ORIGINAL ARTICLE

Cyclodextrin effect on solvolysis of *ortho* benzoyl chlorides

**J. Báscuas · L. García-Río · J. R. Leis ·
M. Méndez-Pérez**

Abstract A kinetic study was carried out on the solvolysis of *ortho* benzoyl chlorides in the presence of α-, β- and γ-Cyclodextrin (CD). The solvolysis mechanism of benzoyl chlorides is sensitive to the substituents, and to the solvent in which the reaction takes place. In water, the behaviour exhibited by benzoyl chlorides which have electron-attracting groups, is consistent with an associative mechanism whilst electron-donating substituents induce a dissociative mechanism. The results obtained in the presence of CD show a decrease in the observed rate constant, k_{obs}, as the CD concentration increases. This behaviour can be explained if these substrates undergo solvolysis through a dissociative path in the presence of α-, β- and γ-CD.

Keywords Benzoyl chloride · Cyclodextrins · Inclusion complex · Pseudophase model · Stability constant

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of glucose units linked by α -1,4 glucoside bonds [1]. The CDs composed of 6, 7 and 8 units are usually referred to as α-, β- and γ-CD. They possess a hollow, truncated cone shape with a non-polar interior and two hydrophilic rims. Much of the interest in CDs arises from their ability to encapsulate a guest molecule inside their annulus to form inclusion complexes [2–4]. This capacity can modulate reactivity because the microenvironment around the reactant in the CD is different from that which prevails in the reaction media [5–7]. The effects of inclusion complexes on reactivity depend on the guest, the CD and the reaction. We have studied the influence of α-, β- and γ-CD on the solvolysis of the benzoyl chlorides shown in Scheme 1. Their mechanism of solvolysis is well known both in water and in different solvents [8–11]. The acyl group transfer was shown to follow one of three mechanisms: dissociative, associative, and concerted displacement.

Experimental

The β-CD was supplied by Sigma (>98%), the α- and γ–CD by Ciclolab (>98%). The benzoyl chlorides were provided by Aldrich (97–98%). All were used without further purification. Reaction kinetics were carried out in an Applied Photophysics stopped flow spectrophotometer with unequal mixing. The benzoyl chloride dissolved in acetonitrile was placed in the smaller syringe (0.1 ml) and the larger syringe (2.5 ml) was filled with the CD. The acetonitrile concentration was
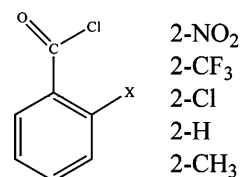
J. Báscuas (✉) · L. García-Río · J. R. Leis ·
M. Méndez-Pérez
Dpto. Química Física, Facultad de Química, Avda. das
Ciencias s/n, Universidad de Santiago de Compostela, 15782
Santiago, Spain
e-mail: qfmariam@usc.es

2-NO₂
2-CF₃
2-Cl
2-H
2-CH₃

Scheme 1

3.85% (v/v). The benzoyl chloride concentration was 1.0×10^{-4} M. All experiments were carried out at 25.0 °C. The kinetic traces were fitted with one exponential equation. All the values of k_{obs} were reproducible to within 3%.

Results and discussion

Solvolytic reactions in the presence of β-CD

Figure 1 shows the influence of the β-CD concentration on k_{obs} for the solvolysis of 2-NO$_2$, 2-Cl and 2-H. In these cases, as occurs with the others benzoyl chlorides, we observe a decrease in k_{obs}, as the CD concentration increases. We can explain these experimental results by the formation of an inclusion complex between the substrate and the β-CD, as shown in Scheme 2.

