Chiral Differentiation in the Deacylation of 6^{A}-*O*-{2-[4-(2-Methylpropyl)phenyl]propanoyl}-β-cyclodextrin

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In 0.1 mol dm^{-3} sodium carbonate buffer at pH 11.5 the pseudo first-order rate constants for the hydrolysis of the diastereoisomers of the title compound to give Ibuprofen {2-[4-(2-methylpropyl)phenyl]propanoic acid} and β-cyclodextrin are 2.97 × 10^{-5} s^{-1} and 3.16 × 10^{-4} s^{-1}, with the diastereoisomer derived from (*R*)-Ibuprofen being the most susceptible to hydrolysis.

Interest in the differentiation between the enantiomers of Ibuprofen {2-[4-(2-methylpropyl)phenyl]propanoic acid}[1,2] stems from the fact that, although the drug is currently administered as a racemate, the physiological activity of (*S*)-Ibuprofen is much greater than that of the (*R*)-enantiomer.[3] In this report we describe the synthesis of the Ibuprofen prodrug 6^{A}-*O*-{2-[4-(2-methylpropyl)phenyl]propanoyl}-β-cyclodextrin **1**.[4] The diastereoisomers of **1** are distinguishable by HPLC and ^{1}H NMR spectroscopy, and at pH 11.5 there is a greater than tenfold difference between the relative rates of their hydrolysis. Acylation and deacylation reactions of cyclic oligomers of D-glucopyranose, or cyclodextrins, have been studied extensively as models of covalent catalysis by enzymes.[5] There have been several reports of the enantioselective acylation of cyclodextrins.[5-7] This selectivity has been attributed to the inherent chirality of the cyclodextrins and their ability to form diastereoisomeric inclusion complexes with chiral guests, and is analogous to the chiral discrimination characteristic of enzymes such as α-chymotrypsin.[7] Both the acylation and deacylation of enzymes have been shown to be stereoselective but to the best of our knowledge this is the first report of chiral differentiation in the deacylation of a cyclodextrin derivative.

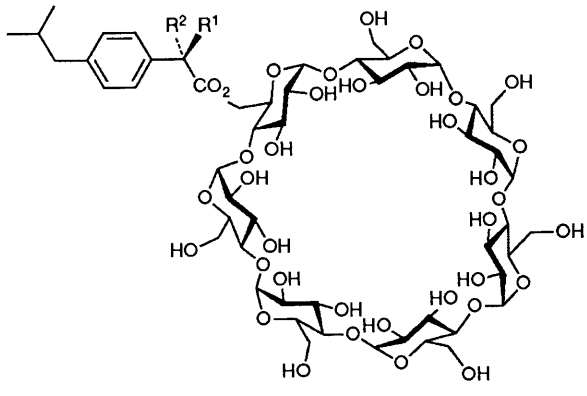
Treatment of 6^{A}-*O*-(4-methylphenylsulphonyl)-β-cyclodextrin[8] with the caesium salt[9] of (*RS*)-Ibuprofen (0.9 equiv.) in *N*,*N*-dimethylformamide at 100 °C for 24 h gave a 59% yield of the regiospecifically monosubstituted cyclodextrin derivative **1**, after chromatography of the crude product on Sephadex G-15 using 85% aqueous acetonitrile as eluent. The diastereoisomers of **1** were produced in approximately equal quantities, as determined by HPLC analysis,† and samples of each diastereoisomer were separated by preparative HPLC. One diastereoisomer **1a** had an HPLC retention time of 0.32 relative to β-cyclodextrin, and a ^{1}H NMR spectrum [300 MHz, $(CD_3)_2SO$] with resonances at δ 7.27 and 7.17 (dd, J_{AB} 8 Hz, 4H), 2.51 (d, *J* 8 Hz, 2H), 1.90 (m, 1H), 1.46 (d, *J* 7 Hz, 3H) and 0.95 (d, *J* 7 Hz, 6H), attributable to protons of the Ibuprofen moiety. The other diastereoisomer **1b** had an HPLC retention time of 0.38 relative to β-cyclodextrin. The resonances for the protons of the Ibuprofen moiety in the ^{1}H NMR spectrum of **1b** were very similar to those of **1a**, except that the aromatic protons of **1b** gave rise to resonances at δ 7.21 and 7.12 (dd, J_{AB} 8 Hz). The diastereoisomers of **1** also gave satisfactory elemental analysis and FAB mass spectral data.

In order to assign the absolute stereochemistry of the diastereoisomers of **1**, the synthesis was repeated using a sample of the (*R*)-enantiomer of Ibuprofen obtained by incubation of the methyl ester of Ibuprofen with horse liver acetone powder.[2] That product was identical in all respects to **1b**.

Each of the diastereoisomers of **1** hydrolysed to give Ibuprofen and β-cyclodextrin. The reactions were studied by HPLC analysis† and the released Ibuprofen was isolated then analysed by ^{1}H NMR spectroscopy. The rate of hydrolysis of **1a** was significantly slower than that of **1b** across the pH range from 1.3 to 13.0. For example, the pseudo first-order rate constant for the hydrolysis of **1a** on incubation at 37 °C in 0.1 mol dm^{-3} sodium carbonate buffer[10] at pH 11.5 was 2.97 × 10^{-5} s^{-1} (calculated from nine data points over four half-lives with r^2 = 0.9968; *r* = linear correlation coefficient), corresponding to a half-life of 6.48 h, while the rate constant for the hydrolysis of **1b** was 3.16 × 10^{-4} s^{-1} (calculated from seven data points over four half-lives with r^2 = 0.9978), corresponding to a half-life of 0.61 h.

The rates of hydrolysis of **1a** and **1b** are sufficiently different to be exploited in a modest kinetic resolution of Ibuprofen. A 1:1 mixture of the diastereoisomers of **1** was incubated at 37 °C in 0.1 mol dm^{-3} sodium carbonate buffer at pH 11.5 for 2 h. The reaction was then terminated by adjusting the pH to 2.0 with hydrochloric acid and the acidified solution was extracted with diethyl ether. In this way (*R*)-Ibuprofen was obtained in approximately 70% enantiomeric excess, as shown by conversion to its methyl ester through treatment with methanol that had been pretreated with thionyl chloride, and analysis of the methyl ester by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent Eu(hfc)$_3$.[2]

The diastereoselectivity observed in the hydrolysis of **1** can be attributed to the proximity of the Ibuprofen and cyclodextrin moieties. The ^{1}H NMR spectra of **1a** and **1b** indicate that the chemical environment of the aromatic protons in **1a** differs from that in **1b**. On this basis it seems likely that the chiral differentiation results from intramolecular inclusion of the Ibuprofen moiety in the annulus of the cyclodextrin, but the specific cause of the discrimination remains an enigma. Nevertheless these results show that the deacylation of cyclodextrin derivatives, as well as the acylation,[5-7] can exhibit diastereoselectivity analogous to that displayed by enzymes. In fact the extent of the chiral differentiation



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

† Analytical and preparative HPLC was carried out using a Waters Carbohydrate Analysis column (3.9 × 300 mm) with 70% aqueous acetonitrile as eluent. Under these conditions β-cyclodextrin had a retention time of 38 min.

observed in the hydrolysis of **1** is similar to that reported for the deacylation step in the hydrolysis of esters catalysed by α-chymotrypsin.[7]

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