)\times10^{-1}$	10±1	220±30	$(3.4\pm0.3)\times10^{-1}$

At higher temperatures (35.0 °C≤T≤45.0 °C), however, k_{obs} increased to a peak value with increasing DM-β-CD concentration and then decreased throughout. This disparate experimental behaviour suggests that 4-NO_2 is complexed in a different manner by DM-β-CD tions of DM-β-CD above 35 °C; also, because solvolysis in the CD cavity was stronger than in the bulk water, k_{obs} increased with increasing DM-β-CD concentration. Once the peak rate was reached, further increasing such a concentration favoured the formation of a 2:1

complex. In addition, the reaction rate approached a limit exceeding that in the bulk water, which confirms that the 2:1 complex is reactive. At the highest DM-β-CD levels studied, k_{obs} was the combination of the reactivity in water and that of the 2:1 complex in the CD cavity.

seen, k_{obs} clearly decreased with increasing DM-β-CD concentration, whatever the temperature.

The previous results are quite consistent with a reaction mechanism involving the formation of a 1:1 CD–G complex and



Scheme 3.

As can be seen from Table 1, the rate constant for the 1:1 complex in the CD cavity invariably exceeded that in the bulk water ($k_{CD}>k_w$); also, the difference increased with increasing temperature. Above 30 °C, the 2:1 complex was also formed, albeit at a lower rate in the cavity than in the bulk water ($k_{CD}>k_w>k_{CD2}$). Also, the corresponding binding constants varied with the temperature. Thus, increasing T favoured the formation of the 2:1 complex ($K_{2:1}$ increased with increasing T) over the 1:1 complex ($K_{1:1}$ decreased with increase in T).

2.3. Influence of the CD concentration on the solvolysis of 4-MeO

In recent work, we found the solvolysis of 4-MeO in water with and without an added cyclodextrin to take place via a dissociative mechanism.[44] The solvolysis of benzoyl chlorides, which involves a dissociative mechanism, is highly sensitive to the solvent polarity.[41,42] Figure 2 illustrates the effect of the DM-β-CD concentration on the observed rate constant for the solvolysis of 4-MeO. As can be

a 2:1 complex only the former of which is reactive. As can be seen from Figure 2, the solvolysis rate tends to zero at high DM-β-CD concentrations. The solid line in the figure represents the fitting of Eq. 3 to the experimental data; based on it, the complex formed has a 2:1 stoichiometry and is therefore unreactive. Table 2 gives the equilibrium formation constants for the host–guest complexes between 4-MeO and DM-β-CD, and the solvolysis rate constants in the bulk water and within the cyclodextrin cavity.

Table 2
Kinetic parameters obtained by fitting Eq. 3 to the experimental data for 4-MeO

T/°C	k_{cd}/s^{-1}	k_w/s^{-1}	$K_{1:1}/M^{-1}$	$K_{2:1}/M^{-1}$
20	$(1.67\pm0.06)\times10^{-1}$	30±1	820±40	20±1
25	$(2.79\pm0.09)\times10^{-1}$	46±2	640±30	29±1
35	$(7.5\pm0.3)\times10^{-1}$	133±5	464±60	35±4

In order to more effectively compare the influence of temperature on our reaction medium, we normalized the rate constants at different temperatures by defining a relative constant k_{rel} such that

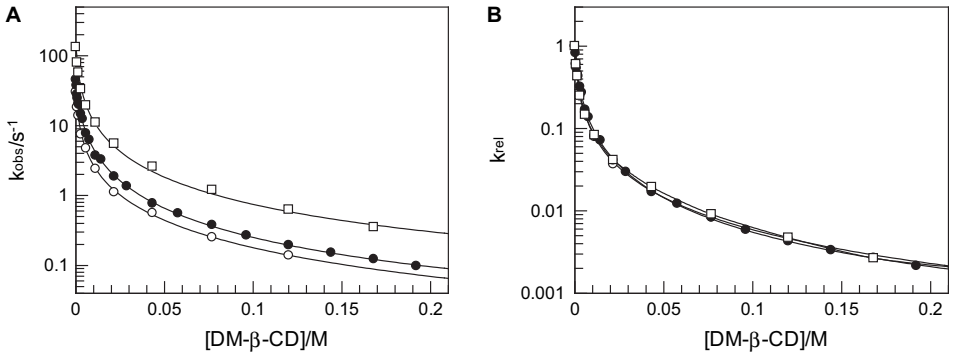


Figure 2. Influence of the DM-β-CD concentration on k_{obs} (left) and k_{rel} for the solvolysis of 4-MeO at (○) 20 °C, (●) 25 °C and (□) 35 °C. The solid lines were obtained by fitting Eq. 3 to experimental data.

