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ORIGINAL RESEARCH

Conceptual density functional theory study on dichloropyridines as ambiphilic molecules

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Abstract Conceptual density functional theory (CDFT) has been employed to compare the electrophilic and nucleophilic characters of the given atomic sites in the complete series of dichloropyridines (DCPs) as ambiphilic molecules. Ambiphilic molecules can act either as electrophiles or as nucleophiles, depending on the reaction partner. In the present work, various chemical reactivity descriptors such as dual descriptor, local hypersoftness and multiphilic descriptor as well as electrostatic potential were computed for the carbon atoms of six position isomers of DCP. Our results show that depending on the position of chlorines in each isomer, electrophilic or nucleophilic attack may occur at the particular sites. This type of study can be used as a theoretical reference for guidance of chemists to select the appropriate reactant and so have a sightly product.

Keywords CDFT · Ambiphilic molecule · Reactivity descriptors · MEP

Introduction

The understanding and prediction of chemical reactivity and site selectivity of molecular systems are critical. The qualitative Density Functional Theory (DFT) [1–3] of chemical reactivity is a branch of DFT which is called Conceptual DFT (CDFT) [4–6] and is a very befitting approach to describe chemical process. This theory provides a powerful theoretical framework for the study of both reactivity and selectivity and proposes a set of local indices such as local hardness [7], dual descriptor [8], electrophilicity access [9], multiphilic descriptor [10], and local hypersoftness [11] aiming to describe local reactivity and site selectivity. Moreover, CDFT includes the global properties such as dipole moment, global hardness, and chemical potential. Chemical reactivity descriptors have been shown useful for predicting the regioselectivity in electrophilic or nucleophilic attack to aromatic and aliphatic compounds [12–17]. Also dual descriptor has been successfully used to derive the Woodward–Hoffmann rules [18] and to study both the regioselectivity and the stereoselectivity of Diels–Alder reactions [19]. More recently, Correa et al. [20] used molecular electrostatic potential and dual descriptor to analyze the nucleophilicity and electrophilicity of substituted silylenes.

Another approach to the interpretation and prediction of reactivity has been through two local properties that are typically computed on molecular surfaces; the molecular electrostatic potential which is particularly useful for noncovalent interactions [21, 22] and the average local ionization energy which is more relevant when some degree of charge transfer is involved [23, 24].

Chemical reactivity descriptors not only can be applied for the ordinary molecules but also may be established for molecules called ambiphilic molecules [25–27]. Ambiphilic molecules cannot be classified either as electrophiles or as nucleophiles. These compounds act as either electrophiles or nucleophiles, depending on the reaction partner or sometimes accept and donate electrons concurrently. More recently reactivity descriptors have been employed by Cardenas et al. [28] to study dual atom, dual molecule, and dual ion–molecule complexes. The aim of the present study is to investigate ambiphilic property in six position isomers of dichloropyridine (DCP). Modification of the pyridine nucleus is a versatile research area which still

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attracts a considerable amount of interest in modern organic chemistry. Due to its presence in numerous natural products and biologically active substances, the pyridine moiety is still regarded as one of the most interesting heteroaromatic ring systems.

In this work, we elaborate on the electrophilic and nucleophilic characters of DCPs through a combined use of CDFT-based descriptors and molecular electrostatic potential. Our main goal is to compare site selectivity in the complete series of DCPs towards the electrophilic or nucleophilic attack. This article is organized as follows: In "Theoretical background" section the theoretical basis for different descriptors used in this work are briefly discussed. "Methodology" section is devoted to computational details and describes the methodology. In "Results and discussion" section, results are presented and discussed. The final section contains our concluding remarks.

Theoretical background

Dual descriptor

The Fukui function was introduced by Parr and Yang [29] as the derivative of the chemical potential with respect to the external potential, or equivalently as the derivative of the total electron density upon changes in the total number of electrons

$$f(r) = \left(\frac{\delta\mu}{\delta\upsilon\,(r)}\right)_N = \left(\frac{\partial\rho\,(r)}{\partial N}\right)_{\upsilon\,(r)} \tag{1}$$

The function $f(r)$ reflects the ability of molecular sites to accept or donate electrons. High values of $f(r)$ are related to a high reactivity at point r. Since the number of electrons N is discrete variable, by applying a finite difference approximation three different types of Fukui functions have been defined [30, 31]

$$f^{+}(r) = \rho_{N+1}(r) - \rho_N(r) \quad \text{For nucleophilic attack} \tag{2}$$

$$f^{-}(r) = \rho_N(r) - \rho_{N-1}(r) \quad \text{For electrophilic attack} \tag{3}$$

$$f^{\circ}(r) = \left(\rho_{N+1}(r) - \rho_{N-1}(r)\right)/2 \quad \text{For radical attack} \tag{4}$$

