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REACTIVITY AND STEREOSELECTIVITY IN THE CLEAVAGE OF COMPLEXES OF ACTIVATED ENANTIOMERIC SUBSTRATES WITH CYCLODEXTRINS.

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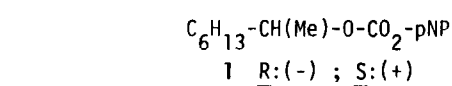
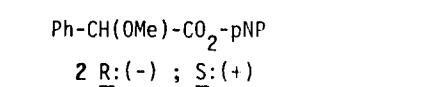
Summary: Remarkable rate accelerations and enantioselectivities in the cleavage of the enantiomers of carbonate **1** and of ester **2** in the presence of α- and β-cyclodextrins are reported.

Processes in which a substrate binds into a cyclodextrin cavity and then undergoes reaction with one of the secondary cyclodextrin's hydroxyls have attracted intense interest[1] as models of enzymatic reactions. Rate enhancements[2-4] and stereoselectivities[3-4] have been reported for a number of reactions, particularly for the cleavage of activated esters.

We have investigated the reactivity of the enantiomers of p-nitrophenyl 2-octyl carbonate[5], **1**, and of p-nitrophenyl α-methoxyphenyl acetate[6], **2**, in the presence of cyclodextrins (CDX). On the basis of previous works[2,3] and recent theories[3], substrates **1** and **2** are very poor candidates for large rate enhancements; in view of that, the rate



1 R:(-) ; S:(+)



2 R:(-) ; S:(+)

accelerations, in one case, and the stereoselectivities observed appear quite remarkable.

Rate measurements were made for aqueous sodium carbonate buffers, pH 9.5-11.4, with added 1% v/v CH_3CN at 25°C. The observed first-order rate constants for the cleavage of substrates in the absence (k_{un}) and presence (k_{obs}) of α- or β-CDX (8 to 10 different CDX concentrations, being [CDX]»[substrate]) were determined. The values of K_d (the dissociation constant of the CDX-substrate complex, assuming a 1:1 stoichiometry) and $k_2=k_c-k_{un}$ (k_c is the first-order rate constant for the cleavage of fully bound substrate) were calculated as described[2]. The results are summarized in the Table.

Carbonate **1** is cleaved within the CDX complexes at a much higher rate than expected if only the p-nitrophenyl moiety were included into the CDX cavity. Typical k_c/k_{un} values for p-nitrophenyl acetate[2a] or p-nitrophenyl phenyl carbonate[2b] are in the range 3-10, as measured under similar conditions and larger for β-CDX complexes, while that for the R-**1** complex with α-CDX is larger by almost two orders of magnitude. This suggests that the more reactive inclusion complex is the one with the alkyl chain inserted into the cavity. Indeed,

Table. Binding and Rate Constants for the Cleavage of **1** and **2** in the Absence[a] and in the Presence of Cyclodextrins, pH 10.5[b], 25°C.

Substrate		CDX	$k_c \times 10^2, s^{-1}$	$K_d \times 10^3, M$	k_c/k_{un}	$\frac{(k_2/K_d)_R}{(k_2/K_d)_S}$
1	R	α	1.2	2.5(2.7)	240 (270)	13.5 (13)
	S	α	0.18	5 (4.5)	35 (37)	
	R	β	0.63	4.4(4.5)	125 (137)	7.7(7.8)
	S	β	0.11	3.3(3.3)	22 (24)	
2	R	α	8.9	9 (8.5)	3 (3.1)	1.5(1.6)
	S	α	7.1	11 (10)	2.5 (2.6)	
	R	β	31	3 (3)	10.5(10.3)	13 (13.8)
	S	β	6.0	4 (4.5)	2 (2.1)	

[a] k_{un}, s^{-1}: 4.95×10^{-5} (**1**) and 2.9×10^{-2} (**2**). [b] The average values determined at pH 9.5, 10.5, and 11.4 are shown in parentheses. Linear plots of log k_c or log k_{un} vs pH of identical slopes were obtained.

molecular models show that, whereas both the aryl and the 2-octyl moieties may easily penetrate the cyclodextrin's cavity, the complex with the alkyl chain inserted is quite properly located for interaction: a) of the carbonyl group with the secondary hydroxy functions, and b) of its chiral centre with the rigid chiral rim of cyclodextrins, thus providing a reasonable explanation for the remarkable accelerations and enantioselectivities observed.

In the case of **2** with α-CDX, the k_c/k_{un} values are similar to that reported for the p-nitrophenylacetate and the enantioselectivity is very small. Molecular models indicate that only the p-nitrophenyl group penetrates the cavity and the aryl group of the mandelic acid portion is prevented from sufficiently deep and productive insertion by the α-methoxy group. Such mode of insertion is allowed, although by a small margin, in the cavity of β-CDX and could give rise to a more reactive complex with R-**2** than the one with p-nitrophenyl moiety inserted. Kinetic data (although not model binding) would suggest that in the case of S-**2** with β-CDX either such a complex is not formed in a significant amount or, if formed, is much less reactive than that with its enantiomer.

Further experiments aimed to substantiate the above hypotheses are in progress.

References and notes

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