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Quantification and Analysis of Intramolecular Interactions

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Abstract: Non-covalent interactions play a prominent role in chemistry and biology. While a myriad of theoretical methods have been devised to quantify and analyze intermolecular interactions, the theoretical toolbox for the intramolecular analogues is much scarcer. Yet interactions within molecules govern fundamental phenomena as illustrated by the energetic differences between structural isomers. Their accurate quantification is of utmost importance. This paper gives an overview of the most common approaches able to probe intramolecular interactions and stresses both their characteristics and limitations. We finally introduce our recent theoretical approach, which represents the first step towards the development of an intramolecular version of Symmetry-Adapted Perturbation Theory (SAPT).[1]

Keywords: Chemical Hamiltonian Approach (CHA) · Interacting Quantum Atoms (IQA) · Intramolecular interactions · Natural Bond Orbital (NBO) · Strictly Localized Orbitals (SLOs) · Symmetry-Adapted Perturbation Theory (SAPT)

Introduction

Non-covalent interactions occur between and within all molecules and dictate a myriad of chemical processes.[2–4] Interactions *between* molecules can be probed experimentally using a diversity of analytical methods such as infrared spectroscopy,[5,6] nuclear magnetic resonance,[7,8] molecular beam experiments,[9] atomic force microscopy,[10] examination of structures by X-ray diffraction,[11] single-molecule fluorescence,[12] *etc.* Theoretical methods represent a highly valuable alternative to either assist in the interpretation of the experimental data or as stand-alone investigation tools. Within this perspective, the analysis and decomposition of intermolecular interactions into energy quantities has motivated the development of a wealth of theoretical methods. The best illustration is perhaps the original Kitaura-Morokuma method[13] for energy decomposition analysis (EDA) along with its variants[14–21] exploiting localized[22–25] or natural orbitals.[26–28] The linear-scaling approaches, which also serve to decompose the energy of a complex system into a sum of physical terms, often rely on the orbital localization onto individual fragments.[29–33] In particular, LMP2[33] derives dispersion energies between fragments by decomposing the MP2 correlation energy. Other approaches rely upon different energy partitioning, either based on symmetry,[34] on the real-space electronic density,[35–37] on density matrices[38] or on the Hamiltonian itself.[39,40] Finally, intermolecular interaction energies can also be obtained readily from the properties of the monomers themselves by using perturbation theory.[41,42] As an example, Symmetry-Adapted Perturbation Theory (SAPT) is one of the most popular EDA as it leads to a natural definition of electrostatic, exchange, induction and dispersion effects[42] and to accurate total interaction energies.[43–46] The theoretical analysis of intermolecular interactions is thus largely documented and has become very efficient and accurate thanks to recent implementation and algorithms.[47–51]

In sharp contrast, there exists only a limited amount of approaches for probing non-covalent interactions *within* molecules. Yet these interactions are omnipresent and govern fundamental phenomena such as the energetic differences between structural isomers,[52] the conformational preference through the anomeric effect,[53] the gauche effect,[54] steric interactions, hyperconjugation,[55] but they are also determinant for the regulation of enzymatic activity[56] and material properties.[57,58] The accurate quantification and analysis of non-covalent intramolecular interactions is as crucial as that of the intermolecular cases. The present account provides an overview of the approaches able to deliver some information regarding these much more subtle intramolecular interactions. The next section comments on the experimental measurements associated with the characterization of these interactions and is followed by a description of the existing theoretical methods relevant to the corresponding analyses. We finally introduce the philosophy behind our recent theoretical approach, which represents the first step towards the development of an intramolecular version of Symmetry-Adapted Perturbation Theory (SAPT).[1]

Experimental Characterization

The examination of experimental structural data provides the first set of hints to detect a non-covalent intramolecular interaction through the identification of re-

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duced bond distances or characteristic orientation of functional groups.[59] X-ray diffraction,[60] electron diffraction,[61] NMR[7] or microwave spectroscopy,[62–64] *etc.* can deliver such information. Alternatively, IR[65] and Raman[66] spectroscopies are highly valuable tools to reveal the presence of structural features and functional groups. In addition, the comparisons of vibrational frequencies give an indication of the relative strengths of an intramolecular interaction in a given class of molecules. As an example, Thomsen *et al.*[65] concluded, based on IR spectroscopy techniques, that 3-aminopropanol exhibits a stronger intramolecular hydrogen bond than 2-aminoethanol.

