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Cyclodextrin effect on solvolysis of substituted benzoyl chlorides

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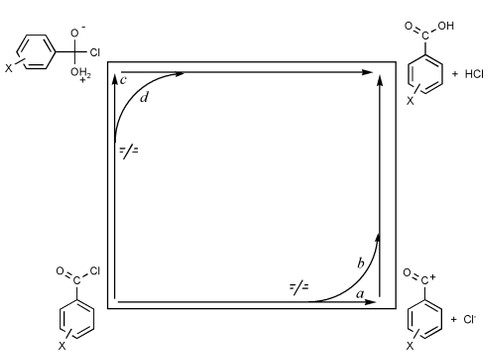
A kinetic study was carried out on the solvolysis of substituted benzoyl chlorides in the presence of α-, β- and γ-CD. Combination of the substituent dependent mechanism for solvolysis of benzoyl chlorides and the complexation ability of the cyclodextrin yields the following experimental behavior: *(i)* catalysis by β- and γ-CD for solvolysis of electron-attracting substituted benzoyl chlorides due to the reaction with its hydroxyl group C(6); *(ii)* absence of α-CD influence on solvolysis of benzoyl chlorides with electron withdrawing substituents; *(iii)* inhibition of solvolysis of benzoyl chlorides with electron-donating groups. This behavior is observed for solvolysis of *meta*/*para* substituted substrates in the presence of β-CD, solvolysis of *meta*-substituted benzoyl chlorides in the presence of α-CD and solvolysis of *para*-substituted benzoyl chlorides in the presence of γ-CD. This decrease in the rate constant is a consequence of the complexation of the substrate in the cyclodextrin cavity and its low solvation ability, causing the rate of solvolysis in its interior to be negligible. *(iv)* The solvolysis of *meta*-substituted benzoyl chlorides in the presence of γ-CD yields a new behavior where the reaction of the complexed substrate is not negligible in the interior of the cyclodextrin cavity, which has been interpreted as a consequence of incomplete expulsion of hydration water from its cavity when the complexation takes place. *(v)* The experimental results obtained in the presence of α-CD show that *meta*-substituted benzoyl chlorides give rise to host : guest complexes with 1 : 1 stoichiometries, whereas those which are *para*-substituted cause a 2 : 1 stoichiometry to be formed. This difference in behavior has been interpreted taking into account the size of the different benzoyl chlorides and their accommodation in the α-CD cavity.

Introduction

The mechanism of solvolysis of benzoyl chlorides is well known both in water and in different solvents.[1] The acyl group transfer was shown to follow one of three mechanisms: dissociative, associative, and concerted displacement. These mechanisms are well-defined, with a clear borderline between them. The term borderline is meaningful in this context: it refers to a reaction series in which a small change in the structure of one of the reactants, or in the reaction conditions, causes a change from a concerted to a stepwise mechanism, or *vice versa*. The first order rate constants for the solvolysis of most substituted benzoyl halides increase with electron-withdrawing substituents and follow a Hammett correlation with a slope of $\rho^+ = 1.7$ (for substituted benzoyl fluorides). There is a change to a negative slope for anisoyl fluoride and for 4-chlorobenzoyl chloride (with a slope of $\rho^+ = -3.0$ for substituted benzoyl chlorides) which indicates a change to a different reaction pathway with a dissociative mechanism.

The change from a dissociative to an associative mechanism can be represented schematically by a More O'Ferrall–Jencks diagram[2] (Scheme 1). The anisoyl chloride reacts through a dissociative mechanism giving rise to an acylium ion intermediate, which rapidly reacts with the solvent (path *a*). With benzoyl chlorides with electron-attracting substituents there is no barrier for reaction of the acylium ion and the potential well no longer exists, although the rate limiting transition state is essentially the same. Therefore the reaction will follow the path indicated by *b*. Electron-withdrawing substituents increase the energy of both the acylium ion and the transition state for the dissociative path and, in contrast, stabilize the upper left-hand corner and the transition state for the associative mechanism. This could eventually favor a change to an associative path with an addition–elimination mechanism through a tetrahedral intermediate (path *c*). However, it is also possible that reaction mechanisms follow path *d* if the addition intermediate does not have a significant lifetime.



Scheme 1

Cyclodextrins are cyclic oligomers of α-D-glucose which are produced by enzymatic degradation of starch[3] and are doughnut-shaped molecules formed by six, seven or eight glucose units (α, β or γ) and are able to form inclusion complexes with a great variety of compounds.[4] The interior of the macrocyclic structure is lined with hydrocarbon and the oxygens linking the glucose units, resulting in a hydrophobic cavity with a water compatible exterior. The use of cyclodextrins (CD) as microreactors to perform chemical reactions has attracted the interest of chemists since the 1960s.[5–7] Cyclodextrins may show two basic forms of catalysis: "noncovalent" and "covalent".[4] In the former case, the cyclodextrin binds to the substrate and provides an environment for the reaction that is different from the bulk solvent; in this case, the effect of cyclodextrins arises from the less polar nature of the cavity (a microsolvent effect) and/or from the conformational restraints imposed on the substrate by the geometry of inclusion. Another factor that may be important for noncovalent catalysis is the differential solvation effects at the interface of the cyclodextrin cavity with the external aqueous environment.[8] Covalent catalysis should involve covalent interactions between the substrate and functional groups on the cyclodextrin in the rate determining step of the reaction. For instance, the anion of the cyclodextrin may act as a basic catalyst towards acidic substrates included in their cavity.[9]

In aqueous phases hydrophobic forces are assumed to be responsible for driving a guest into the CD's hydrophobic

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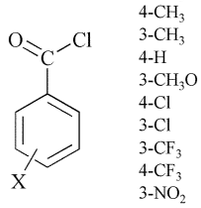
interior usually forming 1 : 1 host–guest complexes. The microenvironment around the reactant in the CD cavity is different from that which prevails in the reaction media. Three different effects are expected: *(i)* microsolvent effects, *(ii)* the protection of unstable intermediates or products, and *(iii)* the solubilization of poorly water soluble reactants. In addition, conformational effects can also be expected: *(iv)* control of reactant conformation, *(v)* control of the orientation between reactants, and *(vi)* control of the size of the molecule.

In this study we have investigated the influence of α-, β- and γ-cyclodextrin on the solvolysis of substituted benzoyl chlorides. As mentioned, the solvolysis mechanism of the benzoyl chlorides is sensitive to the electron-attracting/electron-donating substituents, and to the solvent in which the reaction takes place. We have used eleven substituted benzoyl chlorides in order to cover a reactivity range between a predominantly dissociative mechanism (4-CH_3O) and another which is predominantly associative (4-NO_2) and is shown in Scheme 2.



