JOC Article
pubs.acs.org/joc

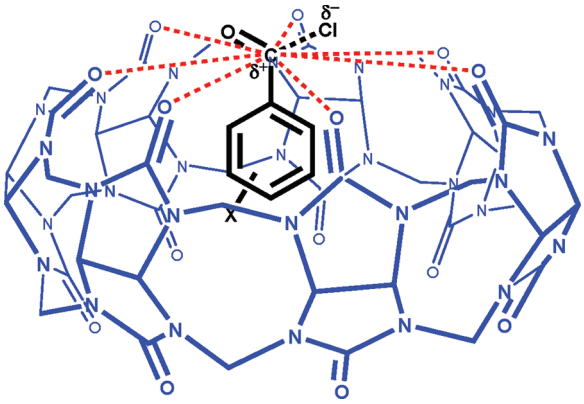
Supramolecular Catalysis by Cucurbit[7]uril and Cyclodextrins: Similarity and Differences

Nuno Basilio,[†] L. García-Río,*[,†] J. A. Moreira,[‡] and M. Pessêgo[†]

[†]*Departamento de Química Física, Facultad de Química, Universidad de Santiago, 15782 Santiago, Spain and* [‡]*CIQA, Departamento de Química, Bioquímica e Farmácia, Faculdade de Ciências e Tecnologia, Universidade do Algarve, Campus das Gambelas, 8005-139 Faro, Portugal*

luis.garcia@usc.es

Received November 11, 2009



To understand the analogies and differences between the cucurbituril and cyclodextrin cavities different solvolytic reactions have been studied in the presence of cucurbit[7]uril, CB7, and β-CD or its methylated derivative, DM-β-CD. Solvolysis of 1-bromoadamantane has been used as a test to evaluate the ability of the cavities to solvate the Br^- leaving group. Obtained results show that in both cases the polarity inside the cavity is similar to that of a 70% ethanol:water mixture. Solvolysis of substituted benzoyl chlorides shows a great difference between the CB7 and DM-β-CD cavity. Solvolysis of electron withdrawing substituted benzoyl chlorides (associative mechanism) is catalyzed by DM-β-CD and inhibited by CB7. However, solvolysis of electron donating substituted benzoyl chlorides (dissociative mechanism) is catalyzed by CB7 and inhibited by DM-β-CD. These experimental behaviors have been explained on the basis of different solvolytic mechanisms. Participation of the hydroxyl groups of the cyclodextrin as a nucleophile can explain the catalytic effect observed for solvolysis of benzoyl chlorides reacting by an associative mechanism. Solvolysis of benzoyl chlorides reacting by a dissociative mechanism is catalyzed by CB7 due to the ability of the CB7 cavity to stabilize the acylium ion developed in the transition state by electrostatic interactions.

Introduction

Cyclodextrins[1] and cucurbiturils[2] are both important host molecules that have been extensively studied and characterized in condensed media. In contrast to the host–guest chemistry of α-, β-, and γ-cyclodextrin which has developed steadily over the past century, the supramolecular chemistry of cucurbit[6]uril only began to develop in the 1980s and 1990s as a result of the pioneering work of Mock,[3] Buschmann and co-workers,[4] and Kim and co-workers.[5,6]

*To whom correspondence should be addressed. Fax: +34-981-595-012.

(1) (a) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: Berlin, Germany, 1978. (b) Szejtli, J. *Cyclodextrins*; Osa, T., Ed.; Elsevier: Oxford, UK, 1996; Vol. 3.

(2) (a) Mock, W. L. In *Comprehensive Supramolecular Chemistry*; Vögtle, F., Ed.; Elsevier: New York, 1996; Vol. 2, pp 477–493. (b) Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844–4870. (c) Kim, J.; Jung, I.-S.; Kim, S.-Y.; Lee, E.; Kang, J.-K.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *J. Am. Chem. Soc.* **2000**, *122*, 540–541.

(3) Mock, W. L. *Top. Curr. Chem.* **1995**, *175*, 1–24.

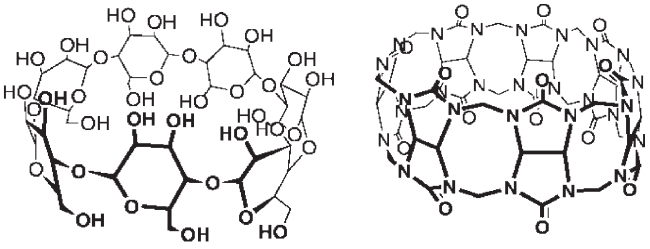
(4) Hoffmann, R.; Knoche, W.; Fenn, C.; Buschmann, H.-J. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1507–1511.

(5) Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H.-J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621–630.

(6) Kim, K. *Chem. Soc. Rev.* **2002**, *31*, 96–107.

Published on Web 01/08/2010 DOI: 10.1021/jo902398z

SCHEME 1



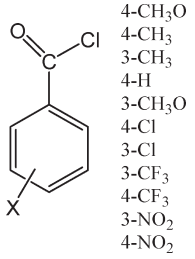
(a) (b)

Interest in the cucurbit[*n*]uril family has increased dramatically in the new millennium following the preparation of four new cucurbit[*n*]uril homologues (CB5, CB7, CB8, and CB10·CB5) by the research groups of Kim and Day.[2c,7]

Scheme 1 compares the structures of β-CD (a) and CB7 (b). Although the sizes and shapes of these two hosts are similar, their structural differences lead to distinct binding differences. CB7 has a symmetric geometry with two identical openings that are lined with electronegative carbonyl groups. However, β-CD has a less symmetric geometry with one opening to the interior lined with primary hydroxyl groups and the other lined with secondary hydroxyls. Several different modes of intermolecular interactions promote the binding of guest by cucurbiturils. First, as for cyclodextrins, a hydrophobic effect applies, i.e., a composite effect derived from an interplay between the release of "high-energy water" upon complexation of nonpolar organic residues and concomitant differential dispersion interactions inside the cavity and in bulk water.[8] Second, ion−dipole interactions of metal cation[4,9] or organic ammonium ions[10] with either ureido carbonyl rim may come into play, while hydrogen-bonding interactions prevail less frequently.[11] As a peculiarity, the complexation of metal cations at the ureido rims can lead to ternary supramolecular complexes composed of host, included guest, and associated metal ion. In fact, it has been suggested that the cations function as "lids" to seal the portal and promote binding.[12]

The confinement imposed by supramolecular inclusion and the associated variations in substrate reactivity are especially important in supramolecular catalysis. Mock[13] and co-workers have studied the influence of CB6 on cycloaddition reactions

SCHEME 2



showing a 10^5 times acceleration that is attributed to bound-substrate destabilization. CB7 and CB8 have been employed to catalyze different types of photocycloaddition reactions.[14] Very recently Nau[15] and co-workers have shown that the supramolecular complexation by CB7 affords a highly efficient inhibition on the activity of proteases, which can be analyzed by a host−substrate complexation model.

