Rate and Enantioselectivity with Complexes of Activated Substrates and Simply Modified Cyclodextrins

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The rate of hydrolytic cleavage of a number of enantiomeric activated substrates, nitrophenyl esters or carbonates, was measured in the presence of some modified β-cyclodextrins: heptakis-[6-deoxy-6-(*N*-methylacetamido)]cycloheptа-amylose (**9**), heptakis-(2,6-di-*O*-methyl)cycloheptа-amylose (**10**), and heptakis-(2,3,6-tri-*O*-methyl)cycloheptа-amylose (**11**). In the presence of (**9**) the rate enhancements were considerably larger and enantioselectivities only slightly smaller than those observed with native β-cyclodextrin. With (**10**) and (**11**) inhibition was observed, the effects being substantially larger in the case of (**10**) than in that of the permethylated cyclodextrin (**11**), and enantioselectivity was virtually absent.

We have recently reported[1] the results of a kinetic study of the hydrolytic cleavage of the enantiomers of esters (**1**)—(**6**) and carbonates (**7**)—(**8**) in the presence of α- and β-cyclodextrins (α-and β-CDs).[2,3] In the present study we have investigated

$PhCR^1R^2–CO_2–L$ $PhCH(Me)–OCO_2-p-NP$ (**7**)

(**1**) R^1 = H, R^2 = Me, L = *p*-NP
(**2**) R^1 = H, R^2 = Me, L = *m*-NP
(**3**) R^1 = H, R^2 = OMe, L = *p*-NP
(**4**) R^1 = H, R^2 = OMe, L = *m*-NP
(**5**) R^1 = CF_3, R^2 = OMe, L = *p*-NP
(**6**) R^1 = CF_3, R^2 = OMe, L = *m*-NP

$C_6H_{13}–CH(Me)–OCO_2-p-NP$ (**8**)

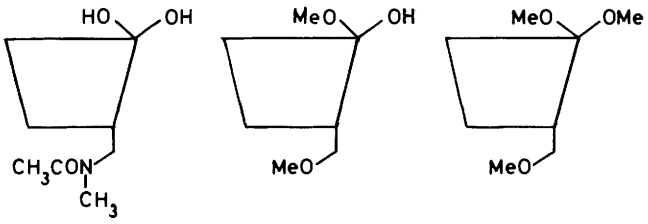
NP = nitrophenyl (*para* or *meta*)

changes in reactivity and enantioselectivity in the cleavage of substrates (**1**)—(**8**) on going from native to simply modified β-CDs: the bottom-capped heptakis-[6-deoxy-6-(*N*-methylacetamido)]cycloheptа-amylose (**9**) (6-NMeAc-β-CD), the partially methylated heptakis-(2,6-di-*O*-methyl)cycloheptа-amylose (**10**) (2,6-Me_2-β-CD), and the permethylated heptakis-(2,3,6-tri-*O*-methyl)cycloheptа-amylose (**11**) (2,3,6-Me_3-β-CD).

A few results concerning the reactivity of complexes of activated esters with these modified CDs have been published. Bender and his co-workers[3,4] observed inhibition (*i.e.* k_c/k_{un}, the ratio of rates for intracomplex cleavage relative to simple hydrolysis, less than one) in the cleavage of a few simple esters in the presence of 2,6-Me_2-β-CD (**10**). On the other hand, Breslow and his co-workers[5] reported that analogues of (**9**) (bearing an *N*-alkylformamido or a tosyl group at C-6 of the β-CD) are normally more effective than the native β-CD and remarkably enantioselective in the cleavage of metallocene substrates.

Results and Discussion

The synthesis of guest and host compounds has been described.[6,7] The kinetic measurements were carried out for reactions in aqueous 20mM-sodium carbonate buffers with added 1% v/v CH_3CN, mostly at pH 10.5 and 25 °C. The observed pseudo-first-order rate constants, k_ψ, were measured both in the absence (k_{un}) and in the presence of (6—10) different concentrations of modified CDs; these values allowed us to estimate for each substrate, by described procedures,[1,3] the rate constant k_c for the fully complexed substrate, and the dissociation constant K_d of the inclusion complex. As discussed elsewhere,[1] the estimated error affecting K_d is rather large and in some cases too large to allow a reasonable evaluation of the constant.



