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Generating CHARMM-compatible force field parameters for atrazine

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Abbreviations:

ATZ - atrazine
QM - quantummechanical
MM - molecular mechanics
AOs - atomic orbitals
MOs - molecular orbitals
HF - Hartree–Fock
MP - Møller–Plesset
GTOs - Gaussian Type Orbitals
VMD - Visual Molecular Dynamics
ffTK - Force Field Toolkit
NAMD - Nanoscale Molecular Dynamics
G09 - Gaussian 09

ABSTRACT

There are many synthetic, drug-like molecules whose interactions with large biomolecules could be partly described by molecular dynamics studies. The parameters necessary to perform an MD simulation are available for biomolecules (proteins, nucleic acids, lipids, carbohydrates) and for many other small chemical compounds with biological relevance. In case of uncharacterized molecules, parameter sets can be calculated using quantummechanical calculations.

The optimized geometry, van der Waals, charge, bond, angle and torsion parameters for the photosystem II-inhibitor herbicide, atrazine, were calculated and integrated into a CHARMM-compatible parameter file. The file (.par) is available, along with the coordinates (.pdb), structure (.psf) and topology (.top), and with this four type of data, atrazine may be part of CHARMM-based molecular dynamics simulations, therefore, its interactions with biomolecules can be studied.

Introduction

In order to get a full parameter set for atrazine (ATZ), calculation of the non-bonded (Lennard–Jones/van der Waals), geometry, charge, bond, angle and dihedral properties is needed through quantummechanical (QM) and molecular mechanics (MM) methods.

In this work, the used LJ/vdW parameters are based on analogous QM data that contain the necessary information on these parameters. These parameters exist for most atoms found in organic small molecules or are largely transferable between highly related atoms [1]. The geometry optimization performed at the QM level is a procedure to find the configuration of a local or global minimum energy of the molecule by calculating the wave function and the energy of an initial structure and searching a new geometry of a lower energy [2]. Partial atomic charges can be determined by creating small ligand-water complexes (explicit solvent) that are subjected to QM calculations. The resulting minimum interaction energies and geometries, along with available dipole moments, are then used as the target data for the MM optimization of the partial atomic charges [3]. The result structure of geometry optimization generally does not have bond lengths and angles that correspond directly to the equilibrium bond and angle parameters. The calculation of bonds and angles needs the QM calculations of the Hessian (the second derivative of potential energy) to reconstruct the potential energy surface associated with distortions along bonds and angles [4]. Dihedral or torsion angles represent the rotations that occur about a bond, leading to changes in the relative positions of atoms 1 and 4. In the parameterization process, a summation of dihedral terms for a single torsion angle, a Fourier series that greatly enhances the flexibility of the dihedral term was used, allowing for more accurate reproduction of the QM energetic target data [5].

In addition to the input atomic data, every QM calculation is specified by a theoretical model and a basis set. A theoretical model is a way to model or represent a system using a specific set of approximations that are combined with a calculation algorithm and are applied to atomic orbitals (AOs), defined by the basis set, in order to compute molecular orbitals (MOs) and energy. The methods can be separated into four main types: semiempirical, *ab initio*, density functional and MM [2]. The Hartree–Fock (HF) method is a basic *ab initio* model. It uses the approximation that Coulombic electron-electron repulsion can be averaged, instead of considering explicit repulsion interactions, but it excludes the electron correlation [2]. In order to get more accurate data, a model starts with an HF calculation is used but the overall results are improved by adding the electron correlation effects. The Møller–Plesset (MP) perturbation theory improves on the HF method by adding electron correlation effects by means of the Rayleigh–Schrödinger perturbation theory [6]. There are various levels of MP calculations (MP2 [7], MP3 [8,9], MP4 [10], MP5 [11]); during the current work, only second order MP calculations were used.

