Isomers of Biologically Active 2-Aminopyrimidinium Picrate through Intrinsic Reaction Coordinate Analysis and Spectroscopic Measurements

T. Karthick, Keshav Kumar Singh, Swapnil Singh, Poonam Tandon, and B. Narayana

ABSTRACT

In the present study, the isomeric forms of a biologically active 2-aminopyrimidinium picrate (2APP) cocrystal were investigated using spectroscopic measurements (FT-IR and FT-Raman) and density functional theory calculations. The vibrational assignments of IR and Raman peaks were predicted and the experimental FT-IR and FT-Raman spectra of the condensed phase of 2APP were compared with the simulated one. The intrinsic reaction coordinate (IRC) analysis was performed on all the possible reaction pathways to identify the isomeric forms of 2APP and transition state geometry. From the IRC analysis, a relatively stable form (named as isomer 2) has been identified in addition to the existing isomeric form (isomer 1) in the crystalline packing of 2APP. The presence of non-covalent interactions within the isomeric forms of 2APP was investigated with the help of quantum topological atoms in molecules analysis. Reactivity descriptors and charge delocalization from lone pair to acceptor entities of both the isomers were predicted to validate the interactions present in the molecule and also to understand the charge distribution within the molecule.

ARTICLE HISTORY

Received 12 June 2021
Accepted 25 October 2021

KEYWORDS

2-Aminopyrimidinium picrate; vibrational spectra; intrinsic reaction coordinates; charge delocalization; non-covalent interactions

Introduction

Picrates are well-known for their explosive properties and used as explosives during the first and second world wars. Picrates are also used to produce aniline; the most important starting material in the chemical synthesis. While adding suitable cations to the picrate anions, biologically important picrate cocrystals are formed. The biological applications of these picrates include anticancer, antitumor, anti-psychotic drugs, etc. Cationic and anionic species in these picrate cocrystals are held together by strong hydrogen bonds. A biologically active 2-aminopyrimidinium picrate (hereafter abbreviated as 2APP) molecule was crystallized by one of our coworkers Narayana and his colleagues and resolved its X-ray crystallography data. Also, Jasinski and coworkers have synthesized biologically active picrates such as lomefloxacinium picrate, acetylpiperaazinium picrate, and 1-(2-methyl-5-nitrophenyl)guanidinium picrate and resolved their crystalline structures. In the present work, the structural properties of 2APP at the atomic level...
were predicted using spectroscopic techniques and quantum chemical computations to identify its isomeric forms. Moreover, the reaction pathways and possible structural isomers were investigated using density functional theory (DFT) computations. The spectroscopic studies were carried out to verify the conformations of 2APP in the crystalline geometry. In general, the biologically active molecules bind with macromolecular targets through hydrogen bonds between the electron donor and acceptor species of the ligand and targets. Moreover, it is necessary to find the electrophilic and nucleophilic sites of the ligand to understand the binding mechanisms. Hence, the Fukui function analysis was performed to reveal the relative electrophilicity and nucleophilicity of 2APP.

Experimental

The compound 2APP was synthesized by conventional synthesis procedures. A yellow color crystalline sample of 2APP approximately 1 mg with potassium bromide (KBr) reference material in the ratio of 1:200 (2APP:KBr) were ground well for 15 min. Using a hydraulic press, a disc-shaped pellet of the sample-reference mixer was made. Fourier transform IR spectrum (FT-IR) of 2APP was recorded in the mid-IR region from 4000 to 450 cm\(^{-1}\) on a Perkin Elmer Spectrum One FT-IR instrument with a spectral resolution of 1 cm\(^{-1}\). The Raman spectrum of 2APP was measured at room temperature in a Horiba Lab-Raman spectrometer equipped with a liquid N\(_2\)-cooled CCD detector. The spectrometer slits were set for a resolution of 2 cm\(^{-1}\). A He–Ne laser of 633 nm line was used as an excitation source.

Methodology

To study the structure and related properties of 2APP, the electronic structure calculations were performed using the Gaussian 16 suite of ab initio program. The electronic structure of 2APP is optimized to the minimum energy using the density functional wB97XD with 6-311++G (d,p) basis set. WB97XD functional is a range separated functional which includes Grimme’s second-order dispersion corrections in its definition. Thus, it is capable of simulating the effect of the London dispersion forces. The inclusion of dispersion correction in DFT is very important while describing the molecular structure consisting of more fragments. Because, they form often intermolecular hydrogen bonds with its neighbors. This functional has been successfully applied for studying the reaction mechanisms of complexes and cocrystals and expected to provide near experimental accuracy. Therefore, WB97XD functional has been chosen to simulate the isomerization in 2APP. The harmonic frequency calculations have been performed on the optimized geometry of 2APP at wB97XD with 6-311++G (d,p) level of approximation to confirm the nature of stationary point as minima as well as to simulate the mid-infrared (IR) and Raman spectra. The transition stat (TS) geometry search has been performed using a quadratic synchronous transit (QST2) approach and investigated the potential energy surface (PES) to locate the different isomers of 2APP and transition state (TS) that exists between the isomers. Full of positive harmonic frequencies obtained in the calculation for both the isomers validate their stationary point minima on the PES and TS structure with one non-negligible imaginary frequency confirms the stationary point maxima on the PES. Intrinsic reaction coordinates (IRCs) were calculated to ensure whether the TS structure acts as an intermediate for both the reactant and product. The spectra generated from the frequency calculations were scaled down using the wavenumber linear scaling (WLS) method to overcome the overestimation of results due to the neglect of anharmonic vibrations. To calculate the local reactivity descriptor and Fukui functions, the partial charges on individual atoms were calculated using Hirshfeld population analysis at wB97XD/6-311++G(d,p). In order to understand the nature of intermolecular and intramolecular
interactions in 2APP, natural bond orbital analysis has been performed using NBO 3.0 interface program as implemented in Gaussian 16.\textsuperscript{45}

