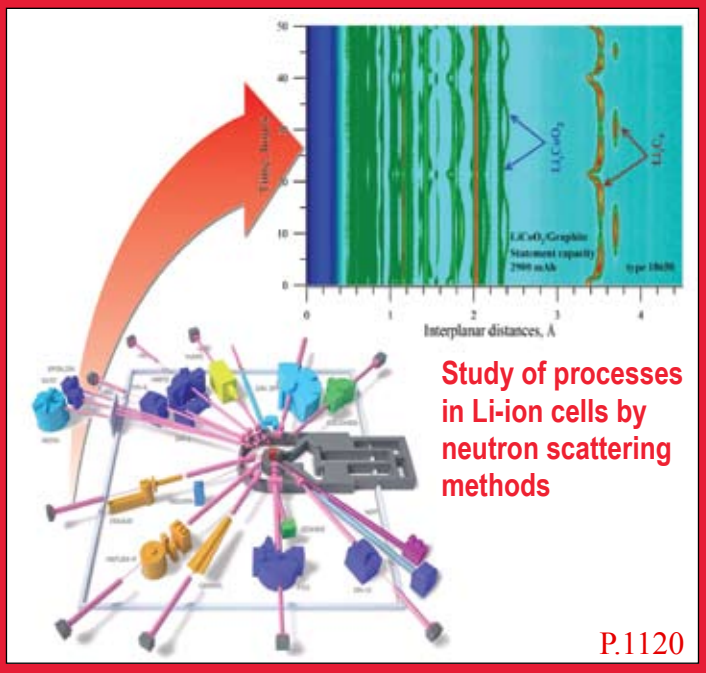
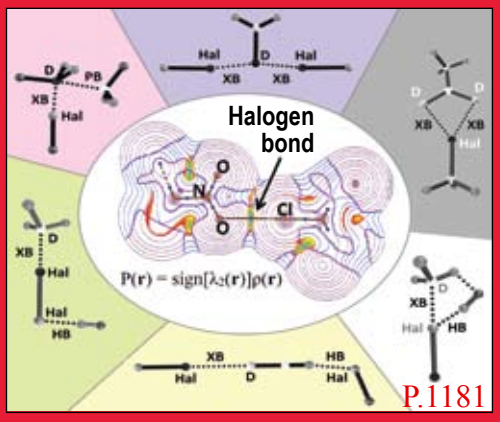
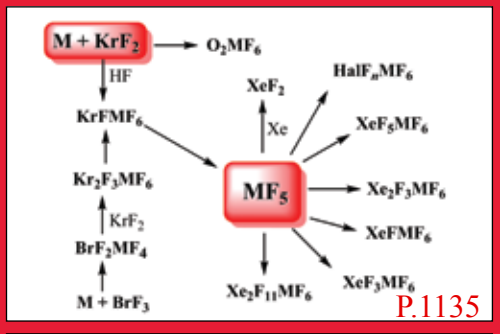
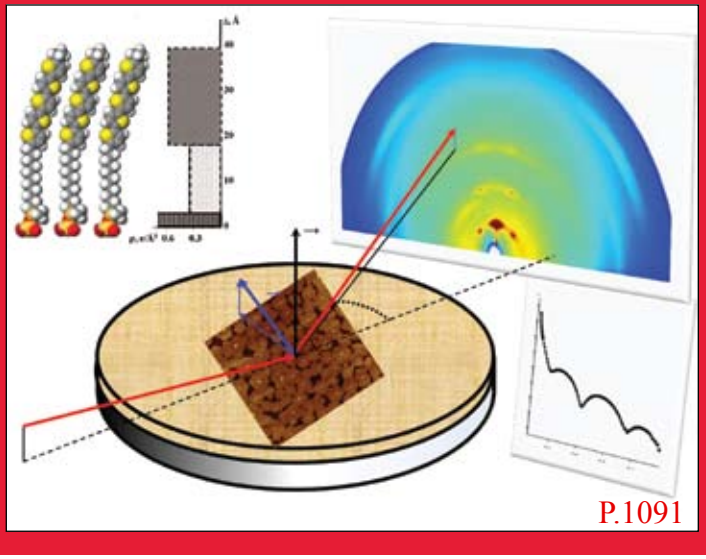
ISSN 0036-021X

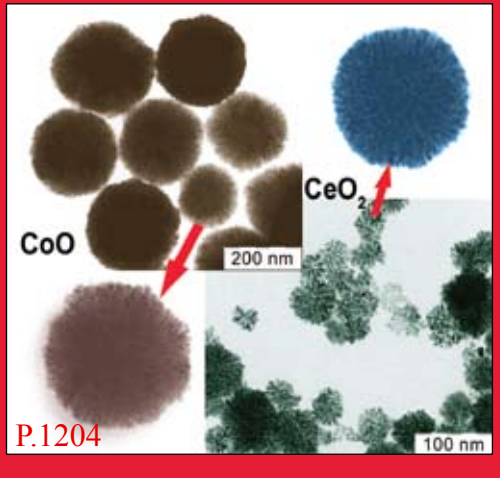
Russian Chemical Reviews











Reviews on current topics in chemistry

International Year of Crystallography

Volume 83 2014 Number 12

Russian Chemical Reviews **83** (12) 1181 – 1203 (2014) © 2014 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RCR4440

Interplay between non-covalent interactions in complexes and crystals with halogen bonds

E V Bartashevich,[a] V G Tsirelson [b]

[a] *South Ural State University (National Research University)*
Lenin prosp. 76, 454080 Chelyabinsk, Russian Federation
[b] *D Mendeleev University of Chemical Technology of Russia*
Miusskaya pl. 9, 125047 Moscow, Russian Federation

Studies on the structure and properties of complexes and crystals with halogen bonding accompanied by different secondary non-covalent interactions are summarized. The signs of halogen bonding are systematized and modern methods and approaches used to provide clear and reproducible estimates of the strength of halogen bonds are analyzed. The halogen bond strength values are compared with the strength of the other non-covalent interactions. The contradictions in the interpretation of the results from different studies of the strength of halogen bond are discussed.
The bibliography includes 249 references.

Contents

I. Introduction 1181
II. Methods and approaches used in comparative evaluation of halogen bonding 1182
III. Halogen bond as compared with other types of non-covalent interactions 1186
IV. Problems and contradictions in evaluation of the halogen bond properties 1193

I. Introduction

Fundamental notions based on systematization and revision of the ideas of various types of non-covalent interactions play a key role in the design of functional materials with preset properties. In particular, the notions 'hydrogen bond' (HB) and 'halogen bond' (XB) are clearly defined [1, 2] and serve as references in the characterization of interactions in molecular complexes, biological systems [3] and crystal engineering.[4–6] Nevertheless, at present researchers continue to give new meaning to these notions and to discuss the filed of their applicability. On the one hand, this is due to accumulation of experimental data on the structures and properties of new compounds with halogen bonds, which often possess specific features of the molecular structure. On the other hand, this is required for progress in novel theoretical methods and approaches aimed to exactly describe and develop the concepts of the properties of halogen bonds and non-covalent interactions in condensed media.

A simple and comprehensive definition of halogen bonding as non-covalent interaction in which the halogen atom acts as acceptor of electron density was reported by Metrangolo and Resnati [7–9] and included in the IUPAC nomenclature.[2, 10] However, signs of meeting the condition 'halogen atom is an electron acceptor' for non-covalently bonded atoms are specific to different methods and approaches. Presently, considerable attention is paid to the competition, or cooperativity effects, of multiple non-covalent interactions that include at least one halogen bond.[11] Correspondingly, this leads to increasing to increasing interest in structural and electronic features of halogen bonds resulting from these competition-driven effects. This interest is driven by progress in new experimental methods and theoretical approaches.

Initially, the properties of a halogen bond were described from the geometry standpoint, as was for the first time reported by Hassel.[12, 13] An analysis of the geometry parameters of halogen bonds in crystals immediately revealed regular elongations of the X—Y covalent bond (X is a halogen atom) if Y is a halogen donor and a correlation between this elongation and the shortening of the internuclear distance D···X in the D···X—Y system, where D is an electron donor. Geometric analysis also underlies the appearance of so-called polar flattening, a

E V Bartashevich Candidate of Chemical Sciences, Assistant Professor, Department of Organic Chemistry of the SUSU (NRU).
Telephone (7-351) 267 95 64, e-mail: kbartash@yandex.ru
Current research interests: structure and properties of organic compounds, chemical bond, intermolecular interactions.
V G Tsirelson Doctor of Physical and Mathematical Sciences, Professor, Head of Department of Quantum Chemistry of the MUCTR.
Telephhone (7-499) 978 95 84, e-mail: tsirel@muctr.ru
Current research interests: chemical bond, intermolecular interactions, structural determinism of properties of molecular and crystalline systems, high-precision X-ray diffraction methods and quantum chemistry methods.

Received 24 December 2013
Uspekhi Khimii **83** (12) 1181 – 1203 (2014); translated by A M Raevskiy

characteristic feature of the specific interactions of halogens (namely, a halogen atom in the crystal should be treated as having a smaller radius along the covalent bond axis). This model was proposed by Nyburg [14–16] and then developed in the studies [17–19] based on systematic observations and concerning the anisotropy of the statistical average values of the distances between the atomic nucleus of a halogen atom and all non-covalently bonded neighbours of this atom in the crystal. An analysis of the effect of polar flattening led to a recommendation to distinguish between the effective radii of a halogen atom in two orthogonal directions. At present, it is accepted that the effective radius of a halogen atom along the extended C—X covalent bond axis is smaller than that in the direction perpendicular to this axis.[20]

Studies by Kitaigorodskii [21] and Zorkii [22] devoted to systematization of halogen–halogen interactions, to the scatter of internuclear distances in crystals and to the search for the reference contacts are basic to the development and improvement of various scales of van der Waals radii. In 1986, Sarma and Desiraju [23] tried to systematize data on shortened Cl···Cl contacts and on the unit cell parameters of chloroaromatic compounds. More recently, these observations became a basis for the concept of halogen bonds as elements of supramolecular synthons in crystals, a key notion in crystal engineering, as was emphasized in Ref. 24.

Eventually, it was understood that the geometric approach to the analysis of halogen bonds is insufficient to explain the nature of the variety of these bonds. An analysis of recent publications on the properties of halogen bonds revealed two research avenues depending on the specific features of the systems under study. One of them is aimed at studying halogen bonds that are usually formed by two or three molecules in complexes. The other is devoted to investigations of the properties of multiple interactions in crystals involving halogen atoms.[25–28] In the latter case, researchers rely on their experience in describing different types of interactions.[20, 29–32]

It was found that the notion 'halogen—halogen interaction', suitable for the description of non-covalent interactions observed in crystals is not equivalent to the notion 'halogen bond'. Not each halogen–halogen interaction exhibits well-defined features of halogen bonds. The conclusion that not all halogen—halogen interactions in crystals should be treated as halogen bonds was discussed in detail by Metrangolo and Resnati.[33] Even the title of their article, '*Type II Halogen···Halogen Contacts are Halogen Bonds*', states that it is Type II interactions of halogens [34, 35] that has some distinctive features. This was experimentally confirmed in a study [36] in which the authors collected information on differences between the physicochemical properties (namely, elastic deformation) of materials based on the compounds with halogen bonds and compounds with van der Waals interactions between halogen atoms. Taking co-crystals of dicarboxylic acids and 4-bromobenzamide as examples, it was shown that their polymorphs are bonded not only through hydrogen bonds, but also through Type I Br···Br contacts (van der Waals interactions) or Type II Br···Br contacts (halogen bonds).[37]

It should be noted that it is an analysis of atom–atom interactions in the crystal structures that revealed the possibility of specifying a particular type of non-covalent interactions corresponding to the new notion 'halogen bonding'. Nevertheless, the key generalizations underlying the present-day specification of indicators of halogen bonds are based on the results of *ab initio* calculations of the electronic properties and energy characteristics of complexes of small molecules. Structural modelling of dihalide complexes is based on the studies by Legon,[38, 39] who collected vast experimental data on the geometry and quadratic stretching force constants of halogen bonds and on the fraction of transferred electrons obtained using pulsed-nozzle Fourier transform microwave spectroscopy in the gas phase. The force constants of halogen bonds (k_σ) can be extracted from centrifugal distortion constants using the Millen model,[40] while the fraction of transferred electrons (δ) can be determined within the framework of the Townes–Dailey model of changes in the nuclear–nuclear quadrupole coupling constants in the reaction of complex formation.[41]

The aim of this review is to analyze the studies published in the last five years and mainly devoted to complexes with halogen bonds accompanied by some alternative or secondary interactions that are usually weaker than the main interaction. The results reported in the earlier studies that were mainly devoted to experimental methods of evaluation of the strength of intermolecular interactions are summarized in Ref. 42. Information on almost all known fields of application of iodine-containing compounds and on experimental methods of assessment of their physicochemical properties is also available.[43, 44] In this review, we will analyze factors responsible for strengthening of halogen bonds in the complexes in which these bonds co-exist with other non-covalent interactions. Also, there is a need to systematize the available information on the present-day descriptors of halogen bonds and to establish which modern methods and approaches give the most stable and clear estimates of the strength of halogen bonds in the presence of other non-covalent interactions.

Experience in modelling non-covalent interactions showed that conclusions drawn for crystals are usually based on the results of calculations of molecular dimers or complexes. Meanwhile, an important role in the recent research is played by analysis of specific features of the distribution of the experimental and theoretical electron density around halogen atoms in crystals. For instance, experimental investigations of the electron density distribution in the presence of interactions involving chlorine atoms were reported.[45–49] This approach is on the cutting edge of research and may influence the concepts concerning the nature and variety of halogen bonds.

II. Methods and approaches used in comparative evaluation of halogen bonding

To date, parameters of single halogen bonds between small organic molecules including dihalides X—X and X—Y have been studied in quite detail. One can state that researchers arrived at a consensus on the relative strength, directionality and relatively high contribution of electrostatic interaction to the interaction energy. Taking dihalides as examples, we will briefly outline main methods and approaches that made it possible to specify the relative position of halogen bonding among non-covalent interactions. The data in Fig. 1 are not comprehensive, but can be used to approximately assess the popularity and relevance of the approaches that were used for comparative assess-

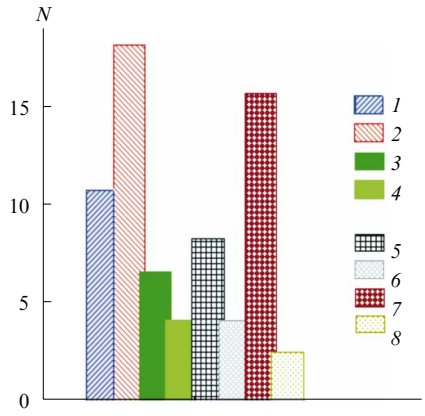


Figure 1. Usage frequency of different methods and approaches in the studies published in 2008 – 2013 and considered in this review. *N* is the number of citations.
Method: NBO (*1*); QTAIM (*1*); SAPT (*3*); other schemes for decomposition of E_{int} (*4*); charges, charge transfer (*5*); dipolar polarization (*6*); MEP (*7*); and ELF (*8*). For notations, see text.

ment of halogen bonds in the studies discussed in this review.

Competition between halogen bonding and other types of non-covalent interactions has been studied by two research groups headed by Li [50 – 53] and Alkorta.[11, 54, 55] Researchers from both groups used a wide range of theoretical methods including three main approaches to quantitative estimation of the energy parameters or electronic properties of non-covalent interactions, namely, the natural bond orbital (NBO) approach,[56, 57] quantum theory of atoms in molecules (QTAIM) [58, 59] and symmetry-adapted perturbation theory (SAPT).[60 – 62]

The NBO analysis manipulates parameters of localized orbitals[63, 64] and is traditionally used to describe the properties of charge-transfer complexes. Complexes with halogen bonds and pronounced polarization of the electron distribution of components were initially qualified as meeting this definition that dates back to Mulliken,[65] who considered so-called inner ($N-X^{+}\cdots Y^{-}$) and outer ($N\cdots X-Y$) complexes. In the latter case, the $N\cdots X$ intermolecular distances are longer than the covalent distances.

The QTAIM method [58, 59] applied to complex systems makes it possible to specify the atomic basins bounded by closed surfaces of zero flux in the electron density gradient. Atom – atom bonds are associated with the maximum electron density lines connecting particular pairs of atomic nuclei, or so-called bond paths. If crystals and complexes under study comprise a number of molecules, the QTAIM approach enables a physically correct identification of halogen bonds in the system by observing the bond path between particular atoms and the corresponding critical point in the electron density distribution (critical point of a chemical bond). This method became an efficient tool for identification of halogen bonds and other non-covalent interactions co-existing with them.

The SAPT approach [60 – 62] is an *ab initio* method based on the Rayleigh – Schrödinger perturbation theory,[66, 67] which is applied to the starting monomers with subsequent imposition of correct permutation symmetry on the multi-electron wave function of the complex. The SAPT Hamiltonian of a dimer has the form

$$H = F_A + W_A + F_B + W_B + V$$

where F_A and F_B are the Fock operators of the monomers A and B, respectively; W_A, W_B and V are respectively the perturbation operators which include the exchange-correlation fluctuations in the monomers (W_A, W_B) and intermolecular interaction (V). A typical expression for the energy of intermolecular interaction in the second order of perturbation theory, which is used to describe molecular complexes with halogen bonds, is as follows:

$$E_{int}^{SAPT} = E_{int}^{SAPT0} + E_{int}^{SAPT2}$$

$$E_{int}^{SAPT0} = E_{pol}^{(10)} + E_{exch}^{(10)} + E_{ind}^{(20)} + E_{exch-ind}^{(20)} + E_{disp}^{(20)} + E_{exch-disp}^{(20)} \quad (1)$$

$$E_{int}^{SAPT2} = E_{pol}^{(12)} + E_{exch}^{(11)} + E_{exch}^{(12)} + E_{ind}^{(22)} + E_{exch-ind}^{(22)} + E_{disp}^{(21)} + E_{disp}^{(22)} \quad (2)$$

Particular terms in Eqns (1) and (2) can be associated with traditional contributions to the energy of intermolecular interaction, namely, electrostatic polarization and exchange-dispersion components. However, the SAPT gives a better detailing of the nature of various energy components compared to conventional perturbation theory. In particular, expression (1) includes the contributions of electrostatic polarization $E_{pol}^{(10)}$ and exchange-dispersion interaction $E_{exch}^{(10)}$ of the unperturbed molecules, as well as the induction $E_{ind}^{(20)}$, exchange-induction $E_{exch-ind}^{(20)}$, dispersion $E_{disp}^{(20)}$ and exchange-dispersion $E_{exch-disp}$ contributions in the first order of perturbation theory. In Eqn. (2), components of the interaction energy correspond to the second order of perturbation theory.

