The Polyhalogenated Molecules in Polarizable Ellipsoidal Force Field

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Abstract
Polyhalogenated compounds are common in industrial, agricultural, and environmental problems. More halogen bonds are possible in such molecules, from the monohalogenated to polyhalogenated molecules. And a few coupled σ-holes exist in the covalent halogen atoms, for which the strong interplay in halogen bonds should be carefully treated in the force field optimization. In this work, the polarizable ellipsoidal force field is successfully applied to many possible halogenated benzenes. The symmetrical feature of the parameters is significantly reproduced without any additional restrictions. The optimized parameters for anisotropic electrostatic potential show good accuracy, stability, transferable with reasonable physical meanings. The parameter fitting protocol is very efficient on a laptop, which may also be completely parallelized for thousands of halogenated homologues.

Introduction
Many halogenated molecules usually contain more than one covalent halogen atom, which are known as polyhalogenated compounds. Polyhalogenated molecules are widespread in industrial, agricultural, and environmental phenomenon. For example, polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyl (PCBs), are known as endocrine-disrupting compounds that induce a wide range of developmental and neurodegenerative effect.\textsuperscript{1-3} The covalent halogen atoms could form halogen bonds with other molecules, which is important in many chemical and biochemical processes.\textsuperscript{4-8} For polyhalogenated molecules, each of the covalent halogen atoms may interact with other molecules \textit{via} halogen bonds. And the coexistence of halogen bonds plays an important and non-negligible role, especially for ortho- and meta- substituted compounds.

Theoretically, the anisotropic charge distribution (namely the σ-hole) for the covalent halogen
atoms should be carefully considered, which is challenging for the atomic point-charge model in traditional force field. Recent years, a few force fields have been developed for halogen atoms or atoms with similar properties as halogen atoms, such as positive extra-point or explicit sigma-hole (ESH) model, force field for biological halogen bonds model (ffBXB), and polarizable ellipsoidal force field (PEff). The anisotropic electrostatic potential distribution is generally recovered by providing additional force field parameters.

The previous studies usually focus on monohalogenated systems, such as rational drug design, and protein-ligand complexes. The simulations for polyhalogenated systems should also be possible, however, the non-additive coupled σ-hole interactions in polyhalogenated molecules require further considerations. For instance, the PEff model proposed by Du et al. use four parameters to describe the electrostatic potential around the covalent halogen atom. As the number of covalent halogen atoms increases, the degree of freedom to be fitted in the polyhalogenated molecules systematically increases and the parameters fitting procedure become very intractable. This problem belongs to the subject of many objective optimization problems (MaOPs) in mathematics. Genetic algorithms and machine learning methods have also been demonstrated as a possible global optimization approach. Take the 1,2,3-tribromobenzene molecule as an example, three covalent bromine atoms should be treated as three optimization objects. Although one can directly optimize the 12 parameters of the three covalent atoms, the optimized parameters are highly dependent on the initial guess or fitting algorithms. In addition, the parameters for three bromine atoms can be fitted one by one, however, the optimized parameters would be strongly dependent on the order of the fitting procedure. The molecule symmetric character is usually destroyed without manual constraint, and usually the optimized parameters cannot provide reasonable physical meanings.

In the present work, the PEff model is applied to a series of polyhalogenated benzene molecules. And the parameter fitting protocol is enhanced, which is designed to be completely compactable with previous work. To keep forward compatibility, the previous fitting protocol for monohalogenated molecules do not need any modification. And the accuracy, stability, transferability, as well as physical meanings of the parameters are discussed in this work. The force filed fitting protocol is very efficient, and the entire procedure can be completely parallelized in the distributed computing systems.
**Theory and Computational Details**

In the PEff model, the halogen bond is a typical noncovalent bond, which consists of three fundamental interactions, and they are the electrostatic interaction and repulsive/dispersion interaction and the polarization interaction.\textsuperscript{13} The PEff model could correctly reproduce the potential energy surface of halogen bonds at quantum mechanism level. The equations of bonded interactions were kept to be consistent with other force field.\textsuperscript{13,36} The parameters for repulsive/dispersion interaction are kept consistent with the previous work, while the polarization interactions require only one parameter to be fitted. Hence, we only need to focus on the electrostatic parameters. And the electrostatic interaction in PEff model is given as follows,

\[ V_{\text{elst}}(r_1, R, r) = Q \left\{ \exp(-\alpha r_1 - \beta R) - \exp(-\zeta r) \right\} \frac{1}{r} \]

And the variables \( r_1 \) are the coordinates in the equatorial area, and \( R \) is the distance from halogen atom along the R-X axis direction. The variable \( r \) is the halogen bond length. And the parameters \((\alpha, \beta, \zeta, Q)\) were derived from the \textit{ab initio} electrostatic potential to mimic the realistic charge distributions. The anisotropic charge distribution was represented with the combination of a negative charged sphere and a positively charged ellipsoid as shown in Figure 1a.