$$k_{rel} = \frac{k_{obs}}{k_{obs}^{[CD]=0}} \quad (4)$$

Figure 2B illustrates the influence of the DM-β-CD concentration on k_{rel} at three different temperatures. By plotting k_{rel} instead of k_{obs} one suppresses the kinetic effect of temperature, so the results can only reflect the dependence of the CD–G complexation equilibria on this variable. As can be seen form Figure 2B, there were no appreciable differences in k_{rel} between temperatures; therefore, as can be inferred from Table 2, constants $K_{1:1}$ and $K_{2:1}$ had a mutual compensation effect. Raising the temperature favoured the formation of the 2:1 complex at the expense of the 1:1 complex. Table 2 illustrates to what extent an increase in temperature decreased the formation rate constant for the 1:1 complex. This effect, however, was countered by an increase in the constant for the 2:1 complex. The reaction rate for the 1:1 complex in the DM-β-CD cavity was invariably about 170 times smaller than in the bulk water (Table 2). The inhibitory effect was identical at any temperature since it was a result of the polarity of the medium. These results, and others of previous studies, confirm that the polarity of the cyclodextrin cavity is similar to that of an alcohol–water mixture.[44]

2.4. Influence of temperature on the solvolysis of 3-CF_3 and 3-Cl

The kinetic study of the solvolytic reaction of the benzoyl halides 3-CF_3 and 3-Cl in the presence of DM-β-CD revealed that raising the cyclodextrin concentration decreased k_{obs} (see Fig. 3). As shown elsewhere,[44] the solvolysis of these chlorides in the presence of cyclodextrins takes place via an associative mechanism. The inhibitory effect observed can be better understood by assuming k_w to be greater than k_{CD} and hence that the observed rate with the substrate completely bound to the cyclodextrin is smaller than in the bulk water, but still markedly different from zero.

Table 3
Kinetic parameters obtained by fitting experimental data for 3-CF_3 and 3-Cl to Eq. 1

	T/°C	k_{cd}/s^{-1}	k_w/s^{-1}	$K_{1:1}$/M^{-1}
3-CF_3	25	$(1.84\pm0.07)\times10^{-2}$	$(3.3\pm0.2)\times10^{-2}$	120±30
3-CF_3	35	$(3.4\pm0.1)\times10^{-2}$	$(8.9\pm0.4)\times10^{-2}$	150±13
3-CF_3	40	$(4.6\pm0.1)\times10^{-2}$	$(1.4\pm0.1)\times10^{-1}$	210±20
3-Cl	15	$(6.1\pm0.2)\times10^{-3}$	$(1.82\pm0.08)\times10^{-2}$	135±13
3-Cl	20	$(7.6\pm0.3)\times10^{-3}$	$(2.7\pm0.1)\times10^{-2}$	260±40
3-Cl	25	$(1.3\pm0.2)\times10^{-2}$	$(4.7\pm0.2)\times10^{-2}$	345±30
3-Cl	30	$(1.95\pm0.04)\times10^{-2}$	$(8.9\pm0.4)\times10^{-2}$	460±25
3-Cl	35	$(2.6\pm0.1)\times10^{-2}$	$(1.45\pm0.06)\times10^{-1}$	560±40
3-Cl	40	$(2.7\pm0.2)\times10^{-2}$	$(2.4\pm0.1)\times10^{-1}$	660±30

3. Discussion

The most salient result obtained in this study is that, based on the equilibrium constants of complexation obtained in the presence of DM-β-CD, the solvolysis of benzoyl chlorides with a *meta* or *para* substituent involves one and two water molecules, respectively. Also, the equilibrium constants are affected in disparate ways by the temperature. Thus, the stability of the 1:1 complexes of the *meta*-substituted benzoyl chlorides increases with increasing temperature and the opposite holds for their *para*-substituted counterparts. In addition, the stability of the 2:1 complexes between a cyclodextrin and a *para*-substituted benzoyl chloride increase with increasing temperature. Accurately interpreting this behaviour entails examining the main factors governing the stability of CD–G complexes.

Thermodynamically, the formation of CD–G complexes is influenced by various factors, namely: (a) penetration of the hydrophobic part of the guest molecule into the cyclodextrin cavity; (b) dehydration of the organic guest; (c) hydrogen-bonding interactions; (d) conformational changes in the cyclodextrin molecule upon complexation; and (e) release of water molecules originally included in the cyclodextrin cavity to the bulk water.[37,45]