From a more quantitative perspective, the most appropriate approach for assessing the relative strength of intramolecular interactions is to extract energetic quantities from the experimental data. Despite the difficulty connected with isolating one given intramolecular interaction within a molecule, indirect information can be extracted from the relative energies of conformational and structural isomers. The value associated with specific noncovalent intramolecular interactions can be unraveled by careful examination of the energy trends within series of molecules structurally similar,[67] or by designing specific reactions balancing all but the interesting energy effects.[68] More direct insight is sometimes possible providing that two conformations of the same molecule are accessible: one with the intramolecular interaction (the 'interacting' conformation) and one where the intramolecular interaction is absent (the 'reference' conformation). Measurements of ionization potentials[70,71] give access to the energy difference between the interacting and reference conformations and provide a close estimate of the intramolecular interaction energy. Estimates of conformer free energy difference are also available from the interplay between computation and relative intensities of vibrational bands in Raman and IR experimental spectra[66] or through the measurement of NMR coupling constants.[69]

While experiment can deliver some energy quantities, the direct connection with a single intramolecular interaction remains subtle. Even in the ideal case where interacting and reference conformations exist, the intramolecular interaction of interest is not the only one to play a role in the measured energy difference.

Localized Orbitals Methods

The theoretical probing of intramolecular interactions relies upon well-defined fragments within a molecule. Using the Born-Oppenheimer approximation, the nuclei are treated classically and are easy to partition. Electrons are described quantum mechanically as an ensemble of indistinguishable and delocalized particles, and their repartition on to the molecular fragments may be achieved through the localization of orbitals. Most common localization schemes operate by rotation of the occupied orbitals to maximize or minimize a predefined localization function such as those of Pipek-Mezey,[70] Boys[71] and Edmiston-Ruedenberg.[72] The resulting localized orbitals have their major contributions on a few atomic centers with generally numerous small contributions arising from all the other basis functions. These small contributions are termed 'orthogonalization tails' as they ensure that localized orbitals remain orthogonal. To relax the orthogonality constraint and eliminate the orthogonalization tails, the orbitals φ_{ix} can be expressed only using basis functions χ from a few atomic centers.

$$\left|\varphi_{ix}\right\rangle = \sum_{\mu\in x} C_{\mu ix} \left|\chi_{\mu}\right\rangle \tag{1}$$

where x is a fragment, usually an ensemble of atoms. The equations first derived by Stoll[73] realize the variational optimization of orbitals φ_{ix}. Later, Gianinetti *et al.* derived similar equations under matrix form,[74,75] and Nagata *et al.* published a variant of these equations as well.[76] This may be the reason why such localized orbitals have appeared in the literature under various terminologies such as Locally Projected Self-Consistent Field for Molecular Interactions (LP-SCF MI),[75,76] Extremely Localized Molecular Orbitals (ELMO),[77] Block-Localized Wavefunction (BLW),[22,78] Absolutely Localized Molecular Orbitals (ALMO)[79] or Non-Orthogonal Localized Molecular Orbitals (NOLMO).[80] Strictly-Localized Molecular Orbitals (SLMO)[81] are similar in spirit but were originally devised for semi-empirical methods[82] and are expressed in terms of a few atomic hybrid functions.[83] Except for SLMO, all the mentioned methods rely on the same orbitals, denoted here Strictly Localized Orbitals (SLOs), and hence have the same way of probing intramolecular interactions. The SLO wavefunction Ψ is defined by:

$$\Psi = \hat{A}\left\{\prod_{ix} \varphi_{ix}\right\} \tag{2}$$

where $\hat{A}$ is the antisymmetrizer operating on the product of SLOs. The wavefunction Ψ lacks any charge transfer or hyperconjugation interaction between SLOs defined on different fragments. The energetic difference between the variationally optimized delocalized orbitals state and the SLOs charge-localized state corresponds to the intramolecular charge transfer and hyperconjugation energies.[76,84,85] Moreover, the effect of electronic delocalization between fragments on the geometry is accessible through geometry optimization of the SLOs state.[86,87] SLOs-based methods do not yet allow for noncovalent intramolecular EDA, however they specifically probe intramolecular processes involving the electronic delocalization between fragments and can thus effectively assess the energy contribution associated with hyperconjugation and resonance.[24,88–91]

