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Deriving force field parameters for coordination complexes

Per-Ola Norrby *, Peter Brandt

Department of Medicinal Chemistry, Royal Danish School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen, Denmark

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* Corresponding author. Tel.: +45-35-306506; fax: +45-35-306040.
E-mail address: peo@dfh.dk (P.-O. Norrby).

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Abstract

The process of deriving molecular mechanics force fields for coordination complexes is outlined. Force field basics are introduced with an emphasis on special requirements for metal complexes. The review is then focused on how to set up the initial model, define the target, refine the parameters, and validate the final force field. Alternatives to force field derivation are discussed briefly. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Molecular modeling is rapidly gaining in importance in all areas of chemistry. Recent advances in computational methods now allow determination of geometry, energy, and/or electronic structure for many materials [1–3]. Various other properties can in turn be calculated from these, either directly by first principles methods, or using linear free energy relationships obtained by correlating calculated primary properties with reference data [4,5].

Methodology for molecular modeling can be divided into two groups: quantum mechanics (QM) and force fields. QM methods primarily determine the electronic structure by solving the Schrödinger equation or it's analogs. All other properties are then derived from the resulting wave function or electron distribution. Application of QM methods to metal complexes is an active field [6–9], but for the purposes of this review, QM results will only be considered insofar as they are relevant to derivation of force fields.

Force field methods ignore the electrons, and instead determine the relationship between energy and structure by application of empirical rules based on classical mechanics [10]. Force field modeling methods are also known as molecular mechanics (MM). Compared to QM methods, the main advantage of MM is the speed and simplicity. Even though rapid advances in electronic structure theory now allow approximate QM calculations to be performed for relatively large systems, MM methods are still several orders of magnitude faster. For applications where MM methods are well defined, the accuracy is better than low level QM calculations (e.g. semiempirical or HF) [11,12] and can match results from correlated calculations (e.g. MP2/6-311G**) [13]. The main drawback of MM is that the method is critically dependent on empirical parameters, generally determined for a small number of model systems. The accuracy of a subsequent application is therefore dependent both upon the quality of the original parameterization, and on the transferability of the parameters to a new molecular environment. When only part of the system can be treated with MM methodology, it is possible to use hybrid methods that divide the structure into QM and MM domains, combining some of the advantages of both methods [14–17].

In organic chemistry, MM is a mature science. Parameters exist for a wide range of structures. The requirements and expected accuracy for various applications are well understood [18]. In coordination chemistry, the picture is less clear. The range of structural motifs is much wider, and the flexibility is generally larger than for organic compounds [19–21]. Force field methodology has been successfully applied to many specific systems [4,22–25], and some general methodologies have been developed [26–28], but frequently each new application requires substantial methods refinement before an acceptable accuracy is achieved.

This review is intended as a help for researchers that need to develop a specialized force field for a specific application in coordination chemistry. Basic force field methodology will be briefly summarized, with an overview of the modification needed for application to metal complexes. The main focus will then be on tools for deriving new parameters, followed by a discussion on validation of the final force field. The intent is to provide pointers on how to introduce a new functional group in a force field, not to give a complete coverage. For examples of applications, and lists of available force fields, the reader is referred to the literature [1,22–25,28] and to the Internet [29].

2. Functional forms of molecular mechanics force fields

Empirical force field methodology is based on the fundamental assumption that the total ‘steric’ energy of a structure can be expressed as a sum of contributions from many interaction types (bond lengths, angles, distances, etc.), according to Eq. (1) [1,3,18,19,30–32]. It is furthermore assumed that the parameters derived for one moiety are transferable to other structures where the structural context is similar. The various interaction types will be discussed below, with notes on special requirements for coordination complexes.

$$E = \sum E_s + \sum E_b + \sum E_t + \sum E_{oop} + \sum E_{el} + \sum E_{vdW} \quad \left(+ \sum E_{other} \right) \tag{1}$$

2.1. Force field basics

2.1.1. Atom types

The basic unit of most force fields is the *atom type*, determining what parameters to apply for all interactions. For example, if two bonds or angles have the same constituent atom types, the same parameters will be applied. Parameters can be further differentiated by structural context (i.e. a bond between two sp^2 carbons can be either single, double, or of intermediate bond order).

Atom types should be *transferable*. As an example, consider two ethers, $\mathbf{CH_3OCH_3}$ and $\mathbf{CH_3OPh}$. The oxygen in the second structure will be conjugated with the aromatic ring, which surely will have an effect also on the **C–O** bond to the methyl group. To avoid an explosive increase in the number of parameters to determine, the oxygens in the two structures will still be considered to be of the same type, and thus to have the same parameters for the methyl **C–O** bond. Note, however, that different **C–O–C** angle parameters will be assigned for the two ethers, as almost any force field will assign different atom types for sp^2 and sp^3 carbons. The number of atom types to be used for each element will depend on factors like the amount and diversity of reference data available, the intended use of the force field, and the target accuracy.

2.1.2. Bond lengths

2.1.2.1. Harmonic bonds. Each bond in a structure will contribute a stretch term to the total energy. Bonds are characterized by a ‘reference’ length, and by a resistance to change from the optimum value, a ‘force constant’. Thus, at least two parameters are needed to describe each bond type. In the simplest case, bond energies are calculated by Hooke’s law, Eq. (2).

$$E_s = k_s(l - l_0)^2 \tag{2}$$

Theoretically, there is one type of bond for each pair of atom types, but in practice, only some of these will ever be determined. For example, force fields with a carbonyl oxygen atom type will include bonds from this to carbon, but rarely to anything else. Thus, the number of bond types in most force fields is only a few times higher than the number of atom types.

2.1.2.2. Anharmonic bonds. The simple Hooke's law can represent the energy increase on small distortions from the reference value. However, for large distortions, the energy of a true bond is better represented by a Morse function, Eq. (3).

$$E_s = D(1 - e^{-\alpha(l - l_0)})^2 \tag{3}$$

Eq. (3) shows a chemically correct elongation behavior, going asymptotically to zero upon dissociation. Note that in addition to the reference bond length l_0, Eq. (3) requires two more parameters: the dissociation energy D and a parameter α that together with D determines the curvature at the minimum (the apparent force constant). Thus, a wider range of reference data is needed for parameterization of Eq. (3). For organic structures, the distortions are small, making the difference between the functions negligible. For coordination complexes, on the other hand, the bonds are usually soft, resulting in large variations of the bond lengths [19]. In such cases, the additional accuracy gained from a well-determined Eq. (3) may well be worth the increase in complexity.

