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General van der Waals potential for common organic molecules

Rui Qi^{a,†}, Qiantao Wang^{b,†}, Pengyu Ren^{a,*}^a Department of Biomedical Engineering, The University of Texas at Austin, Austin, TX 78712, United States^b West China School of Pharmacy, Sichuan University, Chengdu 610041, China

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ABSTRACT

This work presents a systematic development of a new van der Waals potential (vdW2016) for common organic molecules based on symmetry-adapted perturbation theory (SAPT) energy decomposition. The Buf-14-7 function, as well as Cubic-mean and Waldman–Hagler mixing rules were chosen given their best performance among other popular potentials. A database containing 39 organic molecules and 108 dimers was utilized to derive a general set of vdW parameters, which were further validated on nucleobase stacking systems and testing organic dimers. The vdW2016 potential is anticipated to significantly improve the accuracy and transferability of new generations of force fields for organic molecules.

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1. Introduction

Molecular recognition is central to biomolecular processes such as metabolism, signal transduction, and gene expression.¹ In drug discovery processes, one major goal is to identify small ligands that can selectively bind to a macromolecular target with a high affinities and favorable pharmacological properties.^{1b,2} Computational modeling holds the promise of accelerating drug discovery and guiding molecular design by predicting ligand interactions with biomolecular targets.³ Although computational modeling and simulation can provide quantitative understanding of the mechanism underlying molecular recognition,^{2c,4} effective sampling methods and accurate force fields continue to be the main challenges for reliable prediction of molecular interactions.

Classical force fields such as AMBER,⁵ CHARMM,⁶ OPLS-AA,⁷ and GROMOS⁸ typically model the electrostatic interactions with fixed atomic point charges and treat van der Waals (vdW) interactions via simple functions, such as the Lennard–Jones (12–6) potential. As computationally efficient alternatives to quantum mechanical (QM) calculations, such classical point charge models have been widely used in molecular dynamic simulations of biological systems.^{5a,7} Newer models that explicitly represent anisotropic atomic charge distributions and respond to surrounding changes via polarization⁹ can potentially lead to improved transferability between different chemical and physical environments. For

example, the point charge model can be replaced by atomic multipole moments, such as dipole and quadrupole, to capture the anisotropic nature of the electronic structures.¹⁰ The polarization effects have been modeled by interactive atomic induced dipoles,¹¹ fluctuating charges¹² or Drude oscillators models.¹³ The AMOEBA force field, which employs atomic multipole moments and dipole polarizabilities, is one typical example of such newer models.

During the past decade, the AMOEBA polarizable force field¹⁴ has been extensively tested for water,¹⁵ various small molecules,¹⁶ ions,¹⁷ ionic liquids,¹⁸ and proteins systems.¹⁹ However, due to the missing treatment of charge penetration, atomic multipoles are unable to capture electrostatic interactions at very short range where the atomic electron clouds overlap. The current AMOEBA force field and most other widely used fixed-charge force fields address this issue by using a less repulsive van der Waals potential to compensate the charge penetration contribution in short range. The problem with this approach however, is that the resulting vdW parameters are less transferable.²⁰ Given the recent advances in computational chemistry and the computing power, the noncovalent interaction energy components can be computed using highly accurate quantum mechanical methods²¹ such as symmetry-adapted perturbation theory (SAPT).²² Recently, we have developed a general electrostatic model to incorporate the charge penetration effect based on the atomic multipole moments in AMOEBA.²³ This model significantly improves the agreement between point multipoles and quantum mechanical electrostatic energies from SAPT2+ decomposition even at short inter-molecular distances. This improvement leads to the need to revisit vdW

* Corresponding author. Tel.: +1 512 232 1832; fax: +1 512 471 0616.

E-mail address: pren@mail.utexas.edu (P. Ren).

† These authors contributed equally.

potentials that are capable of capturing SAPT repulsion and dispersion energy.

Lennard–Jones (12–6) potential is one of the most common functions to describe the exchange–repulsion and dispersions interactions.²⁴ It has been adopted in a range of force fields²⁵ such as AMBER^{5a} and CHARMM.⁶ This simple function contains only two parameters and it is faster to compute than exponential terms.²⁶ Other Lennard–Jones potential forms include the Lennard–Jones (9–6) function²⁷ and the Lennard–Jones (12–10) function^{25f} which is an alternative to the usual Lennard–Jones (12–6) function in AMBER^{5a} to model hydrogen bonds. As a special case of the Buckingham potential function,²⁸ the exponential-6 potential is widely used in force fields^{25c,29} such as MM2,³⁰ MM3,³¹ and MM4.³² However, both Lennard–Jones and exponential-6 potentials account poorly for the high quality noble gas data while a simple buffered 14–7 (Buf-14-7) potential can accurately reproduce the noble gas potentials over a range of distances.³³ Besides the two interaction-specific parameters, the well depth and minimum-energy distance, the Buf-14-7 functional form is capable of adjusting the curvature of request depending on two shape parameters.

In addition to the functional forms, vdW interactions between unlike atoms (e.g., O and H) depend on the suitable combination of mixing rules to generate the well depth and distance parameters, unless pair-wise parameters are specified for all combinations. Current available force fields employ either geometric or arithmetic mean as the combining rules, which lead to large errors for mixed noble gas atom pairs.³⁴ More elaborate combination rules have been proposed, involving additional parameters such as polarizability, ionization potentials, or dispersion force coefficients.³⁵ Newly derived combining rules, Waldman–Hagler (W–H)³⁴ and Halgren (HHG),³³ require no additional parameters other than the well depth and distance, also well reproduce the experimental values of noble gas interactions.