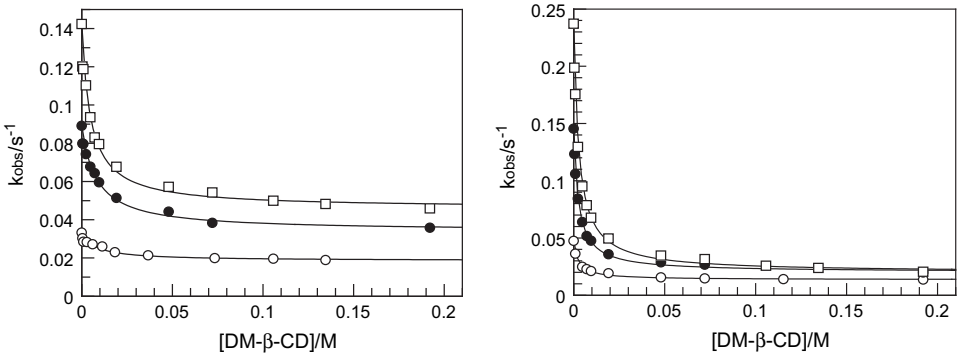


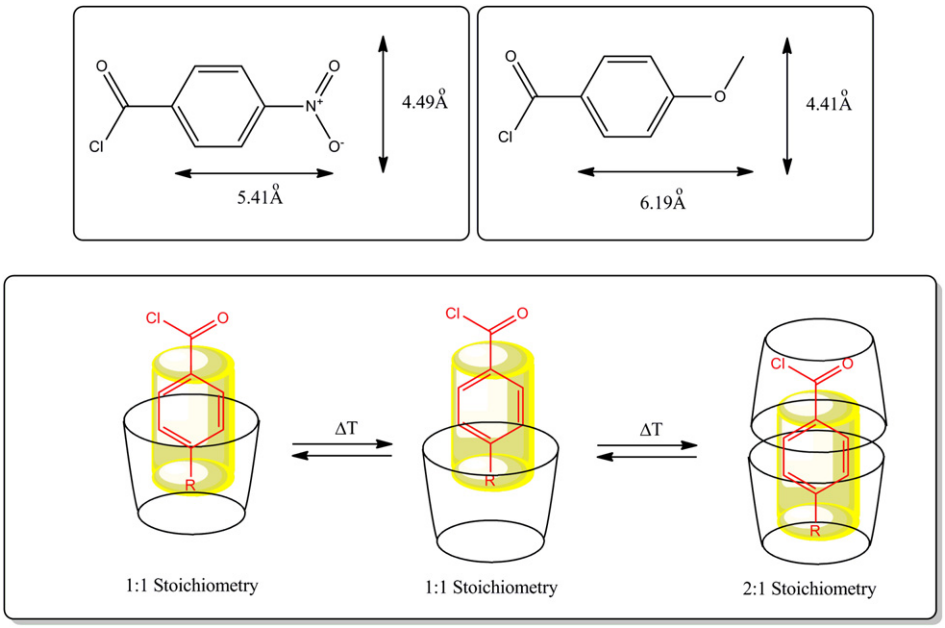
Figure 3. Influence of the DM-β-CD concentration on k_{obs} for the solvolysis of 3-CF_3 (left) and 3-Cl (right) at a variable temperature: (○) 25 °C, (●) 35 °C and (□) 45 °C. The solid lines were obtained by fitting Eq. 1 to experimental data.

The complexation mechanism best fitting the experimental results is that of the simplification of Scheme 1, which assumes the presence of a 1:1 CD–BzCl complex and reaction within the CD cavity. Also, the stoichiometry of the complexes is temperature-independent. Eq. 1 was used to obtain the kinetic parameters given in Table 3.

The rate constant within the CD cavity, k_{CD}, was smaller than that in the bulk water; this accounts for the decrease in k_{obs} with increase in the amount of DM-β-CD present in the medium. It should be noted that the solvolysis of 3-CF_3 and 3-Cl was increasingly inhibited by increasing temperatures. These results suggest that the inhibitory effect is due to the formation of 1:1 complexes. Surprisingly, $K_{1:1}$ increased with increasing temperature (see Table 2).

The benzoyl chlorides studied here have a similar structure and hence an also similar hydrophobicity. The electronic effects of the substituent are usually examined in terms of Hammett parameters. Based on reported data, however, such effects by themselves afford no rationalization of the complexation thermodynamics of cyclodextrins. Careful examination of the data in Tables 1–3 reveals that the most surprising outcome of the kinetic study conducted in this work is the disparate behaviour of *meta*- and *para*-substituted benzoyl halides. Therefore, one must consider the geometry of the compounds (Schemes 3 and 4) and examine its potential effects on the formation of the different complexes.