A number of host−guest studies have been carried out by using the cooperative effect of simultaneous addition of cyclodextrins and cucurbiturils. Cucurbiturils mainly bind cationic guests instead of cyclodextrins distinguishing between guests based on hydrophobic size rather than charge. Formation of ternary complexes has been reported.[16] The pH-responsive movement of the cucurbituril units in the host−guest complexes suggests its application as a basis for stimuli-responsive reconfigurable systems.[17]

The main objective of the present work is to show the differences and similarities between the CB7 and β-CD cavities by using not only the equilibrium constant values for the formation of the host guest complexes, but also the specific interactions that can occur inside the cavities. To this end we have studied two kinds of solvolytic reactions in the presence of CB7 and β-CD because these reactions have extreme sensibility to the physical properties of the reaction medium. We have studied the solvolysis of 1-bromoadamantane, whose solvolytic reaction takes place via an S_N1 reaction mechanism without the possibility of nucleophilic solvent assistance.[18] Moreover we have studied the solvolysis of substituted benzoyl chlorides (Scheme 2). Because these reactions in question exhibit no acid catalysis,[19] any changes in reactivity must be directly related to changes in the physical properties of the environment of the host cavity. This point is of special relevance because it is well-known that complexation by cucurbiturils and cyclodextrins can shift the pK_a value of included guests.[20] Cucurbituril

(7) (a) Day, A. I.; Arnold, A. P.; Blanch, R. J.; Snushall, B. *J. Org. Chem.* **2001**, *66*, 8094–8100. (b) Day, A. I.; Blanch, R. J.; Arnold, A. P.; Lorenzo, S.; Lewis, G. R.; Dance, I. *Angew. Chem., Int. Ed.* **2002**, *41*, 275–277.

(8) (a) Schmidtchen, F. P. *Chem.—Eur. J.* **2002**, *8*, 3522–3529. (b) Buschmann, H.-J.; Jansen, K.; Schollmeyer, E. *Thermochim. Acta* **1998**, *317*, 95–98.

(9) Buschmann, H.-J.; Cleve, E.; Schollmeyer, E. *Inorg. Chim. Acta* **1992**, *193*, 93–97.

(10) (a) Mock, W. L.; Shih, N. Y. *J. Am. Chem. Soc.* **1989**, *111*, 2697–2699. (b) Mock, W. L.; Shih, N. Y. *J. Am. Chem. Soc.* **1988**, *110*, 4706–4710.

(11) Buschmann, H.-J.; Jansen, K.; Schollmeyer, E. *Thermochim. Acta* **2000**, *346*, 33–36.

(12) (a) Jeon, Y. M.; Kim, J.; Whang, D.; Kim, K. *J. Am. Chem. Soc.* **1996**, *118*, 9790–9791. (b) Whang, D.; Heo, J.; Park, J. H.; Kim, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 78–80.

(13) (a) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Adhya, M. *J. Org. Chem.* **1989**, *54*, 5302–5308. (b) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Manimaran, T. L. *J. Org. Chem.* **1983**, *48*, 3619–3620.

(14) (a) Jon, S. Y.; Ko, Y. H.; Park, S. H.; Kim, H.-J.; Kim, K. *Chem. Commun.* **2001**, 1938–1939. (b) Maddipatla, M. V. S. N.; Kaanumalle, L. S.; Natarajan, A.; Pattabiraman, M.; Ramamurthy, V. *Langmuir* **2007**, *23*, 7545–7554. (c) Pattabiraman, M.; Natarajan, A.; Kaanumalle, L. S.; Ramamurthy, V. *Org. Lett.* **2005**, *7*, 529–532. (d) Wang, R.; Yuan, L.; Macartney, D. H. *J. Org. Chem.* **2006**, *71*, 1237–1239.

(15) Henning, A.; Ghale, G.; Nau, W. M. *Chem. Commun.* **2007**, 1614–1616.

(16) (a) Rekharsky, M. V.; Yamamura, H.; Kawai, M.; Osaka, I.; Arakawa, R.; Sato, A.; Ko, Y. H.; Selvapalam, N.; Kim, K.; Inoue, Y. *Org. Lett.* **2006**, *8*, 815–818. (b) Zou, D.; Andersson, S.; Zhang, R.; Sun, S.; Akermark, B.; Sun, L. *Chem. Commun.* **2007**, 4734–4736.

(17) (a) Chakrabarti, S.; Mukhopadhyay, P.; Lin, S.; Isaacs, L. *Org. Lett.* **2007**, *9*, 2349–2352. (b) Ooya, T.; Inoue, D.; Choi, H. S.; Kobayashi, Y.; Loethen, S.; Thompson, D. H.; Ko, Y. H.; Kim, K.; Yui, N. *Org. Lett.* **2006**, *8*, 3159–3162.

(18) (a) Raber, D. J.; Bingham, R. C.; Harris, J. M.; Fry, J. L.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1970**, *92*, 5977–5981. (b) Bentley, T. W.; Carter, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 5741–5747.

(19) Motie, R. E.; Satchell, D. P. N.; Wassef, W. N. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1087–1090.

(20) (a) Bakirci, H.; Koner, A. L.; Schwarzlose, T.; Nau, W. M. *Chem.—Eur. J.* **2006**, *12*, 4799–4807. (b) Saleh, N.; Koner, A. L.; Nau, W. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5398–5401. (c) Wang, R.; Macartney, D. H. *Org. Biomol. Chem.* **2008**, *6*, 1955–1960. (d) Klöck, C.; Dsouza, R. N.; Nau, W. N. *Org. Lett.* **2009**, *11*, 2595–2598.

