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Ab Initio Prediction of Stable Crystal Structure of Procarbazine Molecule

Research Article

R. Meenashi [1], P. Jayalakshmi [1], B. Jothi [1], K. Selvaraju [1,*] and A. David Stephen [2]

[1] *Department of Physics, Kandaswami Kandar's College, Velur 638182 Tamilnadu, India*
[2] *Department of Physics, Sri Shakthi Institute of Engineering and Technology, Coimbatore 641062, Tamilnadu, India*
*__Corresponding author:__ physicsselvaraj@gmail.com

Abstract. The crystal structure of procarbazine molecule was predicted using first principles of quantum mechanics. The gas phase optimization was carried out by density functional theory and the resulted geometric coordinates were utilized for the search of hypothetical packings which reveals the possible stable conformers under a repulsion alone potential field with minimum cell volume. The thermodynamically favor structure was resulted from the lattice energy minimization of these hypothetical structures from the using the repulsion-dispersion potential field. The stability of global minimum structure was confirmed from the hydrogen bond interactions and second derivative properties.

Keywords. Lowest energy conformer; X-ray diffraction; Fingerprint plot; Mechanical stiffness

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1. Introduction

Crystal Structure is the orderly arrangements of atoms, molecules or ions in a lattice, generating dense packing of the molecules [13]. The properties of the bulk materials solely affects on the dense packing of the molecules in solid. This in particular found to be an important area of research in pharmaceutical fields, where the discovery of new crystal forms at final stages of the development may cause wide consequences. The current research priority was to identify the possible stable crystal forms of procarbazine molecule; a pharmaceutical chemotherapy drug

belongs to the class of alkylating agent used for the treatment of brain cancer [3]. The structural analysis of the molecule revealed the hydrazine functional group attached to the aromatic carbon atom along with the formamide group attached to the opposite aromatic carbon atom.

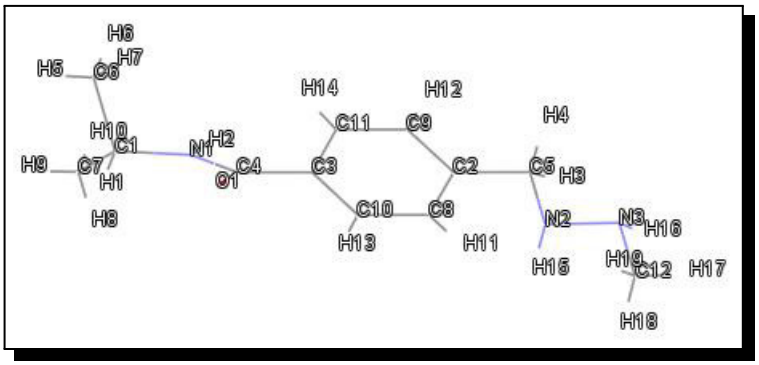

Figure 1. Optimized geometrical structure of procarbazine

As the experimental analysis of the possible dense packing of the procarbazine molecule found to be challenging, ab initio prediction of the packing motifs of the parent molecule from the lattice energy associated gained its vitality.