There are approaches combining the SAPT and density functional theory (DFT) methods. Corresponding software implementations are available, *e.g.*, DFT-SAPT [68] and SAPT(DFT).[69] New aspects of the development of the SAPT methodology including the search for new force fields with inclusion of many-body interactions, *etc.* have been reviewed.[62]

Among the functions that are successfully used to illustrate the ability of molecular structures to form halogen bonds, mention may be made of the molecular electrostatic potential (MEP),[70 – 72] the electron localization function (ELF),[73, 74] the Laplacian of the electron density $\nabla^2\rho(\mathbf{r})$ (see Refs 58 and 75) and the one-electron potential (OEP).[76] All these functions are inappropriate for the detection of a halogen bond; they are used for characterization of the identified halogen bonds.

The MEP at a point $\mathbf{r}$ depends on the electron density $\rho(\mathbf{r})$ and nuclear charges (Z_a)

$$\varphi(\mathbf{r}) = -\int \frac{\rho(\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|}d\mathbf{r}' + \sum_a \frac{Z_a}{|r-R_a|}$$

(it is assumed that MEP is zero at $r \to \infty$). The MEP characterizes the energy of electrostatic interaction between the molecular charge distribution and a unit positive infinitesimal charge located at the point $\mathbf{r}$. In the vicinity of atomic nucleus, the electrostatic potential of an atom or ion

reaches high positive values because of the influence of the atomic nucleus. As the distance from the atomic nucleus increases, the potential monotonically decreases. In neutral atoms, the potential decreases faster than in cations because the effect of atomic nucleus weakens with the distance due to the shielding by electrons. However, the electrostatic potential remains positive at any point. In anions, the electrostatic potential becomes negative at a distance corresponding to completely shielded atomic nucleus. Then it decreases, reaches a minimum value, increases again and approaches the abscissa axis (r) from the negative side.

An analysis of changes in the potential in atoms and ions makes it possible to understand the specific features of the MEP in molecules and to compare the specific features of hydrogen bonding and halogen bonding.[77] It was found that in most molecules the potential around the fluorine atoms characterized by the highest electronegativity remains negative.[78,79] For chlorine, bromine and iodine atoms, a region of positive potential values is formed along the extension of the C–X covalent bond line. This effect was named a σ-hole in the MEP.[71,78] Plotting the MEP values on the 0.001 a.u. electron density envelopes[80] (this is close to the surface specified by the van der Waals radii of atoms) shows that the size of the σ-hole in the MEP increases with the polarizability of the halogen atom (Fig. 2), being also dependent on the intramolecular electronic effects. The ability of halogen atoms to form both halogen bonds and hydrogen bonds can be described in terms of localization of the relative extrema of the potential on the molecular surface (V^{S}_{min} and V^{S}_{max}). Thus, the MEP clearly illustrates that halogen atoms can act as electron acceptors along the extension of the covalent bond axis and as electron donors in the direction perpendicular to this axis (owing to negative values of the potential in the equatorial 'belt').

The Laplacian of the electron density, $\nabla^2\rho(\mathbf{r})$, characterizes the 3D curvature of the plot of the electron density distribution in atoms with the distance from the atomic nucleus. Depending on the ratio of the radial positive curvature along the direction 'from the nucleus' and the curvature along the perpendicular directions, the function $\nabla^2\rho(\mathbf{r})$ will change its sign at points corresponding to different electron shells in the atom. Alternating minima and maxima of $\nabla^2\rho(\mathbf{r})$ make it possible to localize the electron density concentration [$\nabla^2\rho(\mathbf{r}) < 0$] and the electron density depleted [$\nabla^2\rho(\mathbf{r}) > 0$] spatial regions. For molecules, the function $\nabla^2\rho(\mathbf{r})$ becomes anisotropic and local minima of the Laplacian of the electron density in the valence shell, which manifest themselves in the formation of a chemical bond, can serve empirical indicators of localization of the electron pairs. Unfortunately, the electron density concentration regions $\nabla^2\rho(\mathbf{r}) < 0$ of the outer electron shells do not manifest themselves for atoms with $Z > 29$ (Z is the atomic number);[81] therefore, it is appropriate to use some other functions in order to localize the lone electron pairs in molecules containing Br and I atoms. For halogen,[82] the problem can be eliminated using the OEP function[83]

$$P(\mathbf{r}) = \frac{\nabla^2\rho(\mathbf{r})}{4\rho(\mathbf{r})} - \frac{\nabla\rho(\mathbf{r})\,\nabla\rho(\mathbf{r})}{8\rho^2(\mathbf{r})}$$

Negative regions of the OEP approximately correspond to regions characterized by negative values of the Laplacian of the electron density and to small positive values of the local kinetic energy of electrons, which corresponds to electron-rich regions. Alternation of regions with negative and positive OEP values with the distance from the atomic nucleus is due to the shell electronic structure of atoms.

In accordance with the Pauli exclusion principle (PEP), each molecular orbital can be occupied by at most two electrons with antiparallel spins. The corresponding limitation imposed on the spatial distribution of electrons consists in that the region of a molecule, occupied with paired electrons, should be almost inaccessible to any other electrons.[84–86] In the one-determinant approximation, the distribution of electron pairs is given by[87]

$$\eta(\mathbf{r}) = \left[1 + \left(\frac{D_\sigma(\mathbf{r})}{D_{h\sigma}(\mathbf{r})}\right)^2\right]^{-1} \qquad (3)$$

where

$$D_\sigma(\mathbf{r}) = \sum_i |\nabla\varphi_i(\mathbf{r})|^2 - \frac{[\nabla\rho_\sigma(\mathbf{r})]^2}{4\rho_\sigma(\mathbf{r})}$$

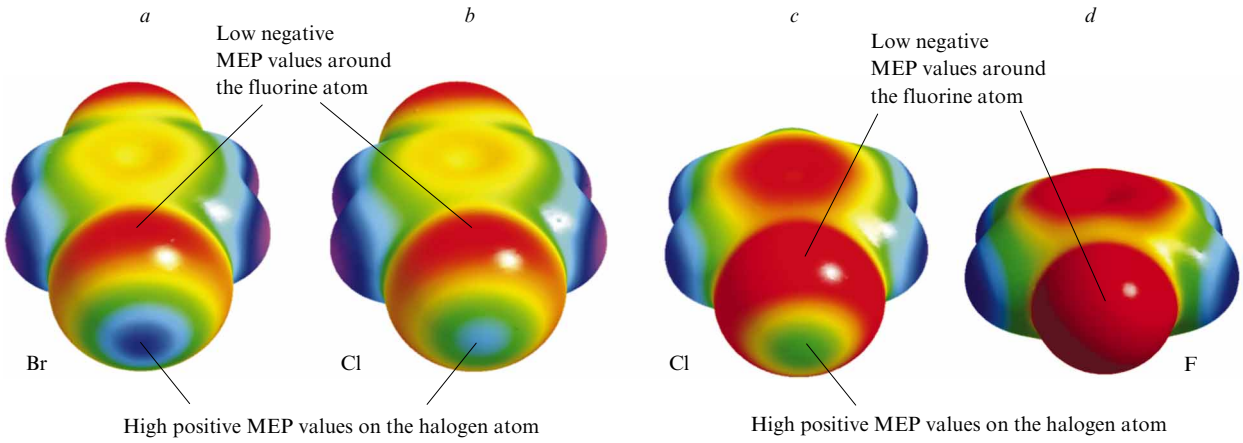


Figure 2. MEP maps on 0.001 a.u. electron density isosurface of 1-bromo-4-chlorobenzene (*a*, *b*), chlorobenzene (*c*) and fluorobenzene (*d*).[10] (*a*, *b*) V^{S}_{max}(Br) = 62.8 kJ mol^{-1}, V^{S}_{max}(Cl) = 33.5 kJ mol^{-1}; (*c*) V^{S}_{max}(Cl) = 16.7 kJ mol^{-1} (B3LYP/6-311**); (*d*) no region of positive MEP values around the fluorine atom.

The function $\sum_i |\nabla\varphi_i(\mathbf{r})|^2$ is the doubled density of the positively defined kinetic energy of electrons with the spin σ, calculated using the spin orbitals appearing in the Slater determinant, *i.e.*, with inclusion of the PEP. Would the PEP be ignored, all N electrons in the system should occupy the lowest-lying spin orbital

$$\varphi_i(\mathbf{r}) = \sqrt{\frac{\rho(\mathbf{r})}{N}}$$

Then, the kinetic energy density for electrons with the spin σ should be written as $(\nabla\rho_\sigma)^2/4\rho_\sigma$. It follows that the function $D_\sigma(\mathbf{r})$ characterizes the local increase in the kinetic energy of electrons, originating from the PEP. The lower the $D_\sigma(\mathbf{r})$ value (*i.e.*, the lower the probability to find the second electron with the spin σ near the point $\mathbf{r}$) the stronger the confinement conditions for the given electron. In closed-shell systems, the function D_σ also characterizes the degree of localization of electron pairs with antiparallel spins; all other electron pairs will be removed from the region surrounding the point $\mathbf{r}$, where a given electron pair is localized. Since in the general case the function D_σ is unbounded, a dimensionless scalar ELF is introduced in the form of Eqn. (3) in which the term

$$D_{h\sigma}(\mathbf{r}) = \frac{3\sqrt[3]{(6\pi^2)^2\left[\rho_\sigma(\mathbf{r})\right]^5}}{5}$$

describes the kinetic energy density of uniform electron gas with the spins σ.

The ELF values span the range $0 \leqslant \eta \leqslant 1$: in the spatial regions characterized by $\eta \to 1$, the kinetic energy of electrons decreases and these regions can be associated with localization of electron pairs; the case $\eta = 1/2$ corresponds to completely delocalized electrons (uniform electron gas). Nealry-zero η values are characteristic of the regions separating the electron pairs, where the local kinetic energy density of electrons is high.

When studying halogen bonds in complexes and crystals, it is important that corresponding indicators be clear for both the entire system and its components and the results obtained be confirmed experimentally. All functions listed above meet these criteria. For instance, the organization principle of structure-forming intermolecular interactions in Cl_2 crystal [45] (namely, mutual orientation of the peak – hole regions of two neighbouring chlorine molecules) is illustrated in Fig. 3 using the ELF function, $\nabla^2\rho(\mathbf{r})$ and OEP. These functions give mutually consistent results obtained in both a high-precision X-ray diffraction experiment and in calculations of an isolated dimer and a 3D crystal taking into account periodic boundary conditions.

Thus, the extension of the covalent bond involving a halogen atom at a distance of the order of a van der Waals atomic radius is characterized by [82]

— relatively high positive MEP values (σ-hole effect);

— relatively low ELF values rapidly tending to a values of 1/2 (low probability of localization of electron pairs);

— low positive values of the Laplacian of the electron density (electron density depletion); and

— high positive regions of the OEP values (electron depletion).

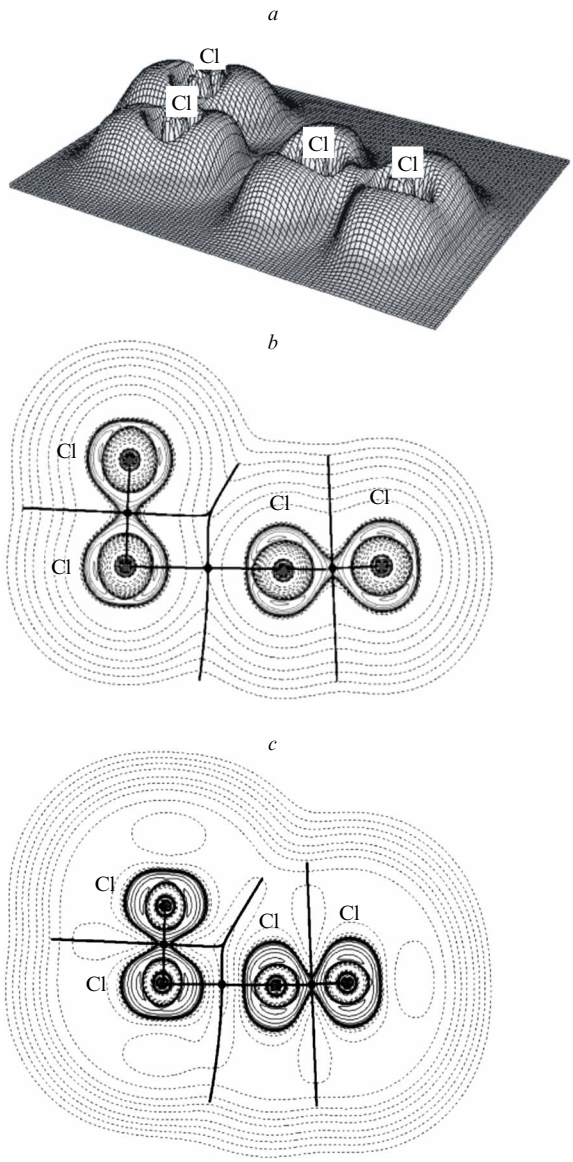


Figure 3. The ELF (*a*), $\nabla^2\rho(\mathbf{r})$ (*b*) and OEP (*c*) plots for Cl_2 dimer. (Taken from Ref. 45; improved).
3D plot of the ELF function (*a*); contour map of the Laplacian of the electron density $\nabla^2\rho(\mathbf{r})$, shown are the boundaries of atomic basins, bond paths and bond critical points obtained from MP2/aug-cc-pVTZ calculations (*b*); contour map of the OEP function (*c*); solid lines confine the electron localization regions.

The values of these functions change in different manner with distance from the atomic nucleus of the halogen along the extension of the covalent bond and in the direction perpendicular to the covalent bond axis. However, they consistently characterize weaker shielding of the positively charged nucleus of the halogen atom by the valence electrons in the region that can be identified as a region of the electron shell of the halogen atom, which ensures the formation of a halogen bond with electron donors.

The wave functions, geometric parameters of complexes with non-covalent interactions as well as their electronic and energy parameters are mainly calculated at the second-order level of Møller – Plesset perturbation theory [88] and by the Kohn – Sham method.[89] A comparison [90] of parameters

of complexes of non-covalently interacting small molecules with the reference geometries obtained from CCSD/aug-cc-pVTZ calculations and the reference interaction energies obtained from Ave-CCSD(T)/(QT) calculations [91] made it possible to recommend a number of functionals that give a ±20% accuracy for energy calculations and a less than 0.045 Å root-mean-square deviation for distances. The M06-2X hybrid functional gave the best results.[92, 93] Methods involving empirical correction to dispersion interactions also give good results.[94 – 98] Calculations of crystals with this accuracy became possible only recently.[99, 100]

The results obtained at different levels of the density functional theory were analyzed [101] in order to evaluate the accuracy of reproduction of the geometry and interaction energy in complexes with halogen bonds. Two functionals with correction for dispersion interactions, namely, M06-2X and ωB97XD, were recommended. It was found that the hydrogen bond lengths [102] and halogen bond lengths [101] calculated using the Grimme empirical dispersion corrections [94] are often underestimated, which reduces the accuracy of calculations.

When calculating the geometry of complexes of small molecules, good results can be obtained using Dunning's extended basis sets,[103] *e.g.*, aVQZ or aVTZ + CP if halogen bonds are studied.[11] However, the results obtained for halogen bonds involving iodine and astatine atoms deviate from common trends. This is due to the need to use the relativistic approximation for heavy atoms starting with $Z > 20$; as a rule, pseudopotentials are used to this end (see, *e.g.*, Ref. 104). For instance, the energy characteristics of iodine atoms in the molecular structures with more lightweight organogens were calculated in the aug-cc-pV*x*Z-PP (x = D, T, Q) basis sets;[105 – 108] for the light atoms in these structures it is more appropriate to use conventional basis sets, aug-cc-pV*x*Z. This strategy is supported by the fact that there are only a few high-quality, full-electron basis sets (6-311G,[109] ANO,[110] pVTZ [111]) and pseudopotentials (LANL08,[112]) for the iodine atom.

Unfortunately, an analysis of the electron density within the framework of the QTAIM approach using pseudopotentials may introduce errors into the characteristics of bonds at critical points because of discontinuity in the region of joining the core (pseudopotential) atomic orbitals with the 'outer' one-electron functions.[113] Here, a combined approach is used, which involves additional calculations of the electron density characteristics in Pople's full-electron basis sets (see, *e.g.*, Ref. 114).

In most cases, studies of systems with halogen bonds using the methods listed above lead to mutually consistent results and conclusions. However, mutual influence of their components for systems with multiple interactions of different nature is still difficult to assess. Contradictions reported in such studies deserve special attention and will be considered below. But first of all we will compare halogen bonds with other types of non-covalent interactions and discuss a number of approaches suitable for solving this problem.

III. Halogen bond as compared with other types of non-covalent interactions

Most often, halogen bonds are compared with hydrogen bonds. An analogy between them is due to the similarity in their properties, namely, stabilizing type of interaction energy, geometric parameters and the relative shifts of the wave numbers in the vibrational spectra.[115] When determining which of the two interactions stabilizes the complex to the greatest extent and thus dominates, the properties of different complexes with the same atomic brutto composition and different configuration of covalent and non-covalent bonding (Fig. 4) are compared.

For instance, a comparison of the interaction energies of a series of hypohalous acids XOH (X = F, Cl, Br, I, At [54]) and a with those of the bases D···XOH and D···HOX containing a carbonyl oxygen atom, thiocarbonyl sulfur atom or nitrogen-containing molecules as electron donors revealed that domination of the hydrogen bond over the halogen bond reduces on going from fluorine to iodine. In complexes of nitrogenous bases, the halogen bond dominates over the hydrogen bond only for X = At. In the formaldehyde complexes with hypohalous acids, predominance of the hydrogen bond also becomes less pronounced with increasing the atomic number of the halogen, *viz.*, competition between the halogen bond and the hydrogen bond begins at X = I.[50] In compounds containing a thiocarbonyl group, the halogen bond dominates starting with X = Br.[51]

Thus, in complexes with the same atomic composition and with isolated hydrogen or halogen bonds the halogen

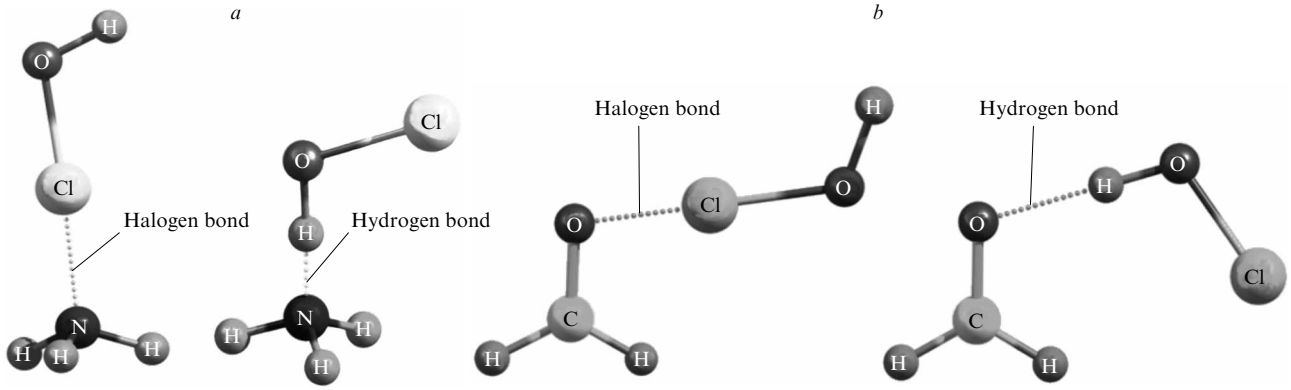


Figure 4. Halogen bonds and hydrogen bonds in different-structure complexes of the same atomic composition. NH_3···ClOH and NH_3···HOCl (*a*) and H_2CO···ClOH and H_2CO···HOCl (*b*).
(The plots are based on materials taken from Refs 50, 54 and 116).

bond dominates over the hydrogen bond only if the halogen used as electron acceptor is characterized by sufficiently high polarizability.