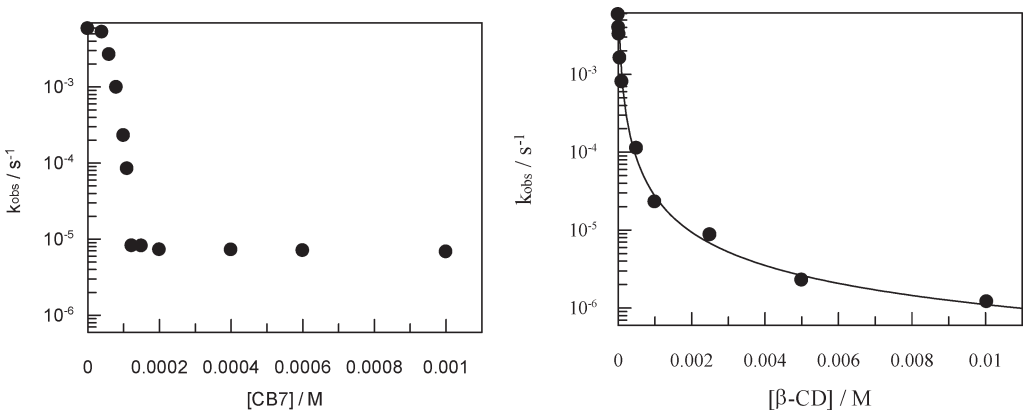


FIGURE 1. Influence of CB7 (left) and β-CD (right) concentration upon the observed rate constant for solvolysis of 1-bromoadamantane at 25.0 °C.

complexation leads to an increase in pK_a (AH^+ as guest) whereas cyclodextrin complexation leads instead to a decrease in pK_a. Thereby complexation may result in either catalysis or inhibition of hydrolysis of acid-labile substrates. As will be shown, a different behavior has been observed when the solvolysis of benzoyl chlorides is studied into the CB7 or the cyclodextrin cavity. The different behavior can be explained on the basis of nucleophilic solvent assistance inside the CB7 cavity. This effect leads to a change in the mechanism of solvolysis of benzoyl chlorides: in the presence of cyclodextrins the reaction follows mainly an associative mechanism, but in the CB7 cavity an S_N1 mechanism prevails.

Results and Discussion

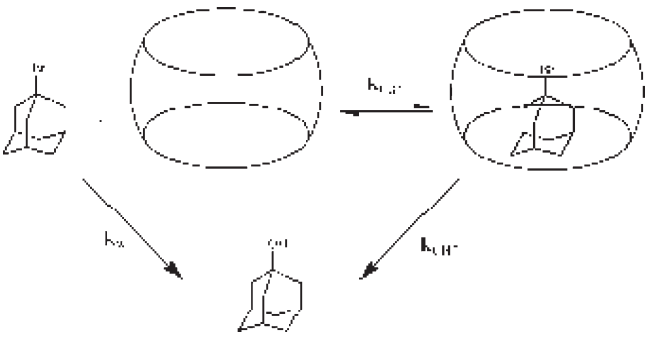
Solvolytic displacement reactions can be affected by solvents in several ways, including nucleophilic solvent assistance and electrophilic solvent assistance. Nucleophilic solvent assistance can be defined as electron donation from solvent to the developing positive dipole of a reacting C−X bond, and electrophilic solvent assistance can be defined as electron acceptance by the solvent from the leaving group. By comparing the sensitivity of various reactions to ionizing power and nucleophilicity, it is possible to deduce mechanistic information.

1. Solvolysis of 1-Bromoadamantane. Bridgehead caged systems such as 1-bromoadamantane can be used as a model for S_N1 reactions. There is extensive experimental evidence consistent with the absence[18,21] of kinetically significant nucleophilic attack in solvolysis of 1-bromoadamantane. Consequently is an excellent substrate for defining a scale of solvent ionizing power for bromides.

Figure 1 shows the effect of the presence of CB7 and β-CD on solvolysis of 1-bromoadamantane. In both cases the observed rate constant decreases as a consequence of formation of host−guest complexes.

These results are consistent with a mechanistic scheme (Scheme 3) considering the formation of a host:guest complex between the 1-bromoadamantane and CB7 or β-CD (K_{CB7} or K_{CD}, respectively) where the solvolytic reaction

SCHEME 3



takes place simultaneously in bulk water and inside the host cavity.

This kinetic scheme takes into consideration the simultaneous existence of two well-differentiated environments: water and host cavity (CB7 or β-CD) between which the substrates are distributed. By considering that solvolysis can take place simultaneously in water, k_w, and the host cavity, k_{CB7} or k_{CD} for CB7 and β-CD, respectively, it is possible to derive the following rate equation:

$$k_{obs} = \frac{k_w + k_{CB7}K_{CB7}[CB7]}{1 + K_{CB7}[CB7]} \quad (1)$$

Kinetic experiments for solvolysis of 1-bromoadamantane were carried out by using a [1-bromoadamantane] = 1.00×10^{-4} M, so that in the presence of CB7 it is impossible to confirm whether [1-bromoadamantane] ≪ [CB7], and so in order to obtain the equilibrium constant it is necessary to resort to a trial and error method (see the Supporting Information). The obtained binding constant, $K_{CB7} = (2.0 \pm 0.2) \times 10^7$ M^{-1}, is in the same order of magnitude as those reported for other adamantane derivatives.[22] The limiting value of k_{obs} obtained for [CB7] > 0.2 mM allow us to obtain the solvolytic rate constant inside the CB7 cavity, $k_{CB7} = (7.1 \pm 0.2) \times 10^{-6}$ s^{-1}. This value is approximately 10^3 times slower than that in bulk water.

Solvolysis of 1-bromoadamantane in the presence of β-CD shows the existence of 1:1 and 2:1 β-CD:adamantane

(21) Bentley, T. W.; Schleyer, P. v. R. *Adv. Phys. Org. Chem.* **1977**, *14*, 1–67.

(22) Liu, S.; Ruspic, C.; Mukhopadhyay, P.; Chakrabarti, S.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2005**, *127*, 15959–15967.

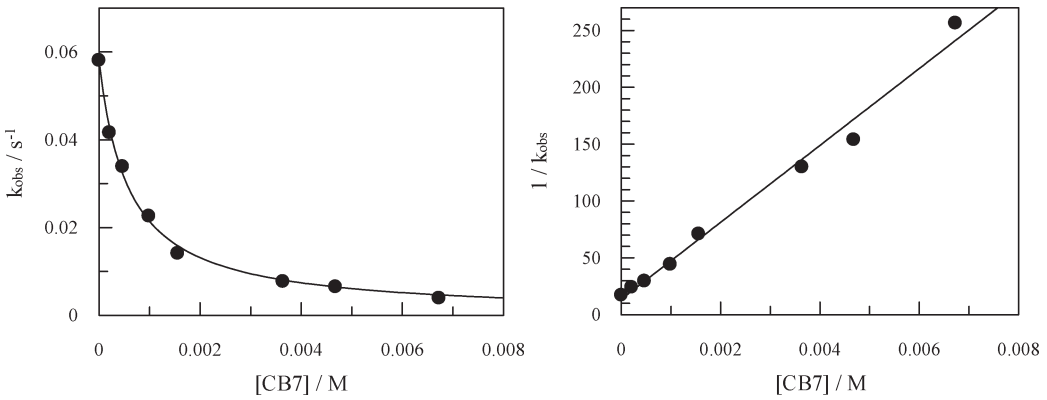


FIGURE 2. (Left) Plot of the influence of CB7 concentration on the pseudo-first-order rate constant for solvolysis of 4-NO_2 at 25.0 °C. (Right) Plot of $1/k_{obs}$ for solvolysis of 4-NO_2 in the presence of CB7 according to eq 3.