The basis sets are a set of wave functions that describe the shape of AOs. The MOs are computed using the selected theoretical model by linearly combining the AOs. The Gaussian Type Orbitals (GTOs) are different from the Slater Type Orbitals but these are much easier to compute. The so-called Pople basis sets allow to specify the number of GTOs to use for core and valence electrons separately. Their general notation is: **K-LMG**, where **K** = number of sp-type inner shell GTOs; **L** = number of inner valence s- and p-type GTOs; **M** = number of outer valence s- and p-type GTOs and **G** = indicates that GTOs are used (e.g. 6-31G) [2,12-13].

Pople basis sets can be modified by adding a polarization function, and letting the AOs distort from their original shape. Polarization can be added as ***** or **(d)**. A **(d) or * type** : d-type functions added on to atoms other than hydrogens and f type functions added on to transition metals and a **(d,p) or ** type** : p-type functions added on to hydrogens, d-type functions added on to all other atoms, f-type functions added on to transition metals (e.g. 6-31G*) [1,14].

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Material and methods

The parameterization workflow contains the following steps and calculations: 1. Assign Missing vdW/LJ Parameters, 2. Geometry Optimization, 3. Water Interaction Energy, 4. Charge Optimization, 5. Hessian Calculation, 6. Bond and Angle Optimization, 7. Torsion Scan, 8. Dihedral Optimization. The ATZ parameterization was made by the plugins of Visual Molecular Dynamics (v1.9.3beta3) (VMD): Molefacture (v1.3) and Force Field Toolkit (v1.1) (ffTK), along with Nanoscale Molecular Dynamics (v2.11) (NAMD) [15,16,17]. The input QM data for ffTK were calculated by Gaussian 09 (Revision B.01) (G09) [18]. The three-dimensional structure of ATZ and its input file for VMD was constructed with Avogadro (v1.1.1) [19]. The ATZ's charge representation was rendered with the VMD plugin, Tachyon [20].

Assign Missing vdW/LJ Parameters

With Molefacture, the partial charges of non-polar hydrogens were fixed to +0.09 for CHARMM-compatible force fields.

After the cross-check of the full topology and parameter set of CHARMM36, 6 bonds, 11 angles, 11 dihedrals and 3 LJ/vdW parameters were found to be missing, the redundant data were not considered. The LJ/vdW parameters were assigned by analogy, the references were also obtained from the topology and parameter data of CHARMM36.

Geometry Optimization

The G09 calculation was run with an MP2/6-31G* theory-basis set combination.

Water Interaction Energy

In order to determine the partial charges of ATZ, it is necessary to characterize the water interaction sites of the molecule in a two-dimensional optimization.

Every partially positively charged atom can possibly interact with the oxygen of water, so those were set as donors, and every partially negatively charged atom can possibly interact with the hydrogens of water, so those were set as acceptors. The only exceptions are the sp^3 carbons of the ethylamine and isopropyl groups, where the approach of a water molecule is obstructed by their bonded hydrogens, therefore, these groups were not included in the optimization. The QM calculations were run with an HF/6-31G* combination.

Charge Optimization

The net charge of ATZ was set to zero, and the fixed charges of non-polar hydrogens were removed. The optimization routine was repeated until two iteration steps showed no difference, and the structure and topology file (.psf, .top) was updated with the final charge values.

Hessian Calculation

The Hessian (the second derivative of potential energy) calculation is an effective method to reconstruct the potential energy surface associated with distortions along bonds and angles.

The calculation was applied on the previously optimized geometry of ATZ. The MP2/6-31G* level of theory was completed with the calculation of frequencies, without using molecular symmetry within the calculation.

Bond and Angle Optimization

The *Geometry Weight* value was set from 1.0 to 2.0 and the *Angles-Eq. Deviation* tolerance was reduced from 10.0 to 5.0. The first modification increases the weight associated with how well the MM-optimized geometry matches the QM-optimized geometry. The latter value sets the threshold below which deviations no longer contribute to the objective function. Overly tight Eq. Deviation thresholds tend to yield large force constants, such that reasonable thresholds are critical to balancing the interplay between obtaining suitably close optimized geometries while reproducing the surrounding potential energy surface. The iterations were performed with NAMD, until the values converged to a minimum.