A SAPT analysis of complexes $H_2C{=}S{\cdots}XY$ (XY = ClF, BrF, BrCl, Br_2) showed [52] that the major attractive contribution to the total interaction energy comes from the electrostatic and induction components and that the former dominates. For the set of compounds studied in Ref. 52, the contribution of the induction energy E_{ind} was from 34% to 50% of the electrostatic energy and the contribution of the dispersion energy E_{disp} varied from 26% to 37% of the electrostatic energy. These contributions increase with increasing the electronegativity of the element Y. However, stability of the O···Cl and O···Br halogen bonds in weak complexes of halomethanes with formaldehyde $H_2C{=}O{\cdots}XCH_3$ (see Ref. 116) is mainly determined by the dispersion rather than electrostatic interactions. However, it is widely accepted [11] that halogen bonds should be mainly governed by electrostatic interactions. Nevertheless, the electrostatic component makes the major stabilizing contribution only for O···I bonds. A study [117] of aryl bromide complexes with acetone showed that the stronger interactions O···Br in the bromine-substituted pyrimidinedione $C_4N_2O_2HBr$ have pronounced electrostatic character compared to bromobenzene.

In complexes of halo-substituted ethers with water [118] the contribution of dispersion forces to the energy of very weak halogen bonds O···Cl (to 3.145 Å long) is twice as high as the electrostatic contribution, unlike hydrogen bonds in these complexes. Dispersion interactions also dominate in complexes of dimethyl ether with haloalkanes at a O···Cl distance of 2.99 Å.[119]

Interactions in the complexes $(CH_3X)(HNC)(HCN)$ (X = Cl, Br) with a very weak halogen bond and the hydrogen bond N···Cl···H are mainly of dispersion character. In these systems, the chlorine atom significantly deviates from the line of the N≡C bond. The contribution of electrostatic component of the N···Cl halogen bond is smaller than the contribution of the secondary interactions N···C in the complex.[120]

Formamidine dimers and trimers as well as halogenated formamidine analogues were considered in order to study the interplay between the hydrogen bond and the N−X···N (X = H, Cl, Br or I) halogen bond in cyclic systems.[121] In the dimers and trimers, the hydrogen bond is stronger than the halogen bond (X = Cl, Br), the bond strengths being almost equal for X = I. However, trimerization leads to weakening of the hydrogen bond and causes the halogen bond involving the iodine atom to strengthen to such an extent that the N···I···N interaction in the trimer is best described as symmetric one. Clearly, the stronger bonding requires an optimum orientation of the N···I bonds relative to the anisotropically distributed electron density of iodine atoms, which occurs in the symmetric iodoformamide trimer.

It is of interest to compare the halogen bonds and pnicogen bonds (N···X and N···P, respectively), which along with the chalcogen bonds (N···S) can be treated as 're-discovered'.[101] It is an analogy with halogen bonds that gave researchers an impetus to look from a new angle at these weak non-covalent interactions that are characterized by strict directionality. In particular, the strengths of the pnicogen, chalcogen and halogen bonds were compared [53, 122 – 126] and interplay between them was assessed in terms of the contributions to the interaction energy E_{int}^{SAPT}. It was shown [53] that going from the pnicogen bond to the halogen bond is accompanied by an abrupt increase in electrostatic attraction in the order N···P, N···S, N···X and that this attraction is compensated by rapidly increasing exchange repulsion. The total interaction energies of the complexes with these types of bonds increase upon introducing electronegative substituents into the electron acceptor molecules.

The bond strengths in complexes of different functional isomers having the same atomic composition are also compared for so-called new types of halogen bonds. For instance, the complexes F−Cl···P≡CH and F−Cl···C(H)≡P were used [127] to compare the stabilization energies of the structures with the halogen bonds Cl···P and Cl···C(sp) in terms of components of the SAPT-DFT energies; the QTAIM, ELF and MEP methods as well as analysis of changes in the calculated values of spin-spin coupling constants were also used.[128, 129] It was found that the halogen bond involving the lone electron pair of phosphorus atom is weaker than the bond involving carbon atom in methynephosphine molecule, one of the first synthetic structures with the triple bond C≡P.[130]

Often, the influence of substitution in a particular fragment of the complex on the strength of a halogen bond is studied. For instance, halogen bonds become stronger and more electrostatic in character upon replacement of hydrogen atoms by fluorine ones in the CH_nF_{3-n} group of electron acceptor molecules $X-CH_nF_{3-n}$ (n = 2, 1, 0).[116] Systems with allowed conjugation including molecules containing acetylene fragments are particularly sensitive to the influence of substitution. A study of the complexes M−C≡C−Br···N≡C−M′ (M and M′ = Li, Na) showed that the halogen bond weakens if the alkali metal (M) is in the halogen donor molecule and strengthens if the metal atom (M′) is in the electron donor molecule.[131]

Thus, the most important general conclusion that can be drawn from analysis of the physical sense of the energy components determined using the SAPT approach is as follows: the relative strengthening of halogen bonds is to a great extent determined by strengthening of electrostatic interactions (E_{els}). Earlier,[72] it was reported that halogen bonding should involve mutual polarization of components of the complex [132] and dispersion interactions between the components. It should also be noted that strengthening of halogen bonds is usually accompanied by an increase in the electrostatic and a decrease in the dispersion contribution to the interaction energy. Here, secondary interactions in the system under study may also play an important role. A comparison of the energies of halogen bonds in different systems showed that both the dispersion and electrostatic contributions increase with increasing the atomic number and, correspondingly, the polarizability of the halogen atom, thus increasing the total interaction energy.

III.1. Halogen bond accompanied by other non-covalent interactions

Alternative interactions in halogen-bonded structures can be of different character, either dominating over the halogen bond or being secondary in importance. Also, a synergistic effect (mutual strengthening of, or cooperativity between two types of interaction) may appear or weakening of the halogen bond may occur. In the latter case, one can expect that the complex with multiple interactions will be

less stable than the complex in which the same molecules are bonded by one halogen bond only.

Manifestation of the interplay between non-covalent interactions in halogen-bonded complexes is often considered taking systems comprised of more than two molecules as examples. A number of studies of the complexes in which the same atom or different atoms from the same molecule are involved in different-type interactions will be considered below. Examples of combinations of non-covalent interactions with the halogen bond are shown in the diagram presented in Fig. 5. Possible situations include involvement of different atoms of a molecule in different-type conjugated interactions (*II*, *III*) or simultaneous involvement of one atom in the donor molecule (*IV*, *V*) or the same halogen atom in a number of intermolecular interactions (*I*, *VI*). Emphasize that here we leave interactions involving hypervalent halogen atoms (this is allowed for, *e.g.*, iodine atom [133]) out of consideration.

Studies of the energy of non-covalent interactions in the systems characterized by two or more types of bonding require evaluation of the synergistic effect. Often,[134–138] conclusions whether or not co-existence of several bonds in trimolecular or larger-size complexes leads to their mutual strengthening are drawn based on analysis of the corresponding energy effect.[139] The energy change $\Delta E = \Delta E_{coop}$ (see Ref. 140) or $\Delta E = \Delta E_{syn}$ (see Ref. 141) is evaluated by subtracting the interaction energy for dimers from the total interaction energy (ΔE_{total}) in bimolecular, trimolecular, or larger-size complexes. Conclusions on the synergism (cooperativity) are then made based on the sign and magnitude of the contributions ΔE of each combination of non-covalent interactions in the system.

Usually, the contributions of two-particle and three-particle interactions to the total binding energy are estimated based on so-called many-body interaction analysis (MBIA). This methodology was for the first time used to assess hydrogen bonding in ice polymorphs;[142] it is based on the following relations:

$$\Delta E_{1-2-3} = \Delta E_{123} - \Delta E_{1-2} - \Delta E_{1-3} - \Delta E_{2-3}$$

$$\Delta E_{total} = \Delta E_{1-2} + \Delta E_{1-3} + \Delta E_{2-3} + \Delta E_{1-2-3} + E_r$$

The three-particle contributions, ΔE_{1-2-3}, are calculated as differences between the total interaction energy of the complex and the interaction energies of each pair of monomers provided that the geometries of the monomers remain the same as those in the complex. The total relaxation energy is defined as the energy difference between the monomers with the optimimzed and fixed geometries. The total interaction energy of the triad equals the sum of the relaxation energies (E_r) and the energies of the pair and triple interactions. This approach requires correction of the basis set superposition error (BSSE).[143] Possible extended schemes of such a correction are available.[144]

A review [11] by Alkorta *et al.* mainly concerns theoretical studies of the cooperativity of multiple interactions and considers all fifteen possible combinations formed by five types of non-covalent interactions, *viz.*, hydrogen bonds, hydride bonds (*h*B), hydrogen–hydrogen bonds H···H (DHB), halogen bonds and interactions between ions and the aromatic ring π-system (ion–π interactions). The classification and examples of combinations of the five types of interaction are visualized in the form of a square matrix. Each matrix element presents an example of the co-existence of two types of non-covalent interactions. In the text below we present a row from this matrix, which illustrates possible combinations of different-type non-covalent interactions with the halogen bond. Emphasize that no examples of the co-existence of (i) two hydride bonds, (ii) a hydride bond and a hydrogen–hydrogen bond and (iii) two hydrogen–hydrogen bonds in the same complex have been reported so far.[11] As far as we know, examples of combinations of the halogen bond with (iv) the hydride bond and (v) hydrogen–hydrogen bond are also unknown. Note that the properties of the hydride–halogen interactions occurring in the same fragment $R^{\delta+}-H^{\delta-}\cdots X-R$ (X is a halogen atom) are well known; they were summarized and comprehensively described in the literature.[145, 146]

Hydrogen bond	Hydride bond	Hydrogen–hydrogen bond	Halogen bond	Ion–π-interactions
XB–HB	XB–*h*B	XB–DHB	XB–XB	XB–ion–π

A number of examples with theoretically estimated synergistic effects of interactions involving the halogen bond (XB–HB; XB–XB; XB–ion–π) is given. Among a vast variety of examples of the co-existence of the halogen bond with other types of interaction, the synergistic effect is more often observed for the XB–HB combination. Contrary to this, the XB–ion–π interactions can mutually weaken one another without stabilizing the complex.

The cooperativity effects in complexes are mainly studied in relation to diatomic molecules XY (X, Y = F, Cl, Br, I). If the best polarizable halogen atom X is bonded to an electron donor, while the Y atom is involved in the hydrogen bond as electron donor (Fig. 6), a synergistic effect will be observed.[52, 140, 147–149]

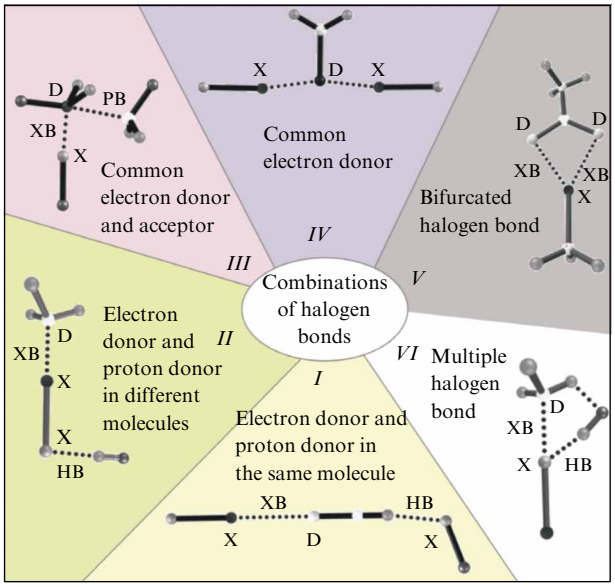


Figure 5. Main types of combinations of halogen bonds with other types of noncovalent interactions in bi- and trimolecular complexes.
For *I*–*VI*, see text; XB is halogen bond, HB is hydrogen bond, PB is pnicogen bond, D is electron donor and X is halogen atom.

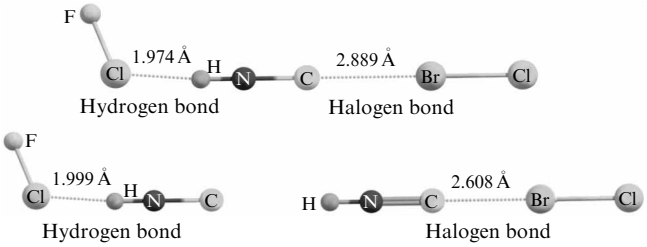


Figure 6. Synergistic effect of the halogen and hydrogen bonds in complex FCl···HNC···BrCl.
(Plotted using data from Ref. 149).

The isosurfaces of the difference electron density obtained by subtracting the electron density on the monomers with the geometry 'as in the complex $F_3CCl\cdots NCH\cdots NCH$' from the electron density on the complex are shown in Fig. 7. The isosurfaces exhibit alternation of the electron density accumulation and depletion regions upon complexation with the synergistic effect of the halogen and hydrogen bonds.[149] In such systems, the hydrogen bond and halogen bond strengthen each other, the influence of the former on the latter being somewhat more evident than *vice versa*. It was concluded [150] that the stronger noncovalent interaction influences the weaker one. Indeed, even if the halogen bond is on the periphery of the complex and the central molecule simultaneously acts as both electron and proton donor as in, *e.g.*, NCH, CNH and FH_2P, the synergistic effect will be observed for both halogen bonds and hydrogen bonds [148, 149] (Fig. 8).

A similar effect was also disclosed in the assessment of synergism between the halogen and pnicogen bonds.[53] This extends the range of possible situations to combinations of the halogen bond with the pnicogen or chalcogen bonds.[122 – 125]

Synergism between the pnicogen and halogen bonds in the complexes $YCl\cdots FH_2P\cdots NH_3$ (Y = F, CCF, OH, CN, NC) was studied;[53] the greatest stabilization of the complexes was observed when the pnicogen bond P···N strengthened in the presence of the halogen bond F···Cl (Fig. 9).

According to results of SAPT analysis, each component of the interaction energy contributes to the mutual strengthening of the halogen and pnicogen bonds, but stabilization

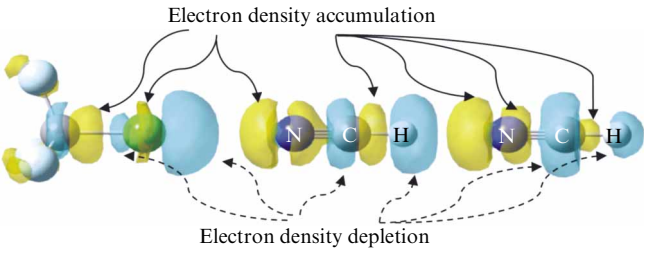


Figure 7. Difference electron density isosurfaces at ±0.0005 a.u. illustrating electron density accumulation (solid arrows) and depletion (dashed arrows) in the formation of interactions in the complex $F_3CCl\cdots NCH\cdots NCH$. (The plot was taken from Ref. 137; adapted).

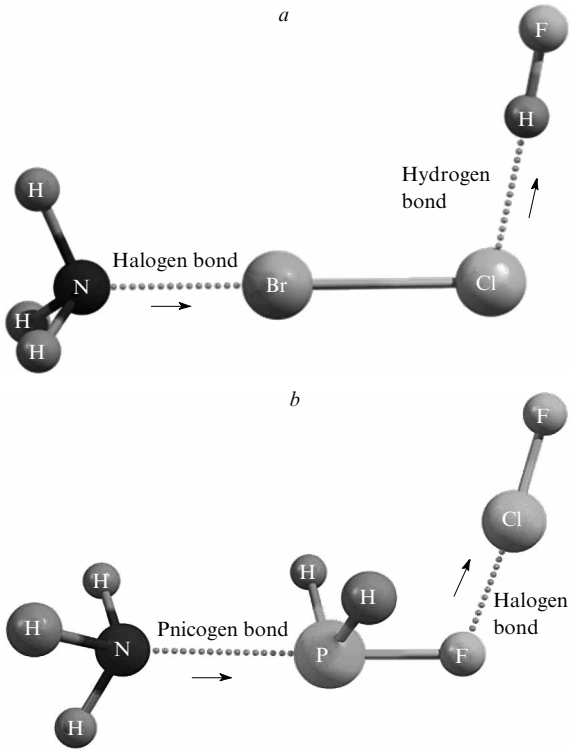


Figure 8. Cooperative effects of halogen bond and hydrogen bond in complex $H_3N\cdots BrCl\cdots HF$ (*a*) and of halogen bond and pnicogen bond in $H_3N\cdots PH_2F\cdots ClF$ (*b*). Arrows denote the charge transfer direction. (The plot is based on materials taken from Refs 148 and 149).

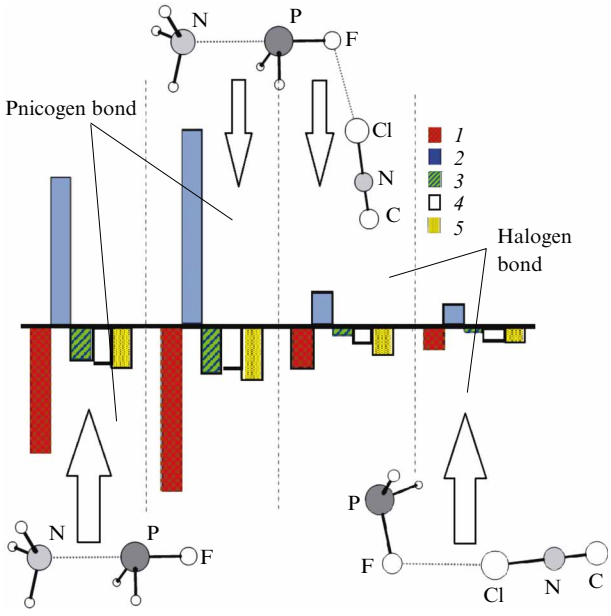


Figure 9. Synergistic effect of the halogen bond and pnicogen bond (an increase in contributions to the total interaction energy) according to SAPT data. (Taken from Ref. 53; improved).
Energy components: electrostatic (*1*), exchange (*2*), induction (*3*), dispersion (*4*); total energy (*5*).

