

Supplementary Material

Polymorphism in S(+)-Clopidogrel-Picrate: Insights from X-ray Diffraction, Vibrational Spectroscopy, Thermal Analysis, and Quantum Chemistry

Aleksandar Cvetkovski *, Petre Makreski, Ljupcho Pejov, Monika Stojanovska Pecova, Valerio Bertolasi,
Paola Gilli, Leonard R. MacGillivray

Table S1. Crystallographic data

Form	1	2
Formula	$(\text{C}_{16}\text{H}_{17}\text{ClNO}_2\text{S})^+\bullet$ $(\text{C}_6\text{H}_2\text{N}_3\text{O}_7)^-\bullet\text{C}_2\text{H}_6\text{O}$	$(\text{C}_{16}\text{H}_{17}\text{ClNO}_2\text{S})^+\bullet$ $(\text{C}_6\text{H}_2\text{N}_3\text{O}_7)^-$
M	596.99	550.92
Space group	$P2_1$	$C2$
Crystal system	Monoclinic	Monoclinic
$a/\text{\AA}$	12.8272(3)	25.4658(6)
$b/\text{\AA}$	7.5546(1)	14.6087(4)
$c/\text{\AA}$	15.2917(4)	13.9702(5)
$\beta/^\circ$	113.3015(8)	108.8426(10)
$V/\text{\AA}^3$	1360.97(5)	4918.7(3)
Z	2	8
T/K	295	295
$D_c/\text{g cm}^{-3}$	1.457	1.488
$F(000)$	620	2272
$\mu(\text{Mo-K}\alpha)/\text{mm}^{-1}$	0.280	0.300
Measured Reflections	12309	18220
Unique Reflections	6221	9544
R_{int}	0.0290	0.0520

Obs. Refl.ns [$I \geq 2\sigma(I)$]	5459	6207
θ_{\min} - $\theta_{\max}/^\circ$	3.84 – 28.00	3.77 – 26.50
hkl ranges	-16,16;-9,9;-20,20	-31,31;-18,16; -17,17
$R(F^2)$ (Obs.Refl.ns)	0.0593	0.0540
$wR(F^2)$ (All Refl.ns)	0.1717	0.1190
No. Variables/Restraints	442/33	685/1
Goodness of fit	1.032	1.070
$\Delta\rho_{\max}; \Delta\rho_{\min} / \text{e } \text{\AA}^{-3}$	0.524; -0.413	0.216;-0.205
CCDC Deposition N.	1448941	1448942

Table S2. Selected bond distances (Å), bond angles and torsion angles (degrees)

Form	1	2	
		A	B
Distances			
N1-C1	1.518(4)	1.509(6)	1.510(5)
N1-C5	1.506(4)	1.509(6)	1.493(5)
N1-C8	1.514(5)	1.508(6)	1.500(5)
C1-C2	1.516(6)	1.493(7)	1.510(6)
C2-C3	1.494(5)	1.488(6)	1.502(6)
C3-C4	1.357(4)	1.352(6)	1.342(5)
C3-S1	1.723(4)	1.712(5)	1.718(4)
C4-C5	1.501(5)	1.505(6)	1.516(5)
C4-C7	1.425(5)	1.422(6)	1.428(6)
C6-C7	1.341(6)	1.362(7)	1.346(6)
C6-S1	1.713(3)	1.697(4)	1.691(4)
C17-O3	1.256(5)	1.242(5)	1.240(5)
C17-C18	1.439(4)	1.444(6)	1.464(6)