complexes. Kinetic results can be fitted by eq 2 (curve in Figure 1, right).

$$k_{obs} = \frac{k_w + k_{CD}K_{CD1}[CD]}{1 + K_{CD1}[CD] + K_{CD1}K_{CD2}[CD]^2} \qquad (2)$$

From the fitting procedure we get $K_{CD1} = (3.9 \pm 0.8) \times 10^4$ M^{-1}; $K_{CD2} = (7 \pm 1) \times 10^3 M^{-1}$ and $k_{CD} = (6 \pm 1) \times 10^{-5} s^{-1}$. The binding constant of 1-bromoadamantane to β-CD, K_{CD1}, is smaller than that to CB7, K_{CB7}. As will be shown latter this result is in agreement with the polarity of the CB7 cavity being smaller that the β-CD one. Moreover the solvolytic rate constant inside the CB7 cavity, k_{CB7}, is smaller than that in the presence of β-CD, k_{CD}. This result is a consequence of the smaller ability of the CB7 cavity than the β-CD one to solvate the transition state.

Because the nucleophilic solvent assistance is negligible for solvolysis of 1-bromoadamantane, experimental results indicate that the solvation of the leaving group inside the cavities of CB7 or β-CD is smaller than that in bulk water. From the results shown in Figure 1 we can conclude that the leaving group solvation inside the CB7 cavity is similar to that found on mixtures of 60% ethanol:40% water ($k_{obs} = 5.1 \times 10^{-6} s^{-1}$) and 70% methanol:30% water ($k_{obs} = 7.3 \times 10^{-6} s^{-1}$). With these results we can estimate that the ionizing power of the cavity of CB7 is between $Y_{Br} = 1.26$ (60% ethanol) and $Y_{Br} = 1.42$ (70% methanol). Experimental results obtained in the presence of β-CD suggest[23] the polarity of the cavity is close to a mixture of 50% ethanol:water.

2. Solvolysis of Benzoyl Chlorides. The mechanism of solvolysis of benzoyl chlorides is well-known both in water and in different solvents.[24] The goal is to compare the observed behavior, in the presence of CB7 or in the presence of the similar β-CD. However, the low solubility of β-CD in water prevents the experimental conditions at which solvolysis of benzoyl chlorides occurs inside the cavity from being reached. This problem can be solved by using the DM-β-CD, since this compound is 20 times more soluble in water than the β-CD without significant changes in cavity properties.

2.1. Inhibitory Effect of CB7 upon Solvolysis of Benzoyl Chlorides. Solvolysis of electron-withdrawing substituted benzoyl chlorides occurs through an associative pathway.[24] As a representative example of an associative mechanism, Figure 2 shows the influence of CB7 concentration on the pseudo-first-order rate constant, k_{obs}, for solvolysis of 4-NO_2 (4-H, 3-Cl, 3-NO_2, and 4-CF_3 should be included in this category). The obtained results show that k_{obs} decreases approximately six times when the concentration of CB7 increases up to 6.7 mM.

These results are consistent with the formation of an inclusion complex between the cucurbituril and benzoyl chlorides, as shown in Scheme 3. The solvolytic reaction will take place simultaneously in bulk water and the CB7 cavity (eq 1). In this case, as with other benzoyl chlorides, the binding constant of the substrate to the CB7 cavity is smaller than that with 1-bromoadamantane. Thus larger CB7 concentrations should be used in such a way that we can neglect the concentration of the host:guest complex (CB7:benzoyl chloride) in comparison with the total host concentration. In this way the host concentration in eq 1 can be considered as the total host concentration and the iterative fitting procedure shown in the Supporting Information for 1-bromoadamantane is not needed.

The fit of the kinetic results to eq 1 (line in Figure 2, left) confirms the inequality of $k_w \gg k_{CB7}K_{CB7}$ [CB7], thus eq 1 can be rewritten as:

$$\frac{1}{k_{obs}} = \frac{1}{k_w} + \frac{K_{CB7}}{k_w}[CB7] \qquad (3)$$

Figure 2, right, shows the fit of experimental data according to eq 3. From the fit we can obtain the value for the complexation equilibrium constant, $K_{CB7} = 1.7 \times 10^3 M^{-1}$, and a maximum value of the rate constant for the solvolysis at cavity, since $k_{CB7} \ll k_w/K_{CB7}$[CB7], $k_{CB7} < 7.2 \times 10^{-4} s^{-1}$ for 4-NO_2 solvolysis in the CB7 cavity (see Table 1).

We must notice that the rate constant inside the cavity of CB7 is approximately 10^2 times smaller than that in bulk water. This difference should be ascribed to the weak solvation of the transition state inside the CB7 cavity, when compared to the transition state solvation in bulk water. It is reported in the literature that CB7 has a very low polarizability ($P = 0.12$) inside its cavity[25] being smaller that the polarizability of the β-cyclodextrin ($P = 0.20$) cavity and smaller than that for *p*-sulfonatocalix[4]arene ($P = 0.25$).

(23) Garcia-Rio, L.; Hall, R. W.; Mejuto, J. C.; Rodríguez-Dafonte, P. *Tetrahedron* **2007**, *63*, 2208–2214.
(24) Song, B. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 8470–8479.
(25) (a) Marquez, C.; Nau, W. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4387–4390. (b) Koner, A. L.; Nau, W. M. *Supramol. Chem.* **2007**, *19*, 55–66.

TABLE 1. Compilation of Binding Constants between Substituted Benzoyl Chlorides and CB7 and DM-β-CD, As Well As Solvolytic Rate Constants in Bulk Water and Inside the Cavities of CD7 and DM-β-CD