(**9**) (**10**) (**11**)

Schematic representation of the modified β-CDs

The Table shows values of k_c/k_{un}, K_d, and the enantioselectivity factors evaluated for the modified CDs as well as those for the native β-CD reported here for comparison. The enantioselectivity factor *R*/*S* is expressed in two forms:[1] as $(k_c)_R/(k_c)_S$ and (within parentheses) as the $(k_c/K_d)_R/(k_c/K_d)_S$ for the two enantiomers of each substrate. The value within parentheses is not shown in the case of (**10**) and (**11**): in fact, k_c/K_d is formally the second-order rate constant for the reaction between the substrate and the CD, which is not the mode of reaction in the case of the methylated CDs, as will be discussed later.

The rates of nitrophenol release from the esters and carbonates here investigated are increased in the presence of the 6-NMeAc-β-CD (**9**) and decreased in the presence of both 2,6-Me_2-β-CD (**10**) and 2,3,6-Me_3-β-CD (**11**). The strength of binding of the substrates to the modified CDs relative to the unmodified CD substantially increases in the case of the 2,6-Me_2-β-CD (**10**) (lower K_d values), whereas it does not change significantly with (**9**) and (**11**). The enantioselectivity effects observed with the β-CD are maintained, although slightly attenuated, in the case of 6-NMeAc-β-CD (**9**) and virtually disappear in the case of the other modified CDs (**10**) and (**11**). These are the main observations from a scrutiny of the data shown in the Table.

The general trend in the rate effects observed here is in line with published data. The high reactivity of the complexes with (**9**), following the work of Breslow and his co-workers,[5a] is due to the presence of the intrusive and flexible floor,† which raises

† Indeed, the induced c.d. spectra of (**9**) show a strong band at 219 nm, diagnostic of the insertion of the carbonyl group of the NMeAc residue; such a band decreases in intensity in the presence of increasing amounts of a complexed substrate.[7]

Table. Hydrolytic cleavage[a] of substrates in the presence of native and modified β-cyclodextrins

	β-CD			(9)			(10)			(11)		
Substrate	$\frac{k_c}{k_{un}}$	10^3K_d/M	R/S	$\frac{k_c}{k_{un}}$	10^3K_d/M	R/S	$\frac{k_c}{k_{un}}$	10^3K_d/M	R/S	$\frac{k_c}{k_{un}}$	10^3K_d/M	R/S
(1) R(+)	8.3	1.7 ± 0.3	9.5	31	0.9 ± 0.1	7	0.095	0.30 ± 0.01	1	0.28	3.5 ± 0.7	1.4
S(−)	0.9			4.5	1.1 ± 0.6	(9)	0.10	0.31 ± 0.001		0.20	4.6 ± 0.6	
(2) R(+)	77.5	3.7 ± 0.4	15.5	2 300	3.0 ± 0.3	10	0.11	0.87 ± 0.03	1.5	*c*		
S(−)	5.0	4.5 ± 1.0	(19)	230	2.3 ± 0.4	(13)	0.07	1.15 ± 0.02		*c*		
(3) R(+)	14.1	3.0 ± 0.7	7.9	157	2.9 ± 0.3	7.4	0.055	0.55 ± 0.04	0.8	0.36	5.0 ± 1.1	0.8
S(−)	1.8	4.5 ± 2.0	(12)	21.5	3.4 ± 0.5	(9)	0.065	0.33 ± 0.04		0.45	2.7 ± 0.9	
(4) R(+)	70.5[b]	2.4 ± 0.2	5.4	910[b]	2.0 ± 0.2	3.9	0.15	1.2 ± 0.2	0.5	0.75	2.4 ± 0.8	1
S(−)	13.1[b]	1.8 ± 0.3	(4.1)	235[b]	1.4 ± 0.3	(5.6)	0.30	0.9 ± 0.2		0.76	1.7 ± 0.8	
(5) R(+)	1.2		3.0	3.8	2.6 ± 1	1.1	0.0045	0.09 ± 0.01	1	0.21	4.7 ± 1.1	1
S(−)	0.4	5.5 ± 2.0		3.4	3.4 ± 0.8	(1.4)	0.0045	0.085 ± 0.01		0.22	3.4 ± 1.0	
(6) R(−)	1.8	5.2 ± 1.9	0.8	*c*			0.046	0.16 ± 0.03	1.5	0.24	1.6 ± 0.6	1.2
S(+)	2.3	8.1 ± 2.1	(1.2)	*c*			0.03	0.15 ± 0.02		0.20	1.5 ± 0.5	
(7) R(+)	3.0	2.1 ± 0.5	0.6	21.5	1.5 ± 0.3	0.35	0.051	0.51 ± 0.04	1.2	0.51	2.2 ± 0.8	0.9
S(−)	5.2	1.6 ± 0.5	(0.5)	60.5	1.7 ± 0.2	(0.3)	0.042	0.44 ± 0.05		0.54	3.4 ± 1.1	
(8) R(−)	125.0	4.4 ± 0.3	5.7	262	3.4 ± 0.2	11.4	0.09	0.37 ± 0.04	1.4	*c*		
S(+)	22.0	3.3 ± 0.4	(4)	23	2.5 ± 0.4	(8.5)	0.065	0.43 ± 0.05		*c*		