2. Computational Details

The prior aim of the research is to analyze the dense crystal structure of the molecule and identification of the space group which it belongs; using which probability of finding new polymorphic forms can be studied in detail. The ab initio prediction of the stable conformer of the procarbazine molecule was initiated from the gas phase optimization of the geometrical structure by virtue of Density field theory approach viaBecke Three-Parameter Hybrid Functionals includinglocal and non local electronic correlation (B3LYP) [6] incorporating 6-31G(d) polarized basis set operation using the Gaussian 09 package [5] to generate the geometric coordinates for the dense packings. The optimized conformer of the procarbazine molecule was subjected for the global search to identify the space group where it belongs. The global search was executed using MOLPAK algorithm [7], where the algorithm was designed to analyze the possible dense packing of the parent molecule within a threshold interaction defined by the degrees of freedom, lattice variables and symmetry operations generated by orientation and repetition of the molecule in a multidimensional grid, in steps of 10° ranging from −90° to 90° generating $(19)^3$ 6859 hypothetical structures. The packing density and the unit cell volume of each generated structure was analyzed with PMIN refinement [8] using a repulsion only UMD potential [16] and optimize the packing arrangements in the commonly encountered space groups P1, P-1, P2, Pm, Pc, $P2_1$, P2/c, $P2_1/m$, P2/m, $P2_1/c$, Cc, C2, C2/c, Pnn2, Pba2, Pnc2, $P22_1$, $Pmn2_1$, Pma2, $P2_12_12_1$, $P2_12_12$, $Pca2_1$, $Pna2_1$,Pnma and Pbca. The PMIN optimized densest structures were exposed to the inner lattice minimization using the DMACRYS algorithm [9].

The densest packing of the molecules inhibited in the common space groups were lattice energy minimized by analyzing the multipole associated with the system. The lattice minimization was carried out in a potential field incorporating the repulsion and

dispersion correlation parameters.

$$U = \sum_{i\in 1,k\in 2} \left[(A_{ii}A_{kk})^{1/2}\right] \exp\left[-(B_{ii}+B_{kk})R_{ik}/2\right] - (C_{ii}C_{kk})^{1/2}/R_{ik}^{6}, \tag{2.1}$$

where i and k are the atoms in different types of molecules 1 and 2. The potential field incorporated in the lattice minimization was generated from the FIT potential, parameterized by Williams and Cox [15], with additional terms for the hydrogen atoms bound to nitrogen later fitted by Coombes et al. [2].

The electrostatic interactions along with intermolecular bindings of the parent molecules were analyzed in detail from the set of multipoles generated from the GDMA algorithm [12] via MP2 level charge density scrutiny through MP2/6-31G(d,p) basis set operation. The lattice minimized procarbazine molecules attaining the Born criteria of mechanical stability [11] with valid Eigen value representations were tabulated on the basis of energy ranking. The thermodynamic stability predicted molecules were authenticated from the second derivative properties calculated from the C_{ij} elements of the Hessian matrix. As the stability of the conformers depends on the ability to achieve the intermolecular short contacts, Ewald summed energies in terms of charge-charge, charge-dipole and dipole-dipole terms were also calculated together with the volume and density of the selected structures using the repulsion-dispersion potential of form (2.1). Detailed studies have been carried out to justify the thermodynamic stability of the predicted conformers by virtue of the XRD patterns along with Hirshfeld surface of interactions.

3. Ab Initio Prediction of the Global Minimum of Procarbazine

The thermodynamically stable crystal packing of the procarbazine molecules was predicted from the lowest energy associated with the conformers satisfying the criteria of (3.1).

$$E_{\text{total}} = U_{\text{lattice}} + \Delta E_{\text{intra}}\,. \tag{3.1}$$

The initial gas phase optimization of the procarbazine molecule to generate the geometric cordinates for all possible dense packing was carried out using DFT approach by virtue of beckes 3 parameter exchange correlation factors using the polarized basis set operations of 6-31G(d p). The global search for the densest conformers was initiated for the optimized procarbazine molecule using the MOLPAK algorithm. The PMIN refined hypothetical structures of procarbazine within the threshold interactions incorporating the repulsion alone potential field was selected with minimum cell volume criteria for inner lattice minimization. The lattice minimization incorporating repulsion-dispersion potential field of form (2.1) incorporating the multipole associated with the system via GDMA algorithm, was carried out for the hypothetical densest structures belonging to the commonly encountered space groups of the CCDC database. The mechanical stability of the lattice energy minimized procarbazine crystal were studied in detail from the Born criteria achieved by the conformers. In the current research the hypothetical structures encountering in valid minimization with non zeroeigen values were reminimized by removing the negative representations in the symmetry constraints. The intermolecular interactions prevailed in the dense packings of the molecule was analyzed in detailed using the ewald summed interactions. The predicted conformers were selected and ranked on the basis of

the total energy associated to determine the global minima of procarbazine; the possible most stable crystal structure of procarbazine (Table 1). The data from the table 1 revealed that the global minima of the parent molecule were generated at the energy of −120.024 KJ/mol with P-1 space group. The structure was found to be dense with exhibited cell density of 1.0933 g/cm^3.