Torsion Scan

Since ffTK excludes dihedrals terminating in hydrogens when their data is read directly from the in-progress parameter file, the previously found 11 dihedrals were added manually. The scan intervals (+/-) were set to 180 degrees and the step size to 10 degrees, so a total of 22 scans were prepared for QM calculations (MP2/6-31G*).

Dihedral Optimization

In the last phase of the parameterization, the data provided by G09 should be refined with an MM method of NAMD to fit to the QM profile. A complete description of dihedrals often requires multiple terms bearing the appropriate periodicity (n) and phase shifts (δ) in addition to a force constant (k). The input n and δ values were taken from analogous dihedral parameters of CHARMM36. The refinement algorithm was set to "downhill" and the *Tolerance* value to 0.0001. The process was iterated until the MM profile became sufficiently close to the QM.

Results and discussions

Since the calculated data are available in the supplemented files, in this chapter only some additional results are discussed.

Assign missing LJ/vdW parameters

During the parameter cross-check, 3 LJ/vdW parameters were found to be missing: a C2, C3 and an Npl type. The assigned parameters (Table 1) were obtained from the topology and parameter data of the CHARMM36 force field.

Table 1. Assigned missing LJ/vdW parameters of ATZ. The ε value is the potential well depth in kcal/mol and R_{min} is the distance where the potential reaches a minimum in Å. The 1-4 interactions are between the end atoms involved in a dihedral angle (see Lennard–Jones potential).

Type	**ε**	**$R_{min}/2$**	**ε, 1-4**	**$R_{min}/2$, 1-4**
C2	-0.040000	2.100000		
C3	-0.078000	2.040000	-0.010000	1.900000
Npl	-0.070000	1.980000		

The C2 type was assigned as a 6-membered aromatic carbon between 2 or 3 nitrogens, double-bound to one of those; C3 as an sp^3 carbon and Npl as neutral nitrogen in aromatic amines.

Optimized Charges

The ATZ's atom charge values can be found in the supplemented psf file, and those are visualized in Fig. 1. The carbons and the N2 of the 1,3,5-triazine ring have the most expressed charge values (Table 2) .

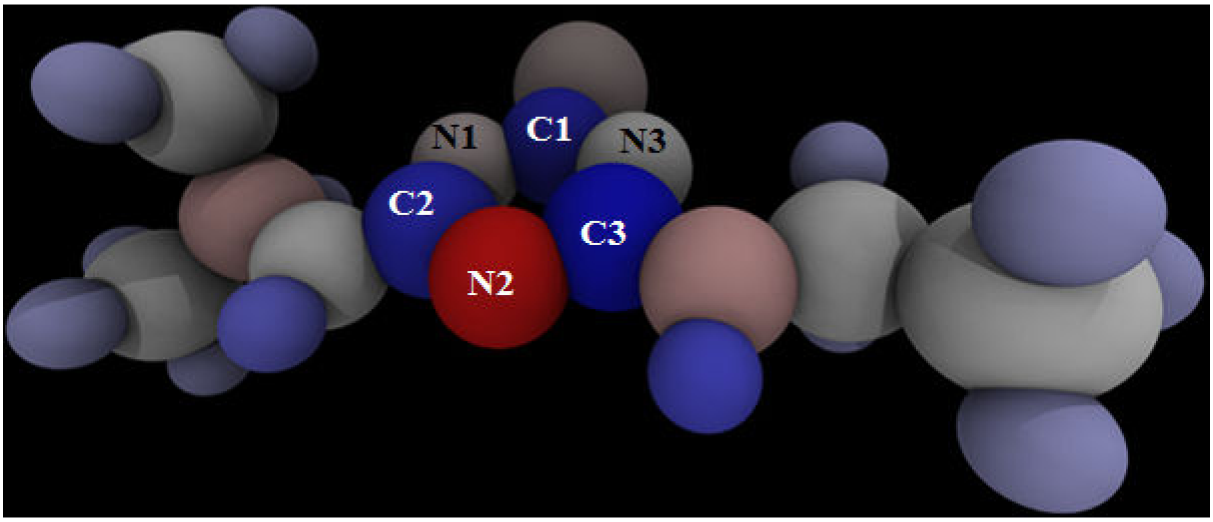

Fig. 1. The ATZ's partial charges. The atoms are coloured by the absolute value of their charges. Positive charges are blue, negative charges are red. The atoms of the 1,3,5-triazine ring are marked with their symbols and numbers.