A correct representation of the energy of distorted structures is only one of the factors influencing the choice of functional form in the force field. Convergence properties are also very important to the efficiency of the model. In everyday use, an important task for force fields is to clean up severely distorted input structures to generate energy minima. Extreme distortions will generally not be found in the final structures, and therefore need not be modeled 'correctly'. It is more important that the chosen function generates a large correcting force to enable a more rapid convergence. From this point of view, Eq. (3) is not optimal, as the force goes to zero upon elongation. Some force fields solve this problem by using the harmonic Eq. (2) for distorted structures, switching to an anharmonic form when the structure approaches the minimum. MM3 instead uses a modification of Hooke's law corrected for higher orders [33], Eq. (4):

$$E_s = k_s(l - l_0)^2[1 + c_s(l - l_0) + q_s(l - l_0)^2] \tag{4}$$

The cubic and quartic stretch terms are chosen to mimic the Morse potential (Eq. (3)) for reasonable distortions, and are determined once for the entire force field. Thus, only two parameters need to be determined for each bond type. Eq. (4) seems to represent a good balance between computational efficiency and a proper description of the potential energy. Dinur and Hagler have proposed an alternate series expansion based on the inverse bond lengths, with all the favorable properties of Eq. (4), but following the true potential energy (as determined by QM calculations) over a wider range, Eq. (5) [34]. To our knowledge, this function has not yet been implemented in any available force field.

$$E_s = E_0 + C_2(l^{-1} - l_0^{-1})^2 + C_3(l^{-1} - l_0^{-1})^3 \tag{5}$$

2.1.3. Bond angles

The simplest approach to obtaining optimized angles close to the reference value is to introduce a quadratic energy penalty similar to Eq. (2), Eq. (6).

$$E_b = k_b(\theta - \theta_0)^2 \tag{6}$$

Two parameters are needed, a reference angle and a force constant. As for bonds, only a fraction of all the possible combinations of atom types correspond to angles found in chemical structures. Still, lack of accurate reference data sometimes forces the use of general parameters, like using a reference value close to 109.5° for all unknown angles around an sp^3 carbon.

Angles are softer than bonds, allowing large distortions in real complexes. This is especially true in coordination complexes, where introduction of steric bulk frequently can change observed angles by 10–20° or even more. To achieve a soft potential without losing the convergence properties for very large distortions, several force fields use extended series expansions similar to Eq. (4) for bonds, but to even higher orders [18,33].

A problem with all polynomial representations of angle energies is that angles of 180° will be described as cusps (unless the reference angle is exactly 180°). In a true picture, the 180° angle should represent a stationary point. To correct this, it is possible to use trigonometric functions [19,35,36]. An example of such a function is given in Eq. (7). This may again lead to convergence problems, as the correcting forces disappear close to the maxima, but for angles the real distortions can well make it necessary to pay that price.

$$E_b = k[1 + \cos(n\theta + \psi)] \tag{7}$$

We also want to note that it is possible to do without specific angle functions entirely. In Urey–Bradley force fields, angle forces are modeled by nonbonded interactions [18]. For purely organic structures, such force fields have fallen out of use, but for coordination complexes, the POS model uses this approach (Section 2.2.2).

2.1.4. Torsional angles

Torsions are even softer than bond angles; all possible values can be found in real structures. Thus, the energy function must be valid over the entire range. The function must also be periodic, and for symmetry reasons, should have stationary points at 0 and 180°. The simplest expression fulfilling these requirements is a cosine function, Eq. (8):

$$E_t = v \cos n\omega \tag{8}$$

The periodicity n is the number of minima for the potential, usually 3 for an sp^3–sp^3 bond and 2 for a conjugated bond. The parameter v is proportional to the rotation barrier.

The definition of a torsion includes two central and two terminal atoms. As a result, the number of possible torsional types is enormous. As for angles, when reference data for a particular type is lacking, it might be necessary to fall back on general parameters based only on the type of the two central atoms.

For a detailed description of a potential energy surface (PES), Eq. (8) might be insufficient, even if augmented with a phase angle. A more flexible description is obtained by utilizing additional terms from a Fourier expansion. It is also conventional to use the form depicted in Eq. (9), in order to set the minimum contribution to zero. Note that metal complexes may require higher terms (Section 2.2).

$$E_t = v_1(1 + \cos \omega) + v_2(1 - \cos 2\omega) + v_3(1 + \cos 3\omega) \tag{9}$$

2.1.5. Out of plane bending

In organic structures, the most important planar atoms are sp^2 carbons with three substituents. To keep the system planar, an energy term E_{oop} is added that increases the energy when one of the atoms deviate from the plane defined by the three others. Several functions have been implemented, for example improper torsions or Hooke's law functions [25,31]. The most important modification when moving to coordination complexes is that the plane of the ligands need no longer be exactly defined. For example, in square planar complexes it is necessary to define an average plane through the ligands (usually the least-squares plane). Alternatives to the regular out of plane function for square planar complexes have included deviation of the metal from the coordination plane [37], functions of the angle of each ligand with the normal to the coordination plane [35], or dummy atoms placed at the axial positions [38,39].

2.1.6. Nonbonded interactions

All interactions between atoms that are not transmitted through bonds are called nonbonded interactions. In addition, some force fields include through space interactions between points that are not centered on nuclei. Common non-atomic centra include lone pairs and other pseudo-atoms, and bond-center dipoles. By convention, interactions between atoms separated by only one or two bonds are not calculated [40]. Atoms in 1,4-position (i.e. with three intervening bonds) are unique in that they interact both via torsional and nonbonded potentials. The two types of interactions thus become partially dependent. To reduce this interdependence, nonbonded 1,4-interactions may be scaled.

2.1.6.1. Electrostatic interactions. The simplest possible treatment of electrostatics is to view all charges as centered on nuclei, and calculate resulting energies from the well-known Coulombs law, Eq. (10):

$$E_{el} = \frac{q_i q_j}{\varepsilon r} \tag{10}$$

To implement this scheme, a charge must be determined for each atom. The charge assignment may be done by fragment matching [41], by considering contributions through bonds [42,43], and possibly the geometry of the molecule (Section 3.1.4) [44]. A major problem lies in the fact that atomic charges are not observables, and it is not always possible to find one set of charges that will reproduce all properties of interest. For most major force fields, one charge determination scheme has been adhered to in the development of the remaining parameter set. Following these rules when adding new functions will generally lead to an internally consistent method. QM calculations are generally a good source of data for electrostatic parameters, as several well-defined methods exist for deriving charges. However, electrostatics of metal complexes are less well known. Any implemented charges should be subjected to extensive validation.

Eq. (10) contains a dielectric constant, ε, which theoretically should be 1 for in vacuo calculations. In reality, the charges will be subject to screening by other parts of the structure or by the environment. Using a higher value for ε, thus reducing the contribution, might be regarded as the simplest possible solvation model. It is also possible to argue that the screening should be proportional to the distance. The resulting distance-dependent dielectric model is computationally efficient, and allows tighter cutoff functions due to the more rapid, quadratic falloff of the interaction. However, the physical validity of the model is doubtful.