Table 1. List of lowest energy conformers of procarbazine molecule

Structure	Spacegroup	Ulattice	a(Å)	b(Å)	c(Å)	α(°)	β(°)	γ(°)	Cell density
str 1	P-1	–120.024	14.530	5.288	13.116	109.843	59.880	72.810	1.093
str 2	Pca21	–119.566	18.242	5.232	13.851	90.000	90.000	90.000	1.112
str 3	P1121	–116.521	27.837	9.547	5.161	90.000	90.000	90.000	1.072
str 4	P21/c	–114.881	9.189	5.277	27.696	90.000	96.617	90.000	1.102
str 5	Pc	–114.875	9.191	5.277	27.695	90.000	96.626	90.000	1.102
str 6	Pbcn	–112.510	29.377	5.204	18.381	90.000	90.000	90.000	1.046
str 7	P21/n	–108.524	5.057	10.020	27.855	90.000	109.224	90.000	1.103
str 8	P2111	–108.079	33.798	5.317	8.389	108.673	90.000	90.000	1.029
str 9	Pna21	–107.793	28.352	9.786	5.239	90.000	90.000	90.000	1.011
str 10	C2/c	–106.363	25.590	5.189	30.120	90.000	46.101	90.000	1.020
str 11	P21	–103.852	21.020	7.257	12.180	90.000	23.403	90.000	0.996
str 12	P212121	–101.689	11.203	13.521	9.109	90.000	90.000	90.000	1.065
str 13	P21212	–98.460	38.891	7.970	5.223	90.000	90.000	90.000	0.908
str 14	P21/c	–98.182	5.481	20.886	12.158	90.000	94.631	90.000	1.060
str 15	Cc	–98.063	4.857	10.839	28.352	90.000	106.933	90.000	1.029
str 16	Pna21	–96.966	7.700	6.617	27.445	90.000	90.000	90.000	1.051
str 17	C2	–96.596	27.957	6.731	8.120	90.000	114.411	90.000	1.057
str 18	Pbca	–96.066	10.919	13.909	18.365	90.000	90.000	90.000	1.054
str 19	P21/c	–94.296	12.728	6.470	18.682	90.000	95.852	90.000	0.961
str 20	P-1	–93.434	12.130	8.243	8.452	86.961	63.901	80.246	0.983
str 21	P1	–89.655	39.992	7.973	10.084	90.000	90.000	90.000	0.914
str 22	Pca21	–89.620	16.284	10.687	8.478	90.000	90.000	90.000	0.996
str 23	P21	–89.069	15.361	9.236	4.953	90.000	96.863	90.000	1.053
str 24	Pna21	–89.051	11.236	17.889	7.207	90.000	90.000	90.000	1.015
str 25	P21	–86.364	8.457	20.945	8.146	90.000	90.000	90.000	1.019
str 26	Pbca	–85.211	18.929	18.464	8.659	90.000	90.000	90.000	0.971
str 27	P1121	–80.863	31.266	5.364	8.717	90.000	90.000	90.000	1.006
str 28	C2/c	–79.639	14.414	11.661	19.048	90.000	72.591	90.000	0.962
str 29	C2/c	–79.310	15.182	10.340	22.685	90.000	125.748	90.000	1.017
str 30	Pna21	–77.916	17.754	12.322	7.243	90.000	90.000	90.000	0.928

The crystalline nature of the global minimum of the procarbazine molecule at 0 K was authenticated from the simulated XRD patterns. The peaks generated at the X-ray diffraction spectrograph, specifically the highest peak at $2\theta = 20°$ indicated the crystalline nature of the procarbazine molecule at 0K which are possibly thermodynamically stable.