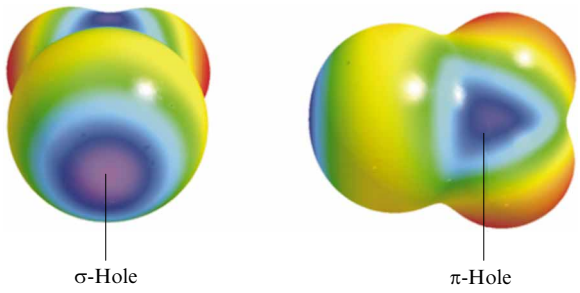


Figure 10. MEP distribution on a 0.001 a.u. electron density surface in $I-NO_2$ molecule. (The plot is based on materials taken from Ref. 152).
Maximum MEP values: $V^{S}_{max} = 129.7$ kJ mol^{-1} in the σ-hole region and $V^{S}_{max} = 113.0$ kJ mol^{-1} in the π-hole region.

of the complex mainly occurs through the electrostatic component. The competitive ability of the pnicogen and halogen bonds may be influenced by the Y substituents, in particular, the P – F covalent bond.[126]

Interesting effects are observed in cyclic systems where additional bonding involves a centre that is immediately adjacent to the halogen atom and participates along with that atom in the electron density delocalization. In such systems, not only atoms or chemical bonds, but also σ-holes and π-holes (local regions of increased positive electrostatic potential values on the van der Waals surfaces of molecules) can be involved in conjgation.[151] Unlike σ-holes, π-holes correspond to high electrostatic potential regions localized orthogonally to the plane of sp^2-hybridized orbitals (Fig. 10).[152]

Synergism in the systems $H_3N\cdots NO_2X\cdots NH_3$ (X = Cl, Br, I) was studied from the standpoint of competition between two electron-rich reaction centres in the NO_2X molecules.[151] In different configurations of these complexes, bonding involves σ-hole and π-hole interactions because these features are pronounced in the NO_2X molecules. It was found that the N···X halogen bond weakens when the lone electron pairs of NH_3 molecules interact with both the σ-hole of the halogen atom and the π-hole of the NO_2X molecule. Also, the interaction $LP(NH_3) \rightarrow \sigma$-hole (LP is the lone electron pair) on the halogen atom (Fig. 11 *a*) is stronger than an analogous interaction $LP(H_3N) \rightarrow$ π-hole on the nitrogen atom in the NO_2 group. Synergistic effect of two interactions in the complex appears if the $LP(H_3N) \rightarrow$ π-hole interaction is replaced by the $H_2N-H\cdots X$ hydrogen bond (Fig. 11 *b*), *i.e.*, if charge transfer is organized in a circular manner, from donors to acceptors. The configurations shown in Fig. 11 *b* and *c* differ in that in the former case the halogen atom simultaneously acts as electron donor and acceptor; in this case, the greatest stabilization of the complex is achieved (except the case X = Cl).

Structures containing halogen and hydrogen atoms that act as electron density acceptors, being simultaneously bonded to the same electron-donating centre (*e.g.*, a Lewis base), have been intensively studied because this type of structural fragments occurs in biological systems. A survey of the Protein Data Bank showed[153, 154] that most halogen atoms in proteins are involved in interactions with the carbonyl oxygen atom. Amino group in proteins appeared to be inaccessible to intermolecular interactions with the formation of halogen bonds.

Systems of bonds with common electron donor atoms were studied[155, 156] and the halogen bond co-existing with the hydrogen bond was characterized. The role of the common electron-donating centre is played by the carbonyl oxygen atom (Fig. 12). This bond is perpendicular to the

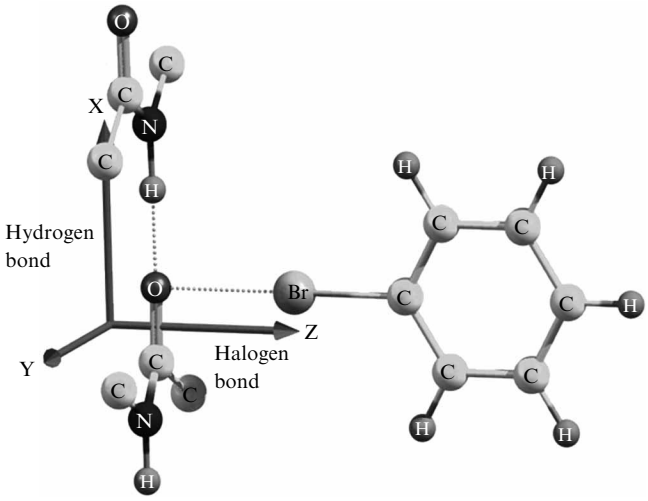


Figure 12. Fragment of a complex with common electron donor atom and orthogonal halogen bond *h*X, occurring in biological systems.
(The plot is based on materials taken from Ref. 155).

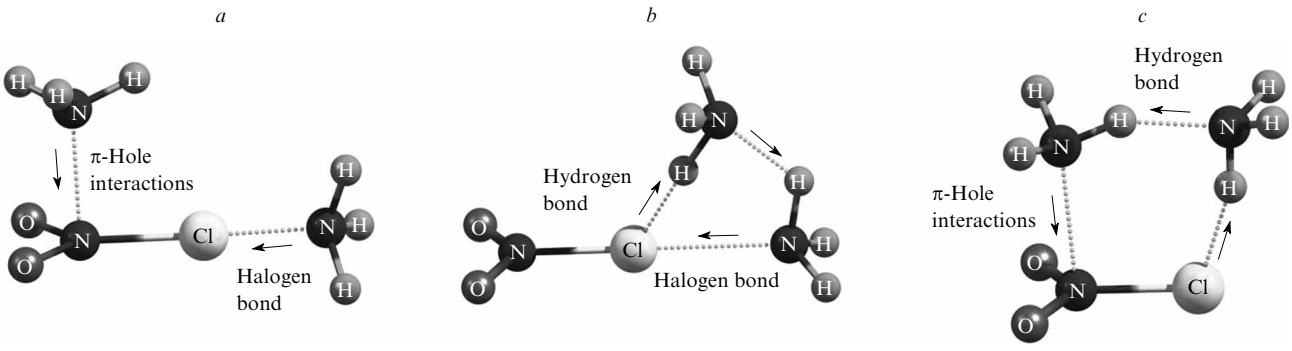


Figure 11. Interactions in $H_3N\cdots NO_2Cl\cdots NH_3$ complexes of different configurations.[151]
Halogen bond and π-hole interactions (*a*), hydrogen bond and halogen bond (*b*) and hydrogen bond and π-hole interactions (*c*).

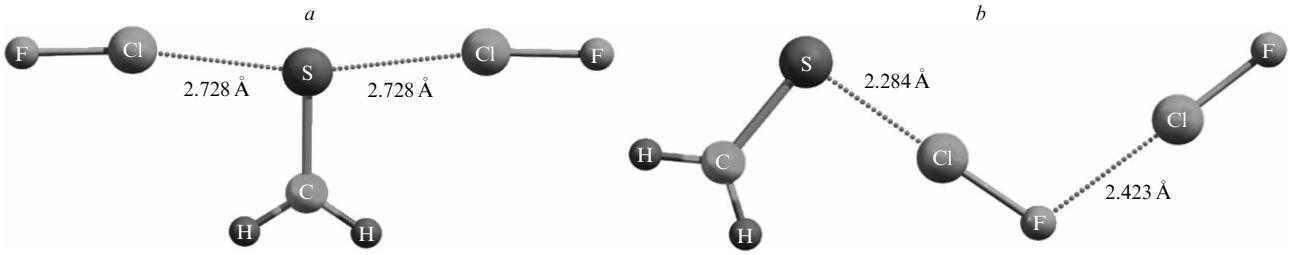


Figure 13. Weakening effect in the complex FCl···(H_2C)S···ClF containing a common electron donor (*a*) and cooperative effect with successive bonding in the complex (H_2C)S···ClF···ClF (*b*). (The plot is based on materials taken from Ref. 52).

double bond in the carbonyl group and was named 'orthogonal bond, *h*X'.[157] The X···O···H (X = Cl, Br, I) angles averaged over a selection of peptide are as follows:[155]

X	Cl	Br	I
X···O···H /deg	88.3	95.0	83.9

This type of bonds plays an important role in biological systems.[158 – 160]

The formation of the *h*X orthogonal halogen bond has no effect on the interaction energy in the model peptide fragments containing hydrogen-bonded carbonyl oxygen atoms.[156] To elucidate whether the *h*X bond energies are independent of the degree of connectivity of their common donor, *viz*., the carbonyl oxygen atom, B3LYP/6-31G(d) calculations of the energies of the interaction between two hydrogen-bonded *N*-ethylpropanamide (NEPA) molecules in the presence and in the absence of the *h*X bond with bromobenzene were carried out.[156] The energy of a complex of bromobenzene with one NEPA molecule in the presence and in the absence of the second NEPA molecule was calculated analogously. Having compared the energies, the authors of that study concluded that the energy of the *h*X bond is independent of the energy of the hydrogen bond.

Systems with evident weakening effect were studied for a case where a common electron donor forms two halogen bonds (Fig. 13 *a*). For instance, if a chlorine atom is simultaneously involved in the pair interaction with the thiocarbonyl sulfur atom Cl···S···Cl in the triad FCl···(H_2C)S···ClF (see Ref. 52), both halogen bonds are weaker than in hypothetical bimolecular system. In the system shown in Fig. 13 *a*, they are even weaker than in the trimolecular system (Fig. 13 *b*) characterized by the cooperativity effect.

The description of halogen bonds in combination with different interactions involving aromatic fragments deserves attention (Fig. 14). An analysis of the competition between electron donors in the XB – π/anion – π/LP – π systems showed that the weakening effect in two combinations, XB – π – anion and XB – π – LP, is observed if each competing interaction is characterized by some concerted direction of charge transfer[141] (see Fig. 14 *a*,*c*). In these cases, the synergistic effect manifests itself if the charge of an anion is transferred by the aromatic system through the conjugation chain to the halogen bond.[114]

Cooperativity effects in the XB – π – π and XB – cation – π systems have been studied recently.[161, 162] Synergistic effect is observed if the aromatic system simultaneously

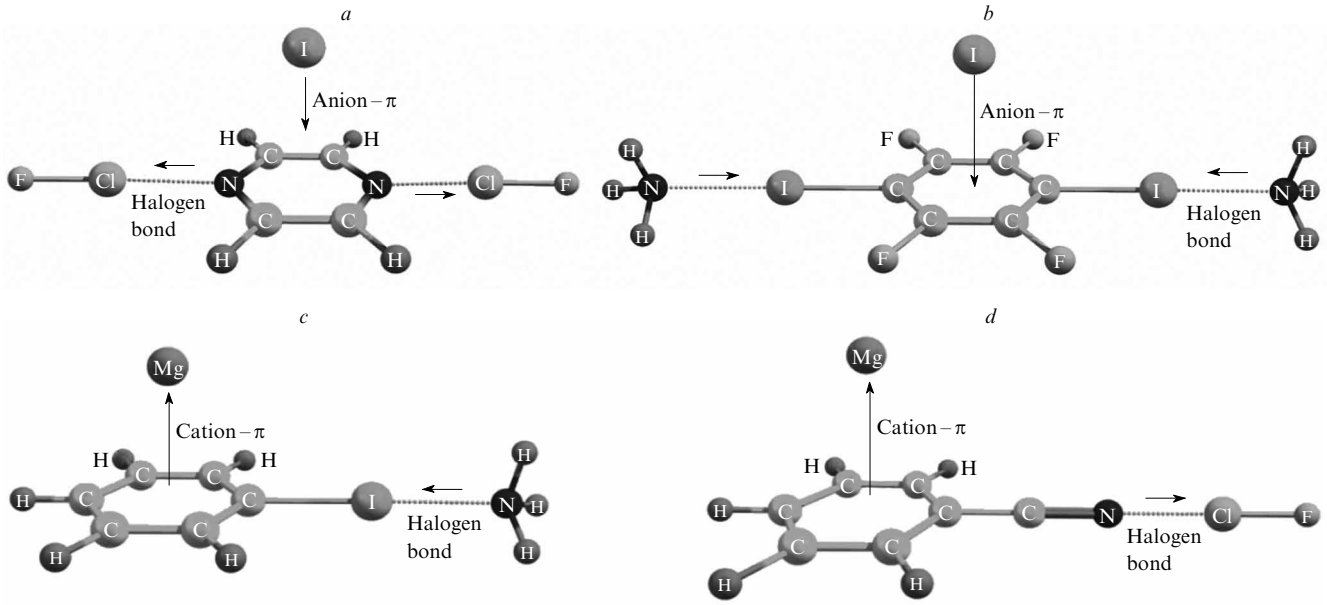


Figure 14. Illustrations of synergistic effects of the XB – π – anion (*a*) and XB – π – cation (*d*) interactions and weakening effects of XB – π – anion (*b*) and XB – π – cation (*c*) interactions. (The plot is based on materials taken from Ref. 141).

acts as an electron donor for the halogen atom and as electron acceptor for π–π interactions. The weakening effect manifests itself if the aromatic system acts as electron acceptor for π–π interactions.[161]

III.2. Multiple halogen bonds in the presence of multiple interactions of halogen atoms

Systematic studies of halogen bonds in complexes where the same halogen atom is simultaneously involved in a number of different non-covalent interactions are few. Indeed, unlike the crystal structures, only indirect experimental data on total identification of multiple interactions are usually available for molecular complexes in solutions. Now we will dwell on the studies on the structure and properties of complexes in which the same halogen atom simultaneously participates in the halogen bond and in the hydrogen bond (see Segment *I* in Fig. 5). We will also consider some examples of bifurcated, or multiple halogen bonds (see Segment *VI* in Fig. 5).

If a halogen atom in complexes is simultaneously involved in more than one non-covalent interaction, a cyclic system is always formed provided that both centres interacting with the halogen atom belong to the same molecule. Such systems are characterized by an increase in the electron density in the regions of both non-covalent interactions. The effect was established for hydrogen bonds in cyclic dimers of carboxylic acids in a comparative quantum chemical study.[163] This is in good agreement with the observed increase in stabilization of interactions in cyclic complexes; these systems are usually characterized by strong synergistic effect. For instance, in the complexes $H_3N\cdots X(Y)\cdots HF$ (X = Cl, Br; Y = F, Cl, Br; see Ref. 149), there are two hydrogen bonds and one halogen bond between three molecules, the halogen atom being simultaneously involved in two N···Cl···H interactions (Fig. 15 *a*). Also, strong co-operative effect of the hydrogen bonds, X···H and Y···H, on the N···X halogen bond was reported.[149]

A comparison of the iodine basicity (pK_{BI2}) values of secondary and tertiary thioamides [RC(S)NHR and $RC(S)NRCH_3$, respectively] showed[164] that the former have higher basicities. The difference can be as large as 0.9 pK_{BI2} units. This was explained[165] by the formation of N–H···I intermolecular hydrogen bond which strengthens the S···I halogen bond.

Methods of determination of pK_{BI2} values allow one to assess the strength of intermolecular interactions involving molecular iodine.[166, 167] Recently, the iodine basicity scale became popular because it can be used to assess the strength of interactions with iodine-containing molecules in crystals.[168] In particular, the pK_{BI2} values of 2-aminopyridine (2.45) and its methylated analogue, (2-*N*,*N*-dimethylamino)pyridine (0.95), were compared.[167] The difference between them equal to 1.50 pK_{BI2} units is partially due to the steric effect. However, the steric effect for 2-methylpyridine (pK_{BI2} = 2.35) and 2-isopropylpyridine (pK_{BI2} = 1.65) was estimated as ~0.70 pK_{BI2} units. To reveal the nature of this discrepancy, the effect of the N–H···I hydrogen bond on the strengthening of the N··· I halogen bond was studied using the quantum topological characteristics of the electron density (QTAIM method) and NBO analysis.[167] It was found that the electron density values at bond critical points are relatively high, a charge of 0.03 e is transferred from the iodine atom to the antibonding orbital of the N–H bond and that the second-order stabilization energy $E^{(2)}$ is 3.3 kJ mol^{-1}. The results obtained thus evidence in favour of synergism between these interactions.

A study of interactions of nitrogenous bases in biologically important systems showed that the halogen bond accompanied by a hydrogen bond (N···Br···H) occurs in adenine complexes with 5-bromouracil, which exhibit mutagenic activity. The bromine atom interacts with the donor centre or with the nitrogen atom in position 1 or 7 of the purine ring and with a hydrogen atom of amino group. The interaction energies of these complexes obtained[169] from *ab initio* calculations in different approximations are low and vary from −11.4 [HF/6-311G(d,p)] to −24.1 kJ mol^{-1} [MP2/6-31G(d,p)].

Desiraju *et al.*[170] were the first who studied so-called Y-shaped three-centre bonds formed in the $NO_2\cdots X$ (X = Cl, Br, I) supramolecular systems (see Fig. 15 *b*); these bonds correspond to Segment *VI* of our classification presented in Fig. 5. The results of a survey of the Cambridge Structural Database[171] and of high-level *ab initio* calculations significantly extended our knowledge of the geometry of $NO_2\cdots X$ interactions.[172] A MP2/aug-cc-pVDZ quantum chemical evaluation of the interaction energies of CH_3X (X = Cl, Br) with CH_3NO_2 and a comparison of the strength of the complexes formed through single (O···X) and bifurcated (O···X···O) halogen bonds showed[173] that complexes with single O···X bonds are by and large more

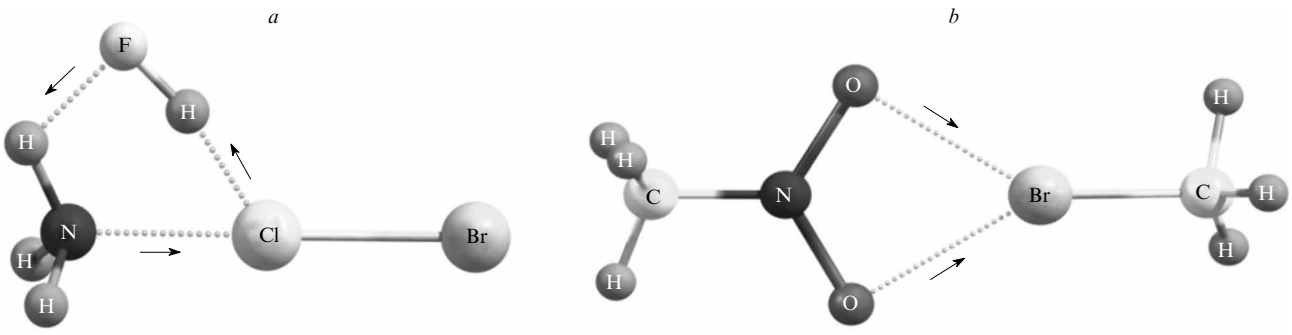


Figure 15. Examples of systems with the multiple halogen bond N···Cl···H (*a*) and bifurcated halogen bond O···Br···O (*b*). (The plot is based on materials taken from Ref. 149).

stable than complexes with multiple O···X···O interactions of the halogen atom with oxygen atoms of the nitro group. An analysis of data retrieved from the Cambridge Structural Database (Versions from 5.22 to 5.29) revealed no structures with O···Cl···O symmetric bifurcated bond in the Cl···O_2N unit.[173] In turn, 'click' synthesis of a series of isomers with modular positioning of Br···O_2N groups in crystals showed that none of the isomers forms O···Br···O units with Y-shaped three-centre interactions.[174] All these observations indicate that bifurcated halogen bonds should be weaker than single ones.