Recently, Morell et al. [8] have proposed a new dual descriptor, $f^{(2)}(r)$, (sometimes also called the second order Fukui function) as follows

$$f^{(2)}(r) \equiv \Delta f(r) = \left(\frac{\partial^2\rho(r)}{\partial N^2}\right)_{\upsilon(r)} = \left(\frac{\partial f(r)}{\partial N}\right)_{\upsilon(r)} \tag{5}$$

Using the well-known finite difference approximation, $f^{(2)}(r)$ can be written as the difference between nucleophilic and electrophilic Fukui functions:

$$f^{(2)}(r) = f^{+}(r) - f^{-}(r) \tag{6}$$

The dual descriptor helps identify simultaneously the nucleophilic and electrophilic regions within a molecule. In other words, since the electrophilic or nucleophilic Fukui functions measure how the electronic density changes when an electron is added or removed from the electronic system, it becomes clear that the sign of the dual descriptor characterizes the electrophilic or nucleophilic behavior of a molecular site within a molecule. If $f^{(2)}(r) > 0$, then the site is favored for a nucleophilic attack (electrophilic region), whereas if $f^{(2)}(r) < 0$, then the site is nucleophilic region and may be favored for an electrophilic attack.

Local hypersoftness

Ayers and Parr [11] defined local hypersoftness, $s^{(2)}(r)$, as the second derivative of electron density with respect to the chemical potential

$$s^{(2)}(r) = \left(\frac{\partial^2\rho(r)}{\partial\mu^2}\right)_{\upsilon(r)} = \frac{f^{(2)}(r)}{\eta^2} + \frac{\eta^{(2)}f(r)}{\eta^3} \tag{7}$$

using finite difference and Koopman's theorem, chemical hardness (η) and hyperhardness ($\eta^{(2)}$) can be approximated as follows [32–34]

$$\eta \approx \varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}} \tag{8}$$

$$\eta^{(2)} \approx \varepsilon_{\mathrm{LUMO}} - 2\varepsilon_{\mathrm{HOMO}} + \varepsilon_{\mathrm{HOMO-1}} \tag{9}$$

where $\varepsilon_{\mathrm{LUMO}}$ is the energy of the lowest unoccupied molecular orbital and $\varepsilon_{\mathrm{HOMO}}$ is the energy of the highest occupied molecular orbital. Previous computations of $s^{(2)}(r)$ show that the second term in Eq. 7 is negligible and can be omitted [35]. The local hypersoftness strongly resembles dual descriptor and the interpretations of $f^{(2)}(r)$ and $s^{(2)}(r)$ are similar; they are positive in electrophilic regions and negative in nucleophilic regions. It means that $f^{(2)}(r)$ and $s^{(2)}(r)$ should give similar reactivity descriptions. However, $s^{(2)}(r)$ augments the regioselectivity information from the dual descriptor with the overall molecular reactivity information from the maximum hardness principle which states that the molecules tend to rearrange themselves to be as hard as possible [36]. Thus, $s^{(2)}(r)$ is an appropriate descriptor for comparing the reactivity of different molecules [18].

Multiphilic descriptor

The electrophilicity index, ω [37], is defined in terms of the chemical potential, μ, and molecular hardness, η

$$\omega = \frac{\mu^2}{2\eta} \approx \frac{\left(\varepsilon_{\mathrm{LUMO}} + \varepsilon_{\mathrm{HOMO}}\right)^2}{8\left(\varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}}\right)} \tag{10}$$

In this equation, the Koopman theory was applied to compute μ and η, i.e., $\mu = \left(\varepsilon_{\mathrm{LUMO}} + \varepsilon_{\mathrm{HOMO}}\right)/2$ and $\eta = \varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}}$.

