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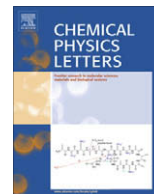


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# Halogen bonding: A lump–hole interaction

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## ABSTRACT

The Laplacian of electron density is employed in the description of halogen bonds between some halogen containing molecules, A–X, and ammonia. We show that a halogen bond is an interaction between a region of charge depletion (a hole) on the halogen atom and a region of charge concentration (a lump) on another molecule. The existence of the hole on the Valence Shell Charge Concentration (VSCC) of halogen atom is a necessary condition in the formation of halogen bonds. In addition, for some chlorine containing molecules, it is shown that the position and properties of the hole determines the geometry and strength of the halogen bond.

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## 1. Introduction

It is well known that halogen atoms can act as electron acceptors and interact with electron donor species [1–5]. This type of noncovalent interaction is usually called ‘halogen bonding’, in order to emphasize the similarity with hydrogen bonding [3,6–8]. A halogen bond, XB, is indicated by A–X...B in which the halogen bond acceptor, B, is often a Lewis base; that is it has an available pair of electrons ( $n$  or  $\pi$ ) [9–13]. X is typically iodine, bromine, chlorine and rarely fluorine, whose strength of the interaction increases in order  $(F) < Cl < Br < I$  [14–16]. A halogen bond is relatively strong and highly directional; the A–X–B angle is always close to  $180^\circ$  [17].

In spite of the importance of halogen bonding in the fields of molecular recognition [7,18,19], crystal engineering [20–23], supramolecular chemistry [24,25] and drug design [23,26–28], the fact that both the halogen atom (X) and the halogen bond acceptor (B) are usually negatively charged, make them more interesting for theoretical studies [29–36]. The different varieties of terms and phrases which has been used to describe this type of interactions, illustrate the struggle to understand the phenomena. ‘bumps-in hollow’, ‘pairs-in-pocket’, ‘exaltation of valency’, ‘donor–acceptor interactions’, ‘charge transfer interactions’ and ‘filling of antibonding orbitals’ are some examples of these descriptive phrases [3,17].

Recently Politzer and co-workers [37,38] and Clark et al. [39] explained the problem by introducing the concept of  $\sigma$ -hole bonding; the lone pairs of halogen atom form a belt of negative electrostatic potential around its central part leaving the outermost region positive, the positive  $\sigma$ -hole, which can interact with negative sites on other molecules to form XB. Politzer and co-workers

[25,37,38] showed that the positive  $\sigma$ -hole accounts for existence, directionality and strength of halogen bonds. However, it seems that the  $\sigma$ -hole concept is useful when the electrostatic forces play the major role in stabilizing the halogen-bonded complexes, and this concept fails when other energy components are also significant. The  $CH_3Cl$  molecule is a good example to explain this problem. The chlorine atom in this molecule does not have a positive electrostatic potential, a positive  $\sigma$ -hole, on its surface and consequently should not be able to form a halogen bond with bases [26,37,40]. But Hobza and co-worker [35] showed that this molecule is able to form a halogen bond with  $OCH_2$ . Meanwhile, they indicated that the largest interaction energy component for this system is dispersion, while electrostatic forces, which have been widely believed to be responsible for halogen bonding interactions, play a smaller role in stabilizing this complex.

On the other hand, the distribution of the Laplacian of the electron density provides a useful tool to describe the acid–base interactions [41]. Very recently, Espinosa and co-workers used experimental electron density and its Laplacian to study halogen–halogen interactions [42]. They showed that a halogen–halogen interaction may be understood as an interaction between charge concentration and charge depletion regions in adjacent halogens.

In this Letter we perform a topological analysis of the Laplacian of electron density, on a series of halogen-bonded complexes formed between ammonia and several halogen containing molecules including  $CH_3F$ ,  $CH_3Cl$ ,  $CH_3Br$  and some A–Cl molecules. Since in the selected A–Cl...B complexes, B is always  $NH_3$ , we will focus on the properties of the chlorine atom in the A–Cl molecules.

## 2. Computational details

Molecular geometries and their electronic wave function have been optimized with GAUSSIAN 03 program [43], at MP2/6-311++G-(d,p)6d level of theory. The AIMPAC suite of programs [44,45] was

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used to obtain critical points in the Laplacian of electron density and to calculate their properties. Three dimensional relief and envelope maps of negative of the Laplacian of electron density have been represented by AIM2000 package [46].

