

## Crystal packing and pharmaceutical properties of salts of diclofenac

The poorly water-soluble drug diclofenac [2-(2,6-dichloroanilino)]phenylacetic acid, D] is a potent anti-inflammatory agent and is also used to treat solar keratoses. Salt formation may optimize its physico-chemical properties for diverse applications since the counter-ion can profoundly affect melting point, solubility, and the tensile strength of compacts. Crystal structures are known for 22 salts of D from the CSD and 6 from our laboratories. Starting with the t-butylammonium (tBut) salt, we compare systematically the structure and properties of 3 salts with larger organic moieties (cyclohexyl, cHex; benzyl, Benz; 1-adamantyl, Adam, CSD refcode PUHTIX) and 3 salts in which 1,2, and all 3 methyl groups of tBut are replaced with hydroxymethyl (AMP1; AMP2; Tris, TUDPIR). In all these cases the  $\text{NH}_3^+$  group is retained.

Crystalline  $\text{RNH}_3^+ \text{OCO}$  salts typically create hydrogen-bonded (HB) columns, built most commonly from successive  $R_4^3(10)$  rings around a  $2_1$  axis or else from alternating  $R_4^4(12)$  and  $R_4^2(8)$  rings around inversion centers. One O atom accepts two HB; the other, just one. Diclofenac salts have an extra donor: the NH group, which can donate an intramolecular HB to the second O atom. Whereas tBut takes the  $R_4^4(12)$  and  $R_4^2(8)$  form, cHex and Adam adopt  $R_4^3(10)$ , while Benz makes distorted  $R_4^4(12)$  rings, accompanied by a drastic drop in melting point. Aqueous solubility decreases as the number of carbon atoms increases. In AMP1 the columns of  $R_4^3(10)$  rings are retained, the hydroxyl group donating a third HB to a carboxylate O atom. A drastic change to HB layers with van der Waals interactions between them is found with AMP2 and Tris. Melting points increase from AMP1 to AMP2 to Tris; but aqueous solubility decreases despite the increasing hydrophilicity of the counter-ion, suggesting the overriding importance of attractive interactions in the crystal. The tensile strength of compacts is disappointingly poor ( $< 1$  MPa) even for the layer structures where slip planes beneficial to compaction might be expected. We thank the UK National Crystallography Service for data collection.

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