The Natural Bonding Orbitals (NBO) method does not rely on the variational optimization of a charge-localized wavefunction, but on an analysis of the canonical wavefunction.[28] For this purpose, NBO are obtained by diagonalization of blocks of the density matrix corresponding to atoms or bonds. The specific process to obtain NBO ensures that they are localized and orthogonal. By construction, NBO are divided into bonding orbitals representing an idealized Lewis structure, and antibonding orbitals representing the deviation of the wavefunction from this ideal Lewis structure. The most straightforward information resulting from an NBO analysis is qualitative: the identification of donating and accepting orbitals within a molecule and of the amount of the charge transferred. The most important hyperconjugative interactions are identified, and their strength confirmed by energetic information. NBO offers two ways to probe the stabilizing energy contribution associated with a specific hyperconjugation or charge transfer interaction. The first and simplest approach is to approximate the exact value by perturbation theory,[28] the second optimizes the orbitals with the interaction of interest deleted from the Fock matrix. The difference between the initial and the final energies corresponds to the delocalization energy upon charge transfer from one orbital to the other and includes orbital relaxation effects. Finally, NBO also assess exchange effects, which are interpreted as steric interactions, by computing the energetic effect of the NBO orthogonalization.[92] In summary, the NBO method, which is widely applicable[28,93–98] gives access to energetic values associated with specific donor–acceptor interactions, quantifies the amount of charge transferred and characterizes the steric contributions through exchange interaction.

Linear-scaling fragment approaches were originally devised to partition a complex molecular system into smaller subsystems to allow for the accurate and more efficient computation of global properties.[29–33] Fragmentation schemes describe the individual fragments using standard quantum chemistry methods and approximate the interaction between fragments in different ways. The Configuration Analysis for Fragment Interaction (CAFI)[30] relaxes the fragment orbitals in a controlled manner based on the Fragment Molecular Orbital (FMO)[32] approach to isolate polarization and charge transfer terms. Further decomposition of the interfragment energy results in the Pair Interaction EDA (PIEDA) method,[99] which leads to electrostatics, exchange, charge transfer and dispersion contributions. Similarly, within the systematic fragmentation method,[100] nonbonded interactions are represented as a sum of electrostatics, induction and dispersion terms,[31] all computed from fragment properties. The Local MP2 method[33] decomposes the total MP2 correlation energy in a pairwise fashion and is thus able to extract dispersion interactions between fragments, although it was originally designed to describe intermolecular fragments and not intramolecular interactions. Note finally that the XPol fragmentation[101,102] method has been combined with selected terms from intermolecular perturbation theory such as exchange and dispersion,[103] and with grand canonical DFT to obtain charge transfer contributions.[104] The XPol fragmentation scheme is however not directly applicable to intramolecular interactions.

Approaches based on fragmentation are ambivalent since they provide a physical analysis of the intramolecular interaction, but at the same time perturb the interaction analyzed through the fragmentation process itself. The approximations associated with the treatment of the interfragment covalent bonds affect significantly the electronic structure of the whole system, especially for small molecules.

Alternative Space Partitioning

All theoretical methods mentioned above employ an orbital-based partitioning of the system. Alternative criteria can be used to identify the molecular fragments and obtain the energetic values associated with their interaction. The most intuitive partitioning scheme may be the definition of atoms in real space represented by the Quantum Theory of Atoms in Molecules (QTAIM) of Bader.[105] A QTAIM atom is defined by the region of space where the electronic density gradient leads to the same nucleus (Fig. 1).

QTAIM partitions a molecule into well-defined, non-overlapping atoms, between which interactions can be computed through the Interacting Quantum Atom (IQA) methodology.[36,110,111] IQA partitions the first-order and diagonal second-order density matrices over the atomic basins, and computes the associated intra- and interatomic energetic contributions.[110] In the chosen partitioning of the first-order density matrix, the kinetic energy is an intraatomic quantity. The electron–nucleus attraction V_{en} is considered as intra- or interatomic, depending on whether the involved electron density and nucleus belong to the same atom or not. The electron-electron repulsion V_{ee} is a more complex quantity involving the partitioning of the diagonal second-order density matrix ρ(1,2), which depends on the coordinates of two electrons. ρ(1,2) is considered as intraatomic when the two electrons belong to the same atomic basin and interatomic otherwise. IQA further partitions ρ(1,2) into a classical, an exchange and a correlation term. As a result:

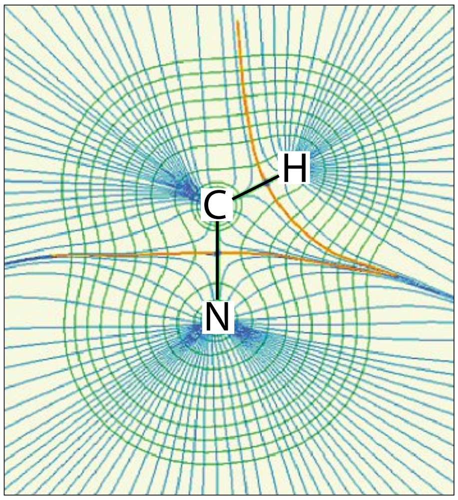


Fig. 1. Example of electronic density gradient paths (in light blue) in the CH_3NH_2 molecule computed with B3LYP[106,107]/6-31G*.[108,109] Electronic density contours are plotted in green and surfaces separating QTAIM atoms are in orange.