While the two benzoyl halides with a *para* substituent form both 1:1 and 2:1 CD–BzX complexes (Scheme 4), their *meta* counterparts only form 1:1 complexes (Scheme 3). Also, as can be

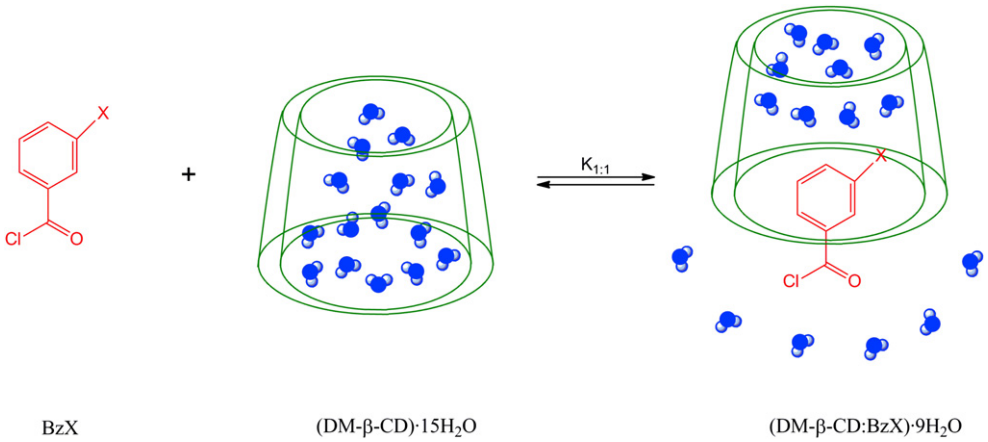


Scheme 4.

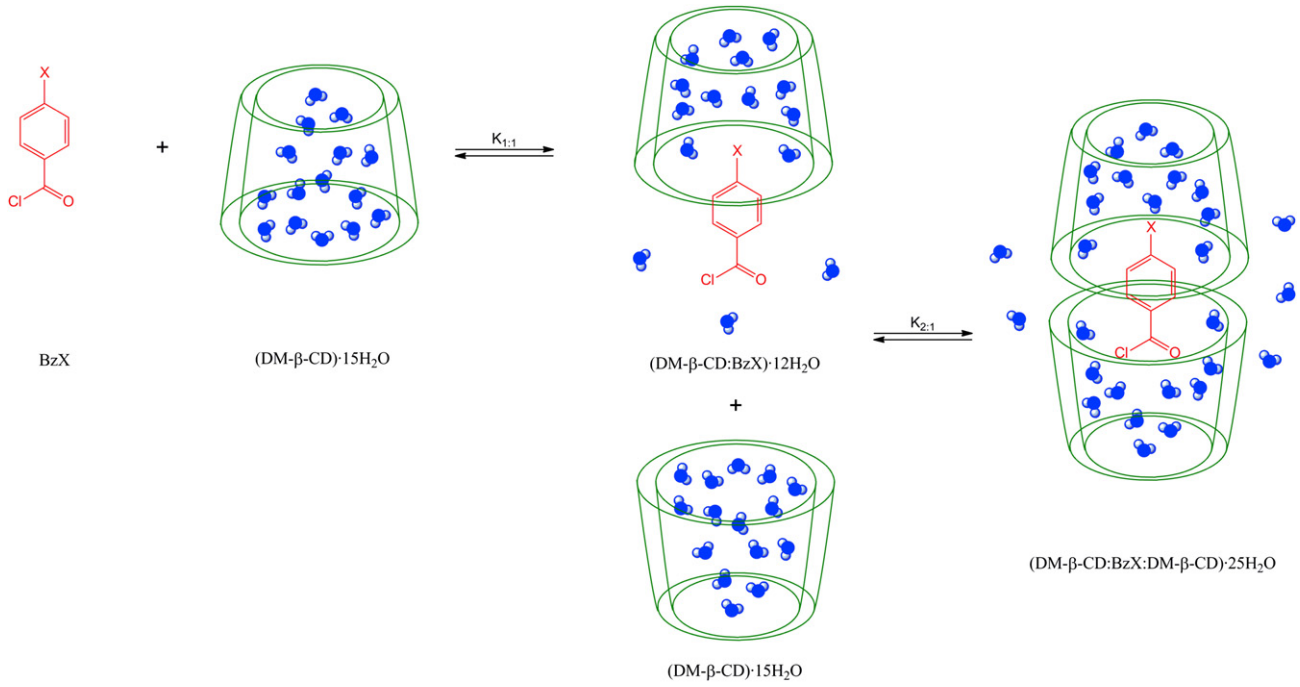
inferred from the data in Tables 1–3, the equilibrium constants for the 1:1 complexes (BzX–CD), $K_{1:1}$, of 4-MeO and 4-NO_2 decrease with increasing temperature, whereas that for the 2:1 complex (CD–BzX–CD), $K_{2:1}$, exhibits the opposite trend. On the other hand, raising the temperature favours the formation of the 1:1 complexes of 3-Cl and 3-CF_3, and increases $K_{1:1}$ as a result. We calculated the enthalpy and entropy of formation of the complexes from the variation of $K_{1:1}$ and $K_{2:1}$ with temperature.