4-CH_3O
4-CH_3
3-CH_3
4-H
3-CH_3O
4-Cl
3-Cl
3-CF_3
4-CF_3
3-NO_2
4-NO_2

Scheme 2

Experimental

The β-CD was supplied by Sigma (purity >98%), and the α-CD and γ-CD by Cyclolab (purity >98%). All were used without further purification. In preparing the solutions the water content supplied by the manufacturer was taken into account. The benzoyl chlorides were provided by Aldrich, all of which had purities between 97–98% and were used without further purification. Their solutions were prepared in acetonitrile (Aldrich) to prevent it from decomposing too rapidly.

Reaction kinetics were carried out in an Applied Photophysics stopped flow spectrophotometer with unequal mixing. The benzoyl chloride dissolved in dry acetonitrile was placed in the smaller syringe (0.1 mL). The larger syringe (2.5 mL) was filled with an aqueous solution of cyclodextrin. The total acetonitrile concentration was 3.85% (v/v). Solutions of benzoyl chlorides were freshly prepared in dry acetonitrile at the appropriate concentration in order to get a final concentration of 1.0×10^{-4} M. All experiments were carried out at 25 °C. The kinetic traces were fitted with one exponential equation using the software of the SF apparatus. The wavelengths used to monitor the reactions were 300, 270, 300, 290, 260, 270, 300, 285, 295, 250 and 260 nm for 4-CH_3O, 4-CH_3, 3-CH_3, 4-H, 3-CH_3O, 4-Cl, 3-Cl, 3-CF_3, 4-CF_3, 3-NO_2 and 4-NO_2 respectively. All the kinetic experiments could be reproduced within an error margin of 3%.

Results and discussion

1. Reaction in bulk water

Fig. 1 shows the results obtained on studying the rate of solvolysis of substituted benzoyl chlorides in bulk water.[10] In the Hammett plot we can observe the existence of two very different slopes: one negative ($\rho^+ = -2.6 \pm 0.3$) and another positive ($\rho^+ = 1.4 \pm 0.5$). The first corresponds to substrates which undergo solvolysis by an eminently dissociative mechanism, while the behavior exhibited by the benzoyl chlorides with electron-attracting groups is consistent with an associative mechanism. The values of the Hammett slopes are consistent

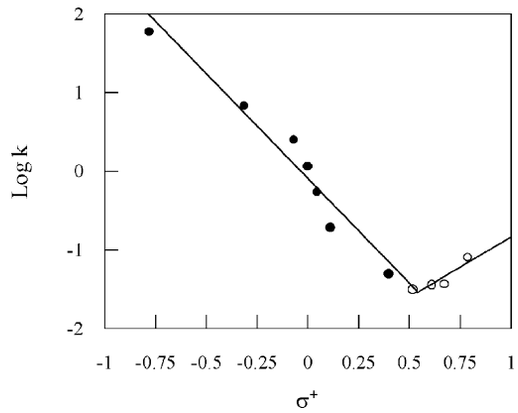


Fig. 1 Hammett plot for solvolysis of substituted benzoyl chlorides in water at 25 °C.

with those found previously by Song and Jencks[1] ($\rho^+ = -3$ and $\rho^+ = 1.7$). The minor discrepancy can be attributed to the fact that in our reaction medium the percentage of acetonitrile is slightly higher than that used by Song and Jencks (1.5–1.0% (v/v) of acetonitrile).

2. Reactions in the presence of β-CD

Fig. 2 shows the experimental behavior observed for the benzoyl chlorides which undergo solvolysis by means of an associative mechanism: 4-CF_3, 3-CF_3, 3-NO_2 and 4-NO_2 (not shown). The observed rate constant, k_{obs}, of 4-CF_3 increases along with the β-CD concentration and tends to reach a maximum value. The results obtained on studying the solvolysis of 3-CF_3 and 3-NO_2 show that k_{obs} increases linearly together with the β-CD concentration. In both cases the influence of the [β-CD] on k_{obs} should be a consequence of the reaction between the benzoyl chloride and the hydroxyl groups of the cyclodextrin.

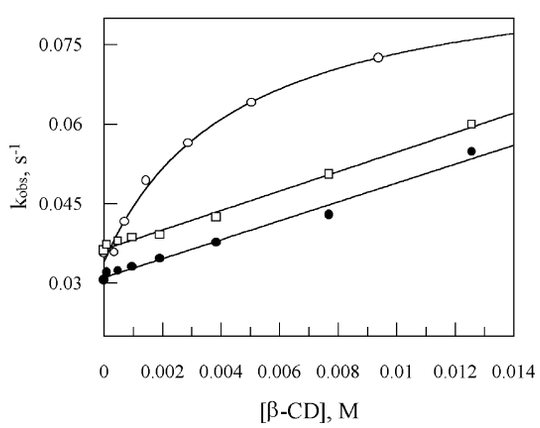
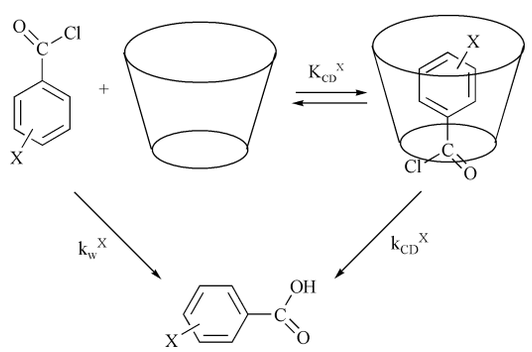


Fig. 2 Influence of β-cyclodextrin concentration on the pseudo-first order rate constant for solvolysis of (○) 4-CF_3, (●) 3-CF_3 and (□) 3-NO_2 at 25 °C.

The α-CD, β-CD and γ-CD have doughnut-like annular structures with wide and narrow hydrophilic ends delineated by O(2)H and O(3)H secondary and O(6)H primary hydroxyl groups.[11–14] The pK_a values assigned to O(2)H and O(3) in α-, β- and γ-CD are pK_a = 12.33, 12.20 and 12.08 respectively and have an important role in the cyclodextrin mediation of the hydrolysis of a range of guests inside the cyclodextrin annulus.[15] The methods that have been developed for the controlled modification of cyclodextrins exploit the different reactivity of the C(2), C(3) and C(6) hydroxyl groups. The primary hydroxyl groups of the cyclodextrins, C(6), are the most basic, they are also the most nucleophilic.[16] Direct O-alkylation of a C(6) hydroxyl group using the corresponding CD alkoxide is not feasible, as the C(2) and C(3) hydroxyl groups are more acidic than those at C(6) and they react prefer-

entially. The C(2) groups are also exposed at the wider end of the cyclodextrin cavity, such that when they deprotonate under basic conditions, the resultant alkoxides often react readily and selectively as nucleophiles. That is, whereas the primary hydroxyl groups are the most nucleophilic under neutral and acidic conditions, above pH = 10–11 it is the C(2) secondary hydroxyl groups which are generally selectively modified through treatment with an electrophilic reagents. The kinetic results for solvolysis of benzoyl chlorides, shown in Fig. 2, occur through a path which is catalyzed by the cyclodextrin. This behavior means that the inclusion of the benzoyl chloride in the cavity of the cyclodextrin must take place with the carbonyl group in the narrow side of the cavity, as shown in Scheme 3.



