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Rare Case of Polymorphism in a Racemic Fluoxetine Nitrate Salt: Phase Behavior and Relative Stability

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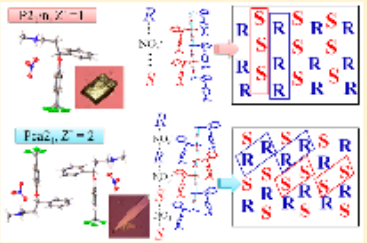
Supporting Information

ABSTRACT: Polymorphism in racemic pharmaceutical compounds is relatively unexplored. However, this phenomenon may provide an additional tool to crystal engineering, opening the doors to rational design of chiral resolution, chiral enrichment, and chiral purification of pharmaceutical compounds. In this work we report two racemic polymorphs occurring for the nitrate salt of the antidepressant drug fluoxetine (FLX): a racemate ($P2_1/n$, $Z = 4$, $Z' = 1$) and a kryptoracemate ($Pca2_1$, $Z = 4$, $Z' = 2$). The relative stability of these polymorphs was established through a combination of techniques, namely, differential scanning calorimetric (DSC), thermogravimetric analysis (TGA), hot stage microscopy (HSM), and solubility measurements. Though the two polymorphs share some structural features, the N^+—H···O^- hydrogen bonds have created dissimilar racemic motifs in their packing, resulting in different enantiomer orientations. The racemate is more stable over the temperature ranges we studied and is monotropically related to kryptoracemate. In our experiments, the obtaining of non-centrosymmetric lattice of racemic fluoxetine nitrate was shown to be dependent on kinetic factors. The thermodynamic relationships between both polymorphs were further confirmed by measuring their water solubility at 20 and 37 °C.



1. INTRODUCTION

Polymorphism is an important topic in crystal engineering, materials, and pharmaceutical sciences.[1−3] Polymorph occurrence has been associated, among other phenomena, with conformational and/or molecular packing diversity.[1,2,4−6] In racemic systems, on the other hand, the presence of two molecular components of opposite absolute configuration (enantiomers)[7] in the crystallization medium is an additional cause of the formation of polymorphs.[3,6,8] Although chiral molecules are less likely to exhibit polymorphism than achiral ones,[6] the different arrangement of enantiomers and the possibility of generation of different racemic motifs can give rise to a special kind of "racemic polymorphism" in a racemic system.[8] Depending on the crystallization conditions, racemate, *kryptoracemates* (also denoted as false conglomerate chiral), or a physical mixture of enantiomers crystals (i.e., conglomerates) can be obtained.[9−11] When a racemate is aggregated, a racemic equimolar arrangement of enantiomers is formed in which the enantiomers are related to one another by a crystallographic inversion or glide operation.[8,9,11,12] Alternatively, the spontaneous resolution of a racemic mixture can produce chiral *kryptoracemates* that are a racemic mixture of enantiomers adopting a chiral packing arrangement in one of the 65 Sohnke space groups.[9,13]

In general, the crystallization of racemic systems results in racemates,[8,12,14] whereas the *kryptoracemates* formation is more rare event.[8] In a survey of the Cambridge Structural Database (CSD),[13] only 181 kryptoracemates structures have been identified showing that they represent only 0.1% of structures deposited in CSD.[13] This fact agrees with the rarity of reports involving racemate and kryptoracemates as polymorphs in the literature.[10,11,13,15−29] In these research articles, chirality and symmetry have been attributed to different structural features of these compounds. While the chiral space group of racemates generates only one enantiomer in the asymmetric unit (ASU), the kryptoracemates show $Z' > 1$, and in most of them[13] (about 60%) they exhibit a pseudosymmetric relationship between the enantiomers.[10,11,13] In addition, the self-assembly of chiral molecules in racemic chains motifs and their supramolecular chirality are the main structural differences between these polymorphs.[21,22,28] The formation of such polymorphs of racemic systems is well recognized, but they remain relatively unexplored. Thus, "racemic polymorphism" potentially provides an additional tool to crystal engineering and opens the door to rational design of chiral resolution, chiral enrichment, and chiral purification of pharmaceutical compounds.

Fluoxetine (FLX), *N*-methyl-3-(4-trifluoromethylphenoxy)-3-phenylpropylamine (Scheme 1), is a selective serotonin reuptake inhibitor (SSRI), which is used in treating a variety of depression cases and other mood disorders.[30−32] This

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