Computational and Theoretical Chemistry 991 (2012) 124–133

Contents lists available at SciVerse ScienceDirect

Computational and Theoretical Chemistry

journal homepage: www.elsevier.com/locate/comptc

Electron density shift description of non-bonding intramolecular interactions

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ARTICLE INFO

Article history:
Received 14 March 2012
Received in revised form 9 April 2012
Accepted 10 April 2012
Available online 14 April 2012

Keywords:
MP2
Intramolecular interactions
Electron density shift
Molecular tailoring

ABSTRACT

A new methodology is described for the study of the electron density shift in intramolecular interactions. The methodology has been tested in an intermolecular complex and compared to the electron density shift obtained as the difference between the complex and the isolated monomers. The molecular fragmentation procedures and its application to hydrogen bonds, chalcogen–chalcogen interactions, nitrogen–boron interactions, dihydrogen interactions and silicon–nitrogen interactions are described. A careful selection of the fragmentation scheme is necessary in order to describe correctly the electron density shift in the intramolecular interactions. For this reason, different orders of fragmentation have been studied and analyzed pointing out the problems and limitations which are inherent to the methodology. It has been found that this methodology is a new tool which provides a good qualitative description of the electron density shift within the interacting region between two or more contacts, in both inter and intramolecular contacts with a reasonable low computational cost.

1. Introduction

Non-covalent interactions are the subject of many studies, some of them very recent. The reason is that they are present in almost every biological system, from small and simple molecules as H_2O [1–4] to large and complex systems as DNA [5,6], from gas phase, liquids and even in solids those interactions play an important role in the structure of matter [7]. The number of non-covalent interactions is quite large, including hydrogen bonds [8–10], halogen bonds [11], ion-π [12,13], pnicogens [14,15], chalcogens [16,17], stacking [18–20], and several others.

These interactions can be classified according to the systems in which they occur as inter- or intra-molecular interactions. As in other partition schemes, the intermolecular case is much simpler than the intramolecular one. For this reason, intermolecular interactions have been extensively studied with different approaches like supramolecular [21,22], and SAPT methodologies [23,24]. The intramolecular interactions have been much less studied due to the difficulties in their description [25]. Nevertheless, the importance of intramolecular hydrogen bonding in medicinal chemistry has been recently stressed [26].

In order to obtain a description of the intramolecular interaction, one has to separate the interacting part from the rest of the molecule. This is a problem which can be approached by the fragmentation of the system in smaller interacting parts. In Fig. 1 we have schematized the inter- and intra-molecular situations: in the first one a non-covalent interaction should be broken while in the second one, a covalent bond has to be broken. However, if we consider that all bonds, covalent and non-covalent, share some common properties, *i.e.* that there is a continuum [27,28], then we could consider a third possibility when both bonds will be broken (new model).

In order to face the molecular scaling problem, some approaches based on molecular fragmentation have been proposed [29,30], in which different approximations are used to describe the molecular energy through the interaction energies between individual molecular fragments. The molecular tailoring approach proposed by Deshmukh et al. [31,32] allows the estimation of the hydrogen bond energies in polyhydroxy compounds and polypeptides [33].

Among all techniques that provide information of the interaction between two different systems, the study of the electron density is one of the most useful, and provides an ideal tool to understand these interactions [34–36]. The study of the electron density in molecules has been in the scope of the scientific community for several decades. Different approaches have been proposed to describe the electron density and its bonding properties [37]. The analysis of the electron transfer within the formation of the complexes as the difference between the electron density of the complex and the isolated monomers provides information in order to characterize these interactions [38–40]. In fact, the electron density shift has been used to analyze the non-bonding intermolecular interactions for different types of complexes as hydrogen bonds [40,41], pnicogen interactions [15,42], π-halogen interactions [43], halogen–hydride interactions [44] and other non-covalent interactions [45,46].

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http://dx.doi.org/10.1016/j.comptc.2012.04.007

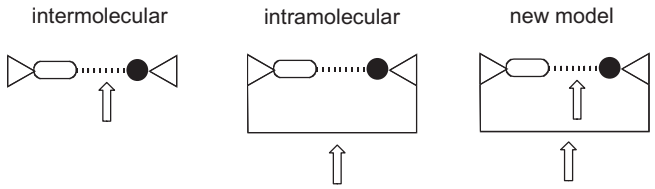

Fig. 1. Three different situations for interactions (the arrows point to the bonds that have to be broken to characterize the interaction).

The main aim of this article is to describe a fragment based method to estimate the electron density shift (EDS) within intermolecular and intramolecular interactions. With this objective in mind, it is very important to perform a partition of the molecule that allows representing properly the electron density shift between the interacting groups.

2. Computational details

All geometries were fully optimized at MP2 computational level [47]. We have used Dunning basis set, aug-cc-pVTZ [48,49] for the heteroatoms (O, Cl, F, N, B), cc-pVDZ for C, and H and pseudopotential LANL2DZ for Te in order to have a good compromise between accuracy and low computational cost. All the calculations have been carried out using the Gaussian-09 program [50]. The topological analysis of the electron density within the atoms in molecules (AIM) methodology [34] has been used to characterize the interactions. For this purpose, the AIMAll program has been used [51].