**Results and discussion**

**IRC analysis and classification of isomers**

The crystal structure of 2APP is optimized at wB97XD/6-311++G(d,p) level of approximation and the optimized structure of 2APP (hereafter abbreviate as isomer 1) are presented in Figure 1. The coplanar structures of picrate (ring 1) and pyrimidine (ring 2) molecules in isomer 1 (total energy = \(-1240.3495\) Hartree, herein total energy = electronic energy + zero-point vibrational energy (ZPVE) corrections) are not much varied during the optimization. It confirms the cocystal formation through higher binding energy. In isomer 1, the pyrimidine ring has NH\(_2\) group and N-H bond and they bind with picrate ring through N-H-O hydrogen bonds. The crystal structure of isomer 1 is predicted to be a polar molecule where ring 2 donates some of its charges to the ring 1 and forms anionic–cationic system.

To understand the chemical reactivity of isomer 1, local reactivity descriptors were calculated using wB97XD/6-311++G(d,p) level of theory. The local reactivity descriptors are important tools to predict the possible binding sites of a particular reaction complex.\textsuperscript{46,47} The picrate molecule (ring 1) of isomer 1 is a highly reactive with strong nucleophilic sites such as O25, O26 and O31. The Fukui descriptors \(s^+\) and \(s\) of isomer 1 and 2 represent the sites prone to nucleophile and electrophilic attack and are tabulated in Tables S1 and S2 (Supplementary Information). Among O25, O26 and O31, the O25 has strong nucleophile character (\(s^- = 0.6523\) a.u.) as compared to the other reactive sites of the ring 1 i.e. O26 (\(s^- = 0.1922\) a.u.) and O31 (\(s^- = 0.1966\) a.u.). On the other hand, there are two atoms of hydrogen (H3 and H6) on the pyrimidine ring (ring 2) in the vicinity of the O25 are prone to be attacked by O25. Hence, the atom O25 makes strong hydrogen bonds O25-H6 (1.6261 Å) and O25-H3 (1.9656 Å). A ring 2 in isomer 1 is a heterocyclic six-membered ring that holds strongly electronegative nitrogen atoms N5 and N13. This results in a less nucleophile character of the heterocyclic ring as the nitrogen atoms withdraw the majority of the electron density from the heterocyclic ring.\textsuperscript{48} Additionally, the amine group (N1H\(_2\)) at C2 position also withdraws some of the electron density. This behavior makes the hydrogen of the N5H6 group strongly positive as nitrogen N5 strip electron from H6 and ring is also depleted from the electron density consequently H6 cannot act as an electron donor. These considerations confirms that atom H6 is stronger electrophilic as compared to H3 of the ring 2 in the isomer 1.

![Figure 1](image-url)  
**Figure 1.** The optimized structure of isomer 1 of 2APP. The dotted line illustrates the hydrogen bonds formed between the picrate and pyrimidine ring.
Additionally, the O25 carries the largest negative partial charge in isomer 1 (−0.273e) while H6 carries the largest positive charge among all the hydrogen atoms in isomer 1 (0.098e). This charge difference creates a strong electrostatic interaction between O25 and H6. Thus, oxygen O25 donates one of its lone pair electrons to H6 inducing a heterolithic dissociation in the N5H6 bond of ring 2. The free hydrogen H6 atom then makes a covalent bond with O25 and forms the product (isomer 2, total energy = −1240.4059 Hartree) as shown in Figure 2. The enthalpy of the formation from isomer 1 to isomer 2 is predicted to be −35.3915 kcal/mol with respect to the isomer 1. This represents a highly exothermic reaction. We were able to locate the TS for this isomer change at −34.0110 kcal/mol (TS total energy = −1240.4037 Hartree). This submerged TS was confirmed by IRC calculations which connect isomer 1 and isomer 2 via TS Figure 3. The presence of submerged TS also confirms that the isomerization is guided by electrostatic attraction as described in its mechanism.