In the Allinger force fields, the major part of the electrostatics arise from bond-center dipoles, Eq. (11) (χ is the angle between the dipoles; the αs are the angles between each dipole and the connecting vector) [18]. This form requires that a dipole parameter is determined for each bond type, but avoids implementation of a charge scheme dependent on bonding environment. The cubic falloff with distance also has the result that possibly non-physical long-range interactions are avoided. On the other hand, the computational implementation is less efficient.

$$E_{\mathrm{el}} = \frac{\mu_i \mu_j}{\varepsilon r^3}(\cos \chi - 3 \cos \alpha_i \cos \alpha_j) \tag{11}$$

2.1.6.2. van der Waals interactions. In addition to electrostatic contributions, nonbonded interactions also contain a short-range repulsive exchange component, and an attraction due to London dispersion. The balance between these result in a shallow energy minimum at the van der Waals distance. A commonly employed functional form is the Lennard–Jones potential shown in Eq. (12).

$$E_{\mathrm{vdW}} = \frac{A}{r^{12}} - \frac{B}{r^6} \tag{12}$$

The two constants A and B are calculated from a set of atomic radius and hardness parameters. Generally, the minimum should come at the sum of the two atomic radii, and the well depth is the geometric average of the atomic hardnesses, but other combination rules exist [27,43,45].

The inverse power of six in the attractive component is the theoretical distance dependence for a pair of resonating induced dipoles, and is used by most force fields. It has been argued that the repulsive component in Eq. (12) is too hard. An exponential falloff is more consistent with certain experimentally observed short contacts, resulting in the Buckingham potential shown in Eq. (13).

$$E_{\mathrm{vdW}} = A\ \mathrm{e}^{-\alpha r} - \frac{B}{r^{6}} \tag{13}$$

The constants are again calculated internally from atomic parameters to give the desired position and depth of the potential.

2.1.6.3. Hydrogen bonding. Hydrogen bonding is an area of active research. Some force fields trust the other nonbonded potentials to reproduce hydrogen bonds, possibly by inclusion of specific pair parameters [46]. Others use special potentials for nonbonded interactions between hydrogen bond donors and acceptors [47], sometimes with an angular dependence [48].

2.1.7. Modifiers

Using a large number of different atom types will enable a high precision in the force field, but may result in a very unwieldy method. Accuracy is therefore sacrificed by combining atoms in related moieties into one ‘average’ atom type. However, the various force field terms differ in their sensitivity to structural environment. It is known that bond lengths vary significantly on substitution, even in purely organic compounds. To reproduce this effect, different atom types might be used for all possible substitution patterns, but this would also result in an extreme increase in the number of angle and torsion parameters to determine. A more flexible way to the same end is to introduce substituent modifiers. A good example is the *electronegativity effect* in the Allinger force fields [49]. In this scheme, substituents will modify the reference bond length, with effects of multiple substitution being slightly reduced. This will necessitate the determination of a substantial number of new bond modification parameters, but as the number of atom types can be kept low, the number of other parameters does not increase. A similar substituent dependence has been used for reference bond angles, mainly based on the number of attached hydrogens on the central atom [18]. It should be noted that an alternative method is to use an atom type replacement scheme, whereby the number of atom types can be high for bond lengths only, but low for other parameters.

For conjugated systems, another type of modifier comes into play. Both the length and the barrier to rotation of a conjugated bond is strongly dependent on the bond order. In simple cases, force fields just rely upon user identification of bond order (e.g. differentiating between single, double, and aromatic $C(sp^2)–C(sp^2)$ bonds). It is also possible to use fragment matching, determining separate parameter sets for each environment [42]. However, a more flexible (if also more time consuming) approach is to calculate the π-bond order for the conjugated system by simplified QM methods [50–52]. This requires additional functions for interpolating parameters depending on bond order, but enables reproduction of effects of remote π-active substituents and geometry changes [53].

2.1.8. Additional terms

The terms described above are generally sufficient for finding positions of energy minima, that is, for optimization to good structures. However, at other points on the PES, or for very strained structures, nonlinear effects are more noticeable. This is especially important in vibrational spectroscopy, where the shape of the PES around the minimum must be very accurately represented. A substantial improvement can be achieved by introduction of cross-terms (also called off-diagonal terms). The importance of these in vibrational force fields has been amply demonstrated [31]. For very strained structures, the cross terms may also have an appreciable effect on structure. Hagler et al. have even demonstrated that inclusion of enough cross terms allows a reduction of the number of atom types (e.g. by dispensing with the need for separate small ring atom types) [43]. Cross-terms are exemplified here by the stretch-bend term (Eq. (14)). The structural effect of this term is to elongate bonds in angles that are severely compressed. For further information on possible cross-terms we refer to the literature [31], but we want to note that an accurate determination of many off-diagonal parameters require extensive reference data on the PES, preferably QM normal modes and non-stationary point data [43].

$$E_{\mathrm{sb}} = k_{\mathrm{sb}}(\theta - \theta_0)(l - l_0) \tag{14}$$

2.2. Coordination complexes

Some of the special requirements in coordination force fields have been noted, like the need for an accurate description of the PES far from the minimum due to the very soft bonds and angles. In this section, we will concentrate on the additional problems introduced by high and flexible coordination modes.

Most organic atom types are highly symmetric. For example, an sp^3 carbon is basically tetrahedral, with an angle close to 109.5° between all substituents. For this reason, all organic force fields were initially developed with the limitation that only one reference angle can be specified for each set. In an octahedral complex, it is obvious that at least two types of reference angles are needed for each ligand–metal–ligand combination, one close to 90° and one close to 180°. A matching scheme is also required to assign which ligands are *trans* to each other (unless separate atom types are used for ligands on the three different axes). This problem is aggravated in pentacoordinate complexes, in particular if the coordination mode can switch between trigonal bipyramidal and square pyramidal in response to steric effects.

Metal complexes frequently also include π-system ligands, with high rotational flexibility [54,55]. Any scheme that relies on bonds to each atom in such ligands will encounter the problems just described [22].

Approaches to solving reference angle problems include matching schemes, treatments ignoring the metal–ligand bonds or just the metal-centered bond angles, functions with multiple minima, and bonding via pseudo-atoms.

Torsional potentials may also require special functions in metal complexes. For example, in octahedral complexes with similar ligands, the symmetry ensures that torsions around the metal–ligand bond are at least 4-fold, requiring a term with $n = 4$ (Eq. (8)) [56].

Ligands in coordination complexes will affect each other through simultaneous interactions with the metal d-orbitals, leading to *trans*-influence and Jahn–Teller effects. Such effects can be handled by addition of extra terms to the force field, sometimes implemented as a direct interaction potential [56] but more commonly as complex cross terms including both bond length and angle contributions [57–59].

2.2.1. Bonds-free coordination

The simplest way of treating metal coordination is to use solely nonbonded interactions, treating the metal–ligand bond as arising from a combination of electrostatic and van der Waals contributions. This has the added advantage of allowing dynamic ligand exchange. However, orientation effects imposed by the metal are completely lacking in the model. Thus, applications are in practice limited to metals without an orientational preference, like the alkali cations [60], or any complex where the geometry is determined solely by ligand–ligand interaction (similar to the POS model, vide infra). Modification of a few atomic parameters (i.e. the van der Waals radius and hardness) may be sufficient, but it may also be advantageous to use specific atom-pair potentials [26,61].

2.2.2. POS

The next step in complexity is to include all metal–ligand bonds, but ignore all metal-centered angles [62]. Torsions including the metal–ligand bond may or may not be included in the model. The coordination geometry is solely determined by ligand–ligand interactions. Structures where the metal directs the coordination, like square planar complexes, cannot be modeled by this approach without addition of specific planarity terms. The POS model is easily combined with bonds-free coordination of certain ligands.