In order to have a quantitative measurement of the similarity of the electron density shifts (EDSs) generated, for the same system in different ways, the Hodgkin similarity index [52] has been used. Based in this index (H_{XY}), the similarity of two EDSs, X and Y, is calculated as expressed by the following equation:

$$H_{XY} = \frac{2\sum_{i=1}^{A} \mathrm{EDS}(X)_i \mathrm{EDS}(Y)_i}{\sqrt{\sum_{i=1}^{A} \mathrm{EDS}(X)_i^2}\sqrt{\sum_{i=1}^{A} \mathrm{EDS}(Y)_i^2}} \quad (1)$$

where EDS(N) (N = X or Y) is the value for the EDS for each molecule at the same point (i) of the three-dimensional grid with A points generated for the same system with two different methods. The maximum value of this index is 1, indicating that both electron densities are identical. It should be noted that the original definition of the Hodgkin index was computed analytically [in Eq. (1) the summation symbols should be changed to integral symbols]. However, in this work all the indexes have been computed numerically. This is for practical reasons, to allow straightforward computation of the molecular properties on a cubic grid and the generation of the three-dimensional maps.

The EDS are constructed using a 3D rectangular grid of approximately 10^6 points in the three directions of the space, in which the molecule is located in the center of the grid and the limit of the generated cube are 5 Å larger than the dimensions on the molecule. The quality of this grid has been checked in some test cases using a denser grid of 8×10^6, obtaining identical results.

The effect of the BSSE correction on the EDS has been explored using the same basis set for all the fragments of a given systems, 1,4-butanediol. The results obtained are identical considering or not the BSSE correction.

3. Methodology

The main aim of the present work is to describe a new tool which allows representing the electron density shift in those regions where non-bonding interactions are expected. The methodology can be applied to both inter and intramolecular interactions. However, since the evaluation of the intermolecular electron density shift can be easily obtained by subtracting the total electron density of the system and the sum of the isolated molecules that form it, we consider that the methodology described here is more suitable for intramolecular interactions.

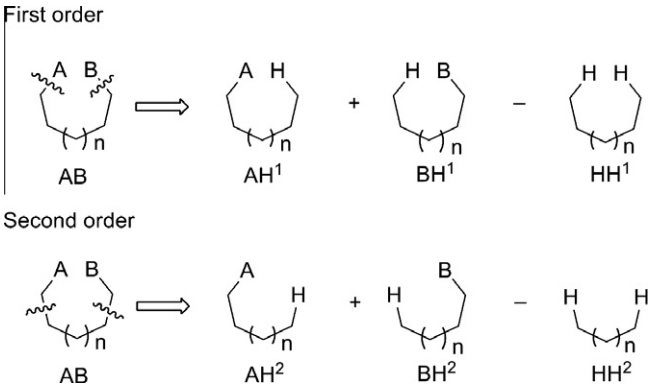

Fig. 2. Schematic representation of first and second order fragmentation in a generic system.

The first step of the procedure corresponds to the fragmentation of the system of interest in different subsystems. In this case, we will consider that the fragmentation of the system will be carried out at the same bond distance of the interacting moieties, A and B. The fragments will maintain the geometry of the original system, except for the addition of hydrogen caps at fixed distances and maintaining the orientation of the bond broken.

Depending on the bond distances between the broken bond and the interacting moieties, the fragmentation order will be defined. First order fragmentation corresponds to the case where the bond broken is the one connecting the interacting moieties with the rest of the system (Fig. 2). Second order fragmentation is when two bonds separate the interacting moieties and the rest of the system and so on. In each case, three fragments are generated named as AH^n, BH^n and HH^n. The superscript n represents the order of the fragmentation and AH^n and BH^n correspond to the fragments without B and A moieties, respectively and HH^n the one without A and B simultaneously.

The electron density shift of fragmentation order n due to the interaction of the A and B moieties can be calculated using the following equation:

$$\mathrm{EDS}^n = \rho_{AB} - \rho_{AH}^n - \rho_{HB}^n + \rho_{HH}^n \quad (2)$$

where ρ_{AB}, ρ_{AH}^n, ρ_{HB}^n and ρ_{HH}^n are the electron densities of the whole system, AH, BH and HH fragments using the fragmentation of n order, respectively.

4. Results and discussion

4.1. Intermolecular interactions

As a test of the methodology proposed, the EDS in an intermolecular complex using the procedure described before has been compared to the one calculated directly from the subtraction of the total electron density from the sum of the isolated molecules. In order to do that, the system chosen has been a dimer of *n*-propanol due to (a) it allows calculating the intermolecular EDS, (b) if we consider it as a whole linked system the intramolecular EDS can be calculated up to the third order of fragmentation, (c) both inter- and intra-molecular EDS can be compared.