9TH CRYSTAL FORMS@BO CONVENTION

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"CRYSTALLIZATION BY DESIGN"

MAKING, DISCOVERING, PROTECTING AND USING CRYSTAL FORMS

Pseudo-polymorphic forms of new molecular salts of the antiplated drug with thienopyridine structure S(+)Clopidogrel

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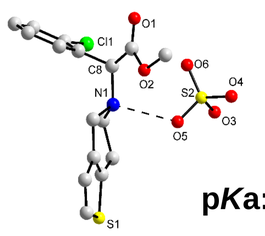
Introduction

Clopidogrel hydrogen sulfate ($ClopH^+•HSO_4^-$) is a potent platelet anti-aggregation drug acting as a selective and irreversible inhibitor of ADP-induced platelet aggregation, or more specifically a thienopyridine class inhibitor of the P2Y12 ADP platelet receptors found on the membranes of platelet cells. Chemically is a (S)-(+)-methyl 2-(2-chlorophenyl)-2-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyridin-5-yl)acetate hydrogen sulfate. Clopidogrel hydrochloride is another salt form of clopidogrel that is available in its generic pharmaceutical formulations.

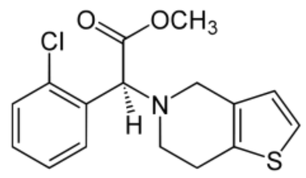
The clopidogrel molecule exists in two enantiomeric forms, the R(−) and S(+) isomers, out of which the dextrorotatory one is more active and better tolerated in pharmaceutical use.[1] The S(+)clopidogrel hydrogen sulfate salt is commercialized as PLAVIX® by Sanofi and Bristol-Myers Squibb, as well as under several generic brand names, and is one of the top-selling drugs in the word . Some different polymorphic and *pseudo*-polymorphic forms of this drug are known, however, only polymorphs I and II are used in pharmaceutical formulations.[2] X-ray crystal structures for both polymorphs, the monoclinic form I [3] and the orthorhombic form II [4], have been previously reported (CSD refcodes FUQMOU01 and FUQMOU). Because only another structure of S(+)clopidogrel salt is known so far, the S(+)clopidogrel isopropylsulfate (refcode YEXHOZ) [5], a systematic co-crystallization screening for molecular salts of clopidogrel with strong organic acids has been performed, in order to obtain new salts of this important drug.

Compounds Studied

$S(+)ClopH^+•HSO_4^-$ polymorph II

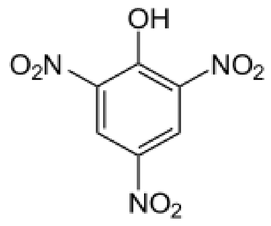


S(+)Clop (free base):



p*K*a: 4.62 (est.)

PicA



p*K*a: 0.36 (NIST)

Salt formation:
Medium-strong H-bonded ($^+$N-H···O$^-$) ionic couples [6-9]

$$\Delta pK_a = pK_a(D{-}H) - pK_a(A{-}H^+) = -4.26$$

Sample Preparation

Compound 1 with Structure 1:

$S(+)ClopH^+•HSO_4^-$: PicA = 1 : 2 *M/M* in 98% ethanol

Compound 2 with the structure 2:

S(+)Clop : PicA = 1 : 1 *M/M* molar ratio in a methanol/*n*-pentanol mixture (50% v/v)

S(+)Clop (free base): Oily liquid
$[\alpha]_{20}^{D} = \sim +57^{o}$(*c* = 1,06, methanol)

Liquid-liquid extraction of Clop in methylenchloride from aqueous solution of $S(+)ClopH^+•HSO_4^-$ treated with $NaHCO_3$

Methods

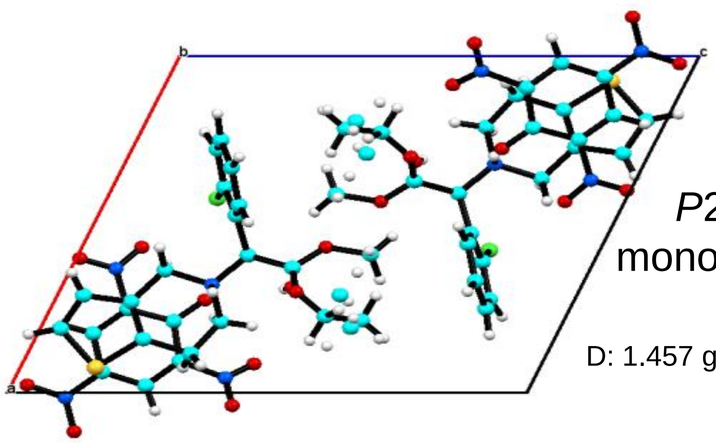
Single yellow crystals of PCC were obtained by slow evaporation of the solvent:

