MS30-P4 Gemfibrozil chain conformation and crystal packing requirements

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To pack efficiently, the antilipidaemic drug gemfibrozil (Gem, Fig. 1) must find interaction partners for both its highly polar carboxyl group and its bulky nonpolar dimethylphenyl group. These can be well separated if the intervening Ph-O-$(CH_2)_3$-CMe_2-COO linkages have an all-*trans* conformation. Structures of Gem free acid [1] and four salts [2] appear in the Cambridge Structural Database. Additionally, we have determined the structures of the adamantylammonium (GAdam), benzylammonium (GBenz), cyclobutylammonium (GCbut), cyclohexylammonium (GChex), and triethanolammonium (GTea) salts. In the free acid the first four link conformations are *trans* and the last two are *gauche*. A Mogul [3] search confirms that these values are preferred for the first five torsion angles, suggesting low energy, while the sixth has no preference. The same arrangement persists in most salts, creating ether O…carboxyl O distances of 5.17-5.89 Å; but with Tris the Gem anions lengthen one such O…O distance to 6.32 Å. Complexed with human transthyretin [4], where Gem occupies the thyroxine T4 binding site, the O…O distances stretch almost 1 Å farther. In the latter two structures the carboxyl(ate) group is *trans* to the rest of the chain.

The carboxyl groups in paired molecules of the free acid form $R_2^2(8)$ dimers. In (aryl)alkylammonium salts the ionic groups form ladders of hydrogen-bonded rings, either $R_4^3(10)$ or alternating $R_4^2(8)$ and $R_4^4(12)$. Cations with one or two OH groups build these into the chains of rings; but in the Tris salt the cations form hydrogen bonded layers [2], retaining two hydrogen bonds to one carboxylate O atom and one to the other. In the non-hydroxylated ladder-forming salts a correlation coefficient of 0.85 between the average of the two O…O distances in Gem and the distance from the N atom to the most distant C atom in the cation suggests that there may be some mutual adaptation. In the transthyretin binding site Gem does not increase its number of hydrogen bonds, so any energy needed to stretch it must be supplied by packing interactions.

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[1] B. Bruni et al. (2005) *Acta Cryst.* E**61**, o1989-o1991. [2] E.Y. Cheung et al. (2007) *J. Solid State Chem.* **180**, 1068-1075. [3] I.J. Bruno et al. (2004) *J. Chem. Inf. Comput. Sci.* **44**, 2133-2144. [4] I. Iakovleva et al. (2015). *J. Med. Chem.* **58**, 6507-6515.

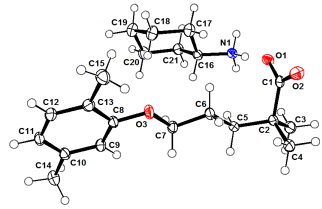

Figure 1. ORTEP drawing of the cyclohexylammonium salt of gemfibrozil

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