### 2.1. An overview on the topology of the Laplacian of the electron density

In the Quantum Theory of Atoms in Molecules, QTAIM [41], the Laplacian of electron density, denoted by  $\nabla^2\rho$ , is characterized by a rich topology which contains a wealth of chemical information complementary to that contained in electron density,  $\rho$ . In essence, the Laplacian of a scalar field measures where the field is locally concentrated and depleted. In our case the scalar field is electron density and its Laplacian indicates where electronic charge is concentrated (when  $\nabla^2\rho < 0$ ) and depleted (when  $\nabla^2\rho > 0$ ). The Laplacian of electron density for an atom (free or in a molecule) oscillates between negative and positive values and reveals an internal fine shell structure of the atom. The outer shell is divided into an inner region over which  $\nabla^2\rho < 0$  and an outer one over which  $\nabla^2\rho > 0$ . The region of the shell where  $\nabla^2\rho < 0$  is called Valence Shell Charge Concentration (VSCC). In discussing molecules, atoms and bonds, the topology of the VSCC is of particular interest to us.

The function  $\nabla^2\rho$  has its own topology, however, the topological discussions always refer to the negative of the Laplacian of the electron density, the function  $L = -\nabla^2\rho$  [41]. Now,  $L$  function is positive in a region of local charge concentration and negative in a region of local charge depletion. The critical points (CPs) in  $L$  occur where  $\nabla(\nabla^2\rho) = 0$  and the eigenvalues of the Hessian of  $\nabla^2\rho$  are the principal curvature of  $\nabla^2\rho$  at the CP. Critical points in  $L$  are classified by rank (the number of nonzero eigenvalues of Hessian matrix, denoted by  $r$ ) and signature (the algebraic sum of eigenvalues signs, denoted by  $s$ ). Each CP is conventionally expressed as  $(r, s)$  in the same way as CPs in  $\rho$ . The VSCC of an atom consist of three types of CPs:  $(3, -3)$ ,  $(3, -1)$  and  $(3, +1)$ . A  $(3, -3)$  is a local maximum in  $L$ , and denoted a local concentration in electronic charge. On the other hand,  $(3, -1)$  and  $(3, +1)$  CPs are saddle points.  $(3, +1)$  CP (which will be important in our discussion) is a minimum on the surface of maximum charge concentration.

## 3. Result and discussion

### 3.1. Halogen bonding in $\text{CH}_3\text{F}$ , $\text{CH}_3\text{Cl}$ and $\text{CH}_3\text{Br}$

As mentioned in the introduction, in halogen bonds, B is an electron rich species and acts as a nucleophile or a Lewis base. On the other hand the halogen atom plays the role of electrophile or Lewis acid. In QTAIM point of view, the basic regions in molecules are in fact zones where the charge is locally concentrated and conversely acidic regions are the zones where the charge is locally depleted [41]. In other words, the Laplacian of the electron density provides a physical basis (via local statement of virial theorem) [41] for the Lewis acid–base interactions. A Lewis acid–base interaction can be regarded as combination of a ‘lump’ in the VSCC of the base with the ‘hole’ in the VSCC of the acid. A lump is a local charge concentration and a hole is a local charge depletion. So, one can reformulate halogen bonding in terms of the topology of the Laplacian of electron density as follows: a maximum in the  $L$  function of B (lump) combines with a minimum (or saddle) in the  $L$  of halogen atom in A–X (hole).

$\text{CH}_3\text{F}$ ,  $\text{CH}_3\text{Cl}$  and  $\text{CH}_3\text{Br}$  are three molecules with different features in halogen bonding. We chose these molecules to investigate the ability of the Laplacian of electron density in discussing the halogen bonds. Let us start with  $\text{CH}_3\text{Br}$  in which the bromine atom

is able to form a halogen bond with bases [31,34,35]. Fig. 1 displays relief map of the  $L$  distribution for this molecule, in a plane containing  $\text{HCBBr}$ . The VSCC of bromine exhibits three maxima and three saddle points lying between them. One of these saddle points is of particular importance in our study. This special saddle point, pointed by an arrow in Fig. 1, indicates the hole in the VSCC of bromine. This hole can be better seen in the 3-dimensional envelope map of  $L$ . Fig. 2 indicates zero envelope map, i.e. the set of points, where  $L = 0$ , for  $\text{CH}_3\text{Br}$  which displays a hole in the VSCC of bromine atom. The existence of this hole indicates the ability of  $\text{CH}_3\text{Br}$  to form a halogen bond. It should be mentioned that this attribute of  $\text{CH}_3\text{Br}$  is also justifiable based on the  $\sigma$ -hole concept; the bromine atom has a positive  $\sigma$ -hole on its surface which can interact with an electronegative atom [37,39,47].