Figure 2. The optimized molecular structure isomer 2 of 2APP. The dotted line illustrates the hydrogen bonds formed between the picrate and pyrimidine ring.

Figure 3. Systematic potential energy diagram for the formation of isomer 2 from the isomer 1 calculated at wB97XD/6-311+G (d, p) level of theory. Relative energies of the structures with respect to isomer 1 in kcal/mol are given in parenthesis.
There is one more possibility of isomerization in this system. The nucleophilic site O25 can also donate its lone pair electrons to the hydrogen H3. The possible local minima structure along this root is studied by breaking up of the bond N1H3 and forming O25H3 bond instead manually followed by optimization of resulting structure. However, it is noticeable that hydrogen H3 always tend to move back to N1 after the optimization. Since no local minima could be located along this root, it is concluded that the local minima structure along this root is not feasible. The primary reason for this would be the instability of the amino group (N1H2) at C2 for proton transfer to O26. Additionally, the distance between the O25 and H3 is quite large (1.9656 Å) as compared to the distance between O25 and H6 (1.6261 Å). Hence, the electron transfer is more feasible between O25 and H6 rather than between O25 and H3.

The isomer 2 seems to be similar as isomer 1 for a quick view. But when we look into the 3D structures, it is observed that pyrimidine ring is slightly moved out-of the plane with respect to pictrate ring whereas in isomer 1 both rings are coplanar. The reason for this shift can be explained as follows: After the formation of isomer 2, the distance between the H3 and O25 has increased and becomes 2.3315 Å while distance between H6 (now attached to O25) and N5 becomes 1.5348 Å (Figure 2). This results in the weakening of the hydrogen bond H3…O25 and strengthening of H6…N5.

The HOMO-LUMO energy gap for the isomer 1 and 2 is observed to be 0.2245 and 0.2808 a.u. respectively. It implies that isomer 2 is less reactive as compared to isomer 1. This is due to the fact that the HOMO of the isomer 2 is completely shifted from picrate ring to the pyrimidine ring. Now, whatever electron density that the pyrimidine ring gains from the transfer of H6 to the picrate ring, it is completely distributed throughout the ring. It increases the stability of pyrimidine ring and of isomer 2 in general and decreases the overall reactivity of isomer 2 (Figure 3).

To reveal more about the mechanism of the formation of isomer 2 from isomer 1, we have analyzed the equidistance points on the IRC (that includes TS) and performed single-point energy calculations on each point. It provides us the wave functions of that particular structure which in turn helps to see the structural changes during the reaction as well as the change in the molecular orbitals and charge delocalization upon change in the energy. The highest occupied molecular orbitals (HOMO) of these intermediate points are displayed in Figure 4. From point 3, it can be seen that the electron cloud of the highest occupied orbital is mostly lying over the picrate ring and over oxygen atoms attached to this ring. The picrate ring is a homogenous carbon ring exhibits π-electron cloud and its electron density is also spreaded over the lone pair electrons of the oxygen atoms. When one electron pair is transferred from the oxygen atom to the nearest hydrogen, it induces a proton transfer. When the hydrogen H6 leaves the –NH group of pyrimidine ring, it gives back its electron which was involved in the NH bonding. In this way, now the pyrimidine ring get one extra electron which results in more reactive pyrimidine ring and shifting the HOMO to the pyrimidine ring (point 0 to –2). After completing the reaction, the electron cloud in the pyrimidine ring will start repelling the electron cloud of the nearest oxygen atoms, therefore, pyrimidine ring bend slightly out of the plane with respect to the plane of the picrate ring in the product complex (point –2).

**Electron density distribution**

Analysis of electron density distribution is a straightforward approach to unravel the hydrogen bonding interactions between the electron donor and acceptor species of the electronic structure of the molecule or cocrystals. Quantum topological atoms in molecules (QTAIM)\(^49\) offers an elegant approach that provides pictorial evidence to the hydrogen bonding interactions in terms of line critical points (LCP) and the type and strength of the interactions can be characterized by quantum topological parameters such as electron density (\(\rho(r)\)), Laplacian of electron density (\(\nabla^2\rho(r)\)), bond ellipticity (\(\varepsilon\)), and hydrogen bond (HB) energies (\(E_{HB}\)). The quantum topological
According to Bader’s theory of QTAIM, the value of $\rho(r)$ is quite small ($\sim 10^{-2}$ a.u. or less for H-bonded complexes and $10^{-3}$ a.u. for van der Waals complexes) and $\nabla^2 \rho(r)$ is positive. The predicted topological parameters of the intermolecular interactions for isomer 1 and 2 are within the range of H-bonded complexes as given by Bader. The intermolecular interactions such as O26--H8, O25--H3, O31--H3, O31--O25, O25--O26 commonly exist in both the isomers, among them O31--O25, O25--O26 are non-classical hydrogen bonds. The prominent intermolecular interactions O25--H6 (isomer 1) and N5--H6 (isomer 2) discriminate the isomeric forms of 2APP. The calculated binding energy of complexes in isomer 1 and isomer 2 are 171.88 and 168.82 kJ/mol respectively. The difference in the binding energy of the complexes isomer 1 and 2 are calculated as 3.06 kJ/mol. The bond ellipticity ($\varepsilon$) measures the extent to which electron density ($\rho(r)$) is accumulated in a given plane containing the bond path. 50 The higher value of $\varepsilon$ illustrates the structural instability and its value close to zero represents the bond is cylindrically symmetrical. 51 Hence, the lesser $\varepsilon$ value and higher hydrogen bonding energy ($E_{HB}$) for the
interactions O25···H6 and O25···H3 are more prominent interactions of isomer 1 while in isomer 2, N5···H6 is the most prominent interaction.