Scheme 3

From this kinetic scheme we can obtain the following rate equation:

$$k_{obs} = \frac{k_w^X + k_{CD}^X K_{CD}^X [\beta\text{-CD}]}{1 + K_{CD}^X [\beta\text{-CD}]} \qquad (1)$$

where k_w^X and k_{CD}^X are the rate constants of the solvolysis of the X-substituted benzoyl chlorides in bulk water and in the inclusion complex with the cyclodextrin. K_{CD}^X is the equilibrium constant of the cyclodextrin–benzoyl chloride X-substituted complex. The experimental results can be fitted perfectly to equation 1, giving the corresponding values of $K_{CD}^{4\text{-}CF_3} = (180 \pm 40)\ M^{-1}$ and $k_{CD}^{4\text{-}CF_3} = 9.62 \times 10^{-2}\ s^{-1}$. The rate constant for the solvolytic process catalyzed by the β-CD is approximately three times greater than the value obtained in bulk water. This result is similar to that found for the solvolysis of 4-NO_2 in water and in mixtures of methanol and water.[17] The rate of solvolysis increases together with the percentage of methanol in the reaction medium until a maximum value of 0.153 s^{-1} is reached for 70% (v/v) of methanol and water. Subsequent increases in the percentage of methanol cause a decrease in the value of the reaction rate constant.

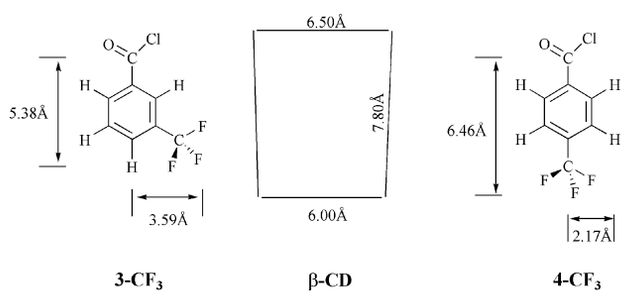
The results in Fig. 2 also show that k_{obs} increases linearly with the β-CD concentration for solvolysis of 3-CF_3 and 3-NO_2. NMR studies indicate that in nitrophenols the nitro group is found in the interior of the cavity,[18] which is consistent with the mode of complexation shown in Scheme 3. This behavior can be explained by equation 1, considering that $1 \gg K_{CD}^X[\beta\text{-CD}]$. In this case equation 1 is reduced to:

$$k_{obs} = k_w^X + k_{CD}^X K_{CD}^X [\beta\text{-CD}] \qquad (2)$$

which satisfies the experimental behavior observed. Table 1 shows the values of the K_{CD}^X and k_{CD}^X parameters obtained from the application of equations 1–4 to the solvolysis of substituted benzoyl chlorides in the presence of β-CD.[19]

The difference between the behavior observed for the 4-CF_3 (k_{obs} increase on increasing [β-CD] to a limiting value) and the other benzoyl chlorides with electron-attracting groups (linear dependence of k_{obs} on [β-CD]) can be attributed fundamentally to a combination of changes in the hydrophobic character of the substrates and to differences in their size. The first factor may be the reason for the difference in behavior between the 4-CF_3 and the substituted benzoyl chlorides with nitro groups, while the difference in size allows us to explain the difference in behavior between the 4-CF_3 and the 3-CF_3. The existing studies in the literature show that the complexation constants of alcohols by cyclodextrins correlate with the partition coefficients between diethyl ether and water.[20,21] These observations are reasonable since, the binding of guests to cyclodextrins is largely governed by their size and hydrophobicity. No data are available for the partition coefficients between water and 1-octanol for the benzoyl chlorides. Likewise the rapidity of the solvolysis reaction makes it impossible to be experimentally determined. We can compare the values of the partition coefficients, log *P*, for substituted phenylacetates.[22] The obtained values, log *P* = 1.28 and 1.38 for the substituted esters with 3-NO_2 and 4-NO_2 groups, are clearly lower than those obtained for esters substituted with 4-Cl (log *P* = 2.35) and 4-CH_3 (log *P* = 2.28) groups. These values show that the hydrophobic character of the phenylacetates decreases as a consequence of the introduction of the nitro groups. What is more significant is the comparison of the incorporation constants of the benzoyl chlorides from the continuous medium to the interface of AOT/isooctane/water microemulsions.[23] The incorporation equilibrium constants must increase as the hydrophobic character of the substrates decreases. In the case of the benzoyl chlorides it can be noted that the incorporation equilibrium constants are approximately $K_{oi} = 5$ for all the substituents and increase to values of $K_{oi} = 121 \pm 9$ and $K_{oi} = 164 \pm 20$ for 3-NO_2 and 4-NO_2 respectively. This behavior is clear evidence of the reduction in the hydrophobic character as a consequence of the nitro substituents. This reduction in the hydrophobic character is a satisfactory explanation for the decrease in the value of the equilibrium constant for the formation of the inclusion complex with the β-CD.

The substituted benzoyl chlorides with the 3-CF_3 and 4-CF_3 groups do not display hydrophobocity, as is the case for the nitro substituents. In fact, the equilibrium constant of the formation of the inclusion constant between the 4-CF_3 and the β-CD presents a value which is entirely compatible with the other benzoyl chlorides (see Table 1). Likewise, the values of the distribution constants for the benzoyl chlorides with the groups 3-CF_3 and 4-CF_3 between the continuous medium and the interface of AOT/isooctane/water microemulsions are similar to those presented by the benzoyl chlorides with substituents 3-CH_3, 4-CH_3, 3-CH_3O, 4-CH_3O, *etc.* Therefore, to explain the decrease in the equilibrium constant for the formation of the 3-CF_3 inclusion complex with the β-CD we must take into account geometric considerations. Simple MM calculations allow us to evaluate the size of the 3-CF_3 molecule (Scheme 4).



