68P

1D AND 2D PROTON NMR STUDIES OF THE CHIRAL RECOGNITION OF FLURBIPROFEN BY β-CYCLODEXTRIN

Carol A. Marchant, Sarah K. Branch,
School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, UK

As a result of the chirality of cyclodextrins (CDs) , inclusion of a racemic drug within their structure gives rise to two diastereomeric complexes. The differing thermodynamic properties of such complexes have been exploited in the resolution of racemic drugs by HPLC using CDs either in the mobile or stationary phase (Coventry 1989). Armstrong et al. (1986) have proposed that interaction between the included host and the unidirectionally hydrogen-bonded network of the secondary hydroxyl groups of the CD is an important feature of the chiral recognition mechanism on the basis of molecular modelling work with (±) propranolol. This theory is now becoming widely accepted, although there appears to be little experimental evidence to support it. We report here ^{1}H NMR studies intended to give further insight into the mechanism of chiral discrimination, using the inclusion complex of flurbiprofen (2-(2-fluoro-4-biphenylyl)propionic acid, FP) in β CD as a model.

Samples containing a mixture of 5 mg FP (either (±), (+) or (-)) and a mole equivalent of β CD were dissolved in 0.8 ml of 0.1 M NaOD/D_2O, and examined at ambient temperature by ^{1}H NMR spectroscopy on a JEOL JNM-GX270 NMR spectrometer, operating at 270 MHz for ^{1}H observation.

Comparison of the ^{1}H NMR spectra of the individual FP enantiomers in the presence of β CD with those of (±) FP and β CD in isolation reveals shifts in both the FP and CD signals which confirm the occurrence of inclusion. The difference in the spectra of these two enantiomers leads to the discrimination of drug enantiomers apparent in the spectrum of the racemate with β CD. The most prominent feature of the racemate spectrum is a duplication, of separation 0.009 ppm, of the FPα methyl doublet at 1.41 ppm.

In the complexes, the resonances arising from the hydrogens which line the CD cavity shift the most. These intermolecular interactions have been further investigated using 2D ROESY (rotating frame Overhauser effect spectroscopy) experiments which give nOe correlations in the rotating frame that are positive and of a reasonable size (Bothner-By et al. 1984). The more common NOESY (2D nuclear Overhauser effect spectroscopy) experiment also gives correlations between nuclei close in space, but may not be applicable for CD complexes because their motional correlation time may be such that nOes are close to the positive to negative crossover point (Inoue et al. 1989). The ROESY spectra for (±), (+) and (-) FP with β CD show correlations between the α methyl and aromatic FP signals and those of the hydrogens lining the CD cavity. These preliminary experiments show the potential of ROESY in identifying intermolecular interactions in CD complexes.

Armstrong D.W. et al. , Science (1986) 232: 1132-1135
Bothner-By A.A. et al. , J. Am. Chem. Soc. (1984) 106: 811-813
Coventry L. , in Chiral Liquid Chromatography ed. W.J. Lough, Blackie (1989), Chapter 8
Inoue Y. et al. , Carbohyd. Res. (1989) 194: c8-c13