**Evidence from natural bond orbitals**

The second-order perturbation energies concerning the donor→acceptor entities of both the isomers of 2APP were predicted by natural bond orbital analysis and the results were depicted in Tables S3 and S4. The donor→acceptor entities of isomer 1 such as LP(2)O25 → BD*(1)N5–H6 and LP(1)O25 → BD*(1)N5–H6 with the stabilization energies of 26.81 and 14.15 kcal/mol confirms the non-bonded interaction O25···H6. The stabilization energies of 6.7 kcal/mol predicted for LP(1)O25 → BD*(1)N1–H3 confirms the non-bonded interaction O25···H3. Moreover, a prominent interaction N5···H6 confirms the presence of isomer 2 and it validates the IRC calculation. LP(1)N5 → BD*(1)O25–H6 with noticeable stabilization energy of about 109.56 kcal/mol supports the presence of non-bonded interaction N5···H6. Apart from these prominent interactions, the donor→acceptor entities of the rest of the molecule were also collected in Tables S3 and S4.

**Analysis of vibration spectra**

To confirm the isomeric conformation in the solid phase, the Fourier-transform mid-IR and Raman spectra of both the isomers of 2APP were recorded and the observed results were compared with their respective theoretically simulated spectra at wB97XD with 6-311+G (d,p) level of approximation (see, Figures 6 and 7). The assignment of the peaks was confirmed with the aid of potential energy distribution (PED) results.

**Vibrational assignment of the bonds involving in the hydrogen bond formation**

A broad and very weak intensity band in the region 3850–3650 cm⁻¹ in the FT-IR spectrum are recognized as N–H stretching vibrations of the amino group of picrate. The scaled wavenumbers of 3772 and 3646 cm⁻¹ for isomer 2 and 3529 and 3274 cm⁻¹ for isomer 1 are ascribed to N–H stretching vibrations of the amino group. It reflects that the stretching modes of N–H bonds in the amino group are greatly affected upon the transfer of hydrogen atom from the pyrimidine ring to picrate ring (from isomer 1 to isomer 2 conversion). The conformational isomerism of 2APP could be identified by the careful investigation of N5–H6 (isomer 1) and O25–H6 (isomer 2) stretching bands. The presence of N5–H6 stretching band and absence of O25–H6 bond confirms isomer 1 of 2APP and the absence of N5–H6 stretching band and the presence of O25–H6 bond confirms isomer 2 of 2APP. A peak identified at 3437 cm⁻¹ belongs to intermolecular O25···H6 stretching mode and the N5–H6 stretching peak centered at 2913 cm⁻¹ in the FT-IR confirms the structure of isomer 1. The assignments of all the vibrational modes of isomers 1 and 2 are given in Tables S5 and S6 (Supplementary Material) respectively.
Our spectroscopic investigations along with theoretical calculations shed light on the structural insights of isomers 1 and 2. We have seen a broad small peak of NH stretching at 2835 cm$^{-1}$ in isomer 1. It is quite evident N5H6 of pyrimidine molecule is involved in the formation of intermolecular H-bonding with an Oxygen atom (O25) of picrate molecule. On the other hand, we have not seen such spectroscopic features (IR and Raman) in isomer 1. Similarly, we have observed the O25H6 stretching at 3106 cm$^{-1}$ in isomer 2 which signifies OH of picrate molecule is involved in H-bonding with a nitrogen atom (N5) of pyrimidine molecule while such traces are completely missing in isomer 1. Additionally, C=O stretching in both the isomers 1 and 2 were found at 1545 and 1534 cm$^{-1}$, respectively which suggests C=O involved in the formation of intermolecular H-bonding. Thus, our spectroscopic results confirmed the theoretical findings and support our predicted molecular structure.