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

$$k_{obs} = \frac{k_w + k_{CD}K_{CD}[\text{CD}]}{1 + K_{CD}[\text{CD}]} \tag{1}$$

$$\frac{1}{k_{obs}} = \frac{\frac{1}{k_w} + \frac{K_{CD}}{k_w}[\text{CD}]}{1 + \frac{k_{CD}K_{CD}}{k_w}[\text{CD}]} \tag{2}$$

where k_w and k_{CD} are the rate constants of the solvolysis of the benzoyl chlorides in bulk water and in the inclusion complex with the CD. K_{CD} is the equilibrium constant of the inclusion complex. The possibility of a reaction between the complexed benzoyl chloride and the CD 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
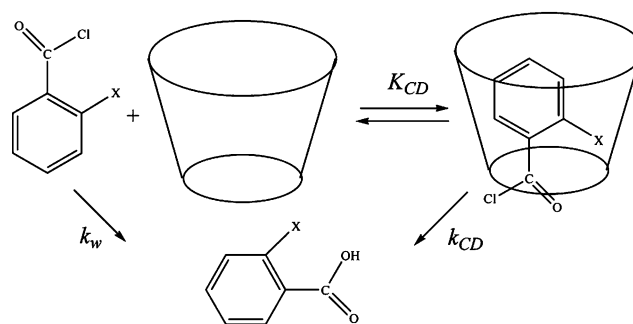
Scheme 2

should be the expulsion of the leaving group assisted by the CD. Given that the solvation ability of the interior of the CD is minimal, it is to be expected that the rate constant k_{CD} would be much lower than the corresponding rate constant in bulk water, in such a way as to confirm the inequality of $k_w \gg k_{CD} K_{CD}$ CD]. Eq. 1 can be rewritten thus:

$$k_{obs} = \frac{k_w}{1 + K_{CD}[\text{CD}]} \tag{3}$$

$$\frac{1}{k_{obs}} = \frac{1}{k_w} + \frac{K_{CD}}{k_w}[\text{CD}] \tag{4}$$

Figure 1 shows the fit of Eq. 3 in its present form, or by means of its linearization (Eq. 4). From the fitting procedure we can obtain the values of K_{CD} (see Table 1).

Solvolytic reactions in the presence of α-CD

The experimental behaviour obtained in the presence of α-CD cannot be explained on the basis of the mechanism proposed in Scheme 2 and Eq. 1–4. As Fig. 2 shows there exists a non-linear dependence of

Fig. 1 Influence of β-CD concentration on k_{obs} for solvolysis of (o) 2-NO$_2$, ($\bullet$) 2-Cl and ($\square$) 2-H at 25.0 °C. Data on the left figure were fitted according to Eq. 3 and according to Eq. 4 on the right
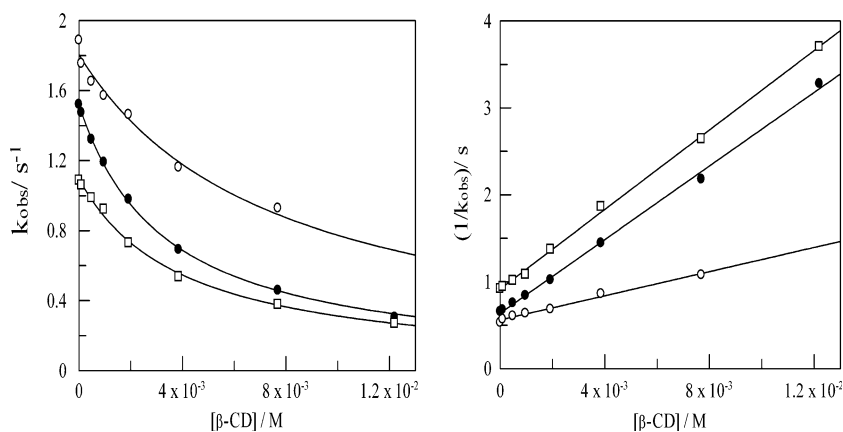
Table 1 Values of the kinetic parameters obtained for the solvolysis of benzoyl chlorides with CDs

	k_w/s^{-1}	β-CD	α-CD		γ-CD		
		K_{CD}/M^{-1}	$K_{1:1}/M^{-1}$	$K_{2:1}/M^{-1}$	k_{CD}/s^{-1}	$K_{1:1}/M^{-1}$	$K_{2:1}/M^{-1}$
2-NO$_2$	1.79	124 ± 6	2.7 ± 0.3	8 ±1	–	57 ± 12	–
2-CF$_3$	0.152	232 ± 6	3.6 ± 0.4	9 ± 1	3.86×10^{-3}	301 ± 45	–
2-Cl	1.57	332 ± 11	3.5 ± 0.3	66 ± 10	–	31 ± 3	161 ± 24
2-H	1.09	250 ± 5	11 ± 1	3 ± 1	–	52 ± 3	–
2-CH$_3$	217	403 ± 40	1.7 ± 0.2	89 ± 13	–	47 ± 5	187 ± 24