Studies on the halogen bonds formed by iodine atoms in complexes with N-heterocycles with sterically hindered basic centres (nitrogen atoms) as well as bifurcated bonds with multiple nonvalent interactions of iodine atom N···I···N were reported.[175, 176] Weakening of the mutual influence of two adjacent donor centres, which manifests itself in weakening of halogen bonds provided that the both donor centres are simultaneously involved in the bonding, was emphasized.

When studying bifurcated halogen bonds, 1,10-phenanthroline attracts considerable attention. This base with two adjacent electron-donating centres is a much better hydrogen bond acceptor than pyridine.[167] However, 1,10-phenanthroline ($pK_{BI2} = 1.91$) is a weaker halogen bond acceptor than pyridine ($pK_{BI2} = 2.22$). This effect can be explained by comparing the Gibbs free energies of complexes, calculated from the expression relating the Gibbs free energy to basicity. Published data[167] including the N(1)···I···N(10) bond lengths, electron density values at bond critical points, degree of charge transfer and the second-order stabilization energy for $n(N) \rightarrow \sigma^*(I-I)$ determined from NBO analysis showed that two interactions in this complex are identified as two nonequivalent bonds, namely, the stronger bond, N(1)···I, and the weaker bond, N(10)···I. Also, the second-order stabilization energies of two different nitrogen atoms differ by a factor of ten.[167] It was shown that the overlap between the LP of the base and the $\sigma^*(X-Y)$ antibonding orbitals is much weaker in the case of a bent orientation of bonds at the iodine atom relative to the pyridine nitrogen atom. In the crystalline state, namely, in the complex 1,4-diiodotetrafluorobenzene – 1,10-phenanthroline, the N(1)···I and N(10)···I distances also significantly differ from each other.[175, 176]

According to B97D/TZVP calculations of the complexes of 1,4-diiodotetrafluorobenzene with 1,10-phenanthroline-5,6-dione and 4,4′,6,6′-tetramethyl-2,2′-bipyrimidine with the TZVPP basis set for the iodine atom, these systems are good candidates for the formation of bifurcated halogen bonds,[177] *viz.*, complexes with symmetric and asymmetric bifurcated halogen bonds N···I···N′ were detected. In the asymmetric complexes of, *e.g.*, 4,5-diazafluoren-9-one with iodine, one N···I bond is 0.17 Å longer than the sum of the van der Waals radii of the N and I atoms (3.61 Å). Vibrational analysis of symmetric molecular structures in the harmonic approximation revealed one imaginary frequency, which does not correspond to the equilibrium state. However, the possibility for N···I···N′ fragments to exist in the crystal structures was confirmed by the synthesis of two co-crystals with symmetric bifurcated halogen bonds.[177]

For organic halides, the bond with donor centres is of pronounced electrostatic character. Indeed, spatial proximity of two lone pairs of nitrogen atom in, *e.g.*, 1,10-phenanthroline, creates a very low negative electrostatic potential in the region between the N(1) and N(10) atoms; its extremal value is $V^S_{min} = -246.8$ kJ mol^{-1}.[167] Pyridine has one lone electron pair and the corresponding minimum of electrostatic potential is only -159.0 kJ mol^{-1}. These data contradict the diiodine basicity data (see above) and point that the MEP is not a universal and self-sufficient descriptor of the bond strength in molecular complexes, as was stated in the literature.[72]

Summing up, elucidation of the role of halogen bonds (among other non-covalent interactions including hydrogen, hydride, pnicogen or chalcogen bonds) in stabilization of molecular complexes and in combination of the interactions of π-systems with cations, anions or carriers of lone electron pairs, leads to the following essential considerations:

— in complexes of the same composition, the halogen bond is usually weaker than the hydrogen bond, but it can dominate over the hydrogen bond if the electrostatic component of the interaction of the halogen atom acting as electron acceptor strengthens due to rather high atomic polarizability; in these cases, the stabilizing energy effect also depends on the electron donor atom;

— halogen bonds in combination with other types of non-covalent interactions (hydrogen bond, pnicogen bond, anion/LP – π interaction, *etc.*) can exhibit synergism if withdrawal of electrons will be accompanied by transfer of the electron density from the halogen atom to the next structural fragment immediately or along the conjugation chain.

IV. Problems and contradictions in evaluation of the halogen bond properties

The vast majority of studies on the structure and properties of halogen-bonded complexes are still based on the comparative assessment of geometric parameters, *e.g.*, internuclear distances D···X. However, the geometric approach gives no comprehensive information on non-covalent interactions in the complexes. A comparative geometric interpretation is particularly different in the case of systems with multiple halogen bonds; therefore, in recent years, the properties of complexes have been characterized using the energy, orbital or charge and electronic parameters. It is of importance that, by and large, elucidation of the hierarchy and a comparison of the strength of halogen bonds and other types of non-covalent interactions using the approaches based on the orbital approach (NBO) and on analysis of the electron density (QTAIM) leads to mutually consistent conclusions.

Nevertheless, there is a variety of systems bonded through weak interactions (in particular, halogen bonds); therefore, a comparison of these bonds is complicated owing to specific features of the chemical structure of such systems. Electronic effects of different nature should also be taken into account. Often, interpretation of the results obtained is complicated by the fact that data are analyzed within the framework of different approximations and even different concepts. As a consequence, the search for universal approach to the interpretation of the data on the strength of halogen bonds also attracts the attention of researchers.

Now we will dwell on the sources of discrepancies or contradictions in the interpretation of results obtained upon retrieval of large data arrays from different comparative studies of the strength of halogen bonds.

IV.1. Schemes for partitioning the total interaction energy

Elaboration of schemes for partitioning the total interaction energy into components is due to the need for physical interpetation of the estimates of the intermolecular interaction energy. Various useful partitioning schemes were proposed,[60–64,68,69] although none of them is universal. Let us consider the most popular schemes for partitioning the total interaction energy, which were used in the last decade to explain the nature of the variety of halogen bonds.

In a simplified form the character and strength of halogen bonds can be characterized from the standpoint of the molecular mechanics using the positive extra-point (PEP) approach.[178,179] For instance, an additional parameter, namely, the extra local positive charge, is introduced to describe the σ-hole in the MEP on the halogen atom. Within the framework of the PEP approach the energies of halogen bonds depend on the balance between the contributions of electrostatic and van der Waals interactions. Although simple, this scheme applied to halogen-bonded systems suggests that the contribution of van der Waals forces is predominant for the chlorine atom, whereas electrostatic interaction dominates in the iodine-containing complexes. This conclusion is similar to that based on the results of quantum chemical calculations.[180]

The energy partitioning scheme based on the SAPT approach was discussed above. In addition, there is the Kitaura–Morokuma (KM) scheme[181,182] which was used much more rarely in the last decade. It also treats the total energy as the sum of different-order perturbation contributions and uses the electrostatic interaction between the charge densities of two unperturbed monomers and the exchange energy of two 'frozen' subunits. The second-order perturbation contribution represents the polarization energy (a stabilizing factor due to any change in the charge of a monomer molecule). The charge-transfer component has the same sense, but it is related to electron transfer from the donor (D) to acceptor (A) and *vice versa*. Emphasize that the degree of charge transfer depends on the approximation used to describe the wave functions of the donor and acceptor, *i.e.*, the physical sense of this notion is ambiguous. The KM scheme ignores the contribution of the dispersion energy.[183] Nevertheless, it was reported[53,122] that both methods, SAPT and KM, give similar estimates of the contributions of the electrostatic component and exchange repulsion for complexes with pnicogen bonds. Correspondingly, the sum of the polarization and charge transfer contributions in the KM scheme for these bonds differs from the induction component in SAPT by at most 17%. Since in SAPT the dispersion component for the N···P bond is small, one can assume that in the case of halogen bonds of more versatile nature a direct comparison of the contributions in the SAPT and KM schemes will not lead to consistent estimates.

The interacting quantum atoms (IQA) concept[184–186] uses yet another approach to energy partitioning into contributions, namely, a complicated system (molecule or molecular complex) is separated into atomic basins according to the QTAIM. Thus, the IQA method uses atomistic ideas in analysis of chemical bonds. Here, the energy contributions are specified based on the pair atom–atom interactions; therefore, the energy parameters are determined by integrating corresponding energy operators over pairs of atomic basins. This requires the use of the one- and two-electron density matrices,[187,188] the calculations being time-consuming. However, an important feature of this approach consists in that there is no need to change the chemical paradigm[189] because the energies of the pair atomic contributions to the total energy are of the order of a few tens of kcal per mole, thus being convenient for interpretation of the chemical processes.

A brief outline of the IQA method is as follows. The contributions of two atoms, A and B ($A \neq B$), to the total energy are divided into the intra-atomic energy (E^{A}_{intra}) and the energy of interatomic interaction (E^{AB}_{inter})

$$E^{A}_{intra} = T^{A} + V^{AA}_{en} + V^{AA}_{ee}$$

$$E^{AB}_{inter} = V^{AB}_{nn} + V^{AB}_{en} + V^{AB}_{ne} + V^{AB}_{ee}$$

Here T^{A} is the kinetic, V_{en} and V_{ne} are the electron–nuclear, V_{ee} is the electron–electron and V_{nn} is the nuclear–nuclear components of the energy. In turn, the electron–electron component is divided into the Coulomb (V^{AB}_{C}), exchange (V^{AB}_{X}) and correlation contributions (V^{AB}_{cor})

$$V^{AB}_{ee} = V^{AB}_{C} + V^{AB}_{X} + V^{AB}_{cor}$$

The total electrostatic interaction energy (E^{AB}_{els}) is given by

$$E^{AB}_{els} = V^{AB}_{nn} + V^{AB}_{ne} + V^{AB}_{en} + V^{AB}_{C}$$

and the total interatomic interaction energy (E^{AB}_{inter}) can be represented by

$$E^{AB}_{inter} = E^{AB}_{els} + V^{AB}_{X} + V^{AB}_{cor}$$

Eventually, the total interaction energy (E) is the sum of the self-atom and diatomic contributions

$$E = \sum_{A} E^{A}_{intra} + \frac{1}{2}\sum_{A}\sum_{B\neq A} E^{AB}_{inter}$$

The boundaries of the atomic basins over which the summation is performed are specified by the zero-flux condition for the electron density gradient.[187,188] Thus, formally, the IQA method is characterized by exact partition of the energy of a molecule into the one-atom and two-atom contributions within the framework of quantified atomistic approach to chemical bonding.[184,190] It was found[191] that the intra-atomic energies of a particular atom vary relatively slightly from one compound to another and that the components of interatomic interactions depend on the strength and type of these interactions.

An analysis of the electronic structure of complexes of organoselenium compounds with halogen bonds (Se···I) and hydrogen bonds (Se···H) within the framework of the IQA approach revealed specifity of the Se···I intermolecular interactions.[192,193] Namely, systems with the Se···I intermolecular are characterized by almost the lack of electrostatic polarization in the complex, which should manifest itself as charge transfer from donor to acceptor similarly to Se···H interactions. In the complexes with the Se···I(1)–I(2) bonds the iodine atom [A = I(1)] loses its electrons compared to its state in isolated iodine molecule. It was shown that the kinetic energy and intra-atomic Coulomb electron–electron repulsion decrease. The

exchange-correlation energy yields the major contribution to the Se···I(1) interatomic interactions, whereas the contribution of electrostatic interaction for the pair A = I(1), B = Se is positive and very small ($\sim$0.13 kJ mol^{-1}). High exchange-correlation energy was explained [192] by considerable covalency of the Se···I bond, which is present together with the electrostatic repulsion between the outer electron shells of two large atoms.

A comparison of electrostatic stabilization of the complexes in the SAPT with the effect of electrostatic interaction of atoms $E_{\rm els}^{\rm AB}$ within the framework of the IQA approach seemingly leads to contradictory conclusions about the nature of the halogen bond. However, one should keep in mind that direct comparison is incorrect because here we deal with the quantities of different nature, although formally both of them are related to electrostatic interactions.

Thus, on the one hand, the variety of schemes for partitioning the interaction energy into physically interpretable components is useful for comparative assessment of parameters of the halogen bonds. On the other hand, one should always keep in mind exact physical sense and mathematical expressions for certain contributions that can be semantically similar but are obtained within the framework of different models. This first of all concerns the contributions of electrostatic interactions. In the schemes based on the perturbation theory, this component of energy represents the average value of the Coulomb interaction operator (**V**) calculated using the unperturbed wave functions of the components ($\Psi_{\rm A}$ and $\Psi_{\rm B}$)

$$E_0 = \langle \Psi_{\rm A}\Psi_{\rm B}|\,\mathbf{V}\,|\Psi_{\rm A}\Psi_{\rm B}\rangle$$

Empirical approaches treat the energy of electrostatic interaction between molecules as the sum of the products of atomic charges by the electrostatic potential and usually use only a few of the first terms in the series of multipole expansion (charge – charge and charge – dipole interactions). The charges and dipole moments are evaluated without internal consistency and include uncontrollable contributions from different origins.

When describing halogen-bonded systems, one should keep in mind that the term 'charge transfer' is ambiguous. This ambiguity origins from the early period of the evolution of charge transfer concept for complexes. Since Mulliken, charge transfer has been treated as electron 'flow' from the occupied orbitals of the donor molecule to the virtual orbitals of acceptor molecule; it is considered as the source of the major contribution to stabilization of the complex. However, now the term 'charge transfer' characterizes mathematical representation of electron polarization in the system of interacting molecules. It was pointed out [194] that differences between the notions 'charge transfer' and 'polarization' are first of all of semantic nature; however, methods of their determination are often different.

Modern approaches based on perturbation theory sometimes treat charge transfer as the source of a specific contribution to the interaction energy. The case in point is that the induction energy can be divided into a contribution associated with excitation of electrons from the occupied orbitals of each monomer to virtual self-orbitals and a contribution describing electronic excitation from the occupied orbitals of one molecule to virtual orbitals of the other molecule. The latter is just used to describe charge transfer as an individual contribution to the interaction energy. This approach was used by, *e.g.*, Hayes and Stone in their intermolecular perturbation theory (IMPT) [195] and in its more recent versions [196] that combine SAPT with DFT methods. The contribution to the energy called charge transfer is also explicitly included in the schemes similar to the Ziegler – Rauk approach,[197, 198] which associates charge transfer with mutual polarization of the molecules in the complex (the wave function of the complex includes states corresponding to ionized components).

One should keep in mind that the contribution of charge transfer to the interaction energy cannot be measured experimentally; therefore it seems appropriate to treat this contribution as a theoretical, auxiliary component of a complex intermolecular interaction.

It should be noted that the classical scheme of energy partition in the SAPT method ignores charge transfer. There are only sporadic attempts [117] to associate the induction component of the interaction energy with charge transfer, *i.e.*, the electron density redistribution in the complex compared to isolated components of the complex.

Modern studies are often concentrated on the role of induction and on the problem of charge transfer. Moreover, Politzer *et al.* [71] characterized complexes with the D···X – Y halogen bonds as 'electrostatically driven interactions'. However, more recently Politzer agreed that the induction and dispersion interactions also contribute substantially.[199]

In his recent study [200] Stone asked: 'Is linearity of the D···X – Y unit due to electrostatics?' He studied a number of D··· X – Y complexes with such electron donors as N_2, CO, HF, H_2O, NH_3, HCN, H_2S, H_2CO and SO_2; in most cases, the X – Y pair was the Cl – F molecule which could rotate about the axes that are perpendicular to the X – Y bond line and pass through the halogen atom X; also, the D···X distance was varied. In carrying out the SAPT(DFT) analysis [69] it was accepted that charge transfer is included in the induction energy and the charge transfer energy was not specified as an individual contribution. Eventually, Stone wrote that 'it is a justifiable generalization to say that the binding in halogen-bonded complexes *BXY* is electrostatically driven, in that the electrostatic energy is usually the largest attractive term...' He also showed that changes in the total interaction energy of the complex caused by deviation of the geometry of D···X – Y from linear is not due to electrostatics. Weakening of interactions upon deviation from linearity is governed by a considerable increase in exchange repulsion (Fig. 16). Thus, a pronounced trend towards linearity of the halogen bond is a consequence of exchange repulsion rather than electrostatics.

Earlier, Adhikari and Scheiner [201] also showed that the energy necessary to change the N···A – Y (A = S, P, Hal) angle in the complexes with ammonia correlates with the exchange repulsion energy rather than electrostatic attraction energy.