Characterization of PCC

Structure determination was performed by Single Crystal X-Ray Diffraction Analysis confirming the structure 1 and structure 2 to be molecular salt forms of New Chemical Entity (NEC) not so far deposited in the Cambridge Structure Database CCDC.

Crystal Structures

Structure 1 CDCC (1448941)

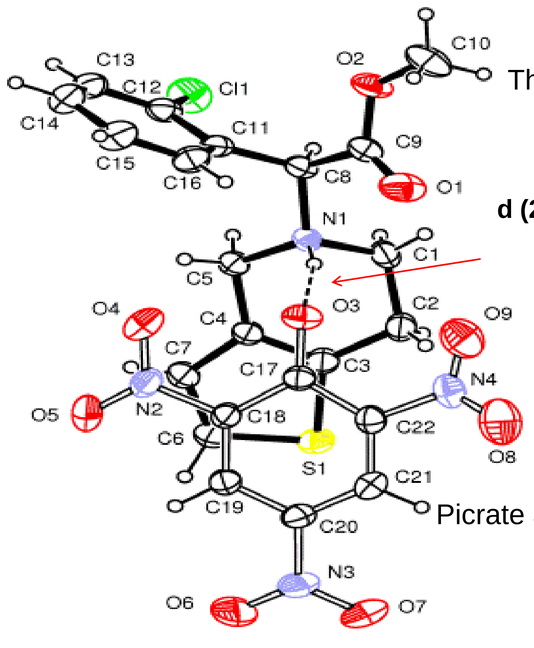


*P*2$_1$
monoclinic

D: 1.457 g cm^{-3}

Discrete $S(+)ClopH^+•Pic^-$ ionic couple

$(C_{16}H_{17}ClNO_2S)^+•(C_6H_2N_3O_7)^-•C_2H_6O$



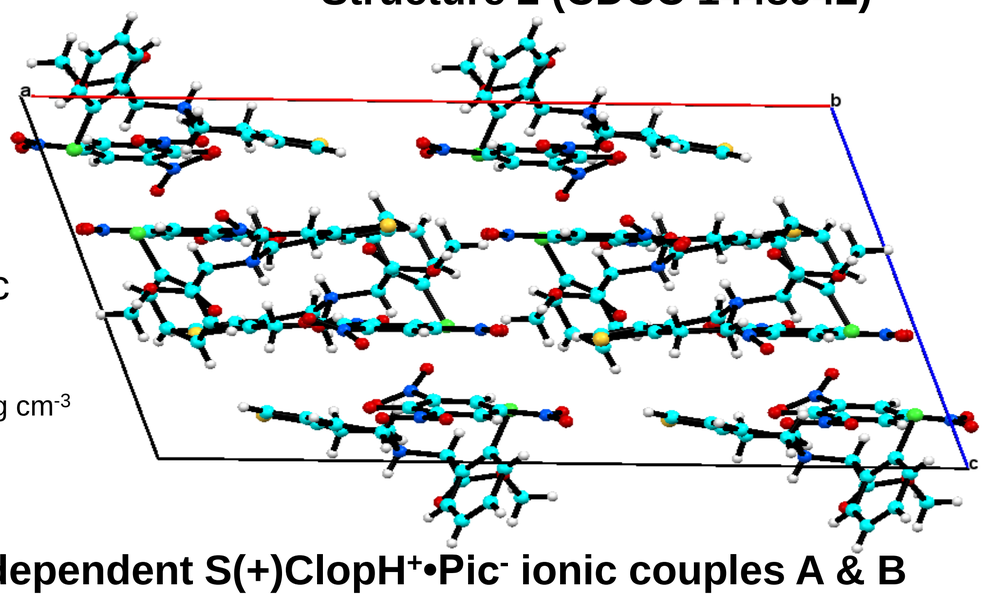
The H-N1-C8(chiral)-H fragment
trans conformation:
Torsion angle: 159°

d (2.815 Å)
170°

E_{HB}= 2.76 kcal mol^{-1}

dihedral angle:
Picrate anion & thiophene ring:
8.6(1)°

Structure 2 (CDCC 1448942)

