Crystal Structures and Physical Properties of Flurbiprofen Salts

Carl H. Schwalbe[a], Simon J. Teat[b], Sarah E. David[a], William J. Irwin[a], Barbara R. Conway[a], Peter Timmins[c], [a]*School of Life & Health Sciences, Aston University, Birmingham B4 7ET, UK.* [b]*Diamond Light Source, Rutherford Appleton Laboratory, Chilton, Didcot OX11 0QX, UK.* [c]*Bristol-Myers Squibb, Reeds Lane, Moreton CH46 1QW, UK.* E-mail: C.H.Schwalbe@aston.ac.uk

Flurbiprofen is a nonsteroidal anti-inflammatory agent bearing a carboxyl group. As the free acid its aqueous solubility is only 0.03 mg mL^{-1}. Hydrophobicity of the counter ion does not fully determine the solubility of its amine salts[1], being 0.37, 2.80, 0.64 and 0.17 mg mL^{-1} for the cyclohexyl(CH)-, hexyl-, octyl- and adamantyl(AD)-ammonium salts respectively. ΔH of fusion is 159.0 J g^{-1} for the CH but only 81.0 J g^{-1} for the hexylammonium salt.

We report structures of the stable CH and AD salts, acquired with synchrotron radiation because they exist as fine needles.

Crystal,T	a/Å	b/Å	c/Å	β/°	ρ/Mgm^{-3}
CH,150K	14.7991	6.3014	19.7845	91.273	1.237
CH,291K	15.0841	6.2988	19.8939	91.146	1.207
AD,150K	39.350	6.3973	16.9976	90	1.228
AD,291K	39.514	6.4257	17.1454	90	1.213

In both cases the cycloalkyl group covers the 2-fold disordered fluorophenyl ring, forming a clear hydrophobic domain. Hydrogen bonds join three ammonium H atoms to two carboxylate O atoms and create infinite ladders along the short b axis, which in CH shows no thermal expansion while the a axis expands by 1.9% over 141K.

[1] Anderson B.D., Conradi R.A., *J. Pharm. Sci.*, 1985, **74**, 815.

Keywords: solubility, thermal expansion, synchrotron radiation