It should be emphasized that the term 'charge transfer' appears in the QTAIM-based methods in different manner compared to the orbital and empirical schemes and that the corresponding contributions to energy [189] and atomic dipole moments [202, 203] are mathematically described in another manner. Namely, they are governed by deformation of the electron density of an atom (molecule) due to transition from free state to the bound state in the molecule (complex). In the IQA method, the change in the energy of an atom upon its transition from the free state with the energy $E_0^{\rm A}$ to the bound state with the energy $E^{\rm A}$ is given by

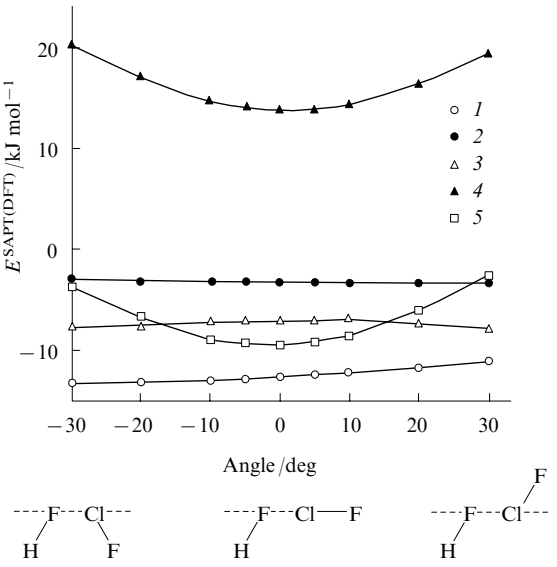


Figure 16. Contributions to the SAPT(DFT) total energy plotted *vs.* F–Cl–F angle as measure of deviation from linear halogen bond geometry. (Taken from Ref. 200; improved).
Contributions: electrostatic (*1*), induction (*2*), dispersion (*3*), exchange (*4*), total energy (*5*).

$$E^{A}_{def} = E^{A} + E^{A}_{0}$$

The sum $\sum_A E^A_{def}$ gives a positive contribution to the binding energy (E_{bind}) that is defined as follows:

$$E_{bind} = \sum_{A} E^{A}_{def} + \frac{1}{2}\sum_{A}\sum_{B\neq A} E^{AB}_{inter}$$

The IQA method deals with two main sources of deformation energy, *viz.*, charge transfer (CT, interatomic process) and charge redistribution (CR) due to changes in the environment (intra-atomic process). Therefore, it is convenient to separate E^A_{def} into the contribution corresponding to the process in the gas phase [E^A_{def}(CT)] and the isoelectronic change in energy upon the formation of a molecule from atoms [E^A_{def}(CR)]. Here, E^A_{def}(CR) is by default independent of the choice of the state of the initial atom, being the one and only source of deformation in homodiatomic molecules (X–X) where no charge transfer occurs. It also compensates changes in the size and variations of the surface area of atomic basins.

In the IQA method, the notion 'charge transfer' is used to characterize redistribution of the electron density upon bonding rather than the energy effect of chemical bonding.[189] Contrary to this, Stone [196] evaluated only the charge transfer energy and emphasized that even the present-day approach based on SAPT(DFT) does not provide the picture of the electron density redistribution in molecules or in the space between the interacting molecules.

One can state that the use of different methods based on different concepts leads to semantic problems that are due to the variety of schemes for energy partitioning into components and to ambiguity of the term 'charge transfer'. This is the current situation. It requires that researchers be accurate in interpreting data and formulating results when comparing the strength and character of halogen bonds.

Often, studies of halogen-bonded complexes involve attempts to evaluate the 'charge transfer value'. Most often, this is done by calculating the difference between the atomic charges or charges of atomic fragments in a complex and in isolated molecules. However, it seems better to call this quantity 'the change in charge' rather than the value of charge transfer.[204–207] Assuming that the strength of the complexes D···X–Y, which is characterized by the halogen-bond force constant k_σ, is related to the change in the charges in the halogen atomic basins, it appears [208] that this dependence characterizes only a trend of influence of the bond polarity in the X–Y molecule. The bonds with the X–Y molecules are stronger than the bonds with the X–X molecules. Moreover, very similar correlations can be established ignoring the influence of donor on the acceptor atomic basin, *i.e.*, by simply considering the charge of the halogen atom in free X–Y molecule. Also, experimental data [38] for halogen-bonded complexes in the gas phase showed that the charge 'transferred' from the donor molecule (D) to the acceptor molecule (X–Y) is very small. It can be determined experimentally as a fraction of charge driven by the corresponding changes in the nuclear quadrupole coupling constants of atoms involved in the formation of the D···X–Y complexes from noninteracting molecules. Usually (except the complexes $H_3P\cdots XY$), the degree of the transferred charge is of the order of a fraction of a per cent. In most complexes with a single halogen bond, *e.g.*, those formed by the chlorine molecule $D\cdots Cl_2$, the degree of intermolecular charge transfer to the acceptor atom is at most 0.01 e.[39] However, the changes in the charges of the chlorine atomic basins obtained from B3LYP/6-311** calculations span a range from 0.004 (for $NH_3\cdots Cl_2$) to 0.041 e (for $H_2S\cdots Cl_2$), which is somewhat overestimated.[208] Summing up, neither the charge of the halogen atomic basin nor its change upon complexation contain quantitative information on the strength of halogen bonds.

IV.2. Problems in evaluation of the energies of halogen bonds in crystals

Generally, the total interaction energy of a molecular complex is defined as the energy difference between the complex and its components, being determined from quantum chemical calculations or using the SAPT and SAPT(DFT) methods. However, in trimolecular and larger-size complexes formed through different-type interactions (*e.g.*, the halogen and hydrogen bonds) and moreover in crystals, correct determination of the energy of each type of interaction is impossible. Also, the computational cost, which depends on the size of the system (N), is high, *viz.*, of the order of N^7 for the SAPT method; this is comparable with the computational cost of CCSD(T) calculations. It can be reduced to N^5 for the SAPT(DFT) analysis with inclusion of correlation effects using the DFT description of monomers,[62] but the results obtained may appear to be dependent on the choice of the functional. The IQA method is of limited use because no relevant software is available; in addition, calculations of the two-electron density matrix of a crystal require huge computing time even using modern parallel computing technologies.

Gavezzotti and Dunitz [209–211] paid attention to the advantages of the method based on atom–atom potentials for evaluation of the energy parameters of intermolecular interactions in crystals.[212] However, in this case researchers face the problem of determination of the empirical param-

eters of potentials and corresponding ambiguity of the physical sense of the results obtained.

Yet another approach is based on the use of a correlation between the interaction energy and the local properties of the electron density or related functions. The electron density at bond critical points [$\rho(\mathbf{r}_b)$] was for the first time compared with the hydrogen bond energy (E_{HB}) by Boid and Choi.[213] More recently, E_{HB} was related to the potential energy density of electrons [$v(\mathbf{r}_b)$] at the critical point of the O···H hydrogen bond [214]

$$E_{HB} = -\frac{1}{2}v(\mathbf{r}_b) \quad (4)$$

(in the atomic system of units). Linear character of this dependence also holds for F···H interactions.[215] Expression (4) was widely used in studies by Antipin and Lyssenko and co-workers [216–218] to evaluate the energies of not only hydrogen bonds, but also various closed-shell non-covalent interactions in complexes and crystals. The dependence (4) was assumed to have a universal character independent of the type of the interacting atoms.

This approach was also used to characterize interactions between halogen atoms that obey the definition of the halogen bond. The energies of contacts with participation of iodine atoms calculated [219, 220] using Eqn (4) were from -7.5 to -73.3 kJ mol^{-1} for O···I interactions in the crystal of α-HIO_3 and -20.1 kJ mol^{-1} for I···I$^-$ interaction in the co-crystal of *N*-methylpyrazine iodide with molecular iodine. The energies of the halogen bonds in these studies were evaluated from parameters of the electron density distribution determined in the course of high-precision X-ray diffraction experiments. The local properties of the calculated and experimental electron densities were also used in the description of the O···Cl, Cl···Cl, F···Cl, F··· F interactions in crystals of halo-substituted aromatic compounds.[47, 48] Taking complexes of bromine-substituted hydrocarbons with bromide ions, R−Br···Br$^-$, as examples, the interaction energy was treated as a linear function of the local kinetic and potential electronic energies. The interaction energies of these complexes span a range from -4.2 to -50.2 kJ mol^{-1} (Ref. 206). In another study,[221] the interaction energies of the complexes with charge-assisted halogen bonds R−X···X$^-$···X−R (X = Br, I) also varied over a wide range from -8.0 to -125.9 kJ mol^{-1}.

More recent studies showed that other electronic properties at bond critical points can also be used to evaluate the energy of contacts based on various correlations.[222–227] It was concluded [228] that the electronic kinetic energy density values at bond critical points better reproduce the experimentally observed sublimation energies for crystals. These values are also in good agreement with the enthalpies of formation of hydrogen bonds calculated according to Iogansen.[229] It was shown [100] that the energies of Cl···Cl contacts in the training set studied can be evaluated using a common linear dependence [225]

$$E_{HB} = 0.429\, g(\mathbf{r}_b)$$

[$g(\mathbf{r}_b)$ is the local kinetic energy] for both van der Waals interactions between halogens and for the halogen bonds.

The possibility of using parameters of the linear correlation between E_{int} and electronic properties at the critical point of the halogen bond was tested taking complexes with typical halogen bonds D···X including NH_3···XY, H_2S···XY, H_2O···XY, HCN···XY, C_2H_4···XY, CO···XY (X = Cl, Br, I; D = N, S, O, C) as examples.[230] Assuming that the halogen bond energy $E_{D\cdots X}$ equals the interaction energy E_{int} of molecules in the complex, it was shown [230] that E_{int} and the local kinetic and potential electronic energies at the critical points of halogen bonds [$g(\mathbf{r}_b)$ and $v(\mathbf{r}_b)$, respectively] can indeed be determined using the following linear relationships

$$E_{int} = \beta v(\mathbf{r}_b)$$

$$E_{int} = -\gamma g(\mathbf{r}_b)$$

However, the coefficients of proportionality β and γ are not universal as it was assumed in the literature,[48, 216–220] being dependent on the nature of the atoms participating in the halogen bond. Agreement between the estimates and the observed E_{int} values is achieved if β and γ vary for the halogen atoms acting as electron density acceptors:

Atom	β	γ
Cl	0.49 ± 0.03	0.47 ± 0.03
Br	0.58 ± 0.02	0.57 ± 0.03
I	0.68 ± 0.04	0.67 ± 0.05

Summing up, equations of the type (4) are useful for evaluating the energy of particular halogen and other non-covalent interactions in crystals. However, the use of a universal parameter in a linear dependence leads to incorrect estimates of the energy of molecular contacts, which is important in the case of non-covalent interactions. These parameters of the linear correlation are not universal and should be determined prior to being used in correlations. Also, linear character of the dependence of the contact energy on the local properties [$\gamma(\mathbf{r}_b)$ or $v(\mathbf{r}_b)$] may violate if strong hydrogen bonds ($-\Delta H > 60$ kJ mol^{-1}; see Ref. 100) and interactions involving halogen atoms in ion pairs are included in the data set.[230]

IV.3. Molecular electrostatic potential on specified electron density isosurfaces

Anisotropy of the electrostatic potential around the terminal halogen atom provides a simple and clear illustration of the variety of forms of non-covalent interactions involving terminal halogen atoms (see Fig. 2). Politzer *et al.* [72] developed a method for evaluating the interaction energies, which is based on the properties of the MEP on a specified electron density surface. Unlike the methods which estimate the electrostatic contributions to the total energy in different manner, positions of extrema of the electrostatic potential on the outer surface surrounding the molecule are located unambiguously, *i.e.*, they are independent and universal quantitative parameters. For the same system, the relative extrema V^S_{min} and V^S_{max} have physical sense. It was reported [72] that the MEP is a self-sufficient tool for prediction of the direction of nucleophilic or electrophilic attacks and the possibility of formation of halogen bonds and even their strength.

A correlation between the interaction energy of halogen-bonded complexes and the MEP minima (V^S_{min}) localized in the regions of potential bonding sites with halogen atoms was reported.[70] However, it was found empirically that

correlations between E_{int} and P_d, where P_d is the energy or electronic characteristic of a property of the donor in the halogen-bonded system, are not universal for extended sets of compounds containing additional, *e.g.*, steric, features or close-lying electron-donating centres.[199] This indicates that the one and only descriptor is insufficient to describe the versatile nature of the electronic properties of the halogen bond in chemically nonequivalent systems.

It is of great importance that the electrostatic potential analyzed on the van der Waals surface of a molecule is convenient for *a priori* assessment of the reactivity. In systems where the anticipated bond has already formed or where multiple interactions occur, the use of the electrostatic potential as the bond strength descriptor is of no sense. Also, the MEP values of molecular complexes and clusters are determined to within a constant, thus being inappropriate for quantitative and comparative description of bond strength in different systems and moreover in the presence of multiple interactions.

IV.4. Identification of non-covalent interactions using the reduced electron density gradient (NCI approach)

Recently,[231] a 'non-covalent interactions' (NCI) approach was proposed to reveal and identify non-covalent interactions in the 3D space using the reduced electron density gradient (RDG).[232] This is a fundamental dimensionless quantity in the density functional theory;[233] it characterizes the deviation of the electron density distribution from a homogeneous case

$$\mathrm{RDG}(\mathbf{r}) = \frac{1}{2(3\pi^2)^{1/3}} \frac{|\nabla\rho(\mathbf{r})|}{\rho(\mathbf{r})^{4/3}}$$

Regions of 2D and 3D minima of the RDG(**r**) function with low electron density values (to this end, a limitation $\rho(\mathbf{r}) < 0.05$ a.u. is introduced usually) serve as indicators of non-covalent interactions. The points $\mathrm{RDG}(\mathbf{r}) = 0$ match the critical points of the electron density, in particular, the saddle points corresponding to 1D minima of the electron density and therefore the (3, −1) critical points which characterize chemical bonds in the QTAIM theory. The curvature of the electron density in the 3D space between atoms or functional groups is visualized using the NCI isosurfaces,[234] *i.e.*, sets of values of the RDG(**r**) function in the vicinity of its minima surrounded by a specified contour. Usually, contours are drawn to make the image clear.

In compact form, information on non-covalent interactions is provided by the $\mathrm{RDG}(\mathbf{r}) - \mathrm{sign}[\lambda_2(\mathbf{r})]\rho(\mathbf{r})$ plots. In these axes, minima of the RDG(**r**) function represent sharp peaks or so-called spikes directed downward. Taking into account the sign of the second eigenvalue of the Hessian of the electron density, $\lambda_2(\mathbf{r})$, at the point **r**, the $\mathrm{RDG}(\mathbf{r}) - \mathrm{sign}[\lambda_2(\mathbf{r})]\rho(\mathbf{r})$ plot in the region of non-covalent interactions has two sleeves, of which the left corresponds to $\lambda_2 < 0$ while the right corresponds to $\lambda_2 > 0$. The interaction is treated as stabilizing at $\lambda_2 < 0$ (in terms of the QTAIM the negative sign of λ_2 corresponds to regions surrounding the bond critical points) and as weak at $\lambda_2 \approx 0$.[234] The region $\lambda_2 > 0$ includes atomic rings and cages. The $\mathrm{RDG}(\mathbf{r}) - \mathrm{sign}[\lambda_2(\mathbf{r})]\rho(\mathbf{r})$ plots for the region $\lambda_2 > 0$ should always exhibit peaks for intermolecular interactions in the complexes with cyclic and cage fragments or in crystals.[235, 236]

The NCI and QTAIM methods were used to compare intra- and intermolecular interactions between halogen atoms in perhalogenated ethanes X_3C-CY_3 (X, Y = F, Cl).[237] For complexes $H_3N\cdots ClF$ and $H_3CCl\cdots ClCF_3$, the NCI isosurfaces were revealed with $\lambda_2 < 0$ between atoms Cl···Cl, Cl···F in each molecule. However, an analysis of data obtained by different methods shows that halogen–halogen intramolecular interactions in perhalogenated ethanes differ from typical halogen bonds in the lack of (i) bond paths in the electron density distribution and (ii) σ-hole on the MEP surface for the halogen atom acting as electron density acceptor. Nevertheless, the NCI method revealed relatively weak (van der Waals type) intramolecular interactions.[237]

Now we will assess the potential of the NCI analysis taking identification of non-covalent interactions in chlorotrinitromethane dimer as an example. This compound has a very short carbon–chlorine bond in the crystal [1.694(1) Å], its nature was studied[238] from the standpoint of specific features of the electrostatic potential. An analysis[239] of the regions of localization of the NCI isosurfaces and $\mathrm{RDG}(\mathbf{r}) - \mathrm{sign}[\lambda_2(\mathbf{r})]\rho$ (**r**) plots revealed the following (Fig. 17). In one chlorodinitromethane dimer, there are three types of regions characterized by low RDG(**r**) values, namely, the O···Cl intermolecular halogen bond; intramolecular interactions between chlorine atom and three oxygen atoms, Cl···O, and three identical intramolecular interactions O···N between nitro groups from the same molecule. Let us compare the first two interactions between chlorine and oxygen atoms. The NCI isosurfaces corresponding to minima of the RDG(**r**) function are shown in Fig. 17 *a*.

The tip of the spike for the intermolecular halogen bond O···Cl (see region *A* in Fig. 17 *b*) coincides with the critical point of the electron density in the 3D space. The fragment of the NCI isosurface for the intramolecular contact Cl···O includes the junction point of three boundary surfaces of four atomic basins (O, N, C and Cl). The electron density gradient has a minimum value in two directions only; as a consequence, no bond path[240] and, correspondingly, no critical point of the electron density appears in this region.

This example shows that the both approaches, NCI and QTAIM, demonstrate the ability to provide clear information on the intermolecular halogen bond O···Cl (because all (3, −1) critical points of the electron density can be assigned to the region of RDG minimum). However, the QTAIM method shows no bond paths and critical points of the electron density for intramolecular contacts Cl···O, whereas the NCI method identifies Cl···O contacts as intramolecular non-covalent interactions.

This implies that the NCI approach is more informative than QTAIM and reveals a number of regions containing 2D extrema of the RDG function in those domains of the 3D space where intramolecular contacts between chlorine and oxygen atoms cannot be interpreted as chemical bonds. Also, indicators of Cl···O intramolecular interactions may resemble halogen bonds.