**Vibrational assignment of the pyrimidine ring**
The scaled wavenumbers at 3118, 3105, 3053 cm$^{-1}$ in isomer 1 and 3065, 3047 cm$^{-1}$ in isomer 2 are attribute to C–H stretching modes of pyrimidine ring. The peaks observed at 1428 cm$^{-1}$ in FT-IR and 1354, 1270 cm$^{-1}$ in FT-Raman are recognized as C–H in-plane bending of the
pyrimidine ring. The scaled wavenumbers at 1718, 1662, 1435, 1261 cm$^{-1}$ in isomer 1 and 1437, 1410, and 1361 cm$^{-1}$ in isomer 2 are assigned to C–H in-plane bending of the pyrimidine ring. The peaks identified at 1055 cm$^{-1}$ in FT-IR and 1042, 802 cm$^{-1}$ in FT-Raman are assigned to C–H out-of-plane bending of the Pyrimidine ring. The peaks predicted at 1029, 998, 810 cm$^{-1}$ in isomer 1 and 1057, 1036, 818 cm$^{-1}$ in isomer 2 are ascribed to C–H out-of-plane bending of the Pyrimidine ring. Deformation modes of the pyrimidine ring predicted at 1010, 657, 593, 526, 410 cm$^{-1}$ in isomer 1 and 1013, 854, 637, 611, 552, 428 cm$^{-1}$ in isomer 2 are assigned.

**Vibrational assignment of the picrate ring**

The scaled wavenumbers at 3108, 3107 cm$^{-1}$ in isomer 1 and 3104 cm$^{-1}$ in isomer 2 are attributed to C–H stretching modes of picrate ring. The peaks found at 1185 cm$^{-1}$ in FT-IR and 1110 cm$^{-1}$ in FT-Raman are identified as C–H in-plane bending of C–H bonds in the picrate ring. A highly coupled mode calculated at 1193 and 1103 cm$^{-1}$ in isomer 1 are identified as in-plane bending of C–H bonds in the picrate ring. The in-plane bending of the C–H bonds are highly coupled with C–C stretching vibrations of picrate ring.

---

**Figure 7.** Experimental FT-Raman spectrum of 2APP in the solid phase and theoretically simulated Raman spectrum of isomer 1 and 2. In the inset, very low intensity peaks/bands in the region 2800–3500 cm$^{-1}$ are shown.
The peaks predicted at 976 and 959 cm\(^{-1}\) in isomer 1 and 1022 and 976 cm\(^{-1}\) in isomer 2 are ascribed to C–H out-of-plane bending of the picrate ring and it matches well with the experimental peak at 976 cm\(^{-1}\) in both FT-IR and FT-Raman. Deformation modes of the picrate ring were predicted at 974, 865, 523, 380, 374 cm\(^{-1}\) in isomer 1 and 860, 748, 734, 540, 537, 195 cm\(^{-1}\) in isomer 2 are assigned.

**Conclusion**

In the present work, the possible isomerization of 2APP cocrystal and reactivity descriptors of isomers were investigated using vibrational spectra and DFT computations. The reaction pathway from isomer 1 to isomer 2 through the TS structure of 2APP has been proposed and the changes in the electron density of atoms on the intermediary points from the reactants to product were investigated to observe the structure changes upon isomerization. With the help of QTAIM, the non-bonded interactions between the pyrimidine and picrate rings were identified and the strength of the bonds was analyzed by quantum topological descriptors viz. electron density, Laplacian of electron density, bond ellipticity, and hydrogen bond energy. The charge delocalization between various donor and acceptor entities of pyrimidine and picrate rings were investigated by NBO analysis and the site prone to electrophilic and nucleophilic attacks were identified by Fukui descriptors. The detailed vibrational assignments of all the harmonic frequencies were predicted and the simulated IR and Raman spectra were compared with the experimental FT-IR and FT-Raman to validate the presence of isomers.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

**Funding**

T. Karthick acknowledges the management of SASTRA Deemed University, Thanjavur, Tamil Nadu, India for providing necessary infrastructure and computational facilities and work was supported by Department of Science and Technology, New Delhi, India under DST-FIST project (Project No. SR/FST/PS-1/2020/135). The financial support to K.K. Singh and P. Tandon from Science & Engineering Research Board (SERB), Department of Science & Technology, and Government of India (Grant No. CRG/2019/006671) is gratefully acknowledged.

**ORCID**

T. Karthick [http://orcid.org/0000-0001-6029-8644](http://orcid.org/0000-0001-6029-8644)
Swapnil Singh [http://orcid.org/0000-0003-1159-7212](http://orcid.org/0000-0003-1159-7212)
Poornam Tandon [http://orcid.org/0000-0002-8120-0498](http://orcid.org/0000-0002-8120-0498)
B. Narayana [http://orcid.org/0000-0001-8945-4516](http://orcid.org/0000-0001-8945-4516)

**Authors’ contributions**

T. Karthick made substantial contributions to the conception or design of the work, data acquisition, analysis, and interpretation of data in the work. Keshav Kumar Singh made significant contribution in drafting some part of the work. Swapnil Singh made contributions in the data acquisition and analysis. Poonam Tandon revised the draft critically for important intellectual content. B. Narayana made contribution in the synthesis of the compound.