Fig. 2 Influence of α-CD concentration on k_{obs} (left) and $1/k_{obs}$ (right) for solvolysis of (o) 2-Cl and (•) 2-CF$_3$ at 25.0 °C. The curve represents the fit of Eq. 6 to the experimental data
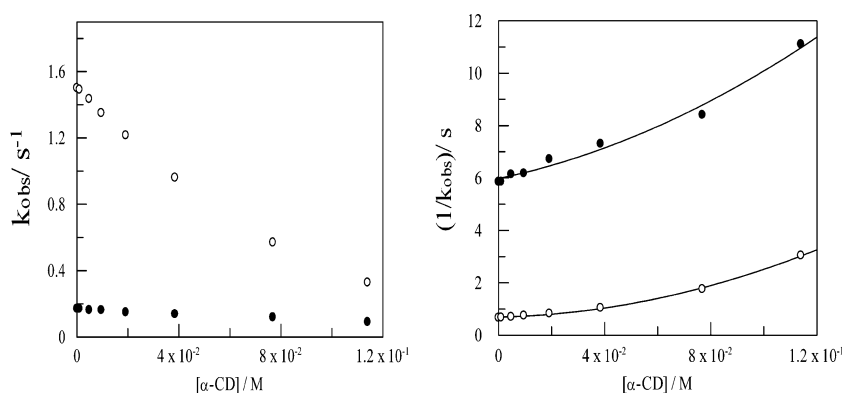
$1/k_{obs}$ on the α-CD concentration. This behaviour is consistent with a mechanism whereby a CD : benzoyl chloride complex is formed with a 2 : 1 stoichiometry, as shown in Scheme 3.

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

$$k_{obs} = \frac{k_w}{1 + K_{1:1}[CD] + K_{1:1}K_{2:1}[CD]^2} \quad (5)$$

$$\frac{1}{k_{obs}} = \frac{1}{k_w} + \frac{K_{1:1}}{k_w}[CD] + \frac{K_{1:1}K_{2:1}}{k_w}[CD]^2 \quad (6)$$

From the fitting of experimental results to Eq. 6 we can obtain the parameters shown in Table 1. It is important to note the difference in behaviour found between α- and β-CD: the benzoyl chlorides form complexes 2 : 1 with α-CD but only 1 : 1 with β-CD. The reason must lie in the geometric restrictions of the cavity of the CDs. In both cases the depth of the cavity is the same: 7.80 Å. 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 to be lower 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 CD molecule.

Solvolytic reactions in the presence of γ-CD

The rate constant of solvolysis of the benzoyl chlorides 2-NO$_2$ and 2-H decreases as a consequence of the formation of the inclusion complex with the γ-CD. The
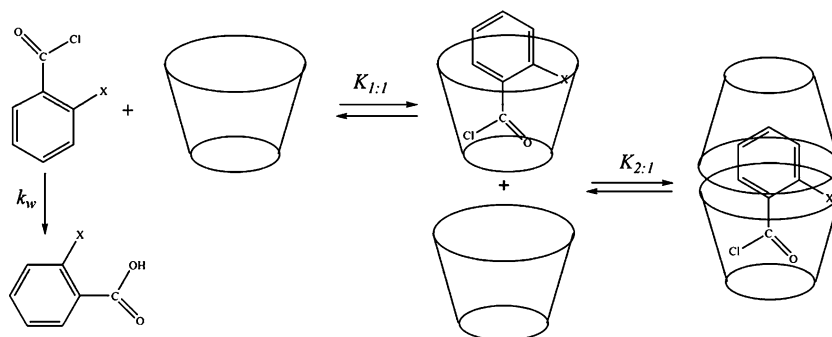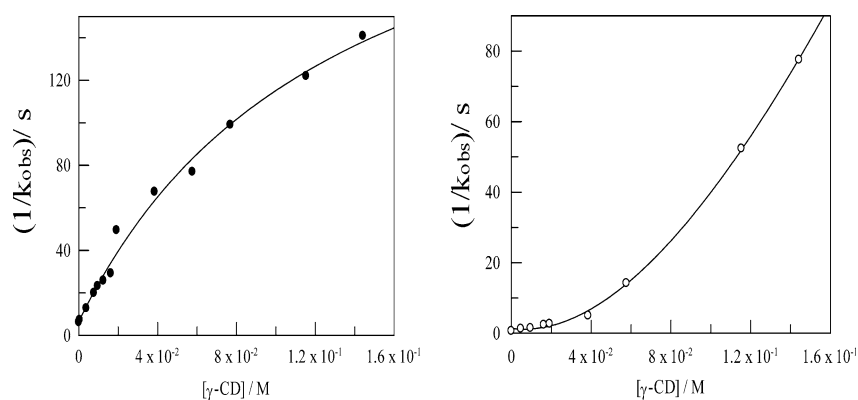
Scheme 3