![Diagram](image)

Figure 1. (a) The PEff model of the covalent halogen atom; (b) the electrostatic potential and (c) the structure of 1,2,3-tribromobenzene.

The situation becomes complicated for polyhalogenated molecules. As shown in Figure 1b, the
1,2,3-tribromobenzene contains three consecutive covalent halogen atoms, and the chemical
environment of first and third bromine atoms should be similar, while the second bromine atom is
different. And there are totally twelve electrostatic parameters to be fitted, which is not an easy task
for the least square method as we used for monohalogenated molecules.\textsuperscript{13} That is to say, the higher
the degree of freedom of the system, the less likely to obtain the optimal solution. This problem is
a multi-objective optimization problem in mathematics\textsuperscript{37,38}. Many local solutions can be obtained if
the parameter sets are large enough. However, these solutions are usually not optimal solutions,
even without any physical significance.

The problem of multi-objective optimization is often transformed into the single objective
optimization. In other words, the polyhalogenated systems optimization can be approximated into a
series of the single halogen issues, which could greatly reduce the difficulty of the optimization.
Take 1,2,3-tribromobenzene as an example (Figure 1c), the parameter values may be derived in a
step-wise fashion. First, the first bromine atom is fitted using PEff model and other bromine atoms
are treated as the point charge, simultaneously. Second, the second bromine atom is fitted using PEff
model, and the parameters of the first bromine is kept fixed. Lastly, the parameters for third bromine
atom are optimized. But the problem is that the fitted parameters would not be self-consistent, since
the fitting order of the halogen atoms would lead a nonnegligible error to the results. In addition,
the fitted parameters can be quite incredible, which may be quite large or small. And unstable
parameters cannot provide a clear physical meaning. Thus, the fitting protocol also needs further
considerations.

\textbf{Scheme 1.} The parameter optimization protocol for polyhalogenated molecules in the PEff
model. Each fitting series (i.e. $X_1X_2\ldots X_n$) only provides a partial depiction of the parameters, and
the series fusion operation could extract the parameters with desirable accuracy, and a simple three-layer feed forward neural network is good enough.

Informatically, one can traverse all possible fitting orders of the halogen atoms (Scheme 1), which can be called the sufficient statistics. And the desired parameters can be derived from such data sets. Thus, one can sample many fitting orders of the halogen atoms, and each fitting order (i.e. $X_1X_2…X_n$) can be called a fitting series or a fitting basis. The least square algorithm is repeatedly applied to each halogen atom for a specific fitting series, and the partial depiction of the parameters can be derived. And then, the obtained data sets would be fed into the series fusion operation, which could be defined by many machine learning algorithms, such as a simple neural network. And a simple three-layer feed forward neural network is good enough with only one hidden layer. Each fitting series can be regarded as a basis in the entire fitting series sets. This is not to say that the result of each fitting series is wrong. On the contrary, the result of any fitting series is also chemically meaningful, which provide a partial description of the desired parameters. This idea is quite similar as the role of delocalized resonance structure of the Kekule formula as discussed in many general chemistry textbooks.

Scheme 1 shows the proposed fitting protocol for parameter optimization. For each fitting series, the halogen atom that appears earlier than the other should be optimized earlier, and it should be fitted as much as possible information. This algorithm makes the optimal choice at each step, which is called the greedy algorithm. Then, one can attempt to extract the overall optimal way to solve the entire problem, which is achieved by a simple three-layer feed forward neural network. The fitting protocol is quite robust, which can even start the optimization from zero initial guess. This protocol is very suitable for parallel computing, because the map and reduce operations are required for each fitting series. If high throughput calculations are desired, this can be easily automatic on a streaming computing framework such as Hadoop. The calculations can also be achieved on a laptop.

Finally, the traditional force field parameters beyond halogens are calculated by GAFF force field. And the electrostatic potential of the polyhalogenated molecule is calculated from ab initio calculations at HF/6-31G* level using ORCA package. And the molecule with iodine atoms is treated with the aug-cc-pVDZ(-PP) basis set. Partial atomic charges were assigned according to the
restrained electrostatic potential approach as recommended in the parameterization protocol of GAFF force field. All the parameter fitting procedure were implemented using Python script. The results are successful as discussed in the following section.