substrate	k_w/s^{-1}	$K_{DM\text{-}\beta\text{-}CD}/M^{-1}$	$k_{DM\text{-}\beta\text{-}CD}/s^{-1}$	K_{CB7}/M^{-1}	k_{CB7}/s^{-1}
4-NO_2	$(8.2 \pm 0.3) \times 10^{-2}$	30 ± 3	0.90 ± 0.04	$(1.7 \pm 0.2) \times 10^{3}$	$\leq 7.2 \times 10^{-4}$
3-NO_2	$(3.8 \pm 0.2) \times 10^{-2}$	5 ± 2	0.29 ± 0.05	430 ± 60	$(1.2 \pm 0.1) \times 10^{-2}$
4-CF_3	$(3.5 \pm 0.1) \times 10^{-2}$	610 ± 100	$(4.1 \pm 0.1) \times 10^{-2}$	68 ± 10	$\leq 7.7 \times 10^{-3}$
3-Cl	0.47 ± 0.02	345 ± 30	$(1.3 \pm 0.1) \times 10^{-2}$	2500 ± 200	$(3.4 \pm 0.4) \times 10^{-2}$
4-Cl	0.19 ± 0.01	435 ± 10	$(4.8 \pm 0.2) \times 10^{-3}$	1500 ± 200	0.71 ± 0.08
3-CH_3O	0.59 ± 0.02	1120 ± 30	$(1.4 \pm 0.2) \times 10^{-3}$	480 ± 80	0.83 ± 0.07
4-H	1.14 ± 0.05	470 ± 30	$(3 \pm 1) \times 10^{-3}$	680 ± 50	0.14 ± 0.03
3-CH_3	2.51 ± 0.07	810 ± 60	$(6 \pm 2) \times 10^{-3}$	4000 ± 1000	3.3 ± 0.6
4-CH_3	6.3 ± 0.2	1050 ± 25	$(3 \pm 1) \times 10^{-2}$	1250 ± 150	19 ± 2
4-CH_3O	46 ± 1	730 ± 35	0.37 ± 0.09	326 ± 40	252 ± 30

Data for DM-β-CD were taken from ref 23.

Table 1 reports the rate constants in bulk water and inside the cavities of CB7 and DM-β-CD, as well as the binding constants. The binding constant for 4-NO_2 with CB7, $K_{CB7} = 1.7 \times 10^3\ M^{-1}$, is approximately 50 times greater than that with DM-β-CD, $K_{DM\text{-}\beta\text{-}CD} = 30$. In general the stability constants of the cucurbiturils are larger than those of the corresponding cyclodextrins with the same guest[26] as a consequence of the lower polarity of the cavity.

From the previous study on solvolysis of 1-bromoadamantane we have concluded that the solvolytic rate constant inside the CB7 cavity is very close to those observed for 60% ethanol or 70% methanol. However, the results obtained[27] for 4-NO_2, $k_{CB7} < 7.2 \times 10^{-4}\ s^{-1}$, are 100−200 times smaller than those obtained in 60% ethanol, $k_{obs} = 6.9 \times 10^{-2} s^{-1}$, and 70% methanol, $k_{obs} = 0.153\ s^{-1}$. Solvent effects for solvolysis of 4-NO_2 in alcohol:water mixtures are mainly due to changes in the solvent nucleophilicity. This means that water nucleophilicity inside the CB7 cavity should be much smaller than that for alcohol:water mixtures.

Figure 3 shows the influence of [DM-β-CD] on the rate constants for solvolysis[23] of 4-NO_2. DM-β-CD shows a clear catalytic effect on solvolysis of the 4-NO_2 derivative; the observed rate constant increases approximately 10 times as a consequence of the reaction between the hydroxyl groups of the cyclodextrin and the included guest.[28,29]

The solvolysis of 4-CF_3 shows a similar behavior to that observed in Figure 2, right. On applying eq 3 a maximum value for the rate constant in the CB7 cavity is obtained. This value is 5 times smaller than that in DM-β-CD (see Table 1). In the solvolysis of other substituted benzoyl chlorides with electron withdrawing groups like 3-NO_2, 3-Cl, and 4-H an inhibitory effect resulting from the addiction CB7 is also observed. In those cases we do not observe the inequality $k_w \gg k_{CB7}K_{CB7}$[CB7] and the experimental results should be fitted to eq 1. The values of the rate constants in the CB7 cavity and the binding constants between the CB7 and substituted benzoyl chlorides are reported in Table 1. For

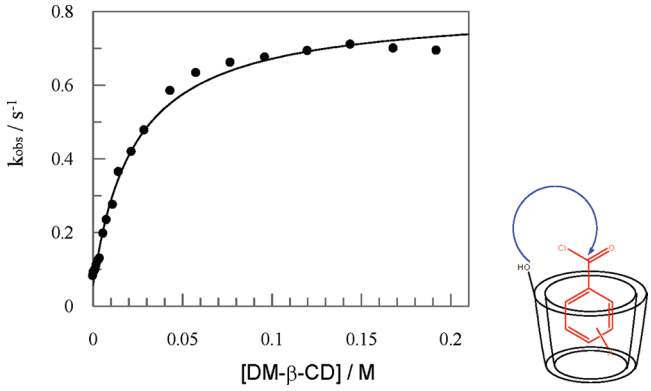


FIGURE 3. Influence of DM-β-CD (data taken from ref 23) concentration on the pseudo-first-order rate constant for solvolysis of 4-NO_2 at 25.0 °C.

the 3-NO_2 derivative, the solvolysis rate constant inside CB7 is approximately 20 times smaller than that inside DM-β-CD, while for 3-Cl and 4-H the rate of solvolysis in the CB7 cavity is greater than that inside DM-β-CD. The cavities of CB7 and DM-β-CD show different affinities to 4-NO_2, 3-NO_2, 4-CF_3, 3-Cl, and 4-H, which is related to the mechanism of reaction, as will be discussed later.

2.2. Catalytic Effect of CB7 upon the Solvolysis of Benzoyl Chlorides. As an example of the behavior of electron-donating substituted benzoyl we consider 4-CH_3O. Figure 4, left, shows the influence of CB7 concentration on the solvolysis of 4-CH_3O where a clear catalytic effect is observed. This experimental behavior is contrary to that observed for solvolysis of 4-NO_2 (Figure 2, left). Solvolysis of 4-CH_3, 3-CH_3, 3-CH_3O, and 4-Cl also shows a catalytic effect exerted by the CB7 concentration (not shown). These experimental results are unexpected on the basis of the CB7 influence on solvolysis of 1-bromoadamantane (Figure 1, left). Results in Figure 1 show that the 1-bromoadamantane solvolytic rate constant inside the CB7 cavity is similar to those observed for 60% ethanol or 70% methanol. However, the 4-CH_3O solvolytic rate constant inside the CB7 cavity is close to $k_{obs} = 200\ s^{-1}$. This value is 10^3 times larger than those observed[30] in 60% ethanol, $k_{obs} = 0.19\ s^{-1}$, and 70% methanol, $k_{obs} = 0.32\ s^{-1}$. As will be shown later the absence of correlation between solvolysis of 1-bromoadamantane and 4-CH_3O is explained as a consequence of the solvent nucleophilic assistance in solvolysis of benzoyl chlorides.