Scheme 4

Given that the diameter of the β-CD cavity oscillates between 6.0–6.5 Å, it is obvious that the 3-CF_3 molecule is too big to be fully included in the β-CD cavity. This difficulty gives rise to the kinetic behavior observed in Fig. 2.

Fig. 3 shows the influence of the β-CD concentration on k_{obs} for the solvolysis of 4-CH_3O and 3-CH_3O. In these cases,

Table 1 Values of the kinetic parameters obtained for the solvolysis of benzoyl chlorides in the presence of cyclodextrins

		β-CD		α-CD		γ-CD	
	k_w^X/s^{-1}	k_{CD}^X/s^{-1}	k_{CD}^X/M^{-1}	$k_{1:1}^X$/M^{-1}	$k_{2:1}^X$/M^{-1}	k_{CD}^X/s^{-1}	k_{CD}^X/M^{-1}
4-NO_2	7.90×10^{-2}	1.87[a]	10.7[a]	—	—	0.119 ± 0.008	33 ± 12
3-NO_2	3.63×10^{-2}	0.233[a]	7.9[a]	—	—	$(3.5 \pm 0.1) \times 10^{-2}$	29 ± 5
4-CF_3	3.56×10^{-2}	9.62×10^{-2}	180 ± 40	1.9 ± 0.1	18 ± 2	—	10 ± 2
3-CF_3	3.10×10^{-2}	0.226[a]	7.9[a]	—	—	$(4 \pm 1) \times 10^{-3}$	25 ± 8
3-Cl	4.90×10^{-2}	—	140 ± 10	12.2 ± 0.7	—	$(9.7 \pm 0.5) \times 10^{-3}$	76 ± 4
4-Cl	0.189	—	225 ± 2	31 ± 5	15 ± 3	—	64 ± 12
3-CH_3O	0.540	—	406 ± 68	20 ± 1	—	$(9 \pm 1) \times 10^{-3}$	78 ± 4
4-H	1.14	—	270 ± 11	11 ± 1	3 ± 1	—	52 ± 3
3-CH_3	2.50	—	568 ± 20	15 ± 1	—	0.37 ± 0.03	116 ± 8
4-CH_3	6.76	—	523 ± 16	20 ± 2	24 ± 3	—	79 ± 19
4-CH_3O	58.2	—	510 ± 15	17.6 ± 0.8	20 ± 1	—	88 ± 14

[a] Maximum values, see text.

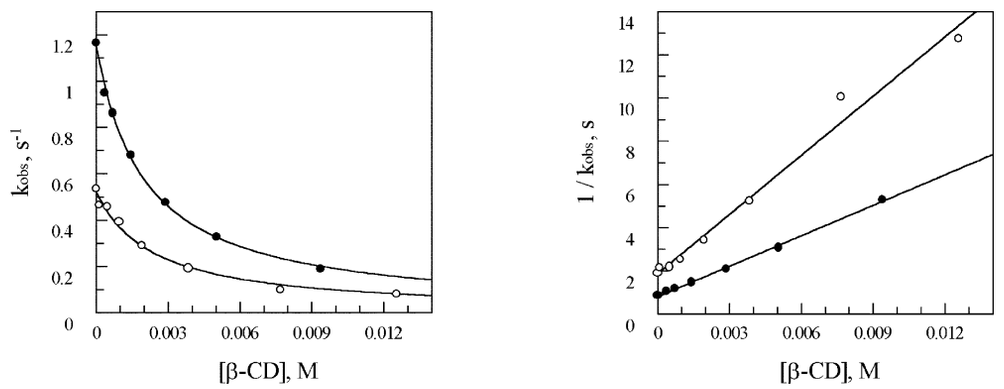


Fig. 3 Influence of the β-CD concentration on the observed rate constant for different benzoyl chlorides: (●) k_{obs}/50 for 4-CH_3O and (○) for k_{obs} 3-CH_3O. Data for the left figure were fitted according to equation 3 and for the right figure according to equation 4.

as occurs with 4-CH_3, 3-CH_3, 4-H, 4-Cl and 3-Cl, it is possible to observe a decrease in the observed rate constant, k_{obs}, as the β-CD concentration increases. This behavior can be easily explained by recourse to the formation of an inclusion complex between the benzoyl chloride and the cyclodextrin, as shown in Scheme 3. The possibility of a reaction between the complexed benzoyl chloride and the cyclodextrin hydroxyl groups can be discarded for those substrates which undergo solvolysis fundamentally by means of a dissociative mechanism. Therefore, in this case the reaction path within the inclusion complex should be the expulsion of the leaving group assisted by the cyclodextrin.

The properties of the water inside the cavity as well as in close proximity to the cavity are quite different from those of bulk water.[20,24–26] The polarity of the interior of the β-CD cavity has been studied using various techniques. Van Etten[27] showed that the ultraviolet absorption spectrum of 4-*tert*-butylphenol in an aqueous solution of α-CD closely matches its spectrum in dioxane. Uno *et al.*[28] concluded, on the basis of blue shifts in the spectra of amine *N*-oxides in the presence of cyclodextrins, that the cavity environment is like methanol or ethanol, depending upon the probe. Studies using fluorescence spectroscopy show that the cyclodextrin cavity has a polarity in the vicinity of alcohols.[29–32] Obtained values for the E_T polarity parameter show that it has similar values to those of *tert*-butyl alcohol or ethylene glycol.[33] However it can be seen that the estimated polarity of the cyclodextrin cavity depends on the compound used to probe it.

In spite of the fact that there is no uniformity, it can be noted that the interior of the cyclodextrin cavity has a much lower polarity than that of pure water. The solvolysis reactions of benzoyl chlorides which occur by means of a dissociative mechanism are very sensitive to the solvent polarity. In fact, for the solvolysis of 4-H, k_{obs} decreases as the percentage of methanol in the reaction medium increases, causing an inhibition of approximately 190 times in the transition from water to mixtures of methanol and water of 90% (v/v).[34] This difference in reactivity increases if we consider 4-CH_3O, a benzoyl chloride which is nearer to the dissociative mechanism, where k_{obs} decreases by approximately 2900 times in the transition from bulk water to a mixture of methanol and water of 95% (v/v).[35]

Given that the solvation ability of the interior of the cyclodextrin is minimal, it is to be expected that the rate constant k_{CD}^X would be much lower than the corresponding rate constant in bulk water, in such a way as to confirm the inequality of $k_w^X \gg k_{CD}^X K_{CD}^X[\beta\text{-CD}]$. Equation 1 can then be rewritten thus:

$$k_{obs} = \frac{k_w^X}{1 + K_{CD}^X[\beta\text{-CD}]} \qquad (3)$$

Fig. 3 shows the fit of equation 3 in its present form, or by means of its linearization (equation 4).

$$\frac{1}{k_{obs}} = \frac{1}{k_w^X} + \frac{K_{CD}^X}{k_w^X}[\beta\text{-CD}] \qquad (4)$$

From the fitting procedure we can obtain the values of the complexation equilibrium constants of the corresponding benzoyl chlorides by the β-CD.

