

Capturing through-bond non-local effects in torsion parameters using fractional bond orders

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Abstract

Accurate small molecule force fields are crucial for predicting thermodynamic and kinetic properties of drug-like molecules in biomolecular systems. Torsion parameters, in particular, are essential for determining conformational distribution of molecules. However, they are usually fit to computational expensive quantum chemical torsion scans and generalize poorly to different chemical environments. Torsion parameters should ideally capture local through-space non-bonded interactions such as 1-4 steric and electrostatics and non-local through-bond effects such as conjugation and hyperconjugation. Non-local through-bond effects are sensitive to remote substituents and are a contributing factor to torsion parameters poor transferability. Here we show that fractional bond orders such as the Wiberg Bond Order (WBO) are sensitive to remote substituents and correctly captures extent of conjugation and hyperconjugation. We show that the relationship between WBO and torsion barrier heights are linear and can therefore serve as a surrogate to QC torsion barriers, and to interpolate torsion force constants. Using this approach we can reduce the number of computational expensive QC torsion scans needed while maintaining accurate torsion parameters. We demonstrate this approach to a set of substituted benzene rings.

1. Introduction

Molecular mechanics (MM) methods rely on Newtonian physics inspired empirical force field to describe the potential energy of the system and are widely used to study larger systems with 10^3 - 10^6 atoms [1]. They are sufficiently cheap and accurate to study biological relevant systems and provide atomistic details of mechanisms in enzymes in solution and can reliably predict thermodynamic properties such as binding free energies [2; 3; CITE free energy]. However, given the larger chemical space small molecule force fields need to cover to adequately represent druglike molecules and common metabolites, they have lagged behind protein force fields [4,5]. In MM forcefields, the potential energy is constructed with terms for bond stretching, angle bending, internal rotations, electrostatics and Lennard-Jones for attractive and repulsive forces [6,7,8]. These free parameters in these functionals are fit to reproduce experimental and quantum chemical (QC) data.

1.1 The torsion functional describes the potential energy of internal rotation

The torsion functional which models internal rotation is particularly challenging to parameterize and the least transferable relative to other bonded terms for several reasons [CITE]. First, torsion parameters are usually fit to computationally expensive QC torsion scans which introduces a bottle neck to setting up simulations. Second, torsion parameters are 'soft' or very flexible degrees of freedom compared to bond and angle parameters [CITE]. Relatively small variations to the torsional potential surface can strongly influence molecular conformation distributions [CITE]. Given how critical torsion parameters are in determining conformation distributions in simulations, it is prudent for them to be accurately parameterized. Third, torsion potentials can be strongly influenced by distal substituents, an effect very difficult to represent in a force field that uses only local chemistry to define parameters. When parameterizing a molecular system, the force field assigns atom types, or a description of the atom's atomic number and chemical environment to every atom in the system [CITE]. These atom types are generally defined by their local chemical environment. A torsion type is defined by the atom types of the four atoms involved in the torsion. These non-local through-bond effects are difficult to capture with local torsion types and is a contributing factor to torsion parameters' poor transferability.

In most force fields (CHARMM [CITE], AMBER [CITE], OPLS [CITE]) the torsion potential is given by a truncated Fourier series:

$$E_{\text{torsions}} = \sum_{\text{torsions}} \sum_{n=1}^N K_{\phi,n} (1 + \cos(n\phi_i - \delta_n)) \quad (1)$$

where the sum is over torsion angles ϕ and multiplicities n . The force constants $K_{\phi,n}$ determine the barrier heights, the multiplicities n determine the number of minima and the phase angles $\delta_{\phi,n}$ determines the phase. In most force fields the N can go up to 6 and the phase angles δ are usually set to 0° or 180° to symmetrize the curve around 0° .

The torsion energy about a bond is determined by a combination of local and non-local effects from conjugation, hyperconjugation, sterics, and electrostatics [CITE]. Steric and electrostatic interactions are, in principle, accounted for by non bonded terms in most force fields, so a torsion profile would ideally primarily capture conjugation or hyperconjugation effects, and only the 1-4 electrostatics. However, conjugation and hyperconjugation are non local properties and remote chemical changes can influence the extent of conjugation and/or hyperconjugation. These effects are not always captured by existing, locally defined torsion types.

Discuss how previous work dealt with this problem

1.2 Fractional bond orders describe the extent of bonding between two atoms

An MM force field first assigns each atom in the system an atom type, or a description of the atom's atomic number and chemical environment [9,10]. This reduces the number of parameters needed to describe the system because parameters developed for one atom can be transferred to other atoms in similar chemical environments.

Bond-stretching and angle-bending terms are considered 'hard' degrees of freedom [11] which means their associated force constants are large and small deviations from b_0 and θ_0 will result in large changes in the potential energy. Therefore, bond and angle terms are straight forward to parameterize. They have historically been fit to vibrational frequency, crystallographic and microwave data [12,13]. QC data have also been used to fit these terms [13]. Parameterizing the torsion dihedral-angle term is less trivial and are the least transferable relative to other bonded terms [14,15]. The torsion angle is a 'soft' or very flexible degree of freedom and relatively small variations to the torsional potential energy surface can strongly influence molecular conformation distributions. Given how critical torsion parameters are in determining conformation distributions in simulations, it is prudent for them to be accurately parameterized.

The torsion energy functional (equation) used to describe the energy of internal rotation of molecules is given as a sum of cosines. In equation 1, the torsion angle ϕ is the angle between the two planes formed by the 1, 2, 3 and 2, 3, 4 atoms of four sequentially bonded atoms. $K_{\phi,n}$ is the torsion force constant which determines the energy barrier height, n is the multiplicity which determines the number of minima and maxima in the curve, and δ is phase angle which determines the shift. The maximum value for n ranges from 3 to 6, depending on the force field. These parameters are usually fit to computationally expensive QC torsion scans.

The physical motivation for the torsion term is to include quantum orbital effects that contribute to resistance to rotations of conjugated and higher multiplicity bonds [16]. The multiplicity terms, n , are chosen based on chemical intuition to reproduce the periodic nature of the torsion profile involved. In reality, the torsion energy about a central bond is determined by a combination of effects that are difficult to separate; 1-4 non-bonded interactions, through-space steric and electrostatic interactions of atoms beyond the 1-4 atoms in the torsion, and electronic delocalization such as conjugation and hyperconjugation [17,18,19,20].

2.2 Fractional bond orders

In quantum mechanics, a molecule is a system of particles - nuclei and electrons. Chemists, however, think of molecules as atoms held together by bonds. The connectivity graph of molecules is a very important mental model in chemistry, based on centuries of chemical observations and knowledge. Many quantum chemists such as Pauling , Coulson , Mulliken , Wiberg , and Mayer have worked on bridging the gap between the physical and chemical conception of atoms in molecules by an analysis of the wave function to arrive at a fractional bond order that is consistent with the chemical concept of the multiplicity of a chemical bond. In this thesis (Chapters 2 and 3) I show how informative the Wiberg bond order, calculated from a cheap AM1 wave function, is for solving several outstanding problems in classical force field development.

The WBO is just one form of quantum mechanical electron density based bond order calculations that aims to quantify the chemical bond, a key concept in chemistry, by computing the electron population overlap between atoms. Many other definitions have been proposed; a non-exhaustive list includes Pauling , Coulson , Mulliken , Mayer , Jug , Politzer , atomic overlap matrix bond order , natural resonance theory bond order , Nalewajski-Mrozek bond order , effective bond order , natural localized molecular orbital bond order , delocalization index , and fuzzy bond order . Here, we compare the Wiberg and Mayer bond orders.

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