The condition is different for fluorine atom in  $\text{CH}_3\text{F}$ . As it is clear in Fig. 3 the non-bonded maxima in the VSCC of fluorine has merged into one and there is no saddle point between them. In other words, the fluorine atom is devoid of a hole in its VSCC to form a halogen bond. This is also in agreement with  $\sigma$ -hole concept which showed that fluorine does not participate in halogen bonding interaction [37].

On the other hand,  $\text{CH}_3\text{Cl}$  is a challenging molecule. Although for  $\text{CH}_3\text{F}$  and  $\text{CH}_3\text{Br}$  both the  $\sigma$ -hole and distribution of the Laplacian of the electron density have similar predictions, it is not the

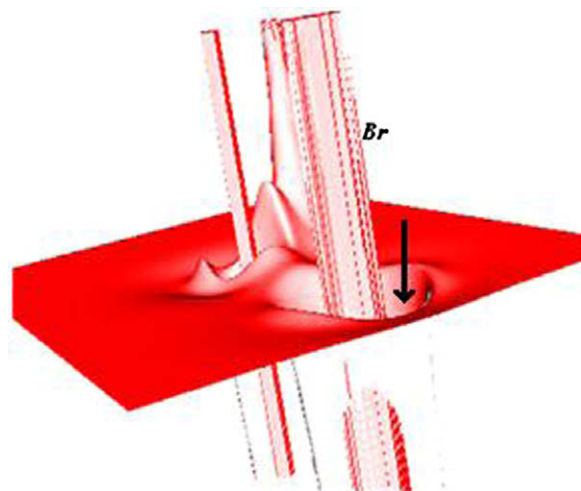


Fig. 1. Relief map of the negative of Laplacian of electron density for  $\text{CH}_3\text{Br}$  in  $\text{HCBBr}$  plane. The arrow points to the ‘hole’ in the VSCC of bromine.



Fig. 2. The hole in the VSCC of bromine in the zero envelope (a set of points where  $L = 0$ ) of  $\text{CH}_3\text{Br}$ .

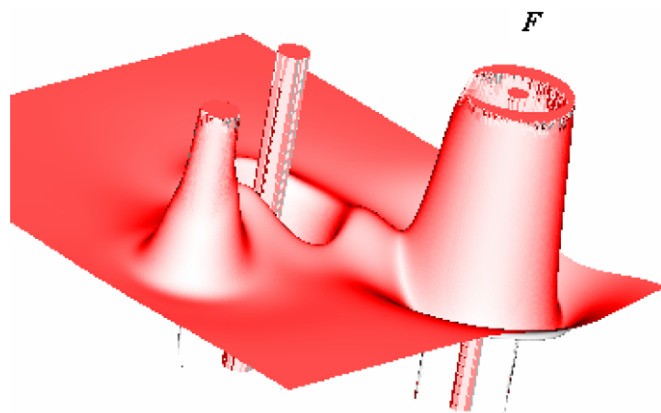


Fig. 3. Relief map of the negative of Laplacian of electron density for  $\text{CH}_3\text{F}$  in HCF plane.