The difference in behavior obtained between the benzoyl chlorides shown in Fig. 2 and those of Fig. 3 is due to the different mechanism whereby the reaction takes place: the electron-donating substituents produce a dissociative mechanism where the reaction rate in the interior of the cyclodextrin is much lower than that which is obtained in bulk water and, therefore, we can observe an inhibiting effect derived from the addition of β-CD to the reaction medium. The results of Fig. 2 show the catalytic effect exerted by the β-CD on the solvolysis rate of

the benzoyl chlorides with electron-attracting substituents. The difference in behavior is due to the fact that the hydroxyl groups of the cyclodextrin can act as efficient nucleophiles if the reaction takes place through an associative mechanism.

3. Solvolytic reactions in the presence of α-CD

The behavior observed on studying the solvolysis of benzoyl chlorides in the presence of α-CD is qualitatively and quantitatively different from that which is found with β-CD. The rate constants of solvolysis of the benzoyl chlorides 3-CH_3O, 3-CH_3 and 3-Cl decrease as a consequence of the formation of the inclusion complex with the α-CD (see Fig. 4 for 3-CH_3O). The experimental results have been fitted satisfactorily to equations 3 and 4, giving the kinetic parameters which are shown in Table 1. The magnitude of the inhibition due to the presence of α-CD is not as great as with β-CD which is attributed to the lower equilibrium constants of formation of the inclusion complexes between α-CD and the benzoyl chlorides. This result is widely documented in the literature showing that complexation of substituted cyclohexanes with α- and β-CD indicates deeper penetration into the wider β-CD cavity.[36,37]

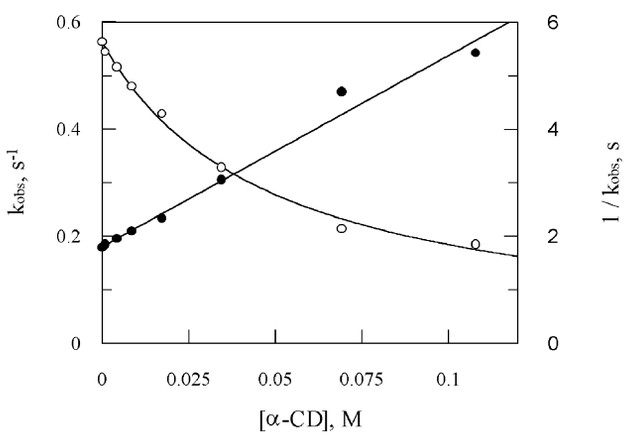


Fig. 4 Influence of α-CD concentration on solvolysis of (○) 3-CH_3O at 25 °C. Experimental results were fitted to equation 3 (○) and 4 (●).

The complexation constants for the benzoyl chlorides by α-CD are approximately 20 times lower than the corresponding complexation constants with β-CD. Therefore, we can conclude that the complexation constants of 3-NO_2, 4-NO_2 and 3-CF_3 must be less than one. Thus, the inequality $1 \gg K_{CD}^{X}$[α-CD] should be observable for all the experimental conditions used (it is important to point out that [α-CD] ≤ 0.12 M). Likewise the rate constant for the cyclodextrin catalyzed path, k_{CD}^{X}, must be only slightly greater than k_w^X, in such a way as to confirm the inequality $k_w^X \gg k_{CD}^{X}K_{CD}^{X}$[α-CD]. This should result in a situation where the observed rate constant would be independent of the α-CD concentration, $k_{obs} = k_w^X$. This behavior is shown experimentally for the benzoyl chlorides 3-NO_2, 4-NO_2 and 3-CF_3, as can be observed in Fig. 5.

More surprising behavior has been observed when studying the solvolysis of *para* substituted benzoyl chlorides (4-CH_3O, 4-CH_3, 4-H, 4-Cl and 4-CF_3). In all cases we can observe that the presence of α-CD causes a reduction in the value of k_{obs}. This behavior is also manifested by 4-CF_3, a substrate which undergoes more rapid solvolysis in the presence of β-CD. It is important to point out that the rates of solvolysis of 4-CH_3O, 4-CH_3 and 4-Cl decrease approximately 8 times when the α-CD concentration increases up to [α-CD] = 0.108 M, while the rate of solvolysis of 4-CF_3 decreases only 1.6 times for the same interval of cyclodextrin concentrations. This behavior is a consequence of the different mechanisms which operate in the solvolysis of 4-CH_3O, 4-CH_3, 4-H and 4-Cl (dissociative mechanism) and 4-CF_3 (associative mechanism). Given that the rate of the associative mechanism is not very sensitive to

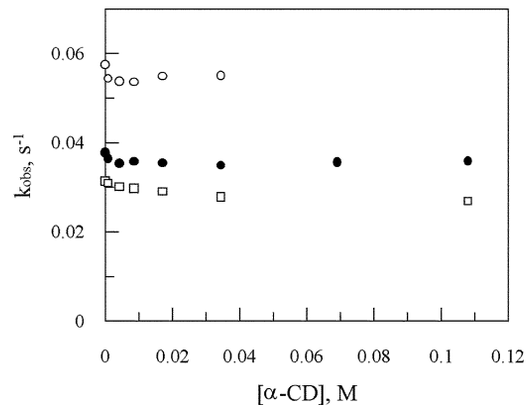


Fig. 5 Influence of α-CD concentration on the observed rate constant for solvolysis of (○) 4-NO_2, (●) 3-NO_2 and (□) 3-CF_3 at 25 °C.

the ability of the medium to solvate the leaving group, it is to be expected that k_{obs} would display a very small decrease when the substrate is incorporated into the α-CD cavity.

The experimental behavior obtained for solvolysis of *para*-substituted benzoyl chlorides cannot be explained on the basis of the mechanism proposed in Scheme 3 and equations 1–4. Fig. 6 shows by way of example how the experimental results obtained for the solvolysis of 4-CH_3O and 4-CF_3 are not justifiable on the basis of equation 4. As Fig. 6 shows there exists a non-linear dependence of $1/k_{obs}$ on the α-CD concentration. This behavior is consistent with a mechanism whereby a cyclodextrin:benzoyl chloride complex is formed with a 2 : 1 stoichiometry, as shown in Scheme 5.