C17-C22	1.446(4)	1.426(6)	1.444(6)
C18-N2	1.459(4)	1.455(5)	1.455(5)
C20-N3	1.432(6)	1.461(6)	1.454(6)
C22-N4	1.447(5)	1.457(7)	1.454(6)
Angles			
C1-N1-C5	109.6(2)	109.4(3)	109.4(3)
C1-N1-C8	110.1(2)	109.9(3)	110.2(3)
C5-N1-C8	111.2(2)	111.8(3)	113.0(3)
N1-C1-C2	111.4(3)	112.1(4)	112.4(3)
C2-C3-C4	124.7(3)	124.0(4)	124.8(4)
C2-C3-S1	124.6(2)	124.5(3)	123.9(3)
C3-C4-C5	122.8(3)	122.6(4)	122.5(3)
C3-C4-C7	113.2(3)	113.3(4)	113.2(4)
S1-C6-C7	112.5(3)	112.9(3)	113.4(3)
C4-C7-C6	112.0(3)	110.9(4)	110.8(4)
O3-C17-C18	124.9(3)	125.2(4)	124.5(4)
O3-C17-C22	123.5(3)	123.4(4)	124.3(4)
C18-C17-C22	111.6(3)	111.3(3)	111.2(3)
C17-C18-C19	124.2(3)	123.7(4)	123.7(4)
C19-C20-C21	124.2(3)	124.3(4)	124.6(4)
C17-C22-C21	124.9(3)	125.2(4)	124.5(4)
Torsion Angles			
C1-N1-C8-C9	-71.2(3)	-67.6(4)	-71.9(4)
C1-N1-C8-C11	166.8(3)	170.3(3)	167.5(3)
C5-N1-C8-C9	167.2(2)	170.7(3)	165.4(3)
C5-N1-C8-C11	45.2(3)	48.6(5)	44.8(4)
N1-C8-C9-O2	167.8(3)	158.2(3)	161.8(3)
N1-C8-C11-C12	-107.9(3)	-121.0(4)	-126.1(4)
H1N-N1-C8-H8	159(4)	169(4)	163(4)

Table S3. Hydrogen bonds parameters (Å and degrees)

D-H...A	Symm. Op.	D-H	D...A	H...A	D-H...A
Form 1					
N1-H1N...O3	x,y,z	0.82(4)	2.815(4)	2.01(4)	170(4)
C1-H1B...O1	x,y,z	0.90(6)	3.084(6)	2.50(6)	123(4)
C2-H2A...O9a	x,y,z	0.96(4)	3.375(8)	2.49(4)	153(3)
C5-H5B...O4a	x,y,z	0.99(4)	3.099(7)	2.41(4)	126(3)
O10-H10...O3	x,y,z	0.90	3.047(6)	2.18	161
C8-H8...O10	x,y+1,z	0.94(5)	3.334(5)	2.49(4)	149(4)
C1-H1B...O8b	-x+2,y+1/2,-z+1	0.90(6)	3.154(11)	2.36(5)	147(5)
C5-H5B...O5a	-x+1,y+1/2,-z	0.99(4)	3.348(6)	2.57(3)	135(3)
C4-H14...O6	-x+1,y+1/2,-z	1.01(5)	3.229(5)	2.47(4)	131(4)
C6-H6...O7	-x+2,y+1/2,-z	1.03(5)	3.669(7)	2.66(5)	167(3)
C15-H15...Cl1	x,y-1,z	1.04(6)	3.438(4)	2.80(5)	120(4)
Compound 2					
N1A-H1NA...O3A	x,y,z	0.89(3)	2.752(4)	1.88(3)	164(4)
C2A-H2A2...O9A	x,y,z	0.97	3.374(6)	2.47	154
C5A-H5A1...O4A	x,y,z	0.97	3.293(5)	2.61	128
C15A-H15A...O3B	x,y,z	0.93	3.234(5)	2.39	150
N1B-H1NB...O3B	x,y,z	0.80(4)	2.770(5)	2.01(4)	158(4)
C2B-H2B2...O9B	x,y,z	0.97	3.322(7)	2.44	150
C16B-H16B...O3B	x,y,z	0.93	3.339(6)	2.53	146
C1A-H1A2...O5A	-x+1/2,y+1/2,-z+2	0.97	3.197(6)	2.41	138
C1A-H1A1...O8B	-x+1/2,y+1/2,-z+2	0.97	3.279(7)	2.52	135
C14A-H14A...O7A	x+1/2,y-1/2,z	0.93	3.246(7)	2.47	141
C1B-H1B2...O5B	-x+1/2,y-1/2,-z+1	0.97	3.324(5)	2.39	161
C5B-H5B1...O8B	-x+1/2,y+1/2,-z+1	0.97	3.249(6)	2.58	126

Table S4. Short contacts with distances shorter than the sum of van der Waals radii in Form 2

D...A	Symm. Op.	D...A
Form 2		
C3A...C17A	x,y,z	3.347(5)
C7A...N2A	x,y,z	3.217(5)
C18A...C19B	x,y,z	3.322(6)
C6A...C4B	x,y,z+1	3.345(6)
S1B...O6B	-x,y,-z+1	3.257(4)

Table S5. The computed DFTB lattice energies ($\Delta E_{\text{latt.}}$) of Form 1, Form 2, and the simulated non-solvated Form 1

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

Technical details related to the DFTB3 calculations.