**References**

1. J. P. Jasinski, R. J. Butcher, Q. N. M. Hakim Al-Arique, H. S. Yathirajan, and B. Narayana, “4-(4-Chloro-Phen-yl)-1-3-(4-Fluoro-Benzo-yl)Prop-y1]-4-Hydroxy-Piperidin-1-Ium 2,4,6-Trinitro-Phenolate (Haloperidol Picrate),” *Acta Crystallographica Section E: Structure Reports Online* 65, no. Pt 10 (2009): o2403–o2404.
2. H. S. Yathirajan, M. A. Ashok, B. Narayana Achar, and M. Bolte, “Promazinium Picrate,” Acta Crystallographica Section E: Structure Reports Online 63, no. 3 (2007): o1432–o1434. doi:10.1107/S1600536807008306.

3. J. P. Jasinski, R. J. Butcher, H. S. Yathirajan, L. Mallesha, and K. N. Mohana, “4-[(E)-(2,4-Difluoro-Phenyl)(Hydroxy-Imino)Methyl]Piperidinium Picrate,” Acta Crystallographica Section E: Structure Reports Online 65, no. Pt 10 (2009): o2365–o2366.

4. H. S. Yathirajan, M. A. Ashok, B. Narayana Achar, and M. Bolte, “Ethopropazinium Picrate,” Acta Crystallographica Section E: Structure Reports Online 63, no. 4 (2007): o1792–o1794. doi:10.1107/S1600536807011543.

5. R. Kant, S. Kohli, L. Sarmal, B. Narayana, and S. Samshuddin, “4-(2-Chloro-Ethyl)Morpholinium Picrate,” Acta Crystallographica Section E: Structure Reports Online 65, no. Pt 10 (2009): o2435.

6. B. K. Sarojini, B. Narayana, M. T. Swamy, H. S. Yathirajan, and M. Bolte, “5-Bromo-3-(Methylaminocarboxyl)Pyridinium Picrate,” Acta Crystallographica Section E: Structure Reports Online 63, no. 10 (2007): o4181. doi:10.1107/S1600536807046934.

7. J. P. Jasinski, R. J. Butcher, M. T. Swamy, H. S. Yathirajan, and A. R. Ramesha, “1-(2-Methyl-5-nitro-phenyl)guanidinium picrate,” Acta Crystallographica Section E: Structure Reports Online 65, no. Pt 11 (2009): o2788–o2789.

8. J. P. Jasinski, R. J. Butcher, H. S. Yathirajan, L. Mallesha, and K. N. Mohana, “4-[(E)-(2,4-Difluorophenyl)(hydroxyImino)Methyl]Piperidinium Picrate,” Acta Crystallographica Section E: Structure Reports Online 65, no. Pt 10 (2009): o2365–o2366.

9. H. S. Yathirajan, M. A. Ashok, B. Narayana Achar, and M. Bolte, “Mepazinium Picrate,” Acta Crystallographica Section E: Structure Reports Online 63, no. 4 (2007): o1691–o1692. doi:10.1107/S1600536807009877.

10. H. S. Yathirajan, M. A. Ashok, B. Narayana Achar, and M. Bolte, “Trifluoperazinium Dipicrate,” Acta Crystallographica Section E: Structure Reports Online 63, no. 4 (2007): o1693–o1695. doi:10.1107/S1600536807009889.

11. W. T. A. Harrison, M. A. Ashok, H. S. Yathirajan, and B. Narayana Achar, “Dioxopromethazinium Picrate,” Acta Crystallographica Section E: Structure Reports Online 63, no. 7 (2007): o3277. doi:10.1107/S1600536807029194.

12. K. Anitha, S. Athimoolam, and S. Natarajan, “l-Prolinium Picrate and 2-Methyl Pyridinium Picrate,” Acta Crystallographica Section C, Crystal Structure Communications 62, no. Pt 9 (2006): o567–o570. doi:10.1107/S0108270106029209.

13. W. T. A. Harrison, S. Bindya, M. A. Ashok, H. S. Yathirajan, and B. Narayana Achar, “Imipraminium Picrate,” Acta Crystallographica Section E: Structure Reports Online 63, no. 7 (2007): o3143. doi:10.1107/S1600536807026050.

14. M. T. Swamy, M. A. Ashok, H. S. Yathirajan, B. Narayana, and M. Bolte, “Desipraminium Picrate,” Acta Crystallographica Section E: Structure Reports Online 63, no. 12 (2007): o4919. doi:10.1107/S1600536807062393.

15. J. P. Jasinski, R. J. Butcher, Q. N. M. Hakim Al-Arique, H. S. Yathirajan, and B. Narayana, “Imatinibium Dipicrate,” Acta Crystallographica Section E: Structure Reports Online 66, no. Pt 2 (2010): o411–o412.

16. J. P. Jasinski, R. J. Butcher, Q. N. M. Hakim Al-Arique, H. S. Yathirajan, and B. Narayana, “Chlorimipraminium Picrate,” Acta Crystallographica Section E: Structure Reports Online 66, no. Pt 2 (2010): o347–o348.