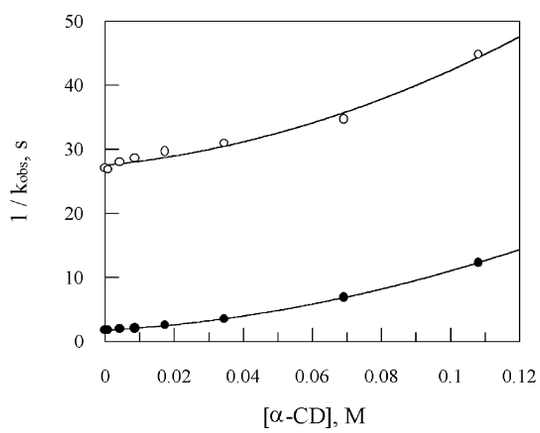


Fig. 6 Influence of α-CD on (○) $1/k_{obs}$ for solvolysis of 4-CF_3 and (●) $100/k_{obs}$ for solvolysis of 4-CH_3O at 25 °C.

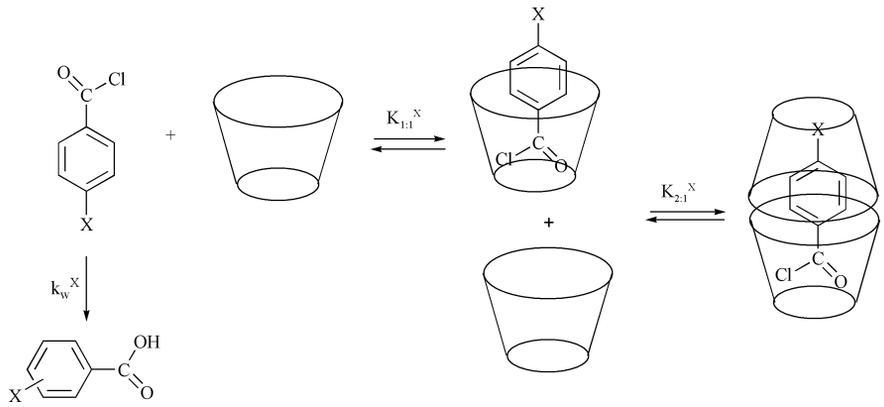
From this complexation scheme we can obtain the following rate equation:

$$k_{obs} = \frac{k_w^X + K_{1:1}^X k_{1:1}^X [\alpha\text{-CD}] + K_{2:1}^X k_{2:1}^X [\alpha\text{-CD}]^2}{1 + K_{1:1}^X [\alpha\text{-CD}] + K_{1:1}^X K_{2:1}^X [\alpha\text{-CD}]^2} \qquad (5)$$

where $k_{1:1}^X$ and $k_{2:1}^X$ are the solvolysis rate constants of the cyclodextrin : benzoyl chloride complexes with stoichiometries 1 : 1 and 2 : 1. Due to the low solvation ability of the cyclodextrin cavity, it is anticipated that these rate constants would be very small in comparison with k_w^X, allowing equation 5 to be rewritten thus:

$$k_{obs} = \frac{k_w^X}{1 + K_{1:1}^X [\alpha\text{-CD}] + K_{1:1}^X K_{2:1}^X [\alpha\text{-CD}]^2} \qquad (6)$$

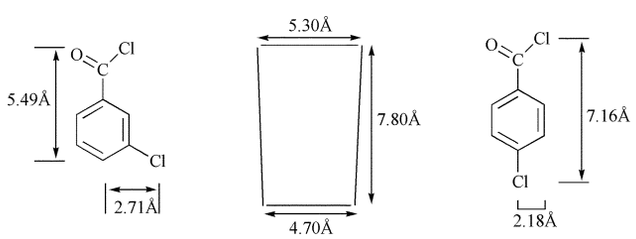
$$\frac{1}{k_{obs}} = \frac{1}{k_w^X} + \frac{K_{1:1}^X}{k_w^X}[\alpha\text{-CD}] + \frac{K_{1:1}^X K_{2:1}^X}{k_w^X}[\alpha\text{-CD}]^2 \qquad (7)$$



Scheme 5

Equation 7 predicts the existence of a linear and quadratic dependence of $1/k_{obs}$ on α-CD concentration, as has been shown experimentally in Fig. 6. From the fitting of experimental results to equation 7 we can obtain the parameters shown in Table 1.

It is necessary to justify the reason why the *para* substituted benzoyl chlorides form inclusion complexes with 2 : 1 stoichiometries, while those which are substituted in the *meta* position form complexes with 1 : 1 stoichiometries. To this end we invoke geometric considerations regarding the α-CD cavity and the size of the substituted benzoyl chloride. Scheme 6 shows the sizes of 3-Cl and the α-CD cavity. As we can observe, the diameter of the α-CD cavity is insufficient to fully accommodate the aromatic ring of the benzoyl chloride 3-Cl. It is important to note that the size of 3-Cl is the smaller of the *meta* substituted benzoyl chlorides. The geometrical restrictions do not allow complexation with a second molecule of α-CD due to the fact that it is impossible to include the aromatic ring in the cavity.



Scheme 6

Scheme 6 also shows the dimensions of the *para* substituted benzoyl chloride. As can be observed, the size of 4-Cl can be fitted to the size of the α-CD cavity. Therefore the benzoyl chlorides substituted in the *para* position can be included in the cavity of α-CD through the aromatic ring or the carbonyl group, and can form inclusion complexes with 2 : 1 stoichiometries, as shown in Scheme 5. It is important to note the difference in behavior found between α-CD and β-CD: the *para*-substituted benzoyl chlorides form complexes with 2 : 1 stoichiometry with α-CD but only with 1 : 1 stoichiometry with β-CD. Once again, the reason must lie in the geometric restrictions of the cavity of the cyclodextrins. In both cases the depth of the cavity is the same: 7.80 Å. Therefore it is to be expected that the *para*-substituted benzoyl chlorides form inclusion complexes with the same stoichiometry in both cases. However, in the case of α-CD the smaller diameter of the cavity (4.7–5.3 Å) causes the penetration of the benzoyl chloride in the cavity to be smaller than in the case of β-CD which has a larger cavity diameter (6.0–6.5 Å). This difference means that part of the benzoyl chloride molecule is outside the α-CD cavity and, consequently, available for complexation with a second cyclodextrin molecule.