case for  $\text{CH}_3\text{Cl}$ . As mentioned in the introduction, based on the electrostatic potentials, Politzer et al. [37] found a completely negative surface around the chlorine atom in this molecule and hence, this atom does not have a positive  $\sigma$ -hole and consequently, based on their conclusion, does not form a halogen bond. Their DFT calculations also showed that  $\text{CH}_3\text{Cl-NH}_3$  complex is not stable, however, MP2 calculations of Zou et al. [31] indicated a small stabilization energy (about 0.5 kcal/mol) for this complex. Up to our knowledge, unfortunately, there are no experimental results for this case, and it seems that the higher-level calculations are required to reveal that the chlorine atom in  $\text{CH}_3\text{Cl}$  is able (or unable) to form a halogen bond with ammonia. But since the nature of the base is not important in our discussions (the ability or inability of Cl in  $\text{CH}_3\text{Cl}$  to form a halogen bond is in question here), we checked the interactions between  $\text{CH}_3\text{Cl}$  and pyridine, furan, and oxirane. Our results show that the chlorine atom in this molecule is able to form halogen bonds with these bases. Their stabilization energies (at MP2/6-311++G(d,p) level) are 1.12, 1.27 and 1.92 kcal/mol for pyridine, furan and oxirane, respectively. In addition, very accurate calculations by Riley and Hobza (with coupled cluster method, CCSD(T), using different basis sets including CBS) confirm the existence of halogen bond between  $\text{CH}_3\text{Cl}$  and  $\text{OCH}_2$  [35]. Interestingly, the distribution of Laplacian of electron density also predicts an ability for the chlorine atom in  $\text{CH}_3\text{Cl}$  to participate in halogen bonding. As indicated in Fig. 4 the chlorine atom has a hole in its VSCC. Although this hole can not be seen in the zero envelope map of  $L$ , it appears when we draw the envelope for  $L = 0.15$  au. So,

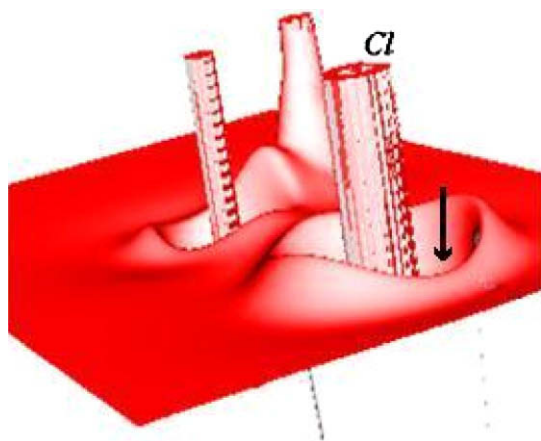


Fig. 4. Relief map of the negative of Laplacian of electron density for  $\text{CH}_3\text{Cl}$  in HCCI plane. The arrow points to the 'hole' in the VSCC of chlorine.

based on the Laplacian of electron density, unlike the  $\sigma$ -hole concept, the chlorine atom in  $\text{CH}_3\text{Cl}$  has this capability to combine with a lump of another molecule and form a halogen bond.

Indeed, the local statement of virial theorem is behind of this advantage of the Laplacian of the electron density; this theorem relates  $L(r)$  to the potential energy density,  $V(r)$ , and kinetic energy density,  $G(r)$ :

$$-\frac{1}{4}L(r) = 2G(r) + V(r)$$

the potential energy density involves the full quantum potential and contains the virial of Ehrenfest force [41]. The electrostatic force, which play a minor role in stabilizing halogen-bonded complexes of  $\text{CH}_3\text{Cl}$  [35], is only one component of this total force.

### 3.2. Properties of the hole

The position of 'lumps' and 'holes' together with some quantitative information can be determined by the position and properties of corresponding CPs in the VSCC of atoms in the molecules. In fact, holes and lumps correspond, respectively, to the (3, +1) and (3, -3) CPs in the topology of negative of Laplacian of electron density. Here, we focused on (3, +1) CPs in some A-Cl monomers.

Fig. 5 indicates four (3, +1) CPs in the VSCC of chlorine in  $\text{CH}_3\text{Cl}$ . The CP which corresponds to the pointed hole in Fig. 4, indicated by an arrow again, interacts with the (3, -3) CP (or lump) on the B when the XB is forming. The properties of this specific CP of the  $\text{CH}_3\text{Cl}$  and other selected A-Cl molecules are listed in Table 1. As indicated in this table, the A-Cl-CP angle is very close to  $180^\circ$ , keep in mind that the A-X-B is also very close to  $180^\circ$ . This means that the geometry of XB is governed by the hole position.