17. H. Li, H. S. Yathirajan, L. Mallesha, K. N. Mohana, and B. Narayana Achar, “Gabapentinum Picrate,” Acta Crystallographica Section E: Structure Reports Online 65, no. Pt 4 (2009): o783.

18. J. P. Jasinski, R. J. Butcher, Q. N. M. Hakim Al-Arique, H. S. Yathirajan, and B. Narayana, “Propiverinium picrate,” Acta Crystallographica Section E: Structure Reports Online 65, no. Pt 8 (2009): o1738–o1739.

19. H. Li, Q. N. M. Hakim Al-Arique, H. S. Yathirajan, B. Narayana Achar, and A. R. Ramesha, “4-(4-Carboxy-Benzyl)-1-Methyl-Piperazin-1-Ium Picrate,” Acta Crystallographica Section E: Structure Reports Online 65, no. Pt 3 (2009): o518.

20. P. Ramesh, R. Akalya, A. Chandramohan, and M. N. Ponnuuswamy, “4-tert-Butyl-Pyridinium Picrate,” Acta Crystallographica Section E: Structure Reports Online 66, no. Pt 4 (2010): o999.

21. J. P. Jasinski, R. J. Butcher, M. S. Siddegowda, H. S. Yathirajan, and C. S. Chidan Kumar, “Cinnarizinum dipicrate,” Acta Crystallographica Section E: Structure Reports Online 67, no. Pt 2 (2011): o500–o501.

22. J. P. Jasinski, A. E. Pek, B. P. Siddaraju, H. S. Yathirajan, and B. Narayana Achar, “Opipramol Dipicrate,” Acta Crystallographica Section E: Structure Reports Online 66, no. Pt 8 (2010): o1979–o1980.

23. G. Dutkiewicz, C. S. Chidan Kumar, H. S. Yathirajan, B. Narayana Achar, and M. Kubicki, “Fluconazolium Picrate,” Acta Crystallographica Section E: Structure Reports Online 66, no. Pt 10 (2010): o2568.

24. R. Peng and Y. Zhao, “2-Amino-Anilinium Picrate,” Acta Crystallographica Section E: Structure Reports Online 66, no. Pt 12 (2010): o3235.

25. B. Narayana, B. K. Sarojini, K. Prakash Kamath, H. S. Yathirajan, and M. Bolte, “2-Amino-Pyrimidinium Picrate,” Acta Crystallographica Section E: Structure Reports Online 64, no. Pt 1 (2007): o117–o118.

26. J. P. Jasinski, R. J. Butcher, M. S. Siddegowda, H. S. Yathirajan, and A. R. Ramesha, “Etoricoxibium Picrate,” Acta Crystallographica Section E: Structure Reports Online 67, no. Pt 1 (2010): o107–o108.
27. J. P. Jasinski, R. J. Butcher, M. S. Siddegowda, H. S. Yathirajan, and A. R. Ramesha, “Levocetirizinium Dipicrate,” *Acta Crystallographica Section E: Structure Reports Online* 66, no. Pt 12 (2010): o3167.

28. J. P. Jasinski, R. J. Butcher, M. S. Siddegowda, H. S. Yathirajan, and Q. N. M. Hakim-Al-Arique, “Lonfloxacinium Picrate,” *Acta Crystallographica Section E: Structure Reports Online* 67, no. Pt 2 (2011): o483–o484.

29. C. N. Kavitha, J. P. Jasinski, M. Kaur, B. J. Anderson, and H. S. Yathirajan, “Crystal Structure of 1-(3-Chloro-Phen-yl)Piperazin-1-Ium Picrate-Picric Acid (2/1),” *Acta Crystallographica Section E: Structure Reports Online* 70, no. Pt 11 (2014): o1210–o1211.

30. T. S. Yamuna, J. P. Jasinski, C. E. Duff, H. S. Yathirajan, and M. Kaur, “3-(1H-Imidazol-1-yl)Propanaminium Picrate,” *Acta Crystallographica Section E: Structure Reports Online* 69, no. Pt 10 (2013): o1572–o1573.

31. J. P. Jasinski, R. J. Butcher, B. P. Siddaraju, H. S. Yathirajan, and B. Narayana, “Orphenadrinium Picrate,” *Acta Crystallographica Section E: Structure Reports Online* 67, no. Pt 1 (2010): o190–o191.

32. J. P. Jasinski, R. J. Butcher, M. S. Siddegowda, H. S. Yathirajan, and B. P. Siddaraju, “Enrofloxacinium Picrate,” *Acta Crystallographica Section E: Structure Reports Online* 67, no. Pt 2 (2011): o432–o433.

33. C. N. Kavitha, M. Kaur, B. J. Anderson, J. P. Jasinski, and H. S. Yathirajan, “1-Piperonylpirperazinium Picrate,” *Acta Crystallographica Section E: Structure Reports Online* 70, no. Pt 2 (2014): o208–o209.