The cyclodextrin cavity can accommodate up to 12 water molecules in β-CD[46] and up to 15 in DM-β-CD.[47] One should bear in mind that the number of water molecules released from the inside of the cavity is usually very small (2–3 for β-CD[28,29]); however, that of water molecules, which undergo a change in some property by effect of the formation of a complex varies. Water molecules can migrate not only from the bulk water to the CD cavity, but also from the CD and substrate hydration shells. Thus, a recent study revealed that up to 20–25 molecules of water can be released to the bulk water by effect of the complexation of 1-adamantanecarboxylic acid by β-CD.[30] In our case, the number of water molecules released to the bulk water must have been influenced by the particular geometry of the different chlorides.

The experimental differences between the 1:1 complexes of the *meta*- and *para*-substituted halides can be ascribed to those in their geometries (see Schemes 3 and 4). Thus, the guest molecule penetrates the cyclodextrin via its most hydrophobic region. If the host molecule is equalled to a cylinder, then the *para* chlorides will occupy a smaller volume of the CD cavity than will the *meta* chlorides; therefore, the former will release fewer water molecules from the CD cavity. Also, the way $K_{1:1}$ varies with T suggests that each benzoyl chloride penetrates the cavity in a different manner. Thus, if the four benzoyl chlorides had penetrated 3.9 Å within the CD cavity (i.e., to one-half its depth), then the volume occupied by 4-NO_2, 4-MeO, 3-Cl and 3-CF_3 would have been 62, 60, 76 and 110 Å, respectively. Therefore, the 1:1 complex of 4-CF_3 would have caused nearly twice as many water molecules to be released as would 4-MeO (Scheme 5). Complexation of the *para*-substituted halides is enthalpy-favoured; also, while some water molecules are inevitable released from the CD cavity (Scheme 6), van der Waals interactions have a stronger effect on the displacement of water in the formation of the 1:1 complex.



Scheme 5.



Scheme 6.

3.1. Thermodynamic parameters for 3-CF_3 and 3-Cl

Table 4 shows the enthalpy and entropy changes for the complexation of *meta*-substituted benzoyl halides by DM-β-CD obtained from the variation of K_{11} with T. Intracavity interactions between CD and the guest can be more accurately described by a 'non-classical' hydrophobic model where the enthalpy and entropy changes (ΔH^0 and ΔS^0, respectively) can be either positive or negative than they are by a 'classical' model where both ΔH^0 and ΔS^0 are positive.[48] Our ΔH^0 and ΔS^0 values for 3-CF_3 and 3-Cl were both positive. As stated above, raising the temperature favoured the formation of the 1:1 complex (i.e., $K_{1:1}$ increases with T). Based on the corresponding thermodynamic parameters, the complexation process is governed by the entropic factor. Although the process is enthalpically unfavourable ($\Delta H_{1:1}>0$), the effect is countered by a positive entropy. Large positive entropy changes can be ascribed to a relatively high flexibility in the guest upon complexation, extensive desolvation from the hydrophilic moieties of the host and guest, or the release and/or restructuring of the water molecules inside and around the cavity.[39] For example Valente et al. discussed the difference in magnitude and sign between α-CD (negative entropy) and β-CD (positive entropy) complexes based on the curvature of the cavity of the CD and suggested that the water molecules inside the α-CD cavity are not able to maintain their hydrogen bond network. Upon complex formation these water molecules are expelled and reform their hydrogen bond network.[37]

Table 4
Thermodynamic parameters for *meta*-substituted benzyl chlorides as calculated from Gibbs free energy values

	$\Delta H_{1:1}$/kJ mol^{-1}	$\Delta S_{1:1}$/J mol^{-1} K^{-1}
3-CF_3	+29±8	+135±25
3-Cl	+45±5	+200±20

The results suggest that the most influential factor in our case is the release of water molecules from the cyclodextrin cavity (Scheme 5). Therefore, the formation of complexes between DM-β-CD and benzoyl halides will depend largely on the number of water molecules that are released from the cavity —and its neighbourhood—, which affects the polarity and nucleophilicity of the reaction medium.