The molecules in Table 1 have been divided into two groups. Although the molecules in these two groups are completely different, we focused on the differences between the VSCC of their chlorine atom. The A part of the A-Cl molecules has been chosen in a manner that the chemical environment of the chlorine atom remain reasonably constant in each group. As it was pointed out earlier, there are three types of CPs in the VSCC of an atom in a molecule; (3, -3), (3, +1) and (3, -1). The chlorine atom is not an exception and its VSCC contains all of these CPs, however, the number and relative positions of them may differ from one molecule to another. As indicated by Popelier [48–50], the CPs and their connectivity scheme can be shown in a planar graph, called VSCC  $L$ -graph. According to Euler, a planar graph obeys

$$V - E + F = 2$$

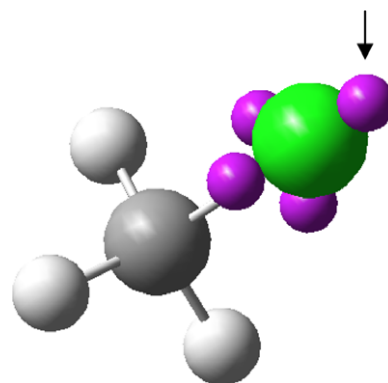


Fig. 5. Four (3, +1) CPs in the VSCC of chlorine atom in the  $\text{CH}_3\text{Cl}$  molecule. One of these CPs (indicated by an arrow) corresponds to the 'hole' in the 'lump-hole interaction'.

**Table 1**

Calculated properties (in a.u.) of hole CP at the Cl atom in the A–Cl monomers. Angles are in degree, interaction energies,  $\Delta E_{XB}$ , are in kcal/mol and relates to complexation between A–Cl and ammonia.

	A–Cl	$G(r)$	$V(r)$	$V(r)/\rho(r)$	Angle <sup>a</sup>	$\Delta E_{XB}$ <sup>b</sup>
Group 1	Me <sub>3</sub> C–Cl	0.2041	−0.4569	−2.3353	180.0	0.26
	Me <sub>2</sub> HC–Cl	0.2040	−0.4555	−2.3348	179.6	0.27
	MeH <sub>2</sub> C–Cl	0.2039	−0.4530	−2.3345	179.5	0.38
	H <sub>3</sub> C–Cl	0.2035	−0.4487	−2.3340	180.0	0.52
	FH <sub>2</sub> C–Cl	0.2024	−0.4485	−2.3310	179.1	1.5
	F <sub>2</sub> HC–Cl	0.2010	−0.4441	−2.3284	179.0	2.19
	F <sub>3</sub> C–Cl	0.1995	−0.4356	−2.3284	180.0	3.19
Group 2	4-NH <sub>2</sub> –Phenyl–Cl	0.2048	−0.4501	−2.3431	179.9	1.05
	Phenyl–Cl	0.2045	−0.4498	−2.3423	180.0	1.36
	4-F-phenyl–Cl	0.2044	−0.4484	−2.3425	180.0	1.6
	4-Pyridyl–Cl	0.2040	−0.4487	−2.3414	180.0	1.87
	4-NO <sub>2</sub> –phenyl–Cl	0.2037	−0.4471	−2.3410	179.8	2.15

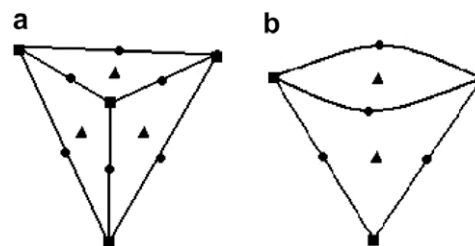
<sup>a</sup> The angle between carbon (in A), chlorine and the hole CP.

<sup>b</sup> From Ref. [31].

where  $V$ ,  $E$  and  $F$  represent the number of vertices, edges and faces in the graph, respectively. In our case, that is the VSCC  $L$ -graph, the  $(3, -3)$  CPs are the vertices, the  $(3, -1)$  CPs the edges and the  $(3, +1)$  CPs are the faces.

Fig. 6 shows the positions of  $(3, +1)$ ,  $(3, -3)$  and  $(3, -1)$  CPs of chlorine atom in CH<sub>3</sub>Cl and phenyl–Cl. Since, the VSCC of chlorine in both molecules obeys the Euler formula (for CH<sub>3</sub>Cl:  $4 - 6 + 4 = 2$  and for phenyl–Cl:  $3 - 4 + 3 = 2$ ), their structures can be shown in planar graphs. The VSCC  $L$ -graph of these molecules has been indicated in Fig. 7. These graphs show that the VSCC structures of chlorine atom in CH<sub>3</sub>Cl and phenyl–Cl belong to two different classes. This is also true for the other molecules of Table 1. In fact, the  $L$ -graph of chlorine atom in molecules of the first group are similar to Fig. 7a, and those of second group are similar to Fig. 7b.