This result is consistent with existing findings in the literature which show that usually guest molecules carrying a phenyl moiety exhibit stronger affinities to β-CD than to α-CD. The insertion of a methylene into the aliphatic chain of phenethylamine, giving 3-phenylpropylamine, leads to an enhancement in affinity toward β-CD, but the affinity increase is much smaller when α-CD is the host, since the extra methylene added is believed to stay outside the α-CD cavity.[38] Phenethylamine and 2-methoxyphenethylamine exhibit similar affinities toward α-CD. However, phenethylamine gives a much higher equilibrium constant for complexation with β-CD than 2-methoxyphenethylamine. A plausible explanation for this contrasting result is that the benzene ring cannot penetrate deeply into the α-CD cavity and the 2-methoxy group is left outside, even after complexation, and in this position it is unable to significantly affect the overall complexation thermodynamics. When the system is switched to the larger β-CD, the cavity may permit deeper penetration of the benzene ring, ironically resulting in a considerable decrease in complex stability owing to the severe steric hindrance caused by the 2-methoxy group. This again leads to the conclusion that the α-CD cavity is too small to accommodate the whole benzene ring. Therefore, part of the molecule will remain outside the α-CD cavity and participate in a second complexation, forming an inclusion complex with 2 : 1 stoichiometry.

4 Solvolytic reactions in the presence of γ-CD

On studying the influence of γ-CD on the solvolytic rate of benzoyl chlorides, we must distinguish three very different types of behavior. The *para* substituted benzoyl chlorides: 4-CH_3O, 4-CH_3, 4-H, 4-Cl and 4-CF_3, show a decrease in k_{obs} as the concentration of γ-CD increases (see Fig. 7 by way of example for 4-Cl). The experimental results can be explained quantitatively by the mechanism proposed in Scheme 3 and equations 3–4. Table 1 shows the values of the kinetic parameters obtained. Fig. 8 shows the behavior obtained on studying the solvolysis of 4-NO_2 and 3-NO_2. In this case we can observe a catalytic effect due to the reaction of the complexed substrate

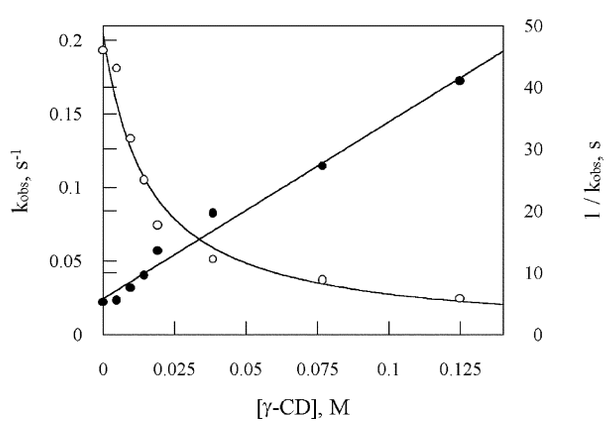


Fig. 7 Influence of γ-CD concentration on solvolysis of (○) 4-Cl at 25 °C. Experimental results were fitted to equation 3 (○) and 4 (●).

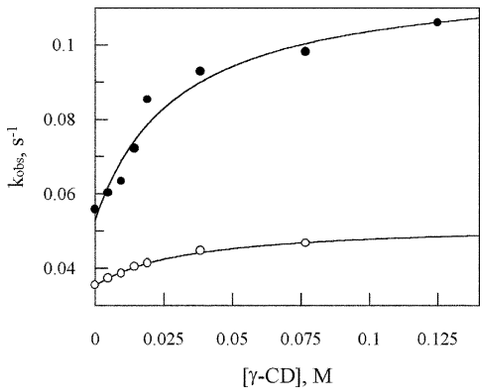


Fig. 8 Influence of γ-CD concentration on solvolysis of (●) 4-NO_2 and (○) 3-NO_2 at 25 °C. Experimental results were fitted to equation 1.

with the hydroxyl groups of the cyclodextrin. Fitting experimental results to equation 1, we obtain the values of $K_{CD}^{4\text{-}NO_2}$ = (33 ± 12) M^{-1} and $k_{CD}^{4\text{-}NO_2}$ = (0.119 ± 0.009) s^{-1}. The obtained value for $k_{CD}^{4\text{-}NO_2}$ is slightly greater than the value obtained in bulk water, $k_w^{4\text{-}NO_2}$ = 7.90 × 10^{-2} s^{-1}. Likewise for the solvolysis of 3-NO_2 we obtain values of $K_{CD}^{3\text{-}NO_2}$ = (29 ± 5) M^{-1} and $k_{CD}^{3\text{-}NO_2}$ = (3.53 ± 0.03) × 10^{-2} s^{-1}. The obtained value for $k_{CD}^{3\text{-}NO_2}$ is practically the same as that obtained in bulk water, $k_w^{3\text{-}NO_2}$ = 3.50 × 10^{-2} s^{-1}. The values of $k_{CD}^{4\text{-}NO_2}$ and $k_{CD}^{3\text{-}NO_2}$ are compatible with those obtained in mixtures of methanol : water:[17] the rate constant increases together with the percentage of methanol, passes through a maximum for a percentage of methanol of around 70% (v/v) and then decreases.

The solvolysis of other benzoyl chlorides substituted in the *meta* position: 3-CH_3, 3-CH_3O, 3-Cl and 3-CF_3, shows clearly differentiated experimental behavior. The rate constant decreases as the concentration of γ-CD increases, however, this experimental behavior cannot be justified on the basis of equations 3–4. Fig. 9 shows a plot of $1/k_{obs}$ against [γ-CD] indicating that the behavior deviates from the linear dependence predicted by equation 4. The experimental results should fit the mechanism shown in Scheme 3 where the substrate complexed with γ-CD can undergo a solvolysis reaction. On the basis of equation 1 we can obtain the following equation:

$$\frac{1}{k_{obs}} = \frac{\dfrac{1}{k_w^X} + \dfrac{K_{CD}^X}{k_w^X}[\gamma\text{-CD}]}{1 + \dfrac{k_{CD}^X K_{CD}^X}{k_w^X}[\gamma\text{-CD}]} \qquad (8)$$

which complies perfectly with the experimental behavior as can be observed in Fig. 9. Table 1 shows the kinetic parameters obtained for the solvolysis of 3-CH_3, 3-CH_3O, 3-Cl and 3-CF_3.

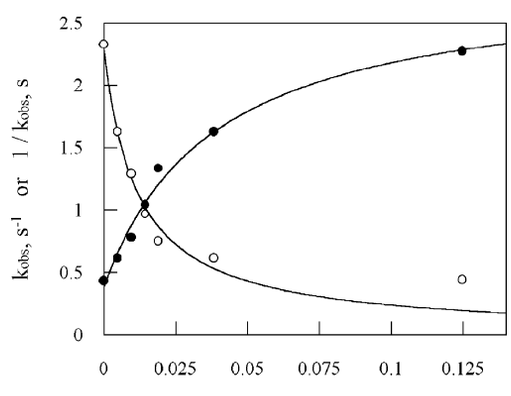


Fig. 9 Influence of γ-CD concentration on the observed rate constant for solvolysis of (○) 3-CH_3 and plot of (●) $1/k_{obs}$ *vs.* [γ-CD] at 25 °C. Experimental results were fitted to equations 1 and 8.