Table 2. The ATZ's partial charge values. The carbons and the N2 of the 1,3,5-triazine ring have the most expressed charge values.

Atom	**Charge**
C1	**0.405**
N1	-0.244
C2	**0.401**
N2	**-0.759**
C3	**0.483**
N3	-0.190

Dihedral Optimization

The Root-mean-square error (RMSE, the square root of the variance) value after the first optimization was 0.446, and after the final (5th), it was 0.225. The result plot of the final refinement (Fig. 2) shows a non-perfect fit to the target QM data.

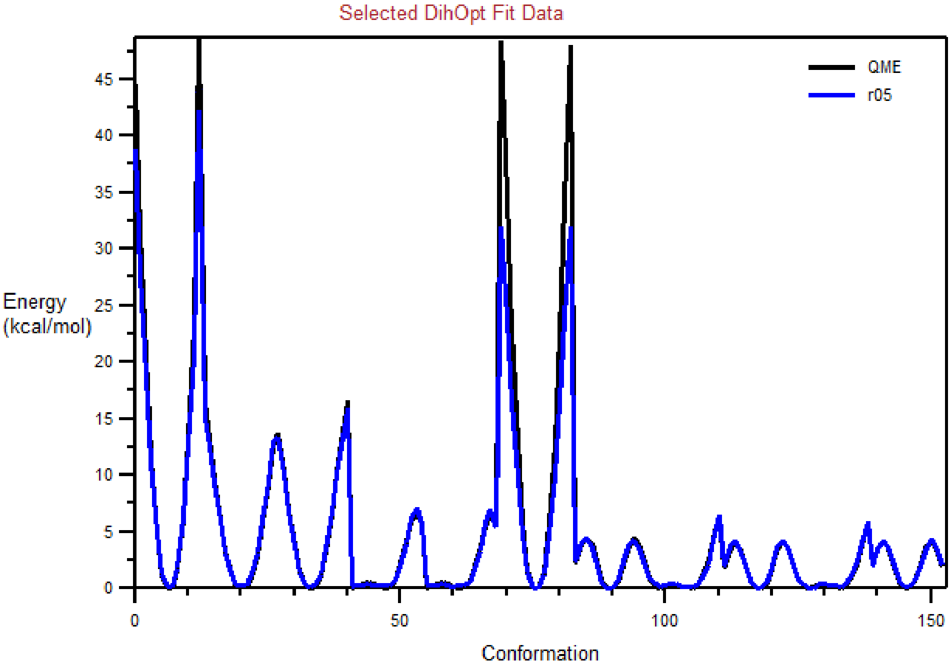

Fig. 2. Final fit data of the ATZ dihedral optimization. The result of the final refinement (r05, blue) shows a good fit to the target QM data profile (QME, black) but in the case of two maxima, the match is not perfect. The reason for the imperfection cannot be determined but it has a negligible effect: the energy content of the two conformers will be slightly lower during the MD simulations than if the fits were perfect.

Conclusions

Most of the publications report parameters taken from the ParamChem webserver, which is a resource for obtaining initial parameters based only on analogy. The problem is that these results contain a so-called penalty score, since the uploaded ligands are cross-checked only with the CHARMM General Force Field (*CGenFF*), therefore, additional calculations would be necesarry to refine the parameters within the novel chemical context. In this work, the amount of data based on analogy are restricted to the 3 non-bonded parameters, the ATZ was cross-checked with every topology and parameter data of the CHARMM36 force field, (including also the CGenFF), and the rest of the output is a result of optimization methods and algorithms.

The end product of the presented workflow is a complete parameter set required to perform MD simulations of atrazine. The necessary data are integrated into the four supplemented files: atrazine.pdb, atrazine.psf, atrazine.top and par_charmm36_atrazine.par.

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