Quantum Chemical calculations of lattice energy for Clopidogrel picrate pseudopolymorphs

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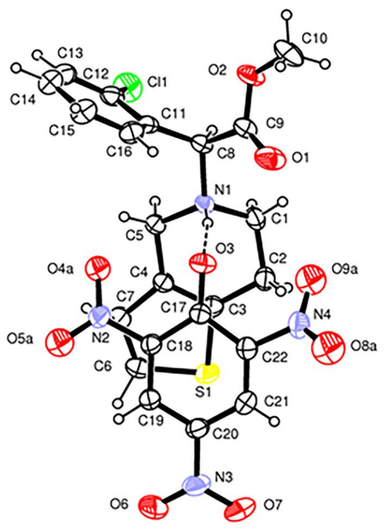
INTRODUCTION

The purpose of engineering multicomponent crystals of drug model Clopidogrel, potent antiplatelet drug, marketed as hydrogen sulfate salt ($ClopH^+ \bullet HSO_4^-$) in Plavix® (BMS-Sanofi), encompassed cocrystallization screening of clopidogrel deprotonated (free) base with coformers from the range of organic acids. The reported crystal structures relate to obtained two pseudopolymorphic forms of S(+)clopidogrel–picrate. Form 1 crystallizes in the monoclinic space group $P2_1$ with an ionic couple $S(+)ClopH+ \bullet Pic^-$ and a molecule of solvent ethanol in the asymmetric unit, while Form 2 crystallizes in the monoclinic space group $C2$ with two ionic couples in the asymmetric unit. The configurations and conformations of the ionic couples, held together by ionized +N-H···O hydrogen bonds, are nearly identical in the structures. [1]

METHODS

The H-bond energies, E_{HB} in kcal mol^{-1}, of the D−H…A bonds (D, A = N, O) in Forms 1 and 2 are evaluated by the Lippincott and Schroeder (LS) method [26–28] as a function of the D…A distance and D-H…A angle. Although more sophisticated methods for estimation of the strength and nature of non-covalent intermolecular interactions have been proposed in the literature, such as the much quoted Bader “atoms-in-molecules” (AIM) electron density analysis technique, the newer NCI technique—which is essentially based on analysis of the reduced density gradient—and the “natural bond orbital” concept (NBO) devised by Weinhold [29–31], relying on the data obtained by the LS analysis is justified by several reasons. All quantitative conclusions based on AIM or NCI approaches are based on the correlation of the data computed for a particular electron density. Due to the size of the presently studied system, the DFTB technique is suitable to compute the energetic properties in the present study. More detailed analyses of electron density-related properties will be the subject of our subsequent investigations, using more exact and advanced periodic DFT methods.

RESULTS



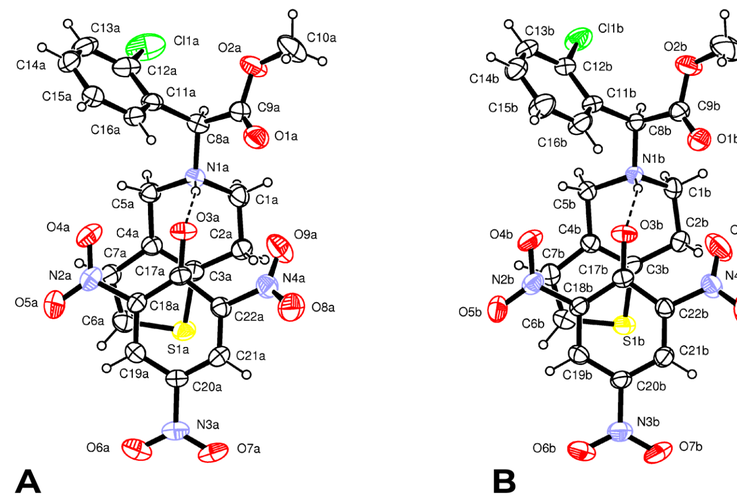
S(+)clopidogrel–picrate. Form 1

The computed DFTB lattice energies ($\Delta E_{latt.}$) of Form 1, Form 2, and the simulated non-solvated Form 1

	$\Delta E_{latt.}$ / (kcal mol^{-1})	$\Delta E_{latt.}$ / (kJ mol^{-1})
Form 1	– 105.8	– 442.5
Form 1 (non-solvated)	– 95.0	– 397.6
Form 2	– 98.5	– 412.3

$$\Delta E_{\text{latt.}} = \frac{E_{u.c.}}{Z} - E_f$$

$E_{u.c.}$ denotes the unit-cell energy and Z is the number of formula units per unit cell, E_f is the total energy of unit cell constituents in the gas phase, isolated from each other (i.e., the sum of energies of unit cell constituents in gas phase, isolated from each other). From a fundamental QM viewpoint, the lattice energy in periodic QM calculations is the expectation value of the crystal Hamiltonian



S(+)clopidogrel–picrate. Form 2

The optimized crystal structure of Form 1 with the DFTB3 methodology: (a) view along a-axis; (b) view along b-axis; (c) view along c-axis

The optimized crystal structure of non-solvated Form 1 with the DFTB3 methodology: (a) view along a-axis; (b) view along b-axis; (c) view along c-axis

LITERATURE

1. Cvetkovski, A., *et al.*, *Crystals* 2024, *14*, 10.
2. Luzzolino, L. *et al.*, *Faraday Discuss.* 2018, *211*, 275–296
3. Rychkov, D.A. *Crystals* 2020, *10*, 81