(26) Wyman, I. W.; Macartney, D. H. *Org. Biomol. Chem.* **2008**, *6*, 1796–1801.
(27) Bentley, T. W.; Jones, R. O. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2351–2359.
(28) (a) Khan, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977–1996. (b) Easton, C. J.; Lincoln, S. F. *Modified Cyclodextrins*; Imperial College Press: London, UK, 1999. (c) Saenger, W.; Niemann, C.; Herbst, R.; Hinrichs, W.; Steiner, T. *Pure Appl. Chem.* **1993**, *65*, 809–817. (d) Saenger, W.; Jacob, J.; Gessler, K.; Steiner, T.; Hoffmann, D.; Sanbe, H.; Koizumi, K.; Smith, S. M.; Takaha, T. *Chem. Rev.* **1998**, *98*, 1787–1802.
(29) (a) Gelb, R. I.; Schwartz, L. M.; Bradshaw, J. J.; Laufer, D. A. *Bioorg. Chem.* **1980**, *9*, 299–304. (b) Gelb, R. I.; Schwartz, L. M.; Laufer, D. A. *Bioorg. Chem.* **1982**, *11*, 274–280.
(30) Bentley, T. W.; Koo, I. S. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1385–1393.

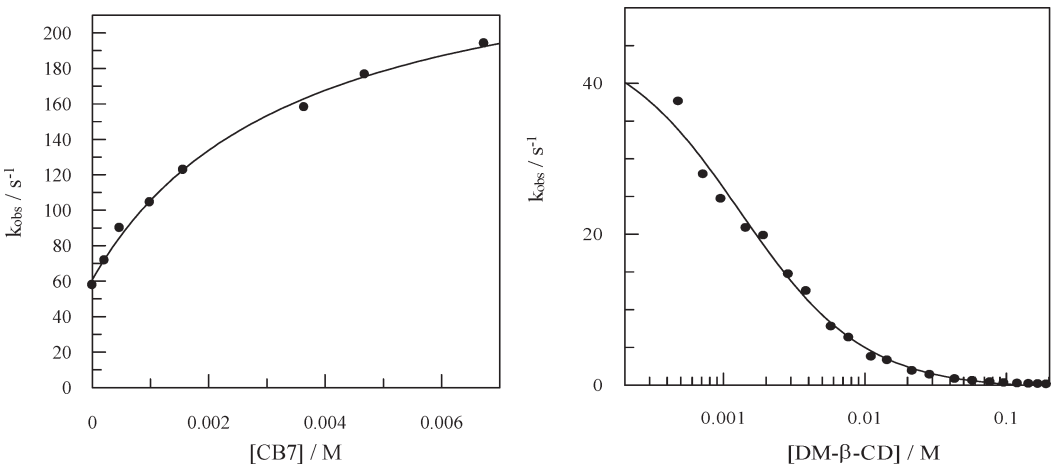


FIGURE 4. Influence of CB7 (left) and DM-β-CD (right, data taken from ref 23) concentration upon the observed rate constant for solvolysis of 4-CH_3O at 25.0 °C.

Results obtained in the presence of CB7 are opposite to those in the presence of DM-β-CD. An increase of k_{obs} up to 300% is observed in the presence of 6 mM CB7 meanwhile the solvolytic rate constant of 4-CH_3O in the presence of DM-β-CD (Figure 4, right) decreases approximately 450 times when increasing the concentration of DM-β-CD up to [DM-β-CD] = 0.15 M.

The inhibitory effect exerted by the DM-β-CD upon solvolysis of 4-CH_3O, as occurs with 4-CH_3, 3-CH_3, 3-CH_3O, and 4-Cl, can be easily explained by recourse to the formation of an inclusion complex between the benzoyl chloride and the cyclodextrin. 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 inside the cavity of the cyclodextrin. The solvolytic rate constant inside the cyclodextrin is smaller than that in bulk water because of the lower polarity of the cavity.[31−38]

The polarity in the CB7 cavity is smaller than that in the DM-β-CD, so an inhibitory effect greater than that shown in Figure 4, right, would be expected. Nevertheless, the experimental results show an important catalytic effect. This result is a consequence of the reaction mechanism being not a pure S_N1 one. In fact, a plot of the logarithm of rate constants for solvolysis of substituted benzoyl chlorides versus Winstein−Grunwal Y_{Cl} shows considerable scatter even for solvents with high ionizing power.[39] Its interpretation is based on considerable information available on the expected trends in S_N2-S_N1-type solvolytic reactivity in a wide range of protic solvents.[40] As Y_{Cl} models S_N1 reactivity, Bentley and co-workers[39a] have concluded that hydrolyses of benzoyl chlorides are not pure S_N1 reactions. It appears that many solvolysis of benzoyl chloride are weakly nucleophilically solvent-assisted (S_N2) to about the same extent as solvolysis of *tert*-butyl chloride. The high reactivity of benzoyl chloride in water and in other solvents of high ionizing power can readily be explained by the relatively good stabilization of the incipient benzoyl cation, i.e., in an S_N1 or an S_N2 pathway via a transition state with high carbocation character. Independent evidence for nucleophilically assisted solvolysis, obtained form rate−product correlations in the presence of added *o*-nitroaniline, support the proposal[35] that even solvolyses in relatively polar solvents are not pure S_N1 processes.

When the solvolysis of 4-CH_3O is studied in a mixture of 70% methanol:water, in which the value of Y_{Cl} is similar to that obtained in the cavity of CB7, an observed rate constant $k_{obs} = 0.316\ s^{-1}$ is obtained. On this basis we expect the 4-CH_3O solvolytic rate constant in the cavity of CB7 to be 150 times lower than the value obtained in bulk water. Surprisingly, as can be see in Figure 4, left, the rate constant increases approximately 4 times when the concentration of CB7 increases. This result suggests that the electrostatic interaction inside CB7 between the carbonyl groups of CB7 and the positive charge developed on the carbony group of the 4-CH_3O increases at least 600 times the solvolytic rate constant. An electrostatic interaction between the positive charge developed on the carbonyl group of benzoyl chloride

(31) (a) Matsui, Y.; Mochida, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2808–2814. (b) Hallen, D.; Schoen, A.; Shehatta, I.; Wadsoe, I. *J. Chem. Soc., Faraday Trans.* **1992**, *88*, 2859–2863. (c) Saenger, W. *Angew. Chem., Int. Ed.* **1980**, *92*, 344–362. (d) Sanemasa, I.; Osajima, T.; Deguchi, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2814–819. (e) VanEtten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242–3253.

(32) Uno, B.; Kaida, N.; Kawakita, T.; Kano, K.; Kubota, T. *Chem. Pharm. Bull.* **1988**, *36*, 3753–3759.

(33) Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325–1357.