At this point, one must consider some essential differences between β-CD and DM-β-CD. Thus, the latter is much more readily soluble in water than is β-CD; also, the water solubility of DM-β-CD has a negative temperature coefficient and that of β-CD a positive one. This reflects in the solubility of DM-β-CD (60 g/100 mL at room temperature, but only 1 g/100 mL above 70 °C).[49] A recent study of DM-β-CD crystallization revealed that water molecules in its hydration shell increase in mobility and diffuse into the bulk water as the more favourable environment when the temperature is raised.[50] Molecular dynamics calculations and Monte Carlo simulations have been used to find a plausible explanation for the negative solubility coefficient of methylated cyclodextrins in water.[51] The prevalence of the hydrophobic effect at high temperatures has been ascribed to massive destruction of hydration shells around the methyl groups. Also, the number of water molecules in the integral hydration shell around DM-β-CD increases dramatically with increasing temperature. Therefore, one must consider the number of water molecules inside the DM-β-CD cavity —which exceeds that for β-CD— and the fact that raising the temperature causes a large number of water molecules in the hydration shell to be displaced to the bulk water. The displacement of water molecules from the hydration shell by effect of an increase in temperature raises the hydrophobicity of the cyclodextrin and the stability of its host–guest complexes as a result.

3.2. Thermodynamic parameters for 4-MeO and 4-NO_2

Table 5 shows the enthalpy and entropy changes for the 1:1 and 2:1 complexes of DM-β-CD with the *para*-substituted benzoyl chlorides. As can clearly be seen, both exhibit identical trends. Thus, $\Delta H_{1:1}<\Delta H_{2:1}$, so the 1:1 complex is enthalpy-favoured and the 2:1 complex entropy-favoured in both cases. This is a result of the aromatic ring, which is the most hydrophobic part of the molecule,

displacing fewer water molecules from the non-polar CD cavity in the first step of the solvolysis process (Scheme 6).

Table 5
Thermodynamic parameters for *para*-substituted benzoyl halides as calculated from Gibbs free energy values

	$\Delta H_{1:1}$/kJ mol^{-1}	$\Delta S_{1:1}$/J mol^{-1} K^{-1}	$\Delta H_{2:1}$/kJ mol^{-1}	$\Delta S_{2:1}$/J mol^{-1} K^{-1}
4-NO_2	−57±4	−16±14	+160±1	+545±4
4-MeO	−28±2	−39±7	+26±9	+115±30

Interactions between the cavity and the aromatic group are favourable and lead to a negative $\Delta H_{1:1}$ value. As widely documented,[48] large negative enthalpy changes are usually due to strong van der Waals interactions arising from the precise matching in size and shape between the host and guest. Likewise, because the entropy is also negative, and based on the classification of Inoue and Rekharsky, we can assume enthalpy-driven complexation ($\Delta H^0<0$, $T\Delta S^0<0$) in our 1:1 complexes.[48] These enthalpic and entropic features are usually assigned to a prevalence of van der Waals interactions arising from the precise CD–G complementariness in size and shape and to the accompanying significant decreases in translational and structural freedom upon complexation. The formation constant for the 1:1 CD–G complexes, $K_{1:1}$, decreases with increase in T; as a result, the benzoyl chloride penetrates to a decreasing depth with increasing temperature. Although van der Waals forces are thermodynamically responsible for the complex formation, 4-NO_2 displaces a greater number of water molecules from the CD cavity at 15 °C than it does at 30 °C.

In the second complexation step, the hydrophilic acid chloride group is —loosely— enclosed in the non-polar cavity of a second CD molecule. Interactions between the group and cavity are unfavourable and lead to a positive $\Delta H_{2:1}$ value. Under these conditions, the formation of the 2:1 complex is facilitated by the entropic factor. In addition, as previously shown for *meta*-substituted benzoyl chlorides, water release from the CD cavity is the most influential factor on the process for their *para* counterparts as well. In the first complexation reaction, the aromatic ring in the benzyl chloride displaces water molecules from the CD cavity and the released molecules solvate the hydrophilic acid chloride group, thereby increasing the overall order of the system. The water molecules are more 'ordered' in this situation than they were in the hydrophilic CD cavity. In the second complexation reaction, the second CD molecule has the acid chloride group inserted into its cavity. This causes the release of further water molecules from the cavity and, more importantly, breaks the solvation of the acid chloride group in the 1:1 BzX–CD complex by the water molecules from the first CD cavity. Thus, although this step involves 1 molecule (CD–Bz*X*–CD) rather than 2 (CD+Bz*X*−CD), the release of the water molecules previously solvating the acid chloride group results in an overall decrease in order and hence in a positive $\Delta S_{2:1}$ value.

4. Conclusion

In this work, we determined thermodynamic properties of the inclusion complexes of benzoyl halides with dimethyl-β-cyclodextrin (DM-β-CD). The results allow us to draw the following thermodynamic conclusions:

(a) The release of water molecules from the CD cavity is enthalpically unfavourable but entropically favourable. The number of molecules released depends on the geometry of the particular benzoyl halide, which dictates to what an extent it can penetrate the cavity.
(b) The desolvation of the halides is entropically favourable but has a positive enthalpy. Because the number of water molecules solvating the four benzoyl halides studied here is very similar, their contribution to the complexation process must be essentially identical.
(c) The inclusion of the halides in the CD cavity is enthalpically favourable and entropically favourable ($\Delta S>0$) or unfavourable ($\Delta S<0$). The process is driven mainly by van der Walls forces between the two species forming the complex.