It is important to analyze the difference in behavior shown by the different substrates. The solvolysis reactions of the substituted benzoyl chlorides with the most strongly electron-attracting groups: 4-NO_2 and 3-NO_2, occur through an eminently associative mechanism. Both reactions are catalyzed by γ-CD due to the reaction with the primary hydroxyl group of γ-CD. This behavior requires that the geometry of the inclusion complex be like that which is shown in Scheme 3. The solvolysis of the other benzoyl chlorides does not present a catalytic effect as a consequence of the addition of γ-CD, and we can observe in all cases a reduction in the reaction rate as the cyclodextrin concentration increases. However, we must distinguish between the behavior presented by the *meta* and *para* substituted substrates.

The cyclodextrins crystallize from water as hydrates of variable composition. α-CD is usually encountered as the hexahydrate,[39,40] β-CD exists as the undecahydrate and as the dodecahydrate.[41] γ-CD is sometimes described as an octahydrate, but it can crystallize with from 7 to 18 molecules of water.[42–46] It is not known exactly how many water molecules (*h*) exist in the cavity of natural cyclodextrins, nor how many water molecules (*i*) are released from the cavity upon complexation, but for α-CD, these numbers (*h* and *i*) are estimated to be 2 or 3 and ≤2, respectively.[24,47,48] In the case of β-CD,[41] six to seven water molecules are distributed within the cavity, even though the cavity is big enough to accommodate up to 11 of them. Taking into account the originally included or interacting water molecules, the 1 : 1 complexation reaction of a guest (G) with a cyclodextrin host (H) may be written as follows:

$$G \cdot gH_2O + H \cdot hH_2O \longrightarrow H \cdot G \cdot (g + h - i)H_2O + iH_2O \qquad (9)$$

where *g* represents the number of water molecules interacting with the free guest, *h* the number of tightly bound hydration water molecules inside the free cyclodextrin cavity, and *i* the net displacement of water upon complexation. There is no accurate information available concerning the values of *g*, *h* and *i* in solution. However it seems clear than the inclusion of a benzoyl chloride in the cavity of a γ-CD should not displace all the existing water molecules in its interior. The more accurate the adjustment of the guest in the cavity of the cyclodextrin, the greater the number of displaced water molecules in its interior.

Water molecules in the α-CD or β-CD cavity cannot saturate their tetrahedral hydrogen bonding capacity as can those in the bulk of the solvent. They may therefore be regarded as molecules of enhanced energy or enthalpy. The cavity of γ-CD is so wide and it may accommodate so many water molecules that their properties resemble water molecules in the bulk solvent. In this way we can consider that the interior of the γ-CD cavity has a high polarity, which is consistent with an approximately 10-fold reduction in the solvolysis rate of the *meta*-substituted benzoyl chlorides, with respect to bulk water.

The results obtained show that for the *para*-substituted benzoyl chlorides no reaction is observable in the interior of the cyclodextrin cavity. This behavior may be due to a greater capacity for penetration in the interior of the cavity. This penetration causes the consequent expulsion of water from the interior of the cyclodextrin and consequently causes γ-CD to have a very hydrophobic interior which is unable to solvate the leaving group for the solvolysis reaction. The *meta*-substituted benzoyl chlorides present a lower capacity of penetration due to the greater steric hindrance. This lower capacity of penetration translates to a lower degree of water expulsion from the interior of the γ-CD and consequently a more hydrophilic environment than in the previous case. The existence of water molecules in the interior of the γ-CD cavity that coexist with the benzoyl chloride can facilitate the solvation of the leaving group and, therefore, facilitate the solvolysis reaction in the interior of the cyclodextrin.

This variation in the polarity of the γ-CD cavity as the complexating substrates vary becomes evident when comparing the values of k_{CD}^{X} and k_{w}^{X}. The values obtained (Table 1) show that k_{w}^{X} is approximately 10 times lower than k_{CD}^{X} for 3-CH_3. In view of the previous considerations, we have not been able to obtain the value of k_{CD}^{X} for 4-CH_3. However we can estimate a maximum value which confirms the inequality which is necessary for the simplification of equation 1 to equation 3, namely $k_{w}^{X} \gg k_{CD}^{X}K_{CD}^{X}$[γ-CD]. We can thus obtain a maximum value of $k_{CD}^{4\text{-}CH_3} = 6.99 \times 10^{-2}$ s^{-1}. The lower polarity of γ-CD motivated by the complexation of 4-CH_3 causes the value of k_{CD}^{X} to be at least 100 times lower than that obtained in bulk water, contrasting with the behavior obtained in 3-CH_3.

It is important to note that this behavior has not been observed in the presence of α-CD or β-CD. This is due to the fact that the aromatic rings of the benzoyl chlorides fit better to the size of the α- and β-CD cavities with the consequent expulsion of a greater number of water molecules. This expulsion causes the interior of the cavities of the complexed α- and β-CD to be more hydrophobic than in the case of γ-CD and consequently the rate constant k_{CD}^{X} will be very small, confirming the inequality $k_{w}^{X} \gg k_{CD}^{X}K_{CD}^{X}$[CD].

Conclusions

The studies carried out allow us to conclude that the solvolysis of benzoyl chlorides in the presence of cyclodextrins shows two clearly differentiated behaviors: when the solvolysis mechanism occurs through an associative path the presence of cyclodextrins catalyzes the process through the reaction with its hydroxyl group C(6). The substituted benzoyl chlorides with electron-donating groups, which undergo solvolysis through a dissociative path, show a reduction of the rate constant caused by the presence of the cyclodextrins. This behavior is due to the complexation of the substrates with the cyclodextrins and also to the limited value of the rate constant in the cavity of the cyclodextrin, due to its low capacity to solvate the leaving group, Cl^-.

The presence of α- and γ-CD causes alterations in behavior which are related to: *(i)* the stability of the substrate–cyclodextrin complexes: it causes the solvolysis rate of the benzoyl chlorides 4-NO_2, 3-NO_2 and 3-CF_3 to be insensitive to the presence of α-CD; *(ii)* the stoichiometry of the complexes, causing the formation of complexes α-CD : benzoyl chloride with 1 : 1 stoichiometries for those which are substituted in the *meta* position and 2 : 1 for those substituted in the *para* position; *(iii)* 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 benzoyl chlorides are used.

Acknowledgements

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