2.2.3. Covalent models

Using a full bonding model with standard potential energy functions introduces angle assignment problems. Several schemes exist for matching angles with the proper parameters, sometimes based on user assignment, but more commonly based on the actual angles in the starting geometry. This is the most common approach with reasonably rigid and well-defined systems, like octahedral complexes. However, in many cases, the angles should be allowed to vary over a wide range of values without undue energy increase (e.g. when Berry pseudo-rotation can occur). Special problems are introduced by π-ligands; these are generally treated by a POS-model or by a pseudo-atom approach.

An alternative approach is to use trigonometric functions for the angles (Eq. (7)). For metal complexes, there are several advantages to this approach. By a proper selection of functions, several minima can be created, corresponding to most common coordination modes [19,35,36]. As an added advantage in soft systems, large angle distortions can be accommodated. Finally, cosine expansions do not display cusps on the PES (as most angle matching schemes based on polynomial functions are prone to do).

2.2.4. Pseudo-atom approaches

In some models, it is advantageous to add bonded entities that do not correspond to real atoms. These are called pseudo-atoms, or dummy atoms. They have two main uses in force fields. The most common is to add nonbonded interactions to points that are close to, but not at a nucleus. This has been done to represent lone pairs [18], but also to ensure a proper geometry of square planar complexes by completing the coordination sphere to a proper octahedron [38]. The second important use of pseudo-atoms is to provide anchor points for bonding. In particular π-ligands are commonly modeled by a bond from the metal to the centroid of the ligand [22,55]. Pseudo-atoms have also been added between metals and normal ligands to allow 'banana-like' distortions where the electron pair of a ligand can point at a position offset from the metal [39].

2.3. Generalized force fields

The potential functions described in the preceding sections require a large number of parameters. Deriving parameters for all relevant atom type combinations is a daunting task even if the target group is common organic molecules. In the area of coordination chemistry, a complete set of accurate parameters will not be produced in the foreseeable future. Thus, each new study will require an initial model development. The aim of the current review is to simplify this task, but we also want to point out that alternative approaches exist. For example, many force fields employ parameter substitution schemes that ensure that *some* parameter will finally be found for any complex. A more complex approach is to include a rule set for deriving all other parameters from a small set of atomic parameters. An example of an extensive current implementation is the UFF force field by Rappé and coworkers, which is able to treat all elements in the periodic table [27,28]. In this context, we also want to mention VALBOND, developed by Landis et al. [63] based on Paulings valence bond theory. It has recently been shown that VALBOND is able to predict very complex coordination geometries [64].

3. Methods for deriving parameters

So far, we have looked at alternative forms of force fields, and what parameters are needed. We will now turn to ways of determining good parameter values for previously undefined or badly defined systems. Before embarking upon a parameterization project, the following questions should be considered:

- What is the goal of the force field? What accuracy is needed for structures? Do conformational energies have to be accurately determined? For some applications, a reasonable structure is all that is needed. If so, it is even possible that an existing force field with generalized parameters can fulfil the goal. At the other extreme, if accurate vibrational modes are to be predicted, it is necessary to reproduce not only relative energies of minima, but also the entire PES for distorted structures.

- What functional form is needed? This is very dependent both upon the goal and upon the type of complex to be calculated. Reasonable structures of octahedral complexes can be achieved with relatively simple functional forms, but accurate barriers to pseudorotation, or sterically induced distortions in coordinatively unfilled complexes (e.g. distortions from planarity in square planar complexes) require an accurate and flexible definition of metal-centered angles.
- What reference data can be obtained? It must always be realized that force fields are empirical, and can never be better than the data that went into creating the force field. Structural data is a necessity, as all other types of molecular modeling predictions depend on good structures. Furthermore, accurate relative energies and other properties require that the relevant type of data has gone into the parameterization. Any prediction that could be seen as an extrapolation outside the defining data set should be carefully validated.

A flow chart outlining the parameterization procedure is shown in Fig. 1. Several of the steps will be outlined in subsequent sections. In real life, a project is seldom as simple and linear as shown in the chart. For example, the functional form is frequently updated during the process, by adding, removing, or changing specific terms. Additional data may also be included during the process.

3.1. Reference data

The goal of a parameterization effort is to fit the model as closely as possible to the input reference data. With a perfect functional form and optimal parameters,

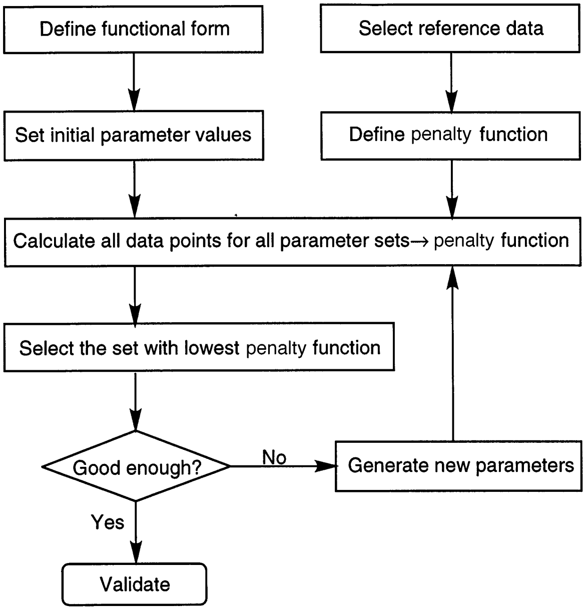

Fig. 1. Parameterization flow chart.

the results from the model will correspond to averages in the training set. Thus, any data used in the parameter refinement should be carefully validated. It is advantageous to include a spread over diverse structural types, but not so diverse that it becomes impossible for the chosen atom types to represent the entire set. A large set of data will also reduce the influence of nonsystematic errors.

The primary goal of most force fields is to yield accurate structures and energies. These two properties are a prerequisite of all others. Energies can be further divided into two types: conformational energies, that is, energy differences between stationary points on the PES, and distortion energies for nonstationary points on the PES. The former will influence any property where more than one conformation might contribute, whereas the latter are important in vibration analysis and dynamic simulations.

Force field calculations basically model an isolated molecule in vacuo, with a condensed phase environment added as a perturbation. Therefore gas phase data is preferred in the parameterization. However, in particular for metal complexes, most of the available reference data has been determined in condensed phase. Furthermore, experimental solution properties are generally averages over several conformations. It is often assumed that effects from the environment and population distributions are nonsystematic and will cancel out if the data set is large enough. On the other hand, environmental effects and population distributions could be included already in the parameterization process, at the cost of longer simulation times [65,66]. An alternative and possibly more efficient approach is to adjust the data to approximate gas phase values by calculating the difference between gas phase and solution using a tentative force field. The procedure lends itself to iterative improvement as the force field is optimized, while still reducing the number of fully solvated calculations to be performed.