The benzoyl halides with a *meta* substituent (3-Cl and 3-CF_3) only form the 1:1 complex, the process involving desolvation of the host molecule and, especially, the release of water molecules. In the *para*-substituted halides (4-MeO and 4-NO_2), the first complexation step is governed by van der Waals interactions and the second by the release of water molecules. As a result, the 1:1 complex is enthalpically favoured and the 2:1 complex entropically favoured. The most salient difference between the two processes is the number of water molecules, that is, displaced from the DM-β-CD. The molecular geometry of the *meta*-substituted halides results in their occupying a larger volume within the CD cavity than the *para*-substituted halides and hence in their displacing a greater number of water molecules from it.

5. Experimental

5.1. General

Dimethyl-β-cyclodextrin (DM-β-CD) was supplied by Sigma in purity higher than 98% and used without further purification. The water content stated on the label was considered in preparing the solutions. The benzoyl chlorides were obtained from Aldrich in 97–98% purity and used as received. Stock solutions containing appropriate amounts of each chloride to obtain a 1.0×10^{-4} M concentration in dry acetonitrile were prepared on a daily basis.

Solvolytic reactions were monitored via the UV absorbance of substrate solutions as measured with a Varian Cary 500 Scan UV–vis–NIR spectrophotometer or an Applied Photophysics stopped-flow spectrophotometer with unequal mixing. For kinetic runs with the stopped-flow spectrophotometer, each benzoyl chloride, dissolved in dry acetonitrile, was placed in the smaller syringe (0.1 mL) and an aqueous solution of the cyclodextrin in the larger one (2.5 mL). The total acetonitrile concentration was always 3.85% (v/v).

All reactions were monitored over the wavelength range 250–350 nm. The ensuing kinetic data fitted a first-order integrated rate law with $r>0.999$. Throughout the paper, k_{obs} denotes *pseudo* first-order rate constants. All kinetic tests were reproducible with an error less than 3%. Also, the final spectrum for each reaction product was checked to match another obtained in pure water in order to ensure that the presence of the cyclodextrin would not alter the outcome of the process.

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References and notes

1. Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743–1754.
2. Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803–822.
3. Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344–362.
4. Bergeron, R. J. *J. Chem. Educ.* **1977**, *54*, 204–207.
5. Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325–1358.
6. Rekharsky, M. V.; Goldberg, N. R.; Schwarz, F. P.; Tewari, Y. B.; Ross, P. D.; Yamashoji, Y.; Yoshihisa, Y. *J. Am. Chem. Soc.* **1995**, *117*, 8830–8840.
7. Rekharsky, M. V.; Schwarz, F. P.; Tewari, Y. B.; Goldberg, R. N.; Tanaka, M.; Yamashoji, Y. *J. Phys. Chem.* **1994**, *98*, 4098–4103.