Chattaraj et al. [38] proposed a generalized concept of philicity containing electrophilic, nucleophilic, and radical reactions. The condensed-to-atom variants for the atomic site "i" have been written as

$$\omega_i^{\alpha} = \omega f_i^{\alpha} \tag{11}$$

where $\alpha = +, -$, and 0 refers to nucleophilic, electrophilic, and radical attacks, respectively. The ω_i^{α} will vary from point to point in a molecule, but the sum of any ω_i^{α} overall atoms is conserved. In light of the local philicity concept and a dual descriptor, Chattaraj and coworkers [10] proposed a multiphilic descriptor which can concurrently characterize both the nucleophilic and electrophilic nature of a chemical species. Multiphilic descriptor is given by

$$\Delta\omega_i = \omega_i^{+} - \omega_i^{-} = \omega\left(f_i^{(2)}(r)\right) \tag{12}$$

If $\Delta\omega_i > 0$ then the site i is favored for a nucleophilic attack, whereas if $\Delta\omega_i < 0$ then the site i may be favored for an electrophilic attack.

Molecular electrostatic potential

The molecular electrostatic potential (MEP) at a point r due to a molecular system with nuclear charges Z_α located at R_α and the electron density $\rho(r')$ is given by

$$V(r) = \sum_{\alpha} \frac{Z_\alpha}{|r - R_\alpha|} - \int \frac{\rho(r')}{|r - r'|} \mathrm{d}r' \tag{13}$$

The first term in the above equation refers to the bare nuclear potential and the second to the electronic contribution. Among the reactivity descriptors used in this work, $V(r)$ is the only one that is a physical observable and can be obtained experimentally [39, 40] as well as computationally. Regions where $V(r)$ is negative are attractive to cations and repulsive to anions; regions where $V(r)$ is positive are attractive to anions and repulsive to cations. In general, the electrostatic potential and the dual descriptor complement each other quite effectively for processes that involve electrophilic or nucleophilic attack, in the sense that the former describes the charge control whereas the second describes the orbital controlled aspects of the reactive attack.

Methodology

For the complete series of DCPs, geometry optimization have been performed at the B3LYP level of theory with the 6-311++G (d,p) basis set using the Gaussian 03 package of program [41]. At the optimized geometry of each DCP, single point calculation was performed for their cations and anions. The HOMO and LUMO energies have been used to calculate μ and η. In this work, the Fukui functions have been approximated by computing the electron densities derived from the AIM 2000 software package [42]. Different chemical reactivity indicators such as dual descriptor, local hypersoftness and multiphilic descriptor were calculated for carbon atoms of all DCPs using Eqs. 6, 7, and 12, respectively. Moreover, the electrostatic potentials at the carbon nuclei were determined and the electrostatic potentials mapped on 0.002 a.u. isodensity surface were depicted for each molecule.

Results and discussion

Unlike benzene, pyridine is generally unreactive with respect to electrophilic aromatic substitution because electrophilic aromatic substitution reactions are performed in acidic condition and pyridine is protonated under such condition so it is very difficult to perform an electrophilic substitution on a positively charged reagent. In DCP electron withdrawing chlorine atoms reduces the basicity of the molecule so that they may undergo electrophilic substitution. Depending on the position of chlorine atoms, selective electrophilic substitution may exclusively occur at particular positions. In this research, the position of chlorines have been changed among all possible locations in pyridine ring and the variation of reactivity descriptors has been evaluated for six produced position isomers.

Table 1 presents the computed values of $f^{(2)}(r)$, $s^{(2)}(r)$, and $\Delta\omega_i$ for all carbon atoms of the complete series of DCPs. Sign and magnitude of these descriptors predict the regioselectivity to electrophilic or nucleophilic attack simultaneously. In 2,3-dichloropyridine the sign of dual descriptor is positive at C4 (electrophilic region) whereas it is negative at C5 and C6 (nucleophilic region). So this molecule undergoes both electrophilic aromatic substitution at C5 or C6 and nucleophilic aromatic substitution at C4. However, comparing the magnitude of $f^{(2)}(r)$ at C5 and C6 reveals that electrophilic substitution at C5 has greater chance. Numerical values of dual descriptor for 2,4-dichloropyridine show that C4 and C6 are electrophilic regions and prone to nucleophilic attack, while C3 and C5 are nucleophilic regions and are favorable to electrophilic substitution. It is obvious that electrophilic and nucleophilic substitutions are more possible to be occurred, respectively, at C5 and C4 rather than C3 and C6. 2,5-dichloropyridine shows completely different behavior so that it cannot be considered as an ambiphilic molecule. Indeed, this molecule is not prone to electrophilic aromatic substitution and C3, C4, and C6 positions are electrophilic regions which are susceptive to nucleophilic attack with the trend of C4 > C6 > C3. In 2,6-dichloropyridine nucleophilic attack is possible at C4 while C3 and C5 are

Table 1 The values of chemical reactivity descriptors as well as electrostatic potential for all carbon atoms of the complete series of dichloropyridines (a.u.)