It was reported[241] that main features of the NCI approach manifest themselves if the electron density in the crystal is approximated by the sum of atomic electron densities (so-called promolecule approximation[242]). The NCI isosurfaces for the unperturbed electron density models are similar to analogous isosurfaces plotted using experimental data on the electron density.[242] It has been stated[234]

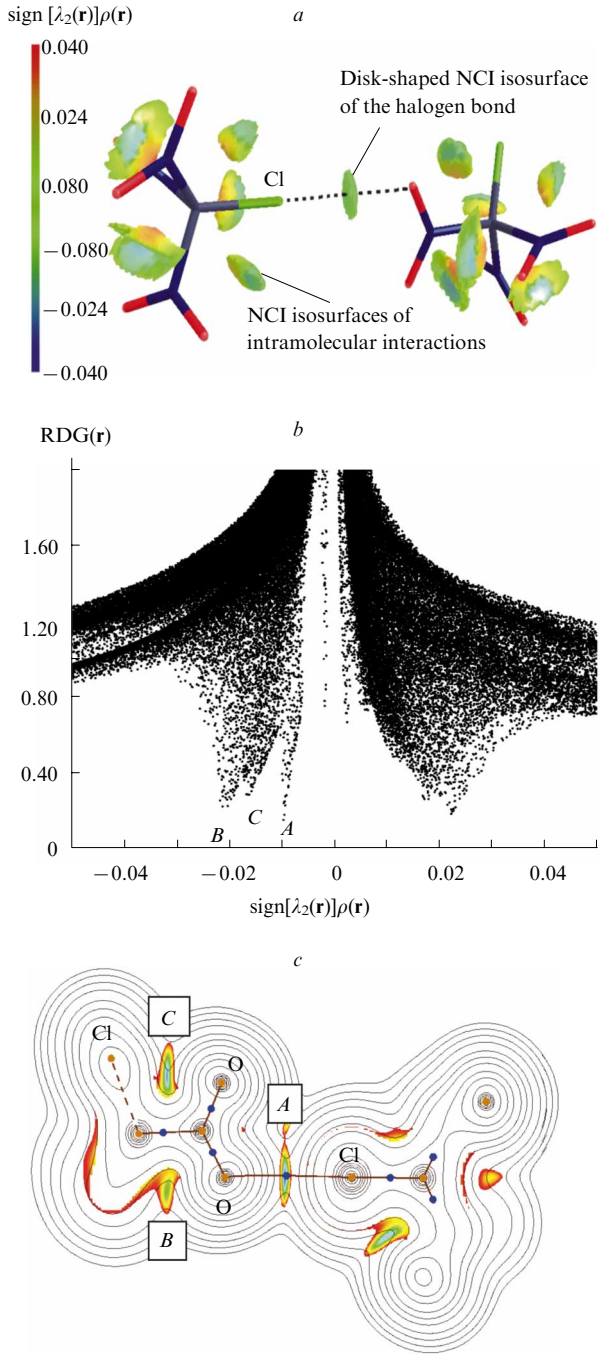


Figure 17. Structure of chlorotrinitromethane dimer with the NCI minima regions specified to a contour corresponding to RDG(**r**) = 0.6 (*a*), RDG(**r**) − sign[λ_2(**r**)]ρ(**r**) plot (*b*) and a superposition of the electron density map and regions corresponding to minima of the RDG(**r**) function (*c*).[239]
The letters *A*, *B* and *C* denote the spikes obtained in different representations.

that this can give an impetus to wider application of the NCI methodology for identification of non-covalent interactions in biosystems. However, a thorough examination [243] showed that in 'real' situations peaks of the electron density gradient are shifted towards more 'bound' states compared to the promolecule and thus characterize greater stabilization of the complex. In addition, the RDG(**r**) parameters of the promolecule are much less structured. These results cast some doubt on the optimism with respect to the data on non-covalent bonding obtained using simple promolecular NCI models in complex biological systems. However, prospects for the development of the NCI methodology for detection and analysis of non-covalent interactions in crystals seem to be bright. Here, some advances are accompanied by the design of new software [CRITIC2 (see Ref. 235) and NCImilano (see Ref. 244)], which enables analysis using the electron density obtained from self-consistent quantum chemical calculations with periodic boundary conditions [CRYSTAL (see Ref. 245)] and the experimental charge density reconstructed using the multipole model [246] [XD2006 (see Ref. 247) and WinXPRO (see Refs 248 and 249].

At the end of this Section, mention may be made that all studies of halogen bonds carried out in the last decade and considered in this review are of complex character and involve an analysis of a set of different characteristics determined using one or more approximations and, in some cases, using different concepts. By and large the approaches based on analysis of both the orbital and atomic characteristics give mutually consistent estimates when comparing the strength of the halogen bond with those of other types of non-covalent interactions.

When the term 'charge transfer' is applied to halogen-bonded complexes without additional comments, there may be some confusion in the interpretation of information because in different methods (Kitaura – Morokuma, IMPT and SAPT schemes, on the one hand and the IQA and QTAIM approaches, on the other hand) it characterizes different effects. The schemes for interaction energy partitioning into components evaluate (ambiguously) only the charge transfer energy and do not treat the electron density redistribution. On the contrary, the QTAIM-type methods include prediction of the electron density redistribution between molecules based on the 'charge transfer' but avoided the binding energy.

Inconsistency in estimates in the course of identification of non-covalent interactions involving halogen atoms may appear when using approaches based on fundamentally different indicators of interactions. For instance, the NCI and QTAIM methods may give mutually inconsistent estimates in detection of non-covalent interactions involving halogen atoms. The NCI approach provides redundant information compared to the QTAIM method with respect to detection of halogen bonds because it reveals a number of regions of the 2D RDG extrema in those spatial domains where intramolecular contacts cannot be treated as halogen bonds. Nevertheless, this provides no obstacles to identification of a variety of regions of non-covalent interactions involving halogen atoms in complexes and crystals using the RDG function.

Summing up, extension of the range of methods and approaches by and large influences favourably the possibility to identify, assess and compare the halogen bond, in particular, in complex systems, where the bonds in question are accompanied by alternative or secondary interactions. Of particuar importance is the possibility to choose complementary methods of investigation. However, conceptual and semantic problems due to the variety of methods and approaches require that researchers be accurate in interpreting data and comparing results obtained using different methods.

* * *

The state of the art in the description of the properties of molecular complexes can be regarded as complete only if competition or cooperativity effects of multiple non-covalent interactions in the system are considered. It is this combination that governs the dependence of the properties of functional compounds on their structure. This fact should be taken into account in crystal engineering and in predicting the structure and properties of novel materials based on halogen-bonded molecular systems. In the text above we systematized recently obtained information on the indicators and properties of halogen bonds that co-exist with other non-covalent interactions. The material presented in this review illustrates that the variety of halogen bonds. It follows that specific features of the molecular structure of compounds should be considered and analyzed in combination with other non-covalent interactions of comparable strength.

It should be emphasized that halogen-bonded structures, with their distinctive features and specific properties, are convenient systems for testing both newly developed and improved methods for identification and quantitative assessment of non-covalent interactions that occur in gas-phase complexes, in solutions and in crystals. Investigations of halogen bonds enable characterization of the structure and properties of candidate functional materials on the most important structural level, *viz*., 3D organization of the electron density.

This review has been written with the financial support from the Russian Foundation for Basic Research (Project Nos 13-03-00767a, 14-03-00961).

References

1. E Arunan, G R Desiraju, R A Klein, J Sadlej, S Scheiner, I Alkorta, D C Clary, R H Crabtree, J J Dannenberg, P Hobza, H G Kjaergaard, A C Legon, B Mennucci, D J Nesbitt *Pure Appl. Chem.* **83** 1619 (2011)
2. G R Desiraju, P S Ho, L Kloo, A C Legon, R Marquardt, P Metrangolo, P A Politzer, G Resnati, K Rissanen *Pure Appl. Chem.* **85** 1711 (2013)
3. P Metrangolo, G Resnati *Science* **321** 918 (2008)
4. D Braga, G R Desiraju, J S Miller, A G Orpen, S S L Price *CrystEngComm.* **4** 500 (2002)
5. P Metrangolo, G Resnati, T Pilati, R Liantonio, F Meyer *Polym. Sci., Part A: Polym. Chem.* **45** 1 (2006)
6. X Ding, M Tuikka, M Haukka, in *Recent Advances in Crystallography* Ch. 7 (InTech., 2012) p. 143
7. P Metrangolo, G Resnati *Chem. – Eur. J.* **7** 2511 (2001)
8. P Metrangolo, H Neukirch, T Pilati, G Resnati *Acc. Chem. Res.* **38** 386 (2005)
9. P Metrangolo, T Pilati, G Resnati *CrystEngComm.* **8** 946 (2006)
10. G Resnati, P Metrangolo, T Pilati, G Terraneo, G Cavallo, in *Book of Abstract of the First International Symposium on Halogen Bonding (ISXB-1), Porto Cesareo, Italy, 2014* p. 54
11. I Alkorta, F Blanco, P M Deya, J Elguero, C Estarellas, A Frontera, D Quinonero *Theor. Chem. Acc.* **126** 1 (2010)
12. O Hassel, J Hvoslef, Vihovde, E Hadler, Sörensen, N Andreas *Acta Chem. Scand.* **8** 873 (1954)
13. O Hassel *Science* **170** 497 (1970)
14. S C Nyburg, J T Szymaiqski *J. Chem. Soc., Chem. Commun.* 669 (1968)
15. S C Nyburg *Acta Crystallogr., Sect. A* **35** 641 (1979)
16. S C Nyburg, C H Faerman *Acta Crystallogr., Sect. B* **41** 274 (1985)
17. S L Price, A J Stone, J Lucas, R S Rowland, A E Thornley *J. Am. Chem. Soc.* **116** 4910 (1994)
18. J P M Lommerse, A Stone, R Taylor, F H Allen *J. Am. Chem. Soc.* **118** 3108 (1996)
19. M Fourmigue, P Betail *Chem. Rev.* **104** 5379 (2004)
20. F F Awwadi, R Willet, K A Peterson, B Twamley *Chem. – Eur. J.* **12** 8952 (2006)
21. A I Kitaigorodskii, T A Khotsyanova, Yu T Struchkov *Zh. Fiz. Khim.* **27** 780 (1953)
22. Yu V Zefirov, P M Zorkii *J. Structur. Chem. (Engl. Transl.)* **17** 851 (1976) [*Zh. Strukt. Khim.* **17** 994 (1976)]
23. J A R P Sarma, G R Desiraju *Acc. Chem. Res.* **19** 222 (1986)
24. G R Desiraju *J. Am. Chem. Soc.* **135** 9952 (2013)
25. G R Desiraju, in *Crystal Engineering: the Design of Organic Solids* (Amsterdam: Elsevier, 1989)
26. B K Saha, R K Jetti, L S Reddy, S Aitipamula, A Nangia *Cryst. Growth Des.* **5** 887 (2005)
27. V R Hathwar, S M Roopan, R Subashini, F N Khan, T N G Row *J. Chem. Sci.* **122** 677 (2010)
28. M E Brezgunova, E Aubert, S Dahaoui, P Fertey, S Lebegue, C Jelsch, J G Angyan, E Espinosa *Cryst. Growth Des.* **12** 5373 (2012)
29. F Bertolotti, A V Shishkina, A Fomi, G Gervasio, A I Stash, V Tsirelson *Crest. Growth Des.* **14** 3587 (2014)
30. N Ramasubbu, R Parthasarathy, P Murray-Rust *J. Am. Chem. Soc.* **108** 4308 (1986)
31. V R Pedireddy, D S Reddy, B S Goud, D C Craig, A D Rae, G R Desiraju *J. Chem. Soc. Perkin Trans. 2* 2773 (1994)
32. W T Pennington, T W Hanks, H D Arman, in *Halogen Bonding: Fundamentals and Applications* (Eds P Metrangolo, G Resnati) (Berlin, Heidelberg: Springer, 2008) p. 65
33. P Metrangolo, G Resnati *Int. Union Crystallogr. J.* **1** 5 (2014)
34. T Sakurai, M Sundaralingam, G A Jeffrey *Acta Crystallogr.* **16** 354 (1963)
35. G R Desiraju, R Parthasarathy *J. Am. Chem. Soc.* **111** 8725 (1989)
36. A Mukherjeea, G R Desirajua *Int. Union Crystallogr. J.* **1** 49 (2014)
37. S Tothadi, S Joseph, G R Desiraju *Cryst. Growth Des.* **13** 3242 (2013)
38. A C Legon, in *Halogen Bonding: Fundamentals and Applications* (Eds P Metrangolo, G Resnati) (Berlin, Heidelberg: Springer, 2008) p. 17
39. A C Legon *Phys. Chem. Chem. Phys.* **28** 7736 (2010)
40. D J Millen *Can. J. Chem.* **63** 1477 (1985)
41. C H Townes, A L Schawlow, in *Microwave Spectroscopy* (New York: McGraw-Hill, 1955) p. 225
42. P Hobza, R Zahradnik, K Muller-Dethlefs *Collect. Czech. Chem. Commun.* **71** 443 (2006)
43. M S Chernov'yants, I V Burykin *Russ. Chem. Bull., Int. Ed.* **58** 1772 (2009) [*Izv. Akad. Nauk, Ser. Khim.* 1716 (2009)]
44. F C Kupper, M C Feiters, B Olofsson, T Kaiho, S Yanagida, M B Zimmermann, L J Carpenter, G W Luther III, Z Lu, M Jonsson, L Kloo *Angew. Chem., Int. Ed.* **50** 11598 (2011)
45. V G Tsirelson, P-F Zou, T-H Tang, R F W Bader *Acta Crystallogr. Sect. A* **51** 143 (1995)
46. E Aubert, S Lebegue, M Marsman, T T T Bui, C Jelsch, S Dahaoui, E Espinosa, J G Angyan *J. Phys. Chem. A* **115** 14484 (2011)
47. V R Hathwar, T N G Row *Cryst. Growth Des.* **11** 1338 (2011)
48. V R Hathwar, R G Gonnade, P Munshi, M M Bhadbhade, T N G Row *Cryst. Growth Des.* **11** 1855 (2011)
49. R Wang, T S Dols, C W Lehmann, U Englert *Chem. Commun.* **48** 6830 (2012)
50. Q Li, X Xu, T Liu, B Jing, W Li, J Cheng, B Gong, J Sun *Phys. Chem. Chem. Phys.* **12** 6837 (2010)

51. Q Li, B Jing, R Li, Z Liu, W Li, F Luan, J Cheng, B Gong, J Sun *Phys. Chem. Chem. Phys.* **13** 2266 (2011)
52. Q Li, R Li, Z Zhou, W Li, J Cheng *J. Chem. Phys.* **136** 014302 (2012)
53. Q Li, R Li, X Liu, Z Zhou, W Li, J Cheng *Chem. Phys. Chem.* **13** 1205 (2012)
54. I Alkorta, F Blanco, M Solimannejad, J Elguero *J. Phys. Chem. A* **112** 10856 (2008)
55. J E Del Bene, G Sanchez-Sana, I Alkorta, J Elguero *Chem. Phys. Lett.* **538** 14 (2012)
56. J P Foster, F Weinhold *J. Am. Chem. Soc.* **102** 7211 (1980)
57. F Weinhold, C R Landis *Chem. Ed.: Res. Pract.* **2** 91 (2001)
58. R F W Bader *Atoms in Molecules: A Quantum Theory* (New York: Oxford University Press, 1990)
59. C F Matta, R J Boyd *The Quantum Theory of Atoms in Molecules; from Solid State to DNA and Drug Design* (Wiley-VCH Verlag GmbH and Co. KGaA, 2007)
60. B Jeziorski, R Moszynski, K Szalewicz *Chem. Rev.* **94** 1887 (1994)
61. R Moszynski, T G A Heijmen, B Jeziorski *Mol. Phys.* **88** 741 (1996)
62. K Szalewicz *Comput. Mol. Sci.* **2** 254 (2012)
63. A E Reed, F Weinhold *J. Chem. Phys.* **78** 4066 (1983)
64. A E Reed, F Weinhold *J. Chem. Phys.* **83** 1736 (1985)
65. R S Mulliken, W B Person *J. Am.Chem. Soc.* **91** 3409 (1969)
66. I G Kaplan *Intermolecular Interactions: Physical Picture, Computational Methods, and Model Potentials* (Chichester: Wiley, 2006)
67. R Eisenschitz, F London *Z. Phys.* **60** 491 (1930)
68. A Hesselmann, G Jansen *Chem. Phys. Lett.* **357** 464 (2002)
69. A J Misquitta, K Szalewicz *Chem. Phys. Lett.* **357** 301 (2002)
70. Z Shields, J S Murray, P Politzer *Int. J. Quant. Chem.* **110** 2823 (2010)
71. P Politzer, J S Murray, T Clark *Phys. Chem. Chem. Phys.* **12** 7748 (2010)
72. P Politzer, K E Riley, F A Bulat, J S Murray *Comput. Theor. Chem.,* **998** 2 (2012)
73. B Silvi, A Savin *Nature (London)* **371** 683 (1994)
74. V G Tsirelson, A I Stash *Chem. Phys. Lett.* **351** 142 (2002)
75. D J R Duarte, G L Sosa, N M Peruchena *J. Mol. Model.* **19** 2035 (2013)
76. F Bertolotti, G Gervasio, D Marabello, A V Shishkina, A I Stash, V G Tsirelson, in *MSSC 2011. Ab initio Modeling in Solid State Chemistry, Turin, 2011* p. 2
77. N Mohan, C H Suresh *J. Phys. Chem. A* **118** 1697 (2014)
78. T Clark, M Hennemann, J S Murray, P Politzer *J. Mol. Mod.* **13** 291 (2007)
79. P Politzer, P Lane, M C Concha, Y G Ma, J S Murray *J. Mol. Mod.* **13** 305 (2007)
80. R F W Bader, M T Carroll, J R Cheeseman, C Chang *J. Am. Chem. Soc.* **109** 7968 (1987)
81. M Kohout, A Savin, H Preuss *J. Chem. Phys.* **95** 1928 (1991)
82. A V Shishkina, Candidate Thesis in Chemical Sciences, Mendeleyev University of Chemical Technology of Russia, Moscow, 2013
83. G Hunter *Int. J. Quant. Chem.* **9** 237 (1975)
84. J Lennard-Jones *Proc. R. Soc. (London), A* **198** 14 (1949)
85. J Lennard-Jones, J A Pople *Proc. R. Soc. (London) A* **202** 166 (1950)
86. J Lennard-Jones *Adv. Sci. (London)* **11** 136 (1954)
87. D Becke, K E Edgecombe *J. Chem. Phys.* **92** 5397 (1990)
88. C Møller, M S Plesset *Phys. Rev.* **46** 618 (1934)
89. W Kohn, L J Sham *Phys. Rev.* **140** A1133 (1965)
90. K Remya, C H Suresh *J. Comput. Chem.* **34** 1341 (2013)
91. I D Mackie, G A Dilabio *J. Chem. Phys.* **135** 134318 (2011)
92. Y Zhao, D G Truhlar *Theor. Chem. Acc.* **120** 215 (2008)
93. Y Zhao, D G Truhlar *Acc. Chem. Res.* **41** 157 (2008)
94. S Grimme *J. Comput. Chem.* **27** 1787 (2006)
95. S Grimme, J Antony, S Ehrlich, H Krieg *J. Chem. Phys.* **132** 154104 (2010)
96. L Goerigk, S Grimme *Phys. Chem. Chem. Phys.* **13** 6670 (2011)
97. S Grimme *Chem. – Eur. J.* **18** 32 (2012)
98. J-D Chai, M Head-Gordon *Phys. Chem. Chem. Phys.* **10** 6615 (2008)
99. A V Shishkina, A I Stash, B Civalleri, A Ellern, V G Tsirelson *Mendeleev Commun.* **20** 161 (2010)
100. M V Vener, A V Shishkina, A A Rykounov, V G Tsirelson *J. Phys. Chem. A* **117** 8459 (2013)
101. S Kozuch, J M L Martin *J. Chem. Theor. Comput.* **9** 1918 (2013)
102. A V Shishkina, V V Zhurov, A I Stash, M V Vener, A A Pinkerton, V G Tsirelson *Cryst. Growth Des.* **13** 816 (2013)
103. T H Dunning *J. Chem. Phys.* **90** 1007 (1989)
104. K A Peterson, B C Shepler, D Figgen, H Stoll *J. Phys. Chem. A* **110** 13877 (2006)
105. B Metz, M Schweizer, H Stoll, M Dolg, W Liu *J. Theor. Chem. Acc.* **104** 22 (2000)
106. B Metz, H Stoll, M Dolg *J. Chem. Phys.* **113** 2563 (2000)
107. K A Peterson *J. Chem. Phys.* **119** 11099 (2003)
108. K A Peterson, D Figgen, E Goll, H Stoll, M Dolg *J. Chem. Phys.* **119** 11113 (2003)
109. M N Glukhovstev, M P McGrath, L Radom *J. Chem. Phys.* **103** 1878 (1995)
110. B O Roos, R Lindh, P-E Malmqvist, V Veryazov, P-O Widmark *J. Phys. Chem. A* **108** 2851 (2005)
111. A J Sadlej, M Urban *J. Mol. Struct. (THEOCHEM)* **234** 147 (1991)
112. L E Roy, P J Hay, R L Martin *J. Chem. Theor. Comput.* **4** 1029 (2008)
113. Yu A Abramov, V G Tsirelson, R P Ozerov, A B Tovbis *Zh. Fiz. Khim.* **66** 1170 (1992) [a]
114. C Estarellas, A Frontera, D Quinonero, P M Deya *Chem. Phys. Chem.* **12** 2742 (2011)
115. A Karpfen, in *Halogen Bonding: Fundamentals and Applications*. (Eds P Metrangolo, G Resnati) (Berlin, Heidelberg: Springer, 2008) p. 1
116. K E Riley, P Hobza *J. Chem. Theor. Comput.* **4** 232 (2008)
117. K E Riley, J S Murray, M C Concha, P Politzer, P Hobza *J. Chem. Theor. Comput.* **5** 155 (2009)
118. W Zierkiewicz, D Michalska, T Zeegers-Huyskens *Phys. Chem. Chem. Phys.* **12** 13681 (2010)
119. B Michielsen, W A Herrebout, B J van der Veken *Chem. Phys. Chem.* **8** 1188 (2007)
120. M Domagala, P Matczak, M Palusiak *Comput. Theor. Chem.* **998** 26 (2012)
121. R D Parr *Comput. Theor. Chem.* **998** 183 (2012)
122. S Scheiner *Int. J. Quant. Chem.* **113** 1609 (2013)
123. S Scheiner *CrystEngComm.,* **15** 3178 (2013)
124. S Scheiner *Acc. Chem. Res.* **46** 280 (2013)
125. A Bauza, D Quinonero, P M Deya, A Frontera *CrystEngComm.* **15** 3137 (2013)
126. J E Del Bene, I Alkorta, G Sanchez-Sanz, J Elguero *J. Phys. Chem. A* **117** 3133 (2013)
127. I Alkorta, G Sanchez-Sanz, J Elguero *J. Phys. Chem. A* **116** 2300 (2012)
128. S A Perera, H Sekino, R J Bartlett *J. Chem. Phys.* **101** 2186 (1994)
129. S A Perera, M Nooijen, R J Bartlett *J. Chem. Phys.* **104** 3290 (1996)
130. T E Gier *J. Am. Chem. Soc.* **83** 1769 (1961)
131. J Cheng, R Li, Q Li, B Jing , Z Liu, W Li, B Gong, J Sun *J. Phys. Chem. A* **114** 37 10320 (2010)
132. M Hennemann, J S Murray, K E Riley, P Politzer, T Clark *J. Mol. Mod.* **18** 2461 (2012)