In classical force fields, electrostatic parameters, such as atomic charges, are normally computed from ab initio quantum mechanics directly.³⁶ The so-called vdW interaction in a force field is actually less well-defined and is essentially utilized to capture everything beyond the charge–charge interactions, including the charge penetration, charge transfer and perhaps some of the many-body polarization effects in condensed-phase. Additional difficulty in force field parameterization lies in the limitations of ab initio methods. A “perfect” ab initio force field will not reproduce experimental condensed-phase thermodynamic properties without explicit quantum corrections such as zero-point energy. Thus deriving vdW parameters by fitting to gas-phase ab initio molecular interaction energy alone is insufficient if the resulting force fields were intended for condensed-phase systems, even with many-body polarization were explicitly accounted for. Given these limitations, the most effective approach, pioneered by Jorgensen and co-workers in developing OPLS and OPLSAA force fields,³⁷ has been to use derive vdW parameters directly against reliable and widely available liquid properties such as density and heat of vaporization.

This work presents the first systematic attempt to develop a new van der Waals potential, vdW2016, for common organic molecules based on SAPT energy decomposition. We first examined several common vdW functions to determine the best functional form based on noble gas interaction energy data. A general set of parameters (element based) was then determined by fitting to the exchange–repulsion and dispersion energies for 756 dimers made of 39 common organic molecules with different configurations and separation distances (S108 ×7 database). This new vdW potential was further validated on nucleobase stacking systems as well as on a testing set of small organic dimers (S36 ×7). Overall, the vdW2016 potential is expect to provide

accurate prediction of vdW interaction energy for common organic molecules, including drug candidates.

2. Computational methods

2.1. Van der Waals functions and mixing rules

The vdW functional form and mixing rules were determined from noble gas systems including helium (He), neon (Ne), argon (Ar), and krypton (Kr), where the non-bonded interactions were dominated by vdW interactions. Three typical vdW functional forms, Buf-14-7, Buckingham, and Lennard–Jones (12–6), were examined using the same sigma and epsilon extrapolated directly from the exchange–repulsion and dispersion energy of SAPT2+/aug-cc-pV5Z calculations (the dispersion energy has been scaled by 0.89 to match the CCSD(T)/CBS total interaction energy).²³ Different combinations of the vdW functions with three sets of mixing rules, Cubic-mean/HHG, W–H/W–H, Cubic-mean/W–H were examined against the SAPT2+/aug-cc-pV5Z potential surfaces. (See different functional forms, mixing rules and parameters in the SI, Table S1.) According to the best fitting results with the perfect match with SAPT (Fig. 1) and the lowest RMSE (Tables 1 and S2), we chose the Buf-14-7 (Eq. (1)) as the functional form, and as mixing rules, Cubic-mean for σ (Eq. (2)) and W–H for ϵ (Eq. (3)). The parameter ϵ_{ij} is the potential well depth, and R_{ij}/σ_{ij} is the ratio between the actual separation of i – j atomic sites and the minimum-energy distance.³³ We also provided the results calculated using the same mixing rules, Cubic-mean/W–H, but the optimized delta and gamma and in the SI, where the Buf-14-7 is still the best choice.

$$E_{vdW} = \epsilon_{ij} \left(\frac{1 + \delta}{\frac{R_{ij}}{\sigma_{ij}} + \delta} \right)^7 \left(\frac{1 + \gamma}{\left(\frac{R_{ij}}{\sigma_{ij}} \right)^7 + \gamma} - 2 \right) \quad (1)$$

$$\sigma_{ij} = \frac{(\sigma_{ii})^3 + (\sigma_{jj})^3}{(\sigma_{ii})^2 + (\sigma_{jj})^2} \quad (2)$$

$$\epsilon_{ij} = (\epsilon_{ii}\epsilon_{jj})^{1/2} \frac{2(\sigma_{ii})^3(\sigma_{jj})^3}{(\sigma_{ii})^6 + (\sigma_{jj})^6} \quad (3)$$

2.2. S108 ×7 fitting database

The interaction energies of seven heterodimers between methane, amine, ethene and water were added to the S101 ×7 database (39 molecules and 101 dimers)²³ to construct the S108 ×7 fitting database. (See newly added energy data in the SI, Table S4). The same structural optimization, distance generation and energy decomposition methods, including the extrapolation scheme and the scaling of dispersion energy, as in the S101 ×7 database construction were used to generate the energy profiles for newly added dimers. The parameters of the vdW model were optimized to match the sum of the dispersion and exchange energy in the S108 ×7 SAPT2+ database, which contains the total interaction energies as well as decomposed energy components for 108 pairwise interactions at seven distances (0.70, 0.80, 0.90, 0.95, 1.00, 1.05, 1.10 times of the equilibrium distances R). The mean unsigned error (MUE), mean signed error (MSE), and root-mean-square error (RMSE) were calculated to examine the performance of different models at all 7 distances for a total of 756 dimers. This set includes 216 dimers at 2 short distances (0.70R and 0.8R), and 540 dimers at 5 near equilibrium distances (0.9R, 0.95R, R, 1.05R and 1.10R).

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