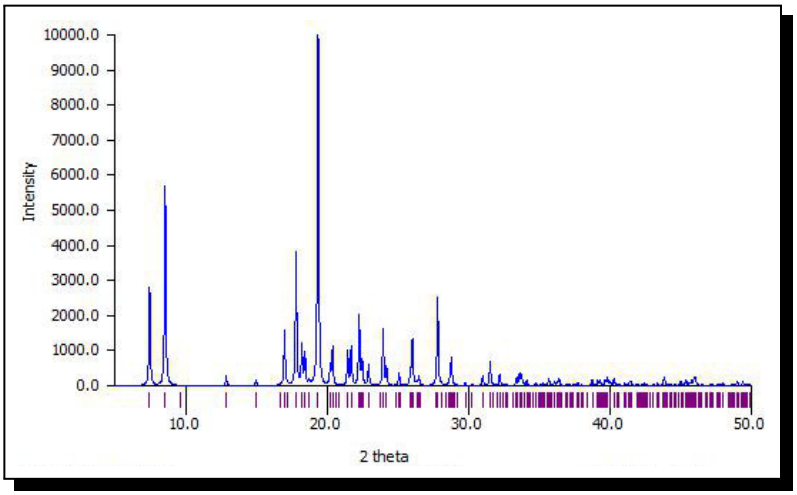

Figure 2. XRD patterns of the predicted procarbazine crystal structure

The probability of a molecule to get crystallized solely depends on the ability to achieve intermolecular Hydrogen bonds and thereby attaining thermo dynamical stability, thus studies have been carried out to analyze the intermolecular H-Bonds of the predicted conformers using PARST algorithm [4] (Table 2).

Table 2. Predicted hydrogen bond interactions prevailed in the procarbazine molecule

Possible H-Bonds of the molecule		
Interactions	**Bond length (Å)**	**Bond angle (°)**
N1-H2…O1	3.111	167.03
C7-H10…O1	3.470	122.40
C11-H14…O1	3.416	124.53
C7-H8…O1	3.485	145.49
C8-H11…N2	3.684	150.70

The PARST analysis gives the details of the possible Hydrogen bonds of the system. The studies exposed that the oxygen atom of the ketone group attached to the aromatic ring contributes to the intermolecular hydrogen bonds prevailed in the system, being the acceptor of the hydrogen atoms. The studies have successfully justified the ability of the predicted crystal structure to get crystallized by virtue of the short contacts incorporating the terminal ketone group attached to the molecule. The strength and contribution of the intermolecular short contacts towards the crystal stability was studied in detail from the 2D finger print plot generated by the crystal explorer software.