$$V_{ee}^{AB} = V_{C}^{AB} + V_{X}^{AB} + V_{corr}^{AB} \qquad (3)$$

where V_{ee}^{AB} is the total electron–electron repulsion between atoms A and B, V_{C}^{AB} is the Coulomb part of the repulsion, V_{X}^{AB} is the exchange and V_{corr}^{AB} the correlation. The IQA analysis is applicable to any real-space partitioning of a molecule into atomic fragments,[36] including those resulting in overlapping atoms such as the Hirshfeld population.[112] IQA can analyze both covalent and noncovalent interactions for any type of wavefunction, as shown for bonding in transition metal carbonyls,[111] halogen bonds[113] or complexes of alkaline metals.[114]

The real-space partitioning into atoms is computationally demanding, and the integration necessary to the computations of the energetic terms is even more expensive. A cheapest partitioning of the system can be achieved through the Hilbert space, *i.e.* the space of basis functions. The Chemical Hamiltonian Approach (CHA) exploits such a partitioning.[39] CHA operates only on basis functions, which can easily be attributed to an atom, usually atom-centered basis functions. CHA possesses a unique particularity among energy decomposition schemes since it relies on an asymmetric interpretation of electronic integrals. For a simple one-electron integral

$$\left\langle \chi_\nu \middle| \hat{V}_X \middle| \chi_\mu \right\rangle \qquad (4)$$

the potential V_X from atom X acts on the electron in basis function χ_μ. The resulting function represents the physical interaction of the electron with the potential, and is then projected on the basis function χ_ν. Similarly, for all electronic integrals the ket is considered to contain the physical part of the interaction with an operator, whereas the bra is only the projection of this interaction on the basis set. Each energetic term can thus be attributed to intra- or interatomic energies depending on the atomic centers present in the relevant integral. The non-unique attribution of some of the terms gives rise to different energy decomposition schemes.[40,115–118] These schemes differ by the attribution of the kinetic energy to the intra- or interatomic terms and on the way to handle the bra of the integrals when it is centered on a different fragment than the physical interaction.

Careful reconsiderations of the different variants by Mayer recently resulted in an improved Chemical Energy Component Analysis (CECA).[40] Improved CECA yields bond energies close to thermodynamic quantities and correct distance dependencies. Within this framework the energetic terms are obtained from the decomposition of the final energy of the entire system, which is applicable to both covalent and noncovalent intramolecular interactions. CHA can thus quantify noncovalent intramolecular interactions, but the physical analysis is currently limited to the electrostatics and exchange terms.[116]

Perturbational Method: Intramolecular SAPT

Intuitively, and in analogy with the intermolecular situations, non-covalent intramolecular interaction energies are defined as the difference between the energy of the interacting and non-interacting systems. The main issue is that the non-interacting system is not physically achievable: two intramolecular fragments cannot stop interacting without dramatically altering their configuration within the molecule. Consequently, all theoretical methods introduced so far probe intramolecular interactions in an indirect or limited manner. The SLOs only annihilate the intramolecular delocalization (*i.e.* charge transfer) but not the full interaction. NBO analysis probes similar effects through a different formalism and provides some information on the steric interactions, but the subsystems are still able to interact. Fragment methods give access to the full interaction energy but their analysis is precluded by the perturbation of the molecular electronic structure resulting from the approximation of interfragment covalent bonds. Finally, wavefunction-based analysis such as IQA and CHA yield physically meaningful energies and decompositions but they exclude the wavefunction relaxation effects occurring upon intramolecular interaction. We here present our efforts towards a theoretical method featuring a non-interacting state closer to our intuitive definition of intramolecular interactions.

The ideal method for computing intramolecular interaction energies would fulfill the following conditions: i) having a reference state excluding completely the intramolecular interaction of interest; ii) preserving the molecular structure by conserving all bonds; iii) naturally decomposing the interaction energy into physically meaningful terms; iv) being accurate. From the perspective of intermolecular interactions, Symmetry-Adapted Perturbation Theory (SAPT) fulfills all four criteria and is hence a well-suited starting point. We consider the development of an intramolecular variant of SAPT as a highly challenging task of fundamental importance, with a potential to truly transform our understanding and quantification of non-bonded intramolecular interactions. The primary challenge is the derivation of a proper reference state to be used in the perturbation expansion. Note however that once the reference state is obtained, the total intramolecular interaction energies can already be estimated without the corresponding perturbation expansion by simple comparison of the energy of the reference non-interacting state with the energy of the interacting state. The non-interacting reference state briefly introduced here corresponds to the zeroth-order wavefunction $\Psi^{(0)}$ on which the future perturbation expansion will be based. More mathematical details are available in the corresponding publication.[1]