133. M Ochai, in *Hepervalent Iodine Chemistry. Modern Developments in Organic Synthesis (Series: Topics in Current Chemistry* Vol. 224) (Ed. T Wirth) (Berlin, Heidelberg: Sringer, 2003) p. 5
134. X Lucas, C Estarellas, D Escudero, A Frontera, D Quinonero, P M Deya *Chem. Phys. Chem.* **10** 2256 (2009)
135. B Gong, B Jing, Q Li, Z Liu, W Li, J Cheng, Q Zheng, J Sun *Theor. Chem. Acc.* **127** 303 (2010)
136. M Solimannejad, M Malekani, I Alkorta *J. Phys. Chem. A* **114** 10261 (2010)
137. M Solimannejad, M Malekani, I Alkorta *Mol. Phys.* **109** 1641 (2011)
138. M Domagala, M Palusiak *Comput. Theor. Chem.* **1027** 173 (2014)
139. R Rivelino, P Chaudhuri, S Canuto *J. Chem. Phys.* **118** 10593 (2003)
140. Q Li, Q Lin, W Li, J Cheng, B Gong, J Sun *Chem. Phys. Chem.* **9** 2265 (2008)
141. Y Lu, Y Liu, H Li, X Zhu, H Liu, W Zhu *J. Phys. Chem. A* **116** 2591 (2012)
142. J C White, E R Davidson *J. Chem. Phys.* **93** 8029 (1990)
143. S F Boys, F Bernardi *Mol. Phys.* **19** 553 (1970)
144. P Valiron, I Mayer *Chem. Phys. Lett.* **275** 46 (1997)
145. M Jablonski, M Palusiak *J. Phys. Chem. A* **116** 2322 (2012)
146. A Mohajeri, M Alipour, M Mousaee *J. Phys. Chem. A* **115** 4457 (2011)
147. S J Grabowski, E Bilewicz *Chem. Phys. Lett.* **427** 51 (2006)
148. Q Li, Sh Ma, X Liu, W Li, J Cheng *J. Chem. Phys.* **137** 084314 (2012)
149. P-P Zhou, W Y Qiu, S Liu, N Z Jin *Phys. Chem. Chem. Phys.* **13** 7408 (2011)
150. Q Zhao, D Feng, J Hao *J. Mol. Model.* **17** 2817 (2011)
151. M Solimannejad, V Ramezani, C Trujillo, I Alkorta, G Sanchez-Sanz, J Elguero *J. Phys. Chem. A* **116** 5199 (2012)
152. J S Murray, P Lane, T Clark, K E Riley, P Politzer *J. Mol. Model.* **18** 541 (2012)
153. P Auffinger, F A Hays, E Westhof, P S Ho *Proc. Natl. Acad. Sci. USA* **101** 16789 (2004)
154. F C Bernstein, T F Koetzle, G J Williams, E E Meyer, M D Brice Jr, J R Rodgers, O Kennard, T Shimanouchi, M Tasumi *J. Mol. Biol.* **112** 535 (1977)
155. A R Voth, P Khuu, K Oishi, P S Ho *Nat. Chem.* **1** 74 (2009)
156. A R Voth, P S Ho *Curr. Top. Med. Chem.* **7** 1336 (2007)
157. C Ouvrard, J Y Le Questel, M Berthelot, C Laurence *Acta Crystallogr., Sect. B* **59** 512 (2003)
158. H S El-Sheshtawy, B S Bassil, K I Assaf, U Kortz, W M Nau *J. Am. Chem. Soc.* **134** 19935 (2012)
159. Y Lu, T Shi, Y Wang, H Yang, X Yan, X Luo, H Jiang, W Zhu *J. Med. Chem.* **14** 2854 (2009)
160. Y Lu, Y Liu, Z Xu, H Li, H Liu, W Zhu *Exp. Opin Drug Discov.* **7** 375 (2012)
161. H Li, Y Lu, Y Liu, X Zhu, H Liu, W Zhu *Phys. Chem. Chem. Phys.* **14** 9948 (2012)
162. Y Lu, Y Liu, H Li, X Zhu, H Liu, W Zhu *Chem. Phys. Chem.* **13** 2154 (2012)
163. O Galvez, P C Gomez, L F Pacios *J. Chem. Phys.* **118** 4878 (2003)
164. F Cristiani, F A Devillanova, A Garau, F Isaia, V Lippolis, G Verani *Heteroat. Chem.* **5** 421 (1994)
165. C Laurence, M J El Ghomari, J-Y Le Questel, M Berthelot, R Mokhlisse *J. Chem. Soc., Perkin Trans. 2* 1545 (1998)
166. C Laurence, J-F Gal, in *Lewis Basicity and Affinity Scales: Data and Measurement* (Chichester, UK: Wiley, 2010) p. 490
167. C Laurence, J Graton, M Berthelot, M J El Ghomari *Chem. – Eur. J.* **17** 10431 (2011)
168. J-Y Le Questel, C Laurencea, J Graton *CrystEngComm.* **15** 3212 (2013)
169. Y Wang, L Li, Y Lu, J Zou *Chin.J. Chem.Phys.* **20** 531(2007)
170. G R Desiraju, V R Pedireddi *J. Chem. Soc., Chem.Commun.* 1112 (1989)
171. F H Allen *Acta Crystallogr., Sect. B* **58** 380 (2002)
172. F H Allen, B S Goud, V J Hoy, J A K Howard, G R Desiraju *J. Chem. Soc., Chem. Commun.* 2729 (1994)
173. Y-X Lu, J-W Zou, Y-H Wang, Q-S Yu *J. Mol. Struct.* **779** 139 (2006)
174. C V Ramana, S Chatterjee, K A Durugkar, R G Gonnade *CrystEngComm.* **11** 143 (2009)
175. J-L Syssa-Magale, K Boubekeur, P Palvadeau, A Meerschaut, B Schoellhorn *CrystEngComm.* **7** 302 (2005)
176. J-L Syssa-Magale, K Boubekeur, B Schollhorn *J. Mol. Struct.* **737** 103 (2005)
177. B Ji, W Wang, D Deng, Y Zhang *Cryst. Growth Des.* **11** 3622 (2011)
178. M A A Ibrahim *J. Comput. Chem.* **32** 2564 (2011)
179. M A A Ibrahim *J. Mol. Model.* **18** 4625 (2012)
180. M A A Ibrahim *J. Phys. Chem. B* **116** 3659 (2012)
181. K Kitaura, K Morokuma *Int. J. Quant. Chem.* **10** 325 (1976)
182. K Morokuma, K Kitaura, in *Chemical Applications of Atomic and Molecular Electrostatic Potentials* (Eds P Politzer, D G Truhlar) (New York: Plenum, 1981) p. 215
183. S M Cybulski, S Scheiner *Chem. Phys. Lett.* **166** 57 (1990)
184. M A Blanco, A M Pendas, E J Francisco *Theor. Comput.* **1** 1096 (2005)
185. A M Pendas, M A Blanco, E J Francisco *J. Chem. Theor. Comput.* **2** 90 (2006)
186. M Garcia-Revilla, E Francisco, A Costales, A M Pendas *J. Phys. Chem. A* **116** 1237 (2012)
187. A M Pendas, M A Blanco, E J Francisco *J. Chem. Phys.* **120** 4581 (2004)
188. A M Pendas, E J Francisco, M A Blanco *J. Comput. Chem.* **26** 344 (2005)
189. A M Pendas, M A Blanco, E J Francisco *J. Comput. Chem.,* **28** 161 (2007)
190. A M Pendas, M Kohout, M A Blanco, E J Francisco, in *Modern Charge-Density Analysis* (Eds C Gatti, P Macchi) (Dordrecht, Heidelberg, London, New York: Springer, 2012) p. 303
191. A M Pendas, E J Francisco, M A Blanco *J. Phys. Chem. A* **110** 12864 (2006)
192. T I Madzhidov, G A Chmutova A M Pendas *J. Phys. Chem., A* **115** 10069 (2011)
193. T I Madzhidov, G A Chmutova *J. Mol. Struct. (THEOCHEM)* **959** 1 (2010)
194. A E Reed, L A Curtiss, F Weinhold *Chem. Rev.* **88** 899 (1988)
195. I C Hayes, A J Stone *J. Mol. Phys.* **53** 83 (1984)
196. A J Stone, A J Misquitta *Chem. Phys. Lett.* **473** 201 (2009)
197. Y Mo, J Gao *J. Phys. Chem. A* **105** 6530 (2001)
198. T Ziegler, A Rauk *Inorg. Chem.* **18** 1558 (1979)
199. K E Riley, J S Murray, J Fanfrlik, J Rezac, R J Sola, M C Concha, F M Ramos, P Politzer *J. Mol. Model.* **19** 4651 (2013)
200. A J Stone *J. Am. Chem. Soc.* **135** 7005 (2013)
201. U Adhikari, S Scheiner *Chem. Phys. Lett.* **552** 31 (2012)
202. R F W Bader, T A Keith. *J. Chem. Phys.* **99** 3683 (1993)
203. R F W Bader, C F Matta *Int. J. Quant. Chem.* **85** 592 (2001)
204. I Alkorta, I Rozas, J Elguero *J. Phys. Chem., A* **102** 9278 (1998)
205. Y Zhang, X-Z You *J. Comput. Chem.* **22** 327 (2001)
206. Y-H Wang, Y-X Lu, J-W Zou, Q-S Yu *Int. J. Quant. Chem.* **108** 90 (2008)
207. J-W Zou, Y-J Jiang, M Guo, G-X Hu, B Zhang, H-C Liu, Q-S Yu *Chem. Eur. J.* **11** 740 (2005)
208. E V Bartashevich, V G Tcirelson *Phys. Chem. Chem. Phys.* **15** 2530 (2013)
209. A Gavezzotti *Top Curr. Chem.* **315** 1 (2012).

210. J D Dunitz, A Gavezzotti *Angew. Chem. Int. Ed.* **44** 1766 (2005)
211. J D Dunitz, A Gavezzotti *Chem. Soc. Rev.* **38** 2622 (2009)
212. A J Pertsin, A I Kitaigorodsky *The Atom-Atom Potential Method. Application to Organic Molecular Solids* (Berlin, Heidelberg, London, New York, Paris, Tokyo: Springer, 1987)
213. R J Boyd, S C Choi *Chem. Phys. Lett.* **120** 80 (1985)
214. E Espinosa, E Molins, C Lecomte *Chem. Phys. Lett.* **285** 170 (1998)
215. I Mata, E Molins, I Alkorta, E Espinosa *J. Chem. Phys.* **130** 044104 (2009)
216. I S Bushmarinov, K A Lyssenko, M Yu Antipin *Russ. Chem. Rev.* **78** 283 (2009)
217. A O Borissova, A A Korlyukov, M Yu Antipin, K A Lyssenko *J. Phys. Chem. A* **112** 11519 (2008)
218. Yu V Nelyubina, M Yu Antipin, K A Lyssenko *Russ. Chem. Rev.* **79** 167 (2010)
219. Yu V Nelyubina, M Yu Antipin, D S Dunin, V Yu Kotov, K A Lyssenko *Chem. Commun.* **46** 5325 (2010)
220. Y V Nelyubina, M Yu Antipin, K A Lyssenko *Mendeleev Commun.* **21** 250 (2011)
221. Q-C Shi, Y-X Lu, J-C Fan, J-W Zou, Y-H Wang *J. Mol. Struct. (THEOCHEM)* **853** 39 (2008)
222. E Espinosa, I Alkorta, I Rozas, J Elguero, E Molins *Chem. Phys. Lett.* **336** 457 (2001)
223. C Gatti, E May, R Destro, F Cargnoni *J. Phys. Chem. A* **106** 2707 (2002)
224. I Mata, I Alkorta, E Molins, E Espinosa *Chem. – Eur. J.* **16** 2442 (2010)
225. I Mata, I Alkorta, E Espinosa, E Molins *Chem. Phys. Lett.* **507** 185 (2011)
226. E V Bartashevich, E A Troitskaya, Y V Matveychik, V G Tsirelson *Comput. Theor. Chem.* **1037C** 53 (2014)
227. E V Bartashevich, E A Troitskaya, V G Tsirelson *Chem. Phys. Lett.* **601** 144 (2014)
228. M V Vener, A N Egorova, A V Churakov, V G Tsirelson *J. Comput. Chem.* **33** 2303 (2012)
229. A V Iogansen *Spectrochim. Acta, A* **55** 1585 (1999)
230. E V Bartashevich, I D Yushina, B V Rudakov, P A Slepukhin, V G Tsirelson, in *Sbornik Tezisov Dokladov XVI Simpoziuma po Mezhmolekulyarnomu Vzaimodeistviyu i Konformatsiyam Molekul, SIICM* (Abstracts of Reports of the XVIth Symposium on Intermolecular Interactions and Conformations of Molecules), Ivanovo, 2012 p. 31
231. E R Johnson, S Keinan, P Mori-Sanchez, J Contreras-García, A J Cohen, Y Weitao *J. Am. Chem. Soc.* **132** 6498 (2010)
232. A J Cohen, P Mori-Sanchez, W Yang *Science* **321** 792 (2008)
233. J P Perdew, A Ruzsinszky, G I Csonka, L A Constantin, J Sun *Phys. Rev. Lett.* **103** 026403 (2009)
234. J Contreras-García, E R Johnson, S Keinan, R Chaudret, J-P Piquemal, D N Beratan, W Yang *J. Chem. Theor. Comput.* **7** 625 (2011)
235. A Otero-de-la-Roza, E R Johnson, J Contreras-García *Phys. Chem. Chem. Phys.* **14** 12165 (2012)
236. E R Johnson, A Otero-de-la-Roza *J. Chem. Theor. Comput.* **8** 5124 (2012)
237. M P Johansson, M Swart *Phys. Chem. Chem. Phys.* **15** 11543 (2013)
238. M Gobel, B H Tchitchanov, J S Murray, P Politzer, T M Klapotke *Nat. Chem.* **1** 229 (2009)
239. E V Bartashevich, A M Pendas, V G Tcirelson *Phys. Chem. Chem. Phys.* **16** 16780 (2014)
240. G R Runtz, R F W Bader, R R Messer *Can. J. Chem.* **55** 3040 (1977)
241. G Saleh, C Gatti, L L Presti, J Contreras-García *Chem. – Eur. J.* **18** 15523 (2012)
242. V G Tsirelson, R P Ozerov, in *Electron Density and Bonding in Crystals* (Bristol: Institute of Physics Publ., 1996)
243. G Saleh, C Gatti, L L Presti *Comput. Theor. Chem.* **998** 148 (2012)
244. G Saleh, L Lo Presti, C Gatti, D Ceresoli *J. Appl. Cryst.* **46** 1513 (2013)
245. R Dovesi, V R Saunders, C Roetti, R Orlando, C M Zicovich-Wilson, F Pascale, B Civalleri, K Doll, N M Harrison, I J Bush, Ph D Arco, M Llunell *Crystal 06 User's Manual* (Torino: University of Torino, 2006)
246. N K Hansen, P Coppens *Acta Crystallogr., Sect. A* **34** 909 (1978)
247. A Volkov, P Macchi, L J Farrugia, C Gatti, P Mallinson, T Richter, T Koritsanszky *User's Manual. SUNY (XD2006)* http://xd.chem.buffalo.edu/
248. A I Stash, V G Tsirelson *J. Appl. Cryst.* **35** 371 (2002)
249. A I Stash, V G Tsirelson, in *Methods and Applications of Computational Chemistry. Fifth Symposium MACC (Book of Abstracts), Kharkiv, 2013* p. 57

[a] — *Russ. J. Phys. Chem. A (Engl. Transl.)*