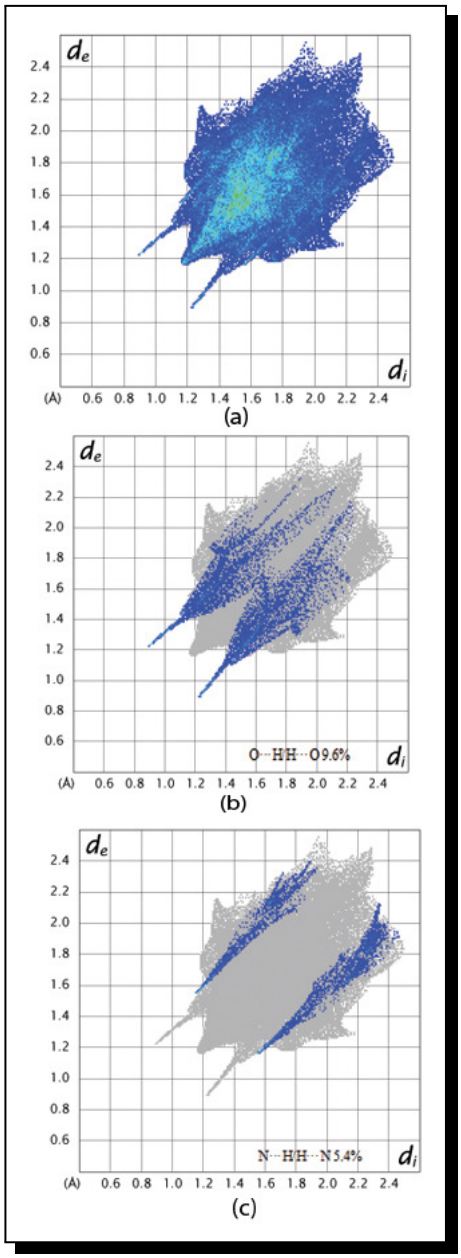

Figure 3. Finger print plot of predicted procarbazine crystal (a) 100 % contribution of all elements, (b) 9.6% of O···H/H···O interaction, (c) 5.4% N···H/H···N interaction

The finger print plots of the intermolecular contacts revealed the pointed nature of the O···H/H···O and N···H/H···N interactions towards the lowest region of the di/de region indicating the strongest interaction with 9.6% and 5.4% contribution towards the hirshfeld surface. The studies have exposed the ability of the predicted procarbazine crystal to achieve thermodynamical stability by virtue of the analyzed short contacts. The mechanical stability and the sensitivity of the dense packing towards the external stress and strain were judged from the diagonal elements of the C_{ij} matrix, exploiting the Born criteria of stability. The crystal structure was found to be hard with elastic stiffness 18.47629 GPa (Young's modulus), proving the mechanical strength.

Table 3. Elements of the mechanical stiffness of predicted procarbazine crystal structure

Predicted conformer	Diagonal elements of elastic stiffness tensor matrix C_{ij}/GPa						Young's modulus (GPa)
Str 1	**C11**	**C22**	**C33**	**C44**	**C55**	**C66**	18.47629
	28.10386	22.51069	17.59210	8.24212	9.15295	8.22676	

As the morphological importance of crystal structure depends on the growth rate and surface area of the crystal phases, studies have been carried out to interpret the morphology and the growth rate of str1 by calculating the interplanar d-spacing through the formula

$$1/d_{hkl}^2 = (1/\sin\beta)(h^2/a^2 + k^2\sin^2\beta/b^2 + l^2/c^2 - 2lh\cos\beta/ac). \tag{3.2}$$

The morphological analysis of the structure have been carried out by using the BFDH theory [14] incorporating the interplanar spacing ($\boldsymbol{d}_{hkl}$) and the crystal symmetry which provide a good insight to the morphology of thepredicted crystal phase of procarbazine. The growth rate of the each miller indices have been noted and tabulated to expose the morphologically importance of the structure. The studies have revealed miller indices of (1 0 0) and (0 0 1) which are morphologically important due to their comparatively less growth rate by exhibiting the higher d_{spacing} [1].

Table 4. Calculated Interplanar d_{spacing} of the procarbazine crystal structures