There are two major sources of reference data for a parameterization: experiment and QM calculations. Experimental data has one big advantage: force fields will reproduce the type of data that has been input, and predicting experimental data is generally more useful than predicting QM data. However, most experimental data has the drawback of being determined in condensed phase. In addition, experimental data must be corrected for differences in paradigm. Relative force field energies are measured as the difference between energy minima, whereas experimental energies may contain vibrational and entropic contributions. For structures, force fields are concerned with position of nuclei, whereas for example X-ray crystallography determines points of maximum electron density [67]. QM results, on the other hand, are eminently suitable for parameterization. QM calculations deliver the same type of modeling data that is desired in force field model, i.e. in vacuo potential energy surfaces based on the position of nuclei. Furthermore, QM calculations can easily yield data on non-stationary points on the PES [43], as well as electrostatic properties [68]. It should be realized though that the target accuracy of force field modeling (frequently 1–2 kJ mol^{-1}) [12] is high. Therefore, it must be ensured that the QM calculation of reference data is performed at a high enough level to avoid deterioration of the force field results. The HF/6-31G* level of theory has been employed frequently in parameterization of organic structures [43,69], but the more recent work by Halgren utilizes correlated levels of theory [13]. For metal complexes, electron correlation in combination with flexible basis sets is highly recommended. Hybrid DFT methods (e.g. B3LYP) have found much recent use [56,70,71]. For heavier elements, relativistic effects have been found to have a profound influence [72,73]. These effects can at least in part be incorporated through the use of quasi-relativistic ECPs [7,8].

Due to the differences in quality of input data, and based on the aim of the force field, deviations should be weighted before evaluation (Section 3.3.1). It should also be noted that most existing force fields include a specific paradigm for source data. For example, the MM2 force field was largely based on experimental gas phase observables [18], whereas the MMFF force field almost exclusively relies on high quality QM calculations [13] and the CFF93 force field utilizes a combination [74]. When new functionality is added to an existing force field, the existing paradigm should be adhered to as closely as possible. When this is impossible (e.g. due to lack of gas phase data for metal complexes), it may be necessary to find new sources of data, but the correspondence of such data to existing force field results should be verified. An example includes determination of charge data for metal complexes in the MM3* force field, where CHELPG charges [75] were found to be suitable after minor modification [56,70].

3.1.1. Structural data

For parameterization, gas phase structures are preferred, but frequently not achievable. With the caveats in the preceding section in mind, QM structures furnish suitable data. However, the most common source of structural information is found in X-ray structures. The crystal environment will always affect the structure, so it is important how structures are compared. Soft modes, like torsions and long-range distances, are easily distorted in crystals, whereas bonds and angles are more resistant. Thus, all-atom overlays should not be used as a measure of the parameter quality. It is better to compare bonds and angles directly, and possibly also torsional angles, albeit with a lower weight [76]. This also allows an extraction of only relevant data from reference structures. For example, in deriving parameters for a metal–ligand bond, data about distant intra-ligand bonds and angles do not contribute any useful information. Long range information might also be included, for example in the form of interatomic distances, but should be scaled down for long distances and generally be given a low weight [71].

Force field bond lengths correspond to the position of a potential energy minimum for nuclei. Experimental structures generally yield bonds that are based on different paradigms, including contributions from vibrational averaging and other effects. For very accurate structures, these effects become important. The interested reader is referred to the literature for a detailed discussion of these effects [18,77].

In the absence of accurate energy data, variations in structure between related compounds may also yield information about energy-related parameters, like force constants. For example, studying the response of one type of bond length to different structural environment, the *average* observed length should be related to the reference length, whereas the *variation* in observed lengths is dependent upon the bond force constant [78].

3.1.2. Conformational energy data

The relative energy between different minima is very sensitive to force constants, torsional profiles, and nonbonded interactions, and is therefore a good probe for the internal balance in a force field. For good accuracy, it is important to convert between the various types of energies available. Experimental energies most often include thermal contributions, and sometimes averaging over several contributing conformations, whereas force field steric energies correspond directly to differences between potential energy minima. Most types of energies can be derived from force fields (by normal mode analysis and Boltzmann averaging), but the calculations can be time consuming. As with environmental effects (vide supra), the relevant difference between steric and experimental energy can be determined a few times during the parameter refinement, and used to correct the reference energy, until convergence is achieved, alleviating the need for costly recalculation of all energy contributions. QM potential energies on the other hand may be compared directly to force field energies.

3.1.3. PES data

If conformational energies are diagnostic of the balance between parameters, the local PES around a minimum yields detailed information about absolute values of force constants. PES information can be obtained experimentally from vibrational spectroscopy (mainly IR and Raman, but also other types of spectroscopy that show a vibrational fine structure). However, for all but the simplest structures, the assignment problem can be overwhelming, severely limiting the usefulness in parameterization. The same type of information can be obtained from QM calculations, and here the assignment is trivial. It is advantageous to use the underlying raw data, the Cartesian second energy derivatives (the Hessian) directly as source data [13,31,43,76,79]. Goddard et al. have demonstrated how the reference data might be improved by replacement of the QM eigenvalues with the experimental counterparts, keeping the QM eigenvectors unmodified [80]. Hagler et al. [43], and later Halgren [13], have based extensive parameterization efforts largely on QM first and second energy derivatives. For metal complexes, the same type of methodology has been used by Norrby et al. [56,70,71]. In this type of parameterization, exactly the same structures should be used without minimization both in QM and force field calculations. It was demonstrated that when using QM energy derivatives for a large number of distorted structures, the parameterization no longer required inclusion of explicit structural information [43], since the first derivatives where automatically zeroed at the position of the energy minimum by the refinement procedure.

A special case of PES data is rotational profiles for torsions. A fully relaxed profile from a QM scan should be compared to a relaxed force field calculation at the same points. However, using relaxed scans introduces the possibility that erroneous contributions from other types of parameters are compensated by a refinement of torsional parameters. To remove such dependencies, torsions could better be parameterized from rigid rotation calculations [81], removing dependencies on all but nonbonded parameters and, if present, torsional cross-terms. In addition to the higher quality, there is also the serendipitous advantage of more rapid single point calculations, both in QM and in the parameter refinement cycle.

3.1.4. Charge data

Electrostatic schemes in force field calculations are primarily based on static atomic charges or bond centered dipoles, but higher order multipoles have also been used [82]. These are not observables, and therefore have to be assigned based on secondary observable properties, like molecular multipoles [18] or solvation properties [83]. Charges and multipoles may be computed quantum mechanically, but again depend on a user-selected scheme for assigning the calculated electron density to specific atoms or bonds [68]. The final selection of electrostatic scheme depends strongly upon the intended application of the force field. However, in the large majority of cases, the primary function of the electrostatic contribution in the force field is in nonbonded interactions with remote fragments or the environment. In such cases, the chosen scheme should as closely as possible reproduce the electrostatic properties of a fragment as seen from outside the molecular surface. Several methods exist for assigning atomic charges and higher multipoles from QM-calculated electrostatic potentials [68]. To reproduce accurately the gas phase electrostatic properties of a molecule, it is necessary to use correlated levels of theory, but it has been argued that for organic molecules the lower quality HF method actually gives a better picture of condensed-phase charges, where a polarization is induced by the environment [69]. However, for metal containing complexes, a correlated method is probably a necessity.