8. Inoue, Y.; Hakushi, T.; Liu, Y.; Tong, L.; Shen, B.; Jin, D. *J. Am. Chem. Soc.* **1993**, *115*, 475–481.
9. Szejtli, L. *Cyclodextrin Technology*; Kluwer Academic: Dordrecht, 1988.
10. Wood, D. J.; Hruska, F. E.; Saenger, W. *J. Am. Chem. Soc.* **1977**, *99*, 1735–1740.
11. Junquera, E.; Tardajos, G.; Aicart, E. *J. Colloid Interface Sci.* **1993**, *158*, 388–394.
12. Gomez-Orellana, I.; Hallen, D. *Thermochim. Acta* **1993**, *221*, 183–193.
13. Munoz de la Pena, A.; Ndou, T.; Zung, J. B.; Warner, I. M. *J. Phys. Chem.* **1991**, *95*, 3330–3334.
14. Herkstroeter, W. G.; Martic, P. A.; Farid, S. *J. Am. Chem. Soc.* **1990**, *112*, 3583–3589.
15. Tee, O. S.; Du, X. X. *J. Org. Chem.* **1988**, *53*, 1837–1839.
16. Connors, K. A.; Paulson, A.; Toledo-Velasquez, D. *J. Org. Chem.* **1988**, *53*, 2023–2026.
17. Kusumoto, Y. *Chem. Phys. Lett.* **1987**, *136*, 535–538.
18. Herkstroeter, W. G.; Martic, P. A.; Farid, S. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1453–1457.
19. Connors, K. A.; Pendergast, D. D. *J. Am. Chem. Soc.* **1984**, *106*, 7607–7614.
20. Kobayashi, N.; Saito, R.; Hino, H.; Hino, Y.; Ueno, A.; Osa, T. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1031–1035.
21. Connors, K. A.; Rosanske, T. W. *J. Pharm. Sci.* **1980**, *69*, 173–179.
22. Liu, L.; Guo, Q.-X. *J. Incl. Phenom. Macrocycl. Chem.* **2002**, *42*, 1–14.
23. Ross, P. D.; Rekharsky, M. V. *Biophys. J.* **1996**, *71*, 2144–2154.
24. Hallén, D.; Shön, A.; Shehatta, I.; Wadsö, I. *J. Chem. Soc., Faraday Trans.* **1992**, *88*, 2859–2863.
25. Bastos, M.; Briggner, L. E.; Shehattaa, I.; Wadsoe, I. *J. Chem. Thermodyn.* **1990**, *22*, 1181–1190.
26. Matsui, Y.; Mochida, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2808–2814.
27. Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer: Berlin, 1978.
28. Fujiwara, H.; Arakawa, H.; Murata, S.; Sasaki, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3891–3894.
29. Barone, G.; Castronuovo, G.; Del Vecchio, P.; Elia, V.; Muscetta, M. *J. Chem. Soc., Faraday Trans. 1* **1986**, *82*, 2089–2101.
30. Taulier, N.; Chalikian, T. V. *J. Phys. Chem. B* **2006**, *110*, 12222–12224.
31. Park, J. W. *J. Phys. Chem. B* **2006**, *110*, 24915–24922.
32. De Sousa, F. B.; Leite Denadai, A. M.; Lula, I. S.; Nascimento, C. S., Jr.; Fernandes Neto, N. S. G.; Lima, A. C.; De Almeida, W. B.; Sinisterra, R. D. *J. Am. Chem. Soc.* **2008**, *130*, 8426–8436.
33. Liu, Y.; Cao, R.; Chen, Y.; He, J.-Y. *J. Phys. Chem. B* **2008**, *112*, 1445–1450.
34. Caballero, J.; Zamora, C.; Aguayo, D.; Yañez, C.; González-Nilo, F. D. *J. Phys. Chem. B* **2008**, *112*, 10194–10201.
35. Terdale, S. S.; Dagade, D. H.; Patil, K. J. *J. Phys. Chem. B* **2007**, *111*, 13645–13652.
36. Tardajos, G.; Montoro, T.; Viñas, M. H.; Palafox, M. A.; Guerrero-Martínez, A. *J. Phys. Chem. B* **2008**, *112*, 15691–15700.
37. Nilsson, M.; Valente, A. J. M.; Olofsson, G.; Söderman, O.; Bonini, M. *J. Phys. Chem. B* **2008**, *112*, 11310–11316.
38. Martin, C.; Sanchez, F.; Jimenez, R.; Prado, R.; Perez-Tejeda, P.; Lopez-Cornejo, P. *J. Phys. Chem. B* **2006**, *110*, 12959–12963.
39. García-Río, L.; Hervés, P.; Leis, J. R.; Mejuto, J. C.; Pérez-Juste, J.; Rodríguez-Dafonte, P. *Org. Biomol. Chem.* **2006**, *4*, 1038–1048.
40. Song, B. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 8470–8479.
41. Bentley, T. W.; Koo, I. S. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1385–1392.
42. Bentley, T. W.; Carter, G. E.; Harris, H. C. *J. Chem. Soc., Perkin Trans. 2* **1985**, 983–990.
43. Bascuas, J.; Garcia-Rio, L.; Leis, J. R. *Org. Biomol. Chem.* **2004**, *2*, 1186–1193.
44. Garcia-Rio, L.; Hall, R. W.; Mejuto, J. C.; Rodriguez-Dafonte, P. *Tetrahedron* **2007**, *63*, 2208–2214.
45. Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875–1918.
46. Lindner, K.; Saenger, W. *Carbohydr. Res.* **1982**, *99*, 103–115.
47. Aree, T.; Hoier, H.; Schulz, B.; Reck, G.; Saenger, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 897–899.
48. Rekharsky, M. V.; Inoue, Y. *J. Am. Chem. Soc.* **2002**, *124*, 813–826.
49. Uekama, K.; Irie, T. In *Cyclodextrins and Their Industrial Uses*; Duchêne., Ed.; Editions de Santé: Paris, 1987.
50. Frank, J.; Holzwarth, J. F.; Saenger, W. *Langmuir* **2002**, *18*, 5974–5976.
51. Starikov, E. B.; Brasicke, K.; Knapp, E. W.; Saenger, W. *Chem. Phys. Lett.* **2001**, *336*, 504–510.