34. C. N. Kavitha, M. Kaur, J. P. Jasinski, and H. S. Yathirajan, “4-Acetyl-Piperazinium Picrate,” *Acta Crystallographica Section E: Structure Reports Online* 70, no. Pt 6 (2014): o717–o718.

35. M. J. Frisch et al., *G16_C01. p. Gaussian 16, Revision C.01* (Gaussian, Inc., Wallin, 2016).

36. J. Da Chai and M. Head-Gordon, “Long-Range Corrected Hybrid Density Functionals with Damped Atom-Atom Dispersion Corrections,” *Physical Chemistry Chemical Physics* 10, no. 44 (2008): 6615–20.

37. M. Das, K. K. Singh, E. Khan, R. K. Sinha, R. K. Singh, P. Tandon, and D. Gangopadhyay, “N-Acetylcysteine versus Arsonic Poisoning: A Mechanistic Study of Complexation by Molecular Spectroscopy and Density Functional Theory,” *Journal of Molecular Liquids* 340 (2021): 117168.

38. D. Gangopadhyay, M. Das, K. K. Singh, R. K. Singh, and P. Tandon, “Attenuating the Increased Level of Creatinine by N-Acetylcysteine: Raman Spectroscopy and Density Functional Theory-Based Monitoring of in Vitro Complexation in Aqueous Solution,” *Journal of Raman Spectroscopy* 51, no. 7 (2020): 1056–66.

39. T. Wjitissuwannakul, T. Mukherjee, M. B. Hall, and J. A. Gladysz, “Computational Investigations of Enantioselection in Carbon–Carbon Bond Forming Reactions of Ruthenium GFunidinobenzimidazole Second Coordination Sphere Hydrogen Bond Donor Catalysts,” *Organometallics* 39, no. 8 (2020): 1149–62.

40. J. Miró, T. Gensch, M. Ellwart, S. J. Han, H. H. Lin, M. S. Sigma, and F. D. Toste, “Enantioselective alke-noate-Claisen Rearrangement Using Chiral Phosphate Catalysts,” *Journal of the American Chemical Society* 142, no. 13 (2020): 6390–99.

41. C. Gonzalez and H. Bernhard Schlegel, “Reaction Path following in Mass-Weighted Internal Coordinates,” *The Journal of Physical Chemistry* 94, no. 14 (2002): 5523–27.

42. K. Fukui, “The Path of Chemical Reactions—The IRC Approach,” *Accounts of Chemical Research* 14, no. 12 (2002): 363–68.

43. H. Yoshida, K. Takeda, J. Okamura, A. Ehara, and H. Matsuura, “A New Approach to Vibrational Analysis of Large Molecules by Density Functional Theory: Wavenumber-Linear Scaling Method,” *The Journal of Physical Chemistry A* 106, no. 14 (2002): 3580–86.

44. P. Kolandaivel, G. Praveena, and P. Selvarengan, “Study of Atomic and Condensed Atomic Indices for Reactive Sites of Molecules,” *Journal of Chemical Sciences* 117, no. 5 (2005): 591–98.

45. J. P. Foster and F. Weinhold, “Natural Hybrid Orbitals,” *Journal of the American Chemical Society* 102, no. 24 (1980): 7211–18.

46. S. Singh, et al. “Combine Experimental and Theoretical Investigation on an alkaidom-Dimethylisoborvererine,” *Journal of Molecular Structure* 1103 (2016).

47. T. Karthick and P. Tandon, “Computational Approaches to Find the Active Binding Sites of Biological Targets against Busulfan,” *Journal of Molecular Modeling* 22, no. 6 (2016). Art. No: 142.doi: 10.1007/s00894-016-3015-z

48. Anna Stachowicz-Kuśniérz, and Jacek Korchowiec, “Nucleophilic Properties of Purine Bases: Inherent Reactivity versus Reaction Conditions,” *Structural Chemistry* 27, no. 2 (2016): 543–55.

49. Richard F. W. Bader, *Atoms in Molecules A Quantum Theory* (Oxford, England: Clarendon Press, 1994).

50. T. Karthick, P. Tandon, K. Srivastava, and S. Singh, “Evaluation of Non-Covalent Interactions of Chlorambucil (Monomer and Dimer) and Its Interaction with Biological Targets: Vibrational Frequency Shift, Electron Density Topological and Automated Docking Analysis,” *Arab Journal of Chemistry* 11, no. 5 (2018): 591–608. doi:10.1016/j.arabjc.2017.10.012.

51. Ofiha O. Browarets’, Ivan S. Voiteshenko, Horacio Pérez-Sánchez, and Dmytro M. Hovorun, “A QM/QTAIM Research under the Magnifying Glass of the DPT Tautomerisation of the Wobble Mispairs Involving 2-Aminopurine,” *New Journal of Chemistry* 41, no. 15 (2017): 7232–43.

52. R. D. Kross and V. A. Fassell, “Regularities in the Infrared Spectra of Picric Acid Molecular Complexes1,” *Journal of the American Chemical Society* 79, no. 1 (1957): 38–41.