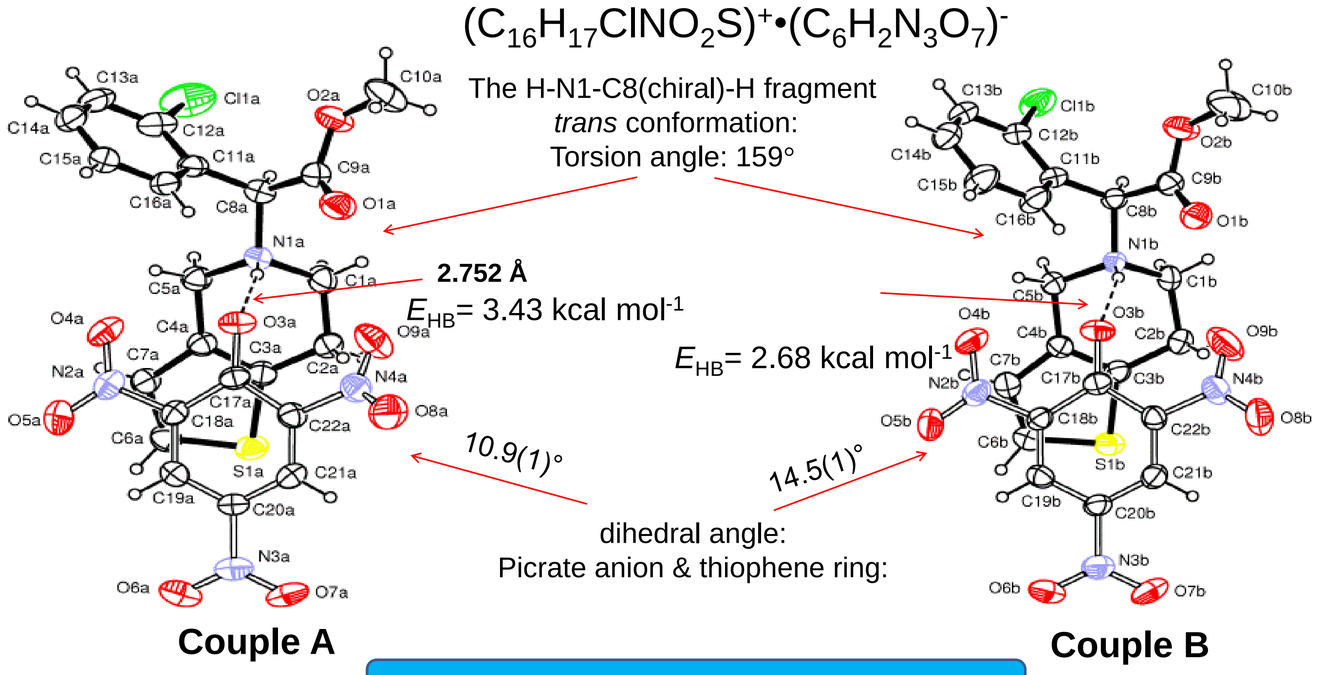


*C*2
monoclinic

D: 1.488 g cm^{-3}

2 independent $S(+)ClopH^+•Pic^-$ ionic couples A & B

$(C_{16}H_{17}ClNO_2S)^+•(C_6H_2N_3O_7)^-$



The H-N1-C8(chiral)-H fragment
trans conformation:
Torsion angle: 159°

2.752 Å

E_{HB}= 3.43 kcal mol^{-1}

E_{HB}= 2.68 kcal mol^{-1}

10.9(1)°

14.5(1)°

dihedral angle:
Picrate anion & thiophene ring:

Couple A

Couple B

Work in Progress

The systematic analysis of the molecular geometries and crystal packing, and the study of the thermodynamic properties are expected to Structure-Properties Relationships for the aforementioned salts of clopidogrel.

References

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