DCPs		$f^{(2)}(r)$	$s^{(2)}(r)$	$\Delta\omega_i \times 10^3$	$V(r)$
2,3-Dichloropyridine	C2	−0.0434	−0.9992	−0.1276	−14.66
	C3	−0.0494	−1.1369	−0.1452	−14.68
	C4	0.1204	2.7720	0.3541	−14.73
	C5	−0.0624	−1.4374	−0.1836	−14.74
	C6	−0.0314	−0.7229	−0.0924	−14.71
2,4-Dichloropyridine	C2	−0.0297	−0.6196	−0.0981	−14.66
	C3	−0.0128	−0.2661	−0.0421	−14.73
	C4	0.1316	2.7432	0.4344	−14.67
	C5	−0.1283	−2.6742	−0.4235	−14.74
	C6	0.0175	0.3642	0.0577	−14.71
2,5-Dichloropyridine	C2	−0.0715	−1.7153	−0.2101	−14.66
	C3	0.0109	0.2605	0.0319	−14.73
	C4	0.1139	2.7303	0.3344	−14.72
	C5	−0.0650	−1.5642	−0.1916	−14.68
	C6	0.0179	0.4288	0.0525	−14.71
2,6-Dichloropyridine	C2	−0.0054	−0.1244	−0.0162	−14.65
	C3	−0.0736	−1.6954	−0.2204	−14.73
	C4	0.1370	3.1539	0.4101	−14.72
	C5	−0.0737	−1.6968	−0.2206	−14.73
	C6	−0.0055	−0.1269	−0.0165	−14.65
3,4-Dichloropyridine	C2	0.0200	0.4250	0.0644	−14.71
	C3	−0.1276	−2.7105	−0.4106	−14.68
	C4	0.1238	2.6291	0.3983	−14.67
	C5	0.0189	0.4016	0.0608	−14.74
	C6	−0.0739	−1.5690	−0.2377	−14.72
3,5-Dichloropyridine	C2	−0.0642	−1.4664	−0.1996	−14.71
	C3	−0.0444	−1.0135	−0.1379	−14.68
	C4	0.1271	2.9021	0.3950	−14.72
	C5	−0.0442	−1.0104	−0.1375	−14.68
	C6	−0.0642	−1.4654	−0.1995	−14.71

nucleophilic zones and are available to electrophilic attack. Here, the molecular symmetry leads to equal likelihood for the electrophilic substitution at C3 and C5. For 3,4-dichloropyridine the results show that the C6 site is favored toward electrophilic substitution while nucleophilic attack occurs at C2, C4, and C5 with preference at C4 and near equal possibility at C2 and C5. Finally from the sign and value of dual descriptors it is seen that in 3,5-dichloropyridine, the C4 site is electrophilic region while C2 and C6 positions are nucleophilic sites. Like to 2,6-dichloropyridine the electrophilic attack occurs with equal probability at C2 and C6. Local hypersoftness and multiphilic descriptors are analogues to dual descriptor and the trends for the reported values of $s^{(2)}(r)$ and $\Delta\omega_i$ in both sign and magnitude are similar to $f^{(2)}(r)$.

In the above, the electrophilic and nucleophilic sites were specified for each DCP. In this part the magnitude of reactivity descriptors at specific positions are considered in order to compare the electrophilicity and nucleophilicity characters of various DCPs with each other. For this purpose, the computed dual descriptors at carbon atoms and bond critical points (BCP) for complete series of DCPs are depicted in Fig. 1. A closer inspection of Fig. 1 reveals that the electrophilic and nucleophilic zones have almost the same trend in various DCPs with a few exceptions. It is clear that C2 and C5 are nucleophilic regions in all DCPs except 3,4-dichloropyridine and similar situation has been observed for C3 and C6 in 2,5-dichloropyridine. This figure shows that in all DCPs, C4 is the zone with maximum electrophilic character irrespective of whether it is chloro-substituted or not. On the other hand, zone that show the most nucleophilic character is not fixed in different DCPs and it is dependent on the chlorines position. In 2,3-, 2,4-, and 2,6-dichloropyridine C5 has the most nucleophilic