The properties of the hole CP in each class of  $L$ -graph, has been analyzed separately. The values of kinetics energy density,  $G(r)$ , potential energy density,  $V(r)$ , and potential energy per electron, the ratio  $V(r)/\rho(r)$ , at the hole CP of A–Cl monomers are listed in Table 1. In addition, the interaction energies of these monomers and ammonia are also indicated in the table. The results show that there are some relationships between these values and halogen bond interaction energies in each group. Increasing the electron-withdrawing power of A portion of A–Cl molecules, decreases the  $G(r)$  and the absolute value of  $V(r)$  at the hole CP and leads to a greater interaction energies. Especially, good linear correlations



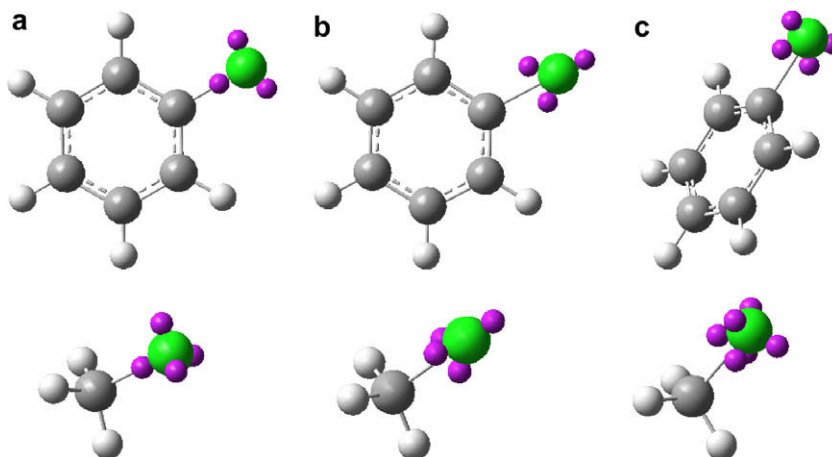
**Fig. 7.**  $L$ -graphs of the VSCC of chlorine atom in (a) CH<sub>3</sub>Cl and (b) phenyl–Cl. A square represents a  $(3, -3)$  CP or vertex ( $V$ ), a dot a  $(3, -1)$  CP or edge ( $E$ ) and a triangle a  $(3, +1)$  CP or face ( $F$ ). The reverse side of the graphs are not displayed.

have been found between interaction energies and  $G(r)$  values (with  $R = 0.997$  and  $0.994$  for the first and second group of molecules, respectively). In addition a linear correlation has been also found between interaction energies and the  $V(r)/\rho(r)$  ratio in both groups.

#### 4. Conclusions

In this work, the Laplacian of electron density and the topology of the VSCC of halogen atom has been used to investigate the halogen bonds. A series of halogen-bonded complexes formed between chlorine containing molecules (with a general formula A–Cl) and ammonia has been examined. It is shown that the formation of halogen bonding can be regarded as the interaction between a  $(3, +1)$  CP (a hole) in the VSCC of halogen atom with a  $(3, -3)$  CP (a lump) in the VSCC of an electron donor atom. The existence of a hole in the VSCC of halogen atom is a necessary condition in the formation of halogen bonds. Fluorine atom, unlike chlorine and bromine, is devoid of a hole in its VSCC and is not able to form a halogen bond. The local virial theorem is the physical rationale behind this ability of the Laplacian of the electron density.

It is shown that the position of the hole in the VSCC of chlorine atom determines the geometry of C–Cl–N in the ACI–NH<sub>3</sub> complexes. Furthermore, as long as the  $L$ -graph of chlorine atom is constant, linear correlations are found between some properties of  $(3, +1)$  CPs and halogen bonding energies. Especially, a good linear correlation is found between kinetic energy density at the CP and interaction energies. This linearity will be more interesting when we remember that the values of these properties at the CP correspond to the A–Cl molecule before complexation and are in the absence of electron donor species.



**Fig. 6.** Three different types of CPs in the VSCC of chlorine atom in CH<sub>3</sub>Cl and Phenyl–Cl. (a)  $(3, -3)$  CPs, (b)  $(3, +1)$  or hole CPs and (c)  $(3, -1)$  CPs.



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