In our proposed scheme, the system of interest is divided into three molecular fragments denoted A, B and C. The noncovalent interaction between A and B must be eliminated before optimizing the wavefunction, whereas fragment C is linked covalently to both A and B. The distribution of electrons amongst the fragments is performed through the use of strictly localized orbitals on each fragment. Once the individual fragments are unambiguously defined, the total energy is partitioned to deliver the intramolecular interactions between fragments A and B. For this purpose, one uses the CHA approach and its improved CECA energy decomposition. The improved CECA was modified to enable the optimization of the zeroth-order energy $E^{(0)}$, excluding any interaction between fragments A and B.[1]

Our validation of $\Psi^{(0)}$ on propane derivatives indicates that the computed intramolecular interaction energies are of the correct order of magnitude, and lead to chemically intuitive substituent effects. Similarly, the interaction energy associated with the intramolecular hydrogen bond in pentane-2,4-diol was found to be attractive and in the range of analogue intermolecular examples. The approach was also demonstrated to be effective at various non-equilibrium geometries.[1]

As an alternative example, Fig. 2 gives the intramolecular interaction energies for the hydrogen bonds in the most stable conformations of 2-aminoethanol and 3-aminopropanol.[65] The intramolecular interaction energy was computed with the 6-31G*,[108,109] aug-cc-pVDZ and aug-cc-pVTZ[119,120] basis sets, with the OH and NH_2 functional groups as interacting fragments.

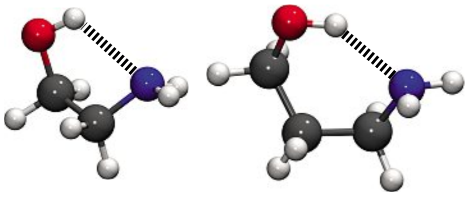
Based on experimental IR spectra, Thomsen *et al.*[65] concluded that the hydrogen bond in 3-aminopropanol was stronger than in 2-aminoethanol. Our computed intramolecular interaction energies are in full agreement (see Fig. 2) with their conclusions. Note however that the computed energies are expected to deteriorate when using large and diffuse basis sets like aug-cc-pVTZ due to the loss of fragment character.[1] Overall, our proposed $\Psi^{(0)}$ yields reasonable energetic trends for a variety of intramolecular interactions and geometries and is hence relevant to the development of intramolecular SAPT. The future application of a perturbation expansion on top of $\Psi^{(0)}$ will give access to the decomposition of the intramolecular interaction energy into physically meaningful terms such as exchange, electrostatics and dispersion and open the door to the accurate quantification and analysis of all types of noncovalent intramolecular interactions.

Conclusion

Non-covalent intramolecular interactions are omnipresent and responsible for many fundamental chemical phenomena. Yet methods to probe and characterize their nature are very scarce compared to the numerous approaches devised for the analysis of intermolecular interactions. Few approaches based on strict orbital localizations or natural bond orbitals can provide some information regarding the intramolecular charge transfer or the steric interaction. Fragment methods yield physically meaningful energy quantities at the expense of perturbing the molecular electronic structure.

The IQA and CHA methods decompose a converged energy by attributing the terms of the Hamiltonian to intra- or interatomic contributions, hence neglect the wavefunction relaxation effects upon interaction.

The current limitations prompted our recent efforts put in the derivation of a correct zeroth-order wavefunction $\Psi^{(0)}$ for intramolecular SAPT. Our proposed $\Psi^{(0)}$ is optimized excluding any interaction between the two fragments of interest. Our zeroth-order wavefunction and energy expression yield unprecedented qualitative and quantitative information in line with our chemical intuition of intramolecular interactions. This primary step is fundamental to the development of intramolecular SAPT. Future prospects will include the derivation of the perturbation expansion and the decomposition of the intramolecular interaction energy into physically meaningful terms, including intramolecular dispersion.



ΔE in kcal/mol		
6-31G*	ΔE=-3.8	ΔE=-6.1
aug-cc-pVDZ	ΔE=-2.9	ΔE=-4.4
aug-cc-pVTZ	ΔE=-1.8	ΔE=-2.1

Fig. 2. Intramolecular interaction energies for the hydrogen bond in 2-aminoethanol (left column) and 3-aminopropanol (right column).

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