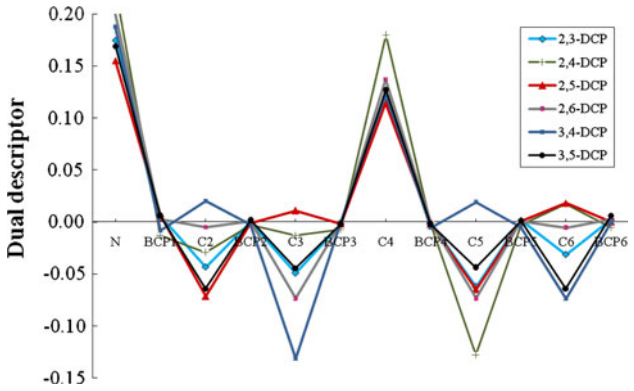

Fig. 1 The computed values of dual descriptor at the atomic sites and the bond critical points of the pyridine ring in all DCP position isomers

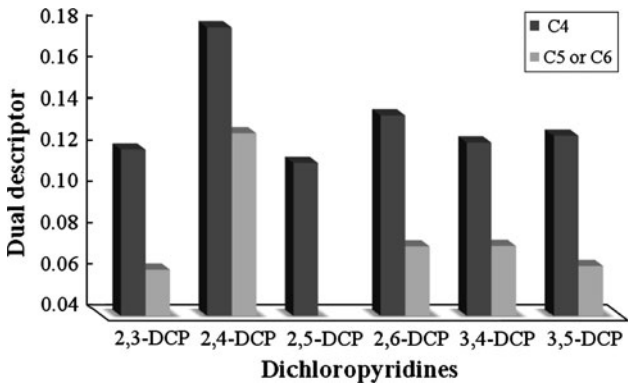

Fig. 2 Absolute values of dual descriptor at C4 (electrophilic site) and C5 or C6 (nucleophilic site) for all DCPs

character while in 3,4- and 3,5-dichloropyridine C6 is the more favorable nucleophilic regions. Figure 2 represents the variation of $f^{(2)}(r)$, regardless of its sign, at the most electrophilic and nucleophilic regions for six studied DCPs. Accordingly, the following order for propensity of DCPs towards nucleophilic attack at C4 are obtained:

$$2,4\text{-dichloropyridine} > 2,6\text{-dichloropyridine} > 3,5\text{-dichloropyridine} > 3,4\text{-dichloropyridine} > 2,3\text{-dichloropyridine} > 2,5\text{-dichloropyridine}$$

Behavior of DCPs under electrophilic substitution can be compared if we consider values of $f^{(2)}(r)$ at C6 in 3,4- and 3,5-dichloropyridine and at C5 for the rest of DCPs. Excluding 2,4-dichloropyridine with an exceptional highly chance to electrophilic attack at C5 from the set of studied DCPs, it can be observed that the remaining DCPs have almost similar tendency toward electrophilic aromatic substitution.

This type of calculations leads to selection of particular reactant to achieve sightly product. For instance 2,6-dichloropyridine should be selected as the most appropriate reactant if we desire to have aromatic electrophilic substitution at C3 or C5 while 3,4-dichloropyridne undergoes electrophilic attack only at C6. These findings are also supported by available experimental evidences on some DCPs. It was experimentally shown that when 2,6-dichloropyridine is lithiated with lithium diisopropylamide on quenching with different electrophiles, 3-substituted complex is obtained as the major product while the minor is the 4-substituted isomer [43]. Also, lithiation of 2,4-dichloropyridine was found to be regioselective at position flanked by the two halogen atoms thus affording 3-substituted product [44].

In addition to chemical reactivity descriptors, the values of electrostatic potential of carbon atoms in all DCPs have been computed. Further, the MEP have been mapped onto the electron density surface of DCPs. The electrostatic maps for polar molecules reveal well the sites that are most electron-rich and electron-poor. The maps represent the potential due to all electrons and thus an electron-poor region in molecule is not necessarily the most electrophilic site. However, the electrostatic potential maps do an excellent predicting for the possibility of charge–dipole, dipole–dipole, and quadrupole–dipole interactions. The electrostatic potentials mapped onto the 0.002 a.u. isodensity have been shown in Fig. 3 for six DCPs. The blue areas are the most positive while the most negative site is colored red. The maps show that hydrogen atoms are the most electron-poor regions while the regions around carbons are less positive. It is evident that the difference between various sites in DCPs cannot be distinguished by either the electrostatic potential map or the computed value of electrostatic potential at carbon nuclei (see Table 1). Thus, the site selectivity cannot be well predicted by using the MEP solely and it is necessary to apply chemical reactivity descriptors for analyzing the molecular regioselectivity.