[a] At pH 10.5 (unless otherwise indicated). For k_{un} values see ref. 1. [b] At pH 9.5. [c] The changes in k_ψ upon addition of CD are too small to allow any reliable evaluation of the kinetic parameters.

the substrate in the shallower cavity and provides a better geometry for the transition state of the reaction without much affecting the strength of binding. Interestingly, the rate benefits are larger in the case of *meta*-nitrophenyl esters than in that of the *para*-isomers, indicating a combined positive effect: that of a twisted mode of inclusion, the so-called *meta*-effect,[3] coupled with a raised position of the substrate.[5]

The different extent of apparent inhibition observed with (**10**) and (**11**) is surprising. In the case of the permethylated CD (**11**), for which the normal substrate–CD interaction[2a,3] is excluded by the absence of available nucleophilic sites, inclusion of any substrate should result in a protective shielding from hydroxide ions which could promote hydrolysis, whereas in the case of 2,6-Me_2-β-CD the possibility of a nucleophilic action by the available hydroxy group at C-3, although less effective than that of the C-2 hydroxy group, could give rise to a minor inhibitory effect compared with (**11**). The opposite is observed in each case: the difference is particularly spectacular in the case of the esters (**5**) and (**6**). The most reasonable explanation is the following: (*a*) the C-3 hydroxy group of (**10**) is virtually inactive as a nucleophile for the guest scissile substrate, probably owing to the effective steric barrier provided by the methyl groups bound to the C-2 hydroxylic oxygen atoms, as suggested by Bergeron and Burton;[8] (*b*) within a complex, hydroxide ions can penetrate[9,10] to a greater or lesser extent, partly according to the size of the included molecule and strongly dependent on electrostatic factors, and promote intracomplex hydrolysis. Thus, the difference in the reactivity between the complexes with (**10**) and (**11**) is mainly due to electrostatic factors: the C-3 hydroxy groups, which are partly dissociated at pH 10.5 (assuming, as indicated by Laufer and his co-workers,[11] that the pK_a of the 2,6-Me_2-β-CD is not much different from that of the β-CD, *i.e. ca.* 12), provide a negatively charged barrier against inclusion of hydroxide ions.

The enantioselectivity effects observed are consistent with this picture. In the case of (**9**), the reaction involves interaction between the C-2 hydroxy group and the carbonyl carbon of the substrate; this implies diastereoisomeric transition states for each pair of enantiomers, just as in the case of the native CD. In the case of complexes with (**10**) and (**11**), the cleavage is a hydroxide-ion-promoted hydrolysis, implying a non-diastereoisomeric transition state for the two enantiomers. Although this is not an argument to exclude, *a priori*, an enantioselectivity effect, since the reaction occurs in a chiral environment, it is conceivable that the selectivity effects would be drastically reduced and different from those measured in the case of β-CD or (**9**), as observed.

Finally, the source of the differential binding effects of the methylated CDs is not obvious. The extension of the receptor hydrophobic cavity wall and the increased hydrophobic character should enhance the binding strength of the complexes with both (**10**) and (**11**). However, only in the case of (**10**) was a substantial effect observed; clearly, other factors are involved.

Experimental

The synthesis of substrates (**1**)—(**8**)[1] and of the modified cyclodextrins (**9**),[10] (**10**),[6] and (**11**)[6] has been reported. In the case of 6-NMeAc-β-CD (**9**) different preparations yielded products with somewhat different elemental analytical figures, suggesting that the C-6 hydroxy groups might not have been fully substituted in each case, the number of NMeAc residues apparently ranging from 6 to 7. Check experiments, however, showed that such a different extent of substitution at C-6 does not lead to appreciably different kinetic effects. The procedure used for the kinetic experiments and for the treatment[1,3,12] of raw kinetic data has been described. The observed constants k_ψ were determined by following the appearance of the nitrophenol by means of a 219 Varian-Cary or a Perkin-Elmer Lambda 5 spectrophotometer occasionally equipped with a Hi-Tech stopped-flow accessory.

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