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Complementary Diastereoselectivity in the Synthesis and Hydrolysis of Acylated Cyclodextrins

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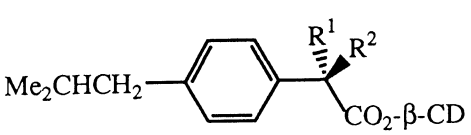
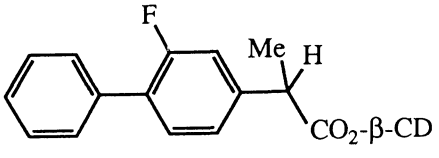
The diastereoselectivity of acylation of β-cyclodextrin with the acid chlorides of Ibuprofen, Flurbiprofen and 2-phenylpropanoic acid is complementary, in absolute and relative terms, to that observed in the hydrolysis of the corresponding cyclodextrin esters.

Acylation and deacylation reactions of cyclic oligomers of D-glucopyranose, or cyclodextrins, have been studied extensively as models of covalent catalysis by enzymes.[1] In this area, there have been several reports of the enantioselective acylation of cyclodextrins and of the stereoselective hydrolysis of esters catalysed by cyclodextrins.[2] This selectivity has been attributed to the inherent chirality of cyclodextrins and their ability to form diastereomeric inclusion complexes with chiral guests. Recently we reported[3] the first example of diastereoselectivity in the deacylation of a cyclodextrin derivative. At 37 °C in 0.1 mol dm^{-3} sodium carbonate buffer at pH 11.5, the pseudo first-order rate constants for the hydrolysis of the diastereomers of 6^{A}-O-{2-[4-(2-methylpropyl)phenyl]propanoyl}-β-cyclodextrin (**1**), to give Ibuprofen {2-[4-(2-methylpropyl)phenyl]propanoic acid} and β-cyclodextrin, were found to be 2.97 x 10^{-5} s^{-1} and 3.16 x 10^{-4} s^{-1}, with the diastereomer **1a** derived from (*R*)-Ibuprofen being the most susceptible to hydrolysis. We now report that the synthesis of the ester **1**, through reaction of the acid chloride of Ibuprofen with β-cyclodextrin, is also diastereoselective, and the stereoselectivity of the acylation is complementary to that of the hydrolysis of the ester **1**. We also describe three other examples of diastereoselective deacylation of cyclodextrin derivatives, in the hydrolysis of the esters **2**-**4**, and the complementary stereoselective acylation of β-cyclodextrin, in the synthesis of the esters **2** and **3**.

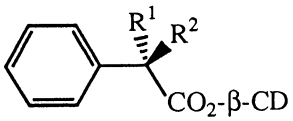
The esters **2**-**4** were obtained, each as a 1:1 mixture of the diastereomers, by treatment of 6^{A}-O-(4-methylphenylsulfonyl)-β–cyclodextrin[4] with the racemic caesium salts of Flurbiprofen {2-[(3-fluoro-4-phenyl)phenyl]propanoic acid}, 2-phenylpropanoic acid and *N*-acetylphenylalanine, respectively, in *N*,*N*-dimethylformamide at 100 °C for 24 h.[5] The diastereomers of the ester **2**, derived from Flurbiprofen, had HPLC retention times of 0.30 and 0.34 relative to β-cyclodextrin, when analysed using a Waters Carbohydrate



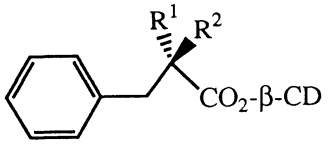
(1)
a) R^1 = H, R^2 = Me
b) R^1 = Me, R^2 = H



(2)



(3)
a) R^1 = H, R^2 = Me
b) R^1 = Me, R^2 = H



(4)
a) R^1 = H, R^2 = NHCOMe
b) R^1 = NHCOMe, R^2 = H

β-CD = 6^A-deoxy-β-cyclodextrin

Analysis column (3.9 x 300 mm) with 70% aqueous acetonitrile as eluent, and their ^{1}H NMR spectra [300 MHz, $(CD_3)_2SO$] showed doublet resonances at δ 1.42 (*J* 8 Hz) and δ 1.45 (*J* 8 Hz), attributable to the methyl groups of the Flurbiprofen moieties. The absolute stereochemistry of the diastereomers of the ester **2** was not determined. The diastereomers of the ester **3**, derived from 2-phenylpropanoic acid, were indistinguishable using ^{1}H NMR spectroscopy, but they were separable using HPLC, having retention times of 0.45 and 0.48 relative to β-cyclodextrin. The more rapidly eluting compound was found to be the diastereomer **3a**, through independent synthesis from the caesium salt of (*R*)-2-phenylpropanoic acid. The HPLC retention times of the diastereomers of the ester **4** were found to be 0.54 and 0.65 relative to β-cyclodextrin. Independent synthesis was used to establish that the diastereomer **4b**, derived from (*S*)-*N*-acetylphenylalanine, had the shorter retention time.