The electrostatic properties of a molecule will change with environment and geometry. Such changes must be modeled for an accurate representation of certain through-space interactions [84,85] There is currently an increasing interest in force fields incorporating environmentally dependent electrostatics (polarizable force fields) [44,84,86]. Parameterization of such schemes require a very diverse data set, usually augmented with QM-calculated polarizabilities [86].

3.1.5. van der Waals data

The influence of non-electrostatic through-space interactions is most noticeable in intermolecular interactions, and thus require data reflecting supramolecular interactions strengths. Refinement of such data may require condensed-phase simulation, for example when heats of sublimation [87–89] or crystal cell constants [89–91] are used as reference. The balance with electrostatic interactions is very important, as is demonstrated in parameterization of water models [83]. Frequently, metals are buried deep enough in coordinating ligands that van der Waals interactions can be neglected. If so, any reasonable literature values for radii can be used. However, it has been possible to optimize van der Waals parameters for crowded systems where intramolecular repulsion becomes significant [39,92].

Note that van der Waals parameters should *not* be derived from production level QM data. The important London dispersion cannot be represented by calculations like HF and most forms of DFT. In addition, QM evaluations of intermolecular interactions are very prone to basis set superposition errors (BSSE), which are frequently larger in magnitude than the van der Waals interactions. High level calculations with large basis sets *can* be used, but generally only for small model systems [45,93]. With the rapid current advances in electronic structure methods, this situation is likely to change, but for the time being, it is recommended that metal van der Waals parameters are obtained from the literature [27,94,95] or derived from experimental data [39,92,96].

3.1.6. Transition state data

Force fields need not necessarily be applied only to the prediction of energy minima. In the estimation of reactivities, it is entirely possible to use force fields to describe also transition states [97] and even non-stationary points on the PES [98]. An entire separate area is to define force fields that describe transition states as minima, allowing easy determination of alternative transition state conformations and relative energies [99]. As very little experimental data is available for transition states, in particular the structures thereof, such parameterizations rely heavily upon QM model systems. The derivation of TS force fields, even for metal catalyzed reactions [71], has been detailed elsewhere [100,101].

3.2. Estimating parameters

The automated refinement cycle in Fig. 1 will improve existing parameters, but in order to start the cycle, a full set of parameters must first be estimated [78,102]. In order to improve convergence, the estimates should be as close as possible to the final values. A badly chosen initial set may even cause the refinement to find a non-physical local optimum. It may also be advantageous to optimize subsets of the parameters separately, especially in the initial stages of the refinement. Estimation of initial parameters is largely based on experience, but some methods for the selection will be outlined here. In some cases, these methods of estimation are similar to what is used in generalized force fields.

The most important goal of the initial estimate is to achieve ‘reasonable’ structures for all molecules in the training set. For very bad parameter sets, the observed structures may no longer correspond to minima on the PES. In such cases, the risk of falling into a false ‘local’ parameter optimum is increased. Thus, it may be necessary to modify some parameters by hand until the structural agreement with the training set is sufficient.

3.2.1. From related parameters

The reason for dividing elements into several atoms types is that different parameters apply in different structural environments. However, the atom types may still be similar enough that parameters for one type may provide a good initial estimate for another type. Several existing force fields employ extensive replacement rules in order to find some parameter for any interaction. The quality of such estimates is dependent on the similarity between the atom types, but also on what type of parameter is being estimated. For example, for bond angles and torsions it is mainly important that the hybridizations of the central atoms are the same, whereas a correspondence in bond length depend upon the similarity in covalent radii of the atoms, and electrostatic parameter transfer require a compatible electronegativity. For van der Waals interactions, related parameters can generally be found in the literature [27,94,95].

3.2.2. From reference data

Several clues to initial parameter values can usually be gleaned from the input data. For example, reference bond lengths and angles should usually be set close to the average of the observed values. From the variability in the data set, and manual inspection of the structures, it is frequently also possible to guess the strain and the stiffness (corresponding to the force constant). In fact, a very efficient initial correction can be obtained by plotting calculated versus observed bond lengths, and then correct the initial estimate from the slope and intercept of the regression line [78]. A similar procedure can be applied to bond angles, but linear dependencies may introduce complications. As a simple example, consider the H–C–H angle in methane. Any initial guess for the reference angle greater than 109.5° will yield the observed tetrahedral structure, irrespective of force constant, and thus no correction will be obtained. This is a general problem in any derivation of angle parameters, and it is usually necessary to introduce the additional requirement that observed angles should be considered relatively unstrained (Section 3.3.2.3).

Torsional parameters can be estimated from the position of observed minima and rotation barriers. Even when the force field employs multi-term Fourier expansions (Eq. (9)), the local symmetry of the central bond will usually identify one term as the main contributor. All other parameters can then be set initially to zero, and added late in the refinement. Note that unless special attention has been paid to a torsional parameter in the initial selection of reference data, the variation may not allow determination of more than one term.

QM-derived reference data usually allows a very straightforward assignment of initial parameter values. For systems with low strain, QM-calculated bond lengths and angles may be used directly as initial reference values. Force constants may be assigned directly from QM normal mode analyses. For rigid-rotor torsional profiles, the difference between force field and QM energies (for exactly the same structures) can be calculated using zeroed parameters. Good initial values for the constants in Eq. (9) can then be obtained by a simple linear regression [81]. Atomic charges and possibly higher multipoles can be directly assigned by fitting the QM-calculated electrostatic potential, or by rules for dividing the electron density among participating atoms [68]. Here, we want to note that the paradigm of certain force fields (e.g. Amber [41]) requires that charges are assigned directly [69], and not further refined.

3.2.3. Rule-based

Some recent force fields, in particular UFF [27], are based entirely upon rules for calculating all required parameters from atomic constants, thus dispensing with the need to determine interaction parameters. However, the rules will by necessity fit only the target functional form, and may not be transferable to other force fields. Application of existing rule sets to new force fields should at the very least be validated by comparison to existing parameters. In some cases, a simple scaling may be sufficient.

Simple rule sets will be exemplified here by examples taken from the MM2 and MM3 force fields [95], but several other rule sets exist [27,103]. Bond lengths are set to the sum of covalent radii, whereas reference angles and torsional parameters are based on the hybridization of the central atom(s). Electrostatic parameters can be derived from electronegativities [103]. For force constants, Badger has based an empirical function on large sets of observed bond lengths [104].

Other types of rules are based on automatic selection of similar, existing parameters, as exemplified in the preceding section. In general, this means replacing an atom type with first others of the same element, then similar elements, until a match has been found.

3.3. Refining parameters

After selection of a functional form and a training set of data, and estimation of initial parameter values, the parameters should be refined to their optimal values. Traditionally, this has been done by hand for one observable at a time [30]. The great advantage of this approach is that it generates a strong familiarity with the data. Each data point will be considered and evaluated in turn, possibly leading to identification of deficient or even faulty data. However, such consideration requires much time, and may well run into a separate research project over several years. With the current explosion of combinatorial methods and high throughput screening, a field may well be exhaustively investigated experimentally before a working computational model has been developed. For specialized force fields, targeted for one specific type of complexes or one project, it may therefore be necessary to utilize more rapid, automated methods for parameter refinement.