Results

The parameter fitting protocol can be automatic and is applied to many possible halogenated benzene compounds. The fitted PEff parameters of halogen atoms are satisfactory. And the average error from the \textit{ab initio} electrostatic potential is usually on the order of $10^{-6}$, which is significantly improve the point charge model of the covalent halogen atoms. The values of the parameters usually fluctuate within limited range for halogen atoms with similar chemical environment, and good parameter transferability is expected. As the number of covalent bromine atoms increases, certain chemical significance can be observed as discussed below.

Figure 2. The fitted electrostatic potential parameters ($\alpha$, $\beta$, $\zeta$, $Q$) of PEff model for the polybromobenzenes. The covalent bromine atoms are ortho-substituted.

Figure 2 shows the fitted electrostatic potential parameters ($\alpha$, $\beta$, $\zeta$, $Q$) for polybrominated benzenes, and the covalent bromine atoms are ortho positions. Take 1,2-dibromobenzene as an example (Figure 1c), the parameter values are very close for both bromine atoms since their chemical environment is equivalent. Compared with single substituted bromobenzene\textsuperscript{13}, it is concluded that the parameter $\beta$ reduced for dibromobenzene, which is consistent with the variation of electrostatic potential around halogen atoms. For bromobenzene, the maximum value of
molecular electrostatic potential ($V_{\text{max}}$) is 9.686 kcal/mol, while for dibromobenzene $V_{\text{max}}$ is 13.143 kcal/mol for each halogen atom. As the increase of the number of halogen atoms, the value $V_{\text{max}}$ increases and the ellipsoidal parameters ($\alpha$, $\beta$) generally decrease. This gives an insight on the parameter significance.

The fitted parameter sets could rationalize the symmetric feature and chemical environment of each halogen atom. For example, two types of bromine atoms exist in the 1,2,3-tribromobenzene molecule. And the chemical environment for the first and third bromine atoms is equal. The fitted parameters also suggest that there are two types of bromine atoms, and the first and third bromine atoms are equal. Meanwhile, different parameter values are assigned for the second bromine atom. This conclusion is also consistent with the electrostatic potential distribution of the 1,2,3-tribromobenzene molecule. The electrostatic potential $V_{\text{max}}$ of first and third bromine atoms is 16.21 kcal/mol, and second bromine atom is 15.93 kcal/mol. In the 1,2,3,4-tetra bromobenzene molecule, two types of bromine atoms are possible. And their parameters also indicates that the first and fourth bromine atoms belong to the same type and the second and third bromine atoms belong to the same type. Similar conclusions can also be found for penta-substituted and full-substituted bromobenzene. This means that the improved parameter fitting protocol could describe the chemical environment of different halogen atoms without any human intervention accurately.

The series fusion operation is important. In fact, significant bias could be observed if only one fitting series (such as $X_1X_2\ldots X_n$) is applied or the series fusion is not applied for the parameter fitting. For example, the parameters of the three bromine atoms for tribromobenzene are greatly different if the optimization algorithm (such as the least square method) is directly applied for one possible fitting series. And numerical bias is even more than 50% for the first and third bromine atoms, which is contrary to the fact that the chemical environment of the two bromine atoms is obviously equal. The series fusion operation could alleviate such unsatisfactory issues, which improves the rationality of the PEff model. Note that the single substituted benzenes could still use the least square method, while the polyhalogenated benzenes required a cascade of actions of least square optimizations. Thus, the fitting protocol is lossless and forward compatible, which provides a good trade-off between the accuracy and stability.
Figure 3. The fitted electrostatic potential parameters ($\alpha, \beta, \zeta, Q$) of PEff model for mixed ortho-, meta- and para- substituted compounds of bromobenzene.

There are 12 possible polyhalogenated compounds as shown in Figure 2 and Figure 3. Figure 3 shows the substituent effect of mixed ortho-, meta- and para- substituted compounds of bromobenzenes. It seems that the parameters are sensitive to the chemical environment of various bromine atoms. Obviously, the electrostatic potential along the R-X axis is more positive than the equatorial area, as revealed by the relationship of $\alpha<\beta$. This would result in the anisotropic charge density on the halogen atom, especially the $\sigma$-hole effect. And the symmetric feature of parameter values is kept for the corresponding bromine atoms, such as dibromobenzene, 1,3,5-tribromobenzene. For the 1,2,4-tribromobenzene, the parameter values for each bromine atom vary along with their chemical environment. Since the value of $Q$ is generally positive in this work, the relationship of $\beta<\zeta$ is an indicator for the attractive electrostatic interaction in the halogen bonds.
Figure 4. The fitted electrostatic potential parameters ($\alpha$, $\beta$, $\zeta$, $Q$) of PEff model for various chlorobenzenes. (a) ortho- substituted chlorobenzenes; (b) mixed ortho-, meta- and para- substituted chlorobenzenes.