h	***k***	***l***	**a(Å)**	**b(Å)**	**c(Å)**	$\alpha(^o)$	$\boldsymbol{\beta}(^o)$	$\boldsymbol{\gamma}(^o)$	***d*(Å)**
1	1	0	14.5304	5.2882	13.116	109.8433	59.8803	72.81	4.97
0	1	-1	14.5304	5.2882	13.116	109.8433	59.8803	72.81	4.90
1	1	-1	14.5304	5.2882	13.116	109.8433	59.8803	72.81	4.68
2	1	0	14.5304	5.2882	13.116	109.8433	59.8803	72.81	4.27
-2	1	0	14.5304	5.2882	13.116	109.8433	59.8803	72.81	4.27
-1	-1	1	14.5304	5.2882	13.116	109.8433	59.8803	72.81	4.68
0	-1	1	14.5304	5.2882	13.116	109.8433	59.8803	72.81	4.90
-1	-1	0	14.5304	5.2882	13.116	109.8433	59.8803	72.81	4.97
1	0	0	14.5304	5.2882	13.116	109.8433	59.8803	72.81	14.50
0	0	-1	14.5304	5.2882	13.116	109.8433	59.8803	72.81	13.09
-1	0	-1	14.5304	5.2882	13.116	109.8433	59.8803	72.81	9.41
1	0	1	14.5304	5.2882	13.116	109.8433	59.8803	72.81	9.41
-1	0	0	14.5304	5.2882	13.116	109.8433	59.8803	72.81	14.50
0	0	1	14.5304	5.2882	13.116	109.8433	59.8803	72.81	13.09

The morphological studies have successfully predicted the needle like shape of the crystal lattice of procarbazine molecule.

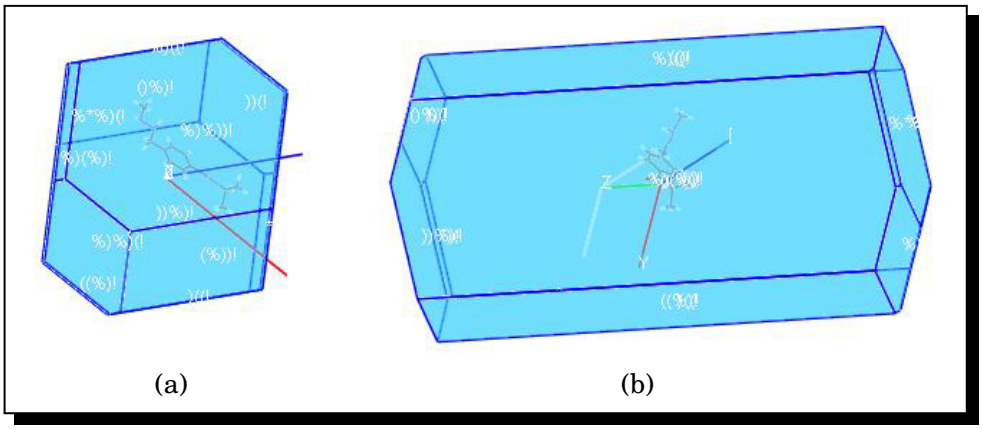

Figure 4. (a) transverse view, (b) longitudinal view of the BFDH predicted procarbazine crystal phase

The theoretical analysis of the str 1 revealed that the structure is a thermodynamically possible stable triclinic crystal system of procarbazine with P-1 spacegroup, which have the ability to crystallize by attaining intermolecular short contacts with stabilized dense packing.

4. Conclusion

The ab initio prediction of the possible crystal packing of procarbazine molecule initiated by a gas phase optimization using the DFT level approach was found to be authentic. The methodology has successfully predicted the possible lowest energy conformers of the gas phase procarbazine encountered in the common space groups of the CCDC database. The global search for the hypothetical conformers of the procarbazine acid successfully generated possible dense packings within the repulsion alone potential field. The structures were selected for the inner lattice minimization, thereby predicting the global minimum of procarbazine crystals. The studies have revealed that the global minima of procarbazine were crystalline at 0K from the simulated XRD pattern. The lowest crystal structure generated at P-1 space group was found to be thermodynamically stable from the intermolecular interactions with the ability to get crystallized via hydrogen bonds initiated through the Oxygen and Nitrogen atoms of terminal functional groups. The hirshfeld surface and the finger print plots also revealed the contribution of the prior interactions towards crystal stability. The studies can be concluded as the lowest energy structures generated in Table 1 as possible crystal phases of gas phase procarbazine acid molecule; global minimum being the most possible crystal phase of the molecule.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

All the authors contributed significantly in writing this article. The authors read and approved the final manuscript.

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