(34) (a) Cramer, F.; Saenger, W.; Spatz, H. C. *J. Am. Chem. Soc.* **1967**, *89*, 738–740. (b) Turro, N. J.; Okubo, T.; Chung, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 3954–3957. (c) Cox, G. S.; Turro, N. J.; Yang, N. C. C.; Chen, M. J. *J. Am. Chem. Soc.* **1984**, *106*, 422–424. (d) Hamai, S. *J. Phys. Chem.* **1990**, *94*, 2595–2600.

(35) Ramamurthy, V.; Eaton, D. F. *Acc. Chem. Res.* **1988**, *21*, 300–306.

(36) Cox, G. S.; Hauptmann, P. J.; Turro, N. *J. Photochem. Photobiol.* **1984**, *39*, 597–601.

(37) Heredia, A.; Requena, G.; Sanchez, F. G. *J. Chem. Soc., Chem. Commun.* **1985**, 1814–1815.

(38) Street, K. W.; Acree, W. E. *Appl. Spectrosc.* **1988**, *42*, 1315–1318.

(39) (a) Bentley, T. W.; Carter, G. E.; Harris, H. C. *J. Chem. Soc., Perkin Trans. 2* **1985**, 983–990. (b) Bentley, T. W.; Carter, G. E.; Harris, H. C. *J. Chem. Soc., Chem. Commun.* **1984**, 387–389.

(40) (a) Swain, C. G.; Mosely, R. B.; Bown, D. E. *J. Am. Chem. Soc.* **1955**, *77*, 3731–3737. (b) Bentley, T. W.; Bowen, C. T.; Morten, D. H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 5466–5475. (c) Peterson, P. E.; Vidrine, D. W.; Waller, F. J.; Henrichs, P. M.; Magaha, S.; Stevens, B. *J. Am. Chem. Soc.* **1977**, *99*, 7968–7976. (d) Kevill, D. N.; Lin, G. M. L. *J. Am. Chem. Soc.* **1979**, *101*, 3916–3919. (e) Fainberg, A. H.; Winstein, S. *J. Am. Chem. Soc.* **1957**, *79*, 1597–1602.

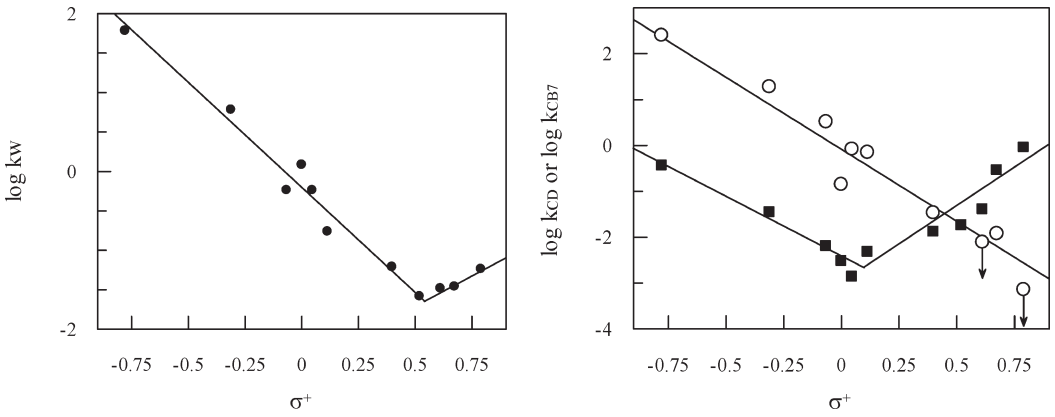
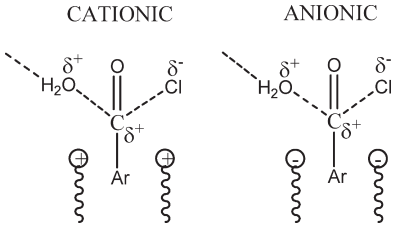


FIGURE 5. Hammett plot for solvolysis of substituted benzoyl chlorides in bulk water (left) and inside the cavity of DM-β-CD (■, right) or the CB7 cavity (○, right) at 25.0 °C. Rate constants for solvolysis of 4-NO_2 and 4-CF_3 inside the CB7 cavity (right) correspond to maximum values.

SCHEME 4



and the cyclodextrin cavity is not possible. In fact, cyclodextrins can form inclusion complexes with inorganic anions[41] (generally with equilibrium constants on the order of 1 M^{-1}). This explains why the value of the rate constant in the cavity of DM-β-CD is $k_{\text{DM-}\beta\text{-CD}} = 0.37\ s^{-1}$, approximately 130 times lower than that in water, and similar to that obtained in 70% methanol:water. This result shows that in the absence of electrostatic interaction, between the CB7 cavity and positive partial charge developed at the carbonyl in the transition state, the qualitative effect of CB7 and DM-β-CD should be the same.

Previous evidence of the electrostatic stabilization of the positive charge developed on the carbonyl group in the solvolysis of benzoyl chlorides has been obtained from kinetic studies in micellar aggregates.[42] Hydrolyses of most acyl derivatives, including carboxylic anhydrides and diaryl carbonates, are micellar inhibited, except for some nitro derivatives,[43] but reactions are faster in cationic than in anionic micelles. The pattern is similar for hydrolyses of substituted benzoyl chlorides in that $k_+/k_- > 1$ for nitro derivatives but is < 1 for methyl and methoxy derivatives[41] ($k_+/k_- = 18, 4, 3.6,$; 0.27, 0.038, and < 0.03 for 4-NO_2, 4-Cl, 4-Br, 4-H, 4-CH_3, and 3-CH_3O, respectively). Interactions of the transition state for hydrolysis of a benzoyl chloride with micellar head groups are illustrated in Scheme 4. The transition state is written as in a concerted S_N1-S_N2 borderline mechanism, with a cationoid acyl center.

Nucleophilic solvation of the transition state on solvolysis of benzoyl chlorides should lead to the catalytic effect of CB7 in the hydrolysis of 4-CH_3O and the different behavior between CB7 and DM-β-CD. Electrostatic effects can play a crucial role in molecular recognition events in both aqueous and organic solution.[44] The electrostatic potential at the portal and within the cavity of CB7 is significantly more negative than that for β-CD. This difference in electrostatic potential has significant consequences for their recognition behavior: CB7 exhibits a pronounced preference to interact with cationic guests whereas β-CD prefers to bind to neutral or anionic guests.[2b,5] The recognition of the dissociative transition state by CB7 could explain the observed catalytic effect as a consequence of the electrostatic interaction between the carbocation developed in the transition state and the electrostatic potential of the CB7 cavity. In the case of DM-β-CD the absence of this interaction could explain the different behavior, shown in Figure 4, and the lower value of $k_{\text{DM-}\beta\text{-CD}}$ with respect to rate constant in water, k_w.