Concluding remarks

Conceptual density functional theory has been employed to probe the reactivity and regioselectivity of DCPs as ambiphilic molecules. Nucleophilic and electrophilic characters of DCPs have been analyzed in terms of electrostatic potential and various chemical reactivity descriptors. It is found that among six position isomers of DCP, 2,5-dichloropyridine is not a dual molecule and is just prone to nucleophilic attack. The remaining five isomers are ambiphilic with both electrophilic and nucleophilic characters at different sites. Thus reactivity descriptors allow to rationally categorize the regioselectivity of various DCPs towards nucleophilic or electrophilic aromatic substitution.

Therefore, our results can be used as theoretical reference for guidance of chemists to select the appropriate reactant and so have a sightly product.

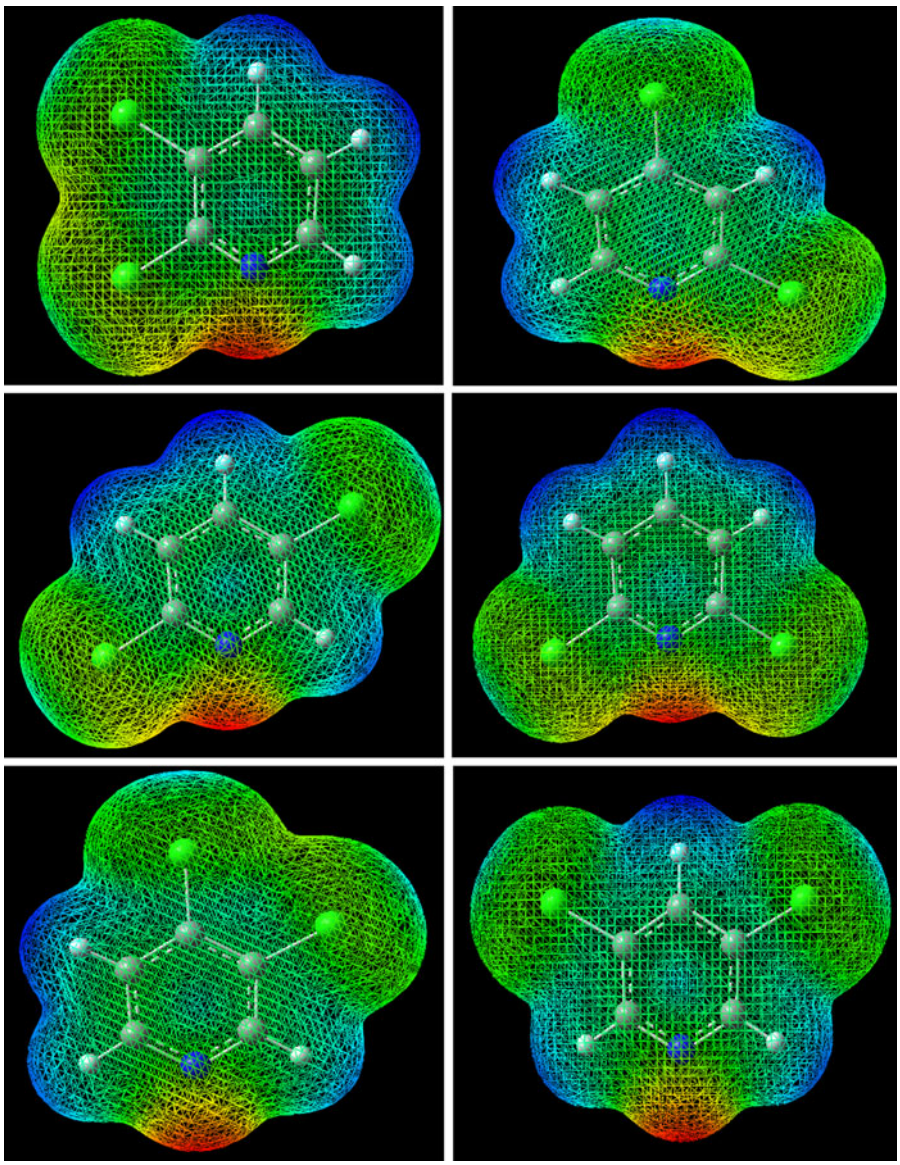

Fig. 3 Electrostatic potentials for six isomers of dichloropyridine mapped on isodensity 0.002 a.u.

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