3.3.1. Parameterization objective

To implement an automated procedure, it is necessary to define the objective of the parameterization mathematically. Thus, for each parameter set is defined a penalty function [105], generally the sum of squares of all deviations of calculated force field data from the training set. In equation 15, χ^2 is the penalty function, y_i is the calculated force field value for point i, y_i° is the corresponding reference value, and w_i is a weight factor. With this definition, the optimum force field is one for which the penalty function is at a minimum with respect to all possible parameter variations.

$$\chi^2 = \sum_i^N [w_i(y_i - y_i^{\circ})]^2 \tag{15}$$

Even though the overall form of the penalty function is simple, the exact definition is still problematic. Different types of data must somehow be weighted and transformed to a common unit (customarily, the penalty function is unitless). The need for some type of scaling is obvious if one compares bond lengths and angles; a deviation of 1 Å should surely be considered more serious than 1°. The weight factors in Eq. (15) can be seen as consisting of three parts; a measure of importance of the type of data, a conversion to a common unit of measure, and a quality compensation for different sources of data [78]. Several factors must be considered when selecting a weighting scheme. The most important is the intended target; the data most highly weighted in the parameterization will generally be best predicted by the final force field. However, downweighting the structural data too much will cause a deterioration of all other properties. Also, the functional form must be complete enough to allow reproduction of the reference data. For example, including vibrational data in the parameterization of a force field lacking sufficient cross-terms might lead to a deterioration in predictivity for *all* properties [76]. Such data might still be desired in order to improve the force constants, but should then be given a low weight in order not to affect parameters for which reliable data already exists within the training set.

Hagler and coworkers [43] used an automated parameterization routine in the derivation of the CFF93 force field. Their initial refinement was based entirely upon QM data for several points on the PES of each molecule in the training set. They utilized calculated energies together with Cartesian first and second derivatives of the energy for each structure, with the weight factors ca. 122:10:1, respectively [106]. Halgren utilized the same method in the derivation of MMFF [13].

Norrby and Liljefors recently introduced a general parameterization scheme allowing inclusion of any type of reference data [76]. In refinement of the MM3* force field, bond length deviations of 0.01 Å were considered equivalent to deviations in angles of 0.5° and in torsional angles of 1°. Thus, the relative weights 100:2:1 were used in the penalty function. This example demonstrates an easy to use, intuitive standard; using the penalty function definition in Eq. (15), the weight factors could simply be the inverse of the acceptable error in each data point. For example, if reproduction of bond lengths to within 0.01 Å is satisfactory, an appropriate weight factor is 100 Å^{-1}. Using this convention, the penalty function becomes unitless, with an admissible deviation of 1 for each data point. It then follows that at the optimum $\chi^2 < N$, i.e. the residual unitless error is lower than the number of data points. In practice, this goal is seldom achieved, as a few large errors can have a disproportionate influence in a sum of squares, but it will serve as a target. The mean absolute deviation (MAD, Eq. (16)), on the other hand, should go below 1 in a well-defined refinement. Other criteria for convergence are outlined in later sections.

$$\text{MAD} = \frac{1}{N} \sum_i^N w_i |y_i - y_i^{\circ}| \tag{16}$$

In work by Norrby et al. [70], deriving MM3* parameters for metal complexes, weight factors were further differentiated according to source and quality of the reference data. When high quality reference data is scarce, it may be necessary to augment the training set with data of lower quality. To avoid an undue influence of deviations that may in fact be caused by inferior data, it is advisable to lower the weight of such points. Obvious errors, possibly identified by strong deviations in partially optimized force fields, should of course be removed from the training set. If the data is expected to include unidentifiable but large errors, it might be proper to make the refinement more robust by basing it on absolute deviations (like Eq. (16)) instead of squared deviations (Eq. (15)) [107].

Different sources of data may show systematic deviations. As an example, bond lengths from HF/6-31G* structures will reflect potential energy minima, with a slight underestimation of bonds to hydrogens due to missing polarization in the basis set, whereas bonds from gas phase electron diffraction will include rovibrational contributions. If the force field is intended to reproduce one type of structures, data from other methods could be corrected to the appropriate type [18,77], or included as is with a lower weight factor [70].

3.3.2. Parameter refinement techniques

When a training set has been selected, initial parameters estimated, and the objective defined, it is time to refine the parameters. Very simply, this is done by varying all parameters, evaluating all data points with the new force field, calculating the penalty function, and selecting the parameter set which has so far yielded the lowest penalty value. This type of model optimization has been extensively described in the literature [107]. A few of the methods that have been implemented for force field refinement will be outlined here.

For a computational chemist, it is probably easiest to think of parameter refinement as analogous to geometry optimization. The techniques are very similar, the only difference is variation of parameters to minimize a penalty function instead of variation of coordinates to minimize the energy. Model optimization techniques can be divided into those that do not need any information beyond the penalty function, and those that require derivatives of χ^2 with respect to each parameter (corresponding to geometry optimization without and with gradients, respectively).

3.3.2.1. Refinement without gradient information

Grid searches. The brute force approach to parameterization is to test all possible combinations of parameter values using a grid. In the most basic implementation, this method scales with the power of N, and thus is only applicable for small subsets of parameters. With iterative cycling through subsets and automatic adjustment of grid spacing, the methodology may still be applied to reasonably large sets.

Monte Carlo. Random variation of the parameters have been applied to derivation of metal force fields [54]. This technique can be efficient for searching large volumes of parameter space, and is easily implemented. Convergence to the minimum is generally slow, but can be improved by simulated annealing techniques [107].

Simplex. The very robust Simplex tool can be applied to any model optimization where the number of variables is small [76,107]. As a guideline, the convergence is generally considered to become too slow with more than ten variables. Basically, a *simplex* (the hypervolume analogue of a tetrahedron) is defined in parameter space as consisting of $N+1$ linearly independent points. The points are ranked according to the penalty function, and a new point is defined by reflecting the worst point through the centroid of all other points. Based on the penalty function value in the new point, the step can be accepted, expanded, or contracted. The best of the new points replace the discarded worst point, defining a new simplex. It has been noted that if the position of the centroid is weighted by the penalty functions values of all contributing points, convergence is accelerated, making the method competitive for up to 30–40 variables [76]. The robustness also makes the Simplex method a valuable adjunct to derivative-based methods for linearly dependent or otherwise troublesome parameters (Sections 3.3.2.2 and 3.3.2.4).

Other methods. Genetic algorithms have become increasingly popular in many types of methods development. Application in parameterization requires estimation of several initial parameter sets, and rules for recombining and mutating the sets. Each ‘generation’ produces several ‘descendants’. Selection of the next generation can then be based both on the penalty function and on diversity criteria. Like the Monte Carlo technique, GA may be used as a tool for finding global optima. In a recent implementation, convergence was speeded up by training a neural network to reproduce the penalty function for new parameter sets [108]. Artificial neural network techniques have also been applied to the prediction of force constants [109]. Usage in force field development has been sparse, but may increase as suitable tools become available.