Hydrolysis of the esters **2**-**4** to give β-cyclodextrin and the corresponding acids, Flurbiprofen, 2-phenylpropanoic acid and *N*-acetylphenylalanine, was studied in sodium carbonate buffer at 37 °C, using HPLC and ^{1}H NMR spectroscopic analysis (Table 1). At pH 11.5, the diastereomer of the ester **2** with the longer HPLC retention time (**2i**) hydrolysed with a pseudo first-order rate constant of 2.3 x 10^{-4} s^{-1}. The other diastereomer (**2ii**) hydrolysed more rapidly, making it difficult to accurately determine the rate constant for this process through analysis of samples taken from the reaction mixture. At lower pH, each of the diastereomers of the ester **2** hydrolysed more slowly,[1,6] and at pH 10.5 the diastereoselectivity of the hydrolysis was *ca.* 7:1 in favour of the isomer **2ii**. Hydrolysis of the ester **3** was found to be less stereoselective and, in sodium carbonate buffer at pH 11.5, the ratio of the rates of hydrolysis of the diastereomers **3a** and **3b** was *ca.* 2:1. The

Table 1. Pseudo first-order rate constants[a] for hydrolysis of the esters **1-4** in 0.1 M sodium carbonate buffer at 37 °C

Ester	pH	Rate Constants	
		$k_{(R)}$	$k_{(S)}$
1	11.5	3.16×10^{-4} s^{-1} b)	2.97×10^{-5} s^{-1} b)
2	10.5	4.8×10^{-4} s^{-1} c)	7.1×10^{-5} s^{-1} c)
3	11.5	1.0×10^{-4} s^{-1}	5.2×10^{-5} s^{-1}
4	10.0	7.7×10^{-5} s^{-1}	4.8×10^{-4} s^{-1}

a) Calculated from data with $r^2 > 0.982$; r = linear correlation coefficient.
b) Data from reference 3.
c) Absolute stereochemistry was not determined in this case.

diastereoselectivity displayed in the hydrolysis of the ester **4** was similar in magnitude to that observed with the ester **2** and, at pH 10.0, the ester **4b** derived from (*S*)-*N*-acetylphenylalanine hydrolysed *ca.* 6 times more rapidly than the diastereomer **4a**. These results, combined with our earlier study[3] of the hydrolysis of the ester **1**, indicate that diastereoselectivity in the deacylation of cyclodextrin derivatives is a general phenomenon.

To examine the relationship between the diastereoselectivity of hydrolysis of the esters **1-3** and of acylation of β-cyclodextrin to give the esters **1-3**, β-cyclodextrin (0.2 M) was treated with a six-fold molar excess of the acid chlorides of (*RS*)-Ibuprofen, (*RS*)-Flurbiprofen and (*RS*)-2-phenylpropanoic acid. The reactions were carried out at room temperature in 0.1 M sodium phosphate buffer, at pH 6.0 in order to minimize hydrolysis of the product esters **1-3**.[1,6] Under these conditions only a portion of the β-cyclodextrin reacts because the major reaction of the acid chlorides is hydrolysis to the corresponding acids. The acid chloride of *N*-acetylphenylalanine is unstable and was therefore unsuitable for use in this study. The esters **1-3** were each obtained as a mixture of diastereomers in approximately 5% yield, and the diastereoselectivity was complementary, in absolute and relative terms, to that of the corresponding deacylation (Table 2), as determined by HPLC analysis of the crude product mixtures. Results were invariant for reaction times between 1-2 hours. The diastereomers of the ester **1** were obtained as a *ca.* 5:1 mixture, with the diastereomer **1a** derived from (*R*)-Ibuprofen being predominant, the ratio of diastereomers of the ester **2** was

Table 2. Diastereoselectivity of synthesis and hydrolysis of the esters **1-3**

Ester	Diastereoselectivity	
	Synthesis	Hydrolysis
1a/1b	5	10
2i/2ii	1.7	7
3a/3b	1.3	2

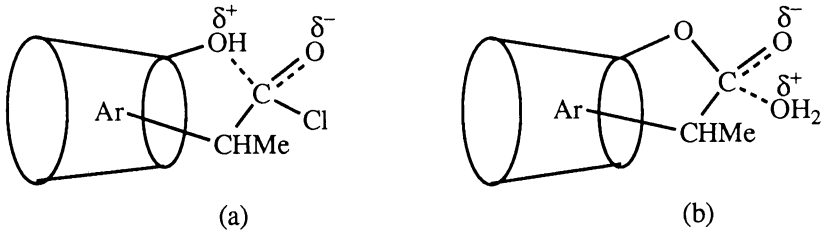


Fig. 1. Transition states (a) for the formation and (b) for the hydrolysis of the esters **1-3**.

ca. 1.7:1, with the major isomer being the one (**2ii**) that hydrolysed more readily, and the diastereomers **3a** and **3b** were produced in the ratio *ca.* 1.3:1. Thus the diastereoselectivity of synthesis and hydrolysis of the esters **1-3** decreases in numerical order. Although the correlation is based on a limited sample, there appears to be direct relationship between the stereoselectivity of the acylation and deacylation reactions. This may reflect similarities between the transition states of these reactions (Fig. 1), in which factors which affect the diastereoselectivity are common to both processes.

For the combined synthesis and hydrolysis of the ester **1**, the overall chiral discrimination in favour of the (*R*)-enantiomer of Ibuprofen is a factor of *ca.* 50. Unfortunately the low yield (5%) for the preparation of the ester **1** from the acid chloride of Ibuprofen limits the synthetic utility of this resolution procedure.

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