Fig. 3 Influence of γ-CD on $1/k_{obs}$ for solvolysis of (•) 2-CF$_3$ and (o) 2-Cl at 25.0 °C. The curves represent the fit of Eq. 2 (left) and Eq. 6 (right) to the experimental data

experimental results have been fitted satisfactorily to Eq. 3–4, giving the kinetic parameters which are shown in Table 1. The rate constant of solvolysis of 2-CF$_3$ decreases as the concentration of γ-CD increases, however, this experimental behaviour cannot be justified on the basis of Eq. 3–4. The experimental results should fit the mechanism shown in Scheme 2 where the substrate complexed with γ-CD can undergo a solvolysis reaction. Figure 3 (left) shows the fit of Eq. 2 to the experimental data. The results obtained show that for the α-CD and β-CD no reaction is observable in the interior of the CD cavity. 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. 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 solvolysis reaction in the CD. Figure 3 (right) shows the behaviour obtained for the solvolysis of 2-Cl. In this case, as occurs with 2-CH$_3$, the experimental results should fit the mechanism shown in Scheme 3. This behaviour 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 CD and consequently causes γ-CD to have a very hydrophobic interior which is unable to solvate the leaving group for the solvolysis reaction.

References

1. Bender, M.L., Komiyama, M.: Cyclodextrin Chemistry, Springer-Verlag, Berlin (1978)
2. Tee, O.S.: The stabilization of transition states by cyclodextrins and other catalysts. Adv. Phys. Org. Chem. **29**, 1–85 (1994)
3. Wenz, G.: Cyclodextrins as synthons for supramolecular structures and functional units. Angew. Chem. Int. Ed. Engl. **33**, 803–822 (1994)
4. Connors, K.A.: The stability of cyclodextrin complexes in solution. Chem Rev. **97**, 1325–1357 (1997)
5. Iglesias, E., Fernández, A.: Cyclodextrin catalysis in the basic hydrolysis of alkyl nitrites. J. Chem. Soc, Perkin Trans. **2**, 1691–1700 (1998)
6. Iglesias, E.: Cyclodextrins as enzyme models in nitrosation and in acid-base-catalyzed reactions of alkyl nitrites. J. Am. Chem. Soc. **120**, 13057–13069 (1998)
7. García-Río, L., Leis, J.R., Mejuto, J.C., Pérez-Juste, J.: Investigation of micellar media containing β-cyclodextrins by means of reaction kinetics: basic hydrolysis of N-methyl-N-nitroso-p-toluenesulfonamide. J. Phys. Chem. B **101**, 7383–7389 (1997)
8. Song, B.D., Jencks, W.P.: Aminolysis of benzoyl fluorides in water. J. Am. Chem. Soc. **111**, 8470–8484 (1989)
9. Jencks, W.P.: General acid-base catalysis of complex reactions in water. Chem. Rev. **72**, 705–718 (1972)
10. More O'Ferrall, R.A.: Relations between E2 and ElcB mechanisms of β-elimination. J. Chem. Soc. B 274–277 (1970)
11. Báscuas, J., García-Río, L., Leis, J.R.: Cyclodextrin effect on solvolysis of substituted benzoyl chlorides. Org. Biomol. Chem. **2**, 1186–1193 (2004)