Figure 4 and 5 show the parameter sets for the chlorine and iodine substituted benzenes. The mixed ortho-, meta- and para- substituted compounds of chlorobenzenes and iodobenzenes are also given. The similar trends were observed as the number of halogen atoms increases. Inserting each halogen atom would strongly change the chemical environment, and thus parameter values. Take the 1,2,3-trichlorobenzene and 1,2,3,5-tetrachlorobenzene as examples, the adding of one chlorine atom at the position 5 as a strong electron withdrawing group, the parameter values of the first and third chlorine atoms would strongly change. The $\beta$ value reduces significantly from 0.031 to 0.001, which means the $\sigma$-hole is enhanced. The $Q$ parameter is usually in the range of 0.1 e for chlorobenzenes and bromobenzenes, and maybe larger than 0.2 e or higher for iodobenzenes. This is reasonable because the polarization of the iodine atoms is more significant than the chlorine or
bromine atoms. The $\beta$ value is quite small for the full substituted counterparts. Considering the substituted effects, only the $\alpha$ and $\beta$ values are weakly affected for para- complexes, which are generally close to the mono-halogenated molecules. Meanwhile, the $\zeta$ and Q are strongly affected by the substituted effects. For ortho-one, the $\alpha$ and $\beta$ are strongly affected by the adjected halogen atoms. Such information is important for us to understand the nature of halogen bonds, especially the $\sigma$-hole effect. Further details of the parameters can be found in the supporting information.

Figure 5. The fitted electrostatic potential parameters ($\alpha$, $\beta$, $\zeta$, Q) of PEff model for iodobenzenes. (a) ortho-substituted iodobenzenes; (b) mixed ortho-, meta- and para- substituted iodobenzenes.

For the monohalogenated molecules, the exponential parameters ($\alpha$, $\beta$, $\zeta$) are suggested as an electrostatic interaction index for halogen atoms\textsuperscript{13}, which provides a very reasonable and meaningful description of the substituent effect for the covalent halogen atoms. Very roughly, this PEff model could also be rationalized by a combination of the HOMO and LUMO pairs, where the
negative charged sphere can be related to a filled HOMO orbital, and positively charged ellipsoid can be related to an empty LUMO orbital. This assumption can be used to interpret some interesting behaviors of the parameter sets. Take the 1,2,3-tribromobenzene molecule as an example, the parameter $\zeta$ of the negative charged sphere is completely zero, which can be rationalized from the frontier molecular orbitals. The second bromine atom does not participate in the HOMO orbital (Figure 6), which is mainly occupied on the first and third bromine atoms. And the electronic density should also delocalize beyond the second bromine atom. Similar trends are also observed for the 1,2,3-chlorobenzenes and 1,2,3-iodobenzenes. The smaller $\zeta$ value indicates the negative charge are more delocalized over the specific halogen atom. Such results further verified the rationality of the PEff model for polyhalogenated molecules.

![Figure 6.](image)

**Figure 6.** The HOMO orbitals of the 1,2,3-trichlorobenzene (a), 1,2,3-tribromobenzene (b), and 1,2,3-triiodobenzene (c). The smaller $\zeta$ value indicates the negative charge are more delocalized over the specific halogen atom.

**Conclusions**

The application of the PEff force field from monohalogenated molecules to polyhalogenated molecules require a sophisticated multi-objective optimization algorithm. This is especially true for the nonlinear parameters in the electrostatic interactions, since each covalent halogen atom requires four parameters. To keep forward compatibility, the monohalogenated molecules can still use least square method, while the poly-halogenated molecules required a cascade of actions of least square optimizations. This fitting protocol is accomplished by a simple series fusion operation. The electrostatic parameters are mainly affected by the chemical environment around the covalent halogen atoms for various ortho-, meta- and para- substituted benzenes. The fitted parameter sets are very reasonable and stable with certain physical significance. Although the calculation time
increase, the fitting protocol can be fully parallelizable with very high computational efficiency. Each fitting can be finished on the laptop. And computations can also be automatically extended to tens of thousands of halogenated homologues.

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Supporting information

Further details of the parameters are given in the supporting information.
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