2.3. CB7 Prevents Mechanistic Changes. Figure 5, left, shows the results obtained on studying the rate of solvolysis of substituted benzoyl chlorides in bulk water. 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.

Figure 5, right, shows a similar correlation when the reaction occurs inside the cavity of DM-β-CD. In this case the observed slopes ($\rho^+ = -2.6 \pm 0.2$ and 3.3 ± 0.5) show that the associative mechanism is more favored than dissociative. In the presence of DM-β-CD the mechanism changes at the benzoyl chloride, 4-H, while in bulk water the mechanism change is observed later at the electron-withdrawing group, 3-CF_3. The DM-β-CD cavity has a poor capacity to contribute in the electrophilic solvation of the

(41) Mochida, K.; Kagita, A.; Matsui, Y.; Date, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3703–3707.
(42) Tascioglu, S. *Tetrahedron* **1996**, *52*, 1113–11152.
(43) (a) Bunton, C. A.; Gillitt, N. D.; Mhala, M. M.; Moffatt, J. R.; Yatsimirsky, A. K. *Langmuir* **2000**, *16*, 8595–8603. (b) Bunton, C. A.; Mhala, M. M.; Moffatt, J. R. *J. Org. Chem.* **1985**, *50*, 4921–4924. (c) Buurma, N. J.; Herranz, A. M.; Engberts, J. B. F. N. *J. Chem. Soc., Perkin Trans. 2* **1999**, 113–119. (d) Possidonio, S.; Siviero, F.; El Seoud, O. A. *J. Phys. Org. Chem.* **1999**, *12*, 325–332. (e) Possidonio, S.; El Seoud, O. A. *J. Mol. Liq.* **1999**, *80*, 231–251. (f) Al-Lohedan, H.; Bunton, C. A.; Mhala, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 6654–6660. (g) Bunton, C. A.; Ljunggren, S. *J. Chem. Soc., Perkin Trans. 2* **1984**, 355–361. (h) Brinchi, L.; Di Profio, P.; Micheli, F.; Germani, R.; Savelli, G.; Bunton, C. A. *Eur. J. Org. Chem.* **2001**, 1115–1120.
(44) Honig, B.; Nicholls, A. *Science* **1995**, *268*, 1144–1149.

leaving group producing a decrease on the dissociative pathway. Likewise, the participation of the C(6) hydroxyl group of the DM-β-CD as a nucleophile favors the associative mechanism.

When the reaction was carried inside the CB7 cavity a single Hammett correlation (Figure 5, right) with slope $\rho^+ = -3.1 \pm 0.3$ is observed. Because rate constants for solvolysis of 4-NO_2 and 4-CF_3 inside the CB7 cavity correspond to maximum values they were excluded from the set for calculating ρ^+. Inside the CB7 cavity all substituted benzoyl chlorides undergo solvolysis through a dissociative path. The ρ^+ value is equal to that obtained in 97% trifluoroethanol[45] ($\rho^+ = -3.1$) suggesting the existence of a dissociative mechanism (S_N1 type). However, the results in Figure 5, right, show that in the reaction an important nucleophilic assistance must be present. Substituted benzoyl chlorides with electron-donating groups show a rate constant inside the CB7 cavity 10^2 times bigger than that in the DM-β-CD cavity. Nevertheless the study of solvolysis of 1-bromoadamantane shows that the cavities of CB7 and β-CD have similar electrophilic solvation ability and therefore similar values of Y_{Br}. The fact that reactivity cannot be correlated only with the solvent ionizing power clearly indicates nucleophilic assistance on solvolysis of substituted benzoyl chlorides in the CB7 cavity. The nucleophilic assistance results from the electrostatic interaction between the CB7 cavity and the transition state of the solvolysis reaction.

Conclusions

Obtained results for solvolytic reactions in the presence of CB7 and β-CD or DM-β-CD can be explained on the basis of the different properties of their cavities. Pure S_N1 reactions, 1-bromoadamantane, are inhibited by both cucurbituril and cyclodextrin. In both cases the ability of the cavity to solvate the Br^- leaving group is similar to that of a 70% methanol:30% water mixture. However important discrepancies have been observed in the solvolysis of substituted benzoyl chlorides. For electron donating substituted benzoyl chlorides the solvolytic reaction is catalyzed in the cucurbituril cavity and is inhibited in the cyclodextrin. This behavior is a consequence of the poor ability of both cavities to solvate the Cl^- leaving group; however, inside the cucurbituril cavity the interaction between the electrostatic potential at the portal of the cavity and the acylium cation developed in the transition state can decrease the energy barrier for the reaction. Experimental differences for solvolysis of electron withdrawing substituted benzoyl chlorides between the CB7 or cyclodextrin cavities can be explained as a consequence of the participation of the cyclodextrin hydroxyl groups in the reaction.

Experimental Section

CB7 was synthesized by using the procedure described by Nau et al.,[46] and after separation of CB7 from others homologues, the sulfuric acid was exchanged with chlorhydric acid by dissolving the product in concentrated HCl, diluted with water, and precipitated with acetone. This procedure was repeated two times and finally the product was dissolved in water and precipitated several times with acetone until the pH of the solution was neutral as seen by indicator paper. Finally the product was dried on high vacuum at 140 °C for several days. The pH of a 5 mM solution was checked with a glass electrode and was found to be 5.7. The product was characterized by proton nuclear magnetic resonance and electrospray ionization mass spectrometry based on known literature data.[2c]

The benzoyl chlorides were commercially available, all of which had purities between 97% and 98%, and were used without further purification. Their solutions were prepared in acetonitrile to prevent it from decomposing too rapidly.

Reaction kinetics was 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 the macrocyclic. 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 obtain a final concentration of 5.0×10^{-5} M. All experiments were carried out at 25.0 °C. The kinetic traces were fitted with one exponential equation by 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. Solvolysis of 1-bromoadamantane was followed by conductometry; the kinetic data were treated both by the integral method and by the initial rate method. All the kinetic experiment could be reproduced within an error margin of 3%.

Acknowledgment. This work was supported by Ministerio de Ciencia y Tecnología (Project CTQ2008-04420/BQU) and Xunta de Galicia (PGIDIT07-PXIB209041PR). N.B. acknowledge FCT for PhD Grant SFRH/BD/29218/2006.

Supporting Information Available: A description of the fitting procedure for solvolysis of 1-bromoadamantane in the presence of CB7. This material is available free of charge via the Internet at http://pubs.acs.org.

(45) Bentley, T. W.; Harris, H. C. *J. Chem. Soc., Perkin Trans. 2* **1986**, 619–624.

(46) Marquez, C.; Huang, F.; Nau, W. M. *IEEE Trans. Nanobiosci.* **2004**, *3*, 39–45.