We hereby rely on the so-called third order DFTB (DFTB3 [35]). In the full third-order self-consistent charge (SCC) DFTB, the total electronic energy is expressed as the following Taylor series expansion:

$$E_{\text{DFTB3}} = \sum_i n_i \sum_{\mu\nu} c_{\mu i} c_{\nu i} H_{\mu\nu}^0 + \frac{1}{2} \sum_{ab} \Delta q_a \Delta q_b \gamma_{ab} + \frac{1}{3} \sum_{ab} \Delta q_a^2 \Delta q_b \Gamma_{ab} + \frac{1}{2} \sum_{ab} V_{ab}^{\text{rep}} \quad (1)$$

In (1), the $c_{\mu i}$ and $c_{\nu i}$ are wavefunction expansion coefficients, $H_{\mu\nu}^0$ denotes the Hamiltonian matrix elements, Δq_a and Δq_b represent the charge fluctuation terms (at atoms a and b correspondingly), while V_{ab}^{rep} is the short-range repulsive energy term between a and b . The γ function in (1) is a representation of Coulomb repulsion occurring between the corresponding density fluctuations for spherically constrained atomic densities. The analytical form of γ is represented as:

$$\gamma_{ab} = \frac{1}{r_{ab}} - S(r_{ab}, U_a, U_b) \cdot h(r_{ab}, U_a, U_b) \quad (2)$$

where the short-range function S has been introduced to provide a correct convergence behavior of γ as r_{ab} approaches zero, while h is a damping function which helps in accurate description of the hydrogen bonding interactions. It has the form:

$$h(r_{ab}, U_a, U_b) = \begin{cases} \exp \left[- \left(\frac{U_a + U_b}{2} \right)^\zeta r_{ab}^2 \right]; \exists a, b = \text{H} \\ 1; \text{in all other cases} \end{cases} \quad (3)$$

In (3), $U_{a,b}$ are the atomic Hubbard parameters, while ζ is a parameter that has been obtained by fitting to hydrogen bond energies calculated at high theoretical levels in case of series of representative clusters. The parameter Γ_{ab} in the third order correction term in (1) represents the derivatives of γ function with respect to the nuclear charges. For example:

$$\Gamma_{ab} = \left(\frac{\partial \gamma_{ab}}{\partial q_a} \right)_{q_a^0} = \left(\frac{\partial \gamma_{ab}}{\partial U_a} \frac{\partial U_a}{\partial q_a} \right)_{q_a^0}; a \neq b \quad (4)$$

etc. for other possibilities. DFTB is a DFT-based approximative scheme, *i.e.* in a sense, a “semiempirical” approach [32–35]. Hubbard parameters are computed directly with DFT, while e.g. the repulsive potential (along with other parameters) are obtained by fitting to the DFT results. In essence, the efficiency of the DFTB approach is due to the fact that the evaluation of the Hamiltonian matrix elements is carried out within a minimal basis set (consisting of pseudo-atomic orbitals), employing the two-center approximation. Such precomputed values of $H_{\mu\nu}$, along with the values of the overlap matrix elements are tabulated for different distances, within the Slater-Koster approach. The coefficients in the LCAO – MO expansion are calculated as solutions of the Kohn-Sham secular-type equations, which have the form:

$$\sum_\nu c_{\nu i} (H_{\mu\nu} - \varepsilon_i S_{\mu\nu}) = 0; \forall \mu, i \quad (5)$$

In the last equation, $S_{\mu\nu}$ denotes the corresponding overlap matrix element. The Hamiltonian matrix elements, on the other hand, contain the Mulliken charges, the γ functions and their charge derivatives:

$$H_{\mu\nu} = H_{\mu\nu}^0 + S_{\mu\nu} \sum_c \Delta q_c \left[\frac{1}{2} (\gamma_{ac} + \gamma_{bc}) + \frac{1}{3} (\Delta q_a \Gamma_{ac} + \Delta q_b \Gamma_{bc}) + \frac{\Delta q_c}{6} (\Gamma_{ca} + \Gamma_{cb}) \right] \quad (6)$$

The need for a self-consistent solution of (5) is obvious.