3.3.2.2. Utilizing derivatives of the penalty function. The gradient of the penalty function with respect to the parameters defines the optimal direction of change. Convergence can be accelerated if information about the curvature is also included (the matrix of second derivatives, the Hessian). Many methods have been described in the literature [107]. We will first cover some problems in determining derivatives of the penalty function, whereupon we will give a brief outline of some of the major optimization methods.

Determining penalty function derivatives. Using the chain rule, the first and second derivatives of the penalty function with respect to parameters can be expressed in terms of first derivatives of each data point, Eqs. (17) and (18). The neglect of the second term in the chain expansion in Eq. (18) is due to the expectation that the difference between calculated and reference data points are randomly distributed around zero, at least in the final stages of the refinement [107,110].

$$\frac{\partial \chi^2}{\partial p_\mathrm{a}} = 2\sum_i^N w_i^2 (y_i - y_i^\circ)\frac{\partial y_i}{\partial p_\mathrm{a}} \tag{17}$$

$$\frac{\partial^2 \chi^2}{\partial p_\mathrm{a}\partial p_\mathrm{b}} = 2\sum_i^N w_i^2\left[\frac{\partial y_i}{\partial p_\mathrm{a}}\frac{\partial y_i}{\partial p_\mathrm{b}} + (y_i - y_i^\circ)\frac{\partial^2 y_i}{\partial p_\mathrm{a}\partial p_\mathrm{b}}\right] \approx 2\sum_i^N w_i^2\frac{\partial y_i}{\partial p_\mathrm{a}}\frac{\partial y_i}{\partial p_\mathrm{b}} \tag{18}$$

Thus, it is sufficient to determine the matrix of first derivatives of all data points with respect to each parameter, the Jacobian **J** of the system. For some types of data, this is trivial. In the works by Hagler et al. [43] and Halgren [13], the only data used in the refinement was energies and energy derivatives calculated for fixed geometries. The force field derivatives of these properties are easily calculated from Eq. (1), leading to a very rapid analytical method. However, inclusion of experimental reference data points introduces complications. Most experimental properties are determined for energy minima. Thus, calculation of the corresponding force field data requires reoptimization of all geometries for each trial parameter set. For such data, the most straightforward way of obtaining the required derivatives is by numerical differentiation, that is, change each parameter in turn by a small value and recalculate the entire data set [76]. The main drawback of this methodology is that it is very time consuming. A not too obvious advantage is that the response of the force field will be reflected truly. Determination of analytic derivatives requires knowledge of all details of the functional form, whereas numerical differentiation in principle can be applied without any information about the inner workings of the force field.

Lifson and Warshel [111], and later Dillen [91], have derived approximate expressions of the penalty function derivatives that includes the expected geometry change upon small parameter variations, allowing fully analytical parameterization including data for energy minima.

Gradient-based methods. The steepest descent method simply steps the parameters along the gradient. The method does not employ any information allowing determination of the optimum step length, and is therefore usually augmented by a linear search routine, locating the minimum along a line before calculating a new gradient. The method works best when the gradient is large, but converges only very slowly close to the optimum. Convergence can be improved by including information about preceding steps, as in conjugate gradient methods.

Methods employing the Hessian. With the Jacobian of the system available, the additional effort required for calculating the approximate Hessian (Eq. (18)) is negligible. The Hessian contains information about the local curvature of the parameter space, allowing a determination of optimum step size according to equation 19 ($\Delta\mathbf{P}$ is the vector of parameter changes, whereas $\Delta\mathbf{Y}$ denotes the deviations in all data points).

$$\Delta\mathbf{P} = -(\mathbf{J}^T\mathbf{J})^{-1}(\mathbf{J}^T\Delta\mathbf{Y}) \tag{19}$$

For a fully quadratic system with independent parameters, Eq. (19) will converge to the optimum in one step. For real systems, the curvature may not correspond to a quadratic function, and Eq. (19) might even diverge. In particular in the initial phase of the refinement, it is advisable to include some type of dampening, usually by increasing the diagonal elements of the approximate Hessian before inversion [76,107].

Due to linear dependencies, the Hessian will frequently be close to singular. The singularities can be removed by addition of suitable Lagrange multipliers (simultaneously dampening the solution), or the system can be solved directly utilizing singular value decomposition (SVD) [76,107]. With a quadratic definition of the penalty function (Eq. (15)), SVD is equivalent to performing a principal component regression (PCR).

3.3.2.3. Dependencies and tethering. Automated optimization schemes are plagued by the problem of dependent parameters [112]. Two parameters are dependent if changing them induces the same change in all data points. Expressed another way, if *any* simultaneous change of two parameters can be found that does not affect any data point, the two parameters are dependent. In a more general sense, if any column in the Jacobian can be expressed as a linear combination of other columns, the system is linearly dependent and singular. In force field refinement, it must be recognized that a complete set of angles around a common center is *always* linearly dependent. Consider the simple example of formaldehyde. Increase in the H–C–H reference angle can always be compensated by a simultaneous increase for O=C–H. A similar dependence is observed for force constants. The resulting singular systems can be solved by SVD, but the effect will just be that the dependent parameters will be kept close to their starting values. A possible solution is to resort to parameter tethering.

Parameters can be tethered in a very simple manner by adding deviations from the desired value to the penalty function, with the weight factor set to the inverse of the allowed variation. The effect is that of a harmonic restraining potential. For bond angles, it is recommended that a tethering value is added based on observed values in what could be expected to be unstrained structures [78]. Tethering should also be applied to any other parameters that are badly defined by the data. Such parameters are readily identified from the Jacobian in any scheme employing penalty function derivatives. If all derivatives in one column of the Jacobian are low, the corresponding parameter is ill-defined. Similarly, linearly dependent parameters can be identified through SVD or analysis of the covariance matrix.

3.3.2.4. Combining refinement techniques. Each of the refinement techniques in the preceding sections has advantages and disadvantages. A synergistic effect might be achieved by combining several techniques. For Hessian-based techniques, convergence is only rapid for parameters for which the second derivative of the penalty function (the curvature) is strongly positive. Parameters far from their optimal value may even display a negative curvature, which in undampened refinement can cause a step in the wrong direction. It would be possible to use Lagrange multipliers to improve the convergence of selected parameters, but it is also possible to do subset refinements for selected parameters using a more robust optimization technique. A combination that has been found to work well is to alternate between Hessian-based refinement of the entire set, selection of ill-defined parameters, and Simplex optimization of the subset [71,78].

3.3.3. Convergence criteria

In any automated optimization, it is necessary to define when to stop further refinement. Basically, this should be when no significant improvement can be obtained by changing any combination of parameters. What level constitutes 'significant' must in each case be based on the intended use and target accuracy of the force field. The total value of the penalty function should also be low enough to show that most data points are reproduced within an acceptable accuracy (Section 3.3.1).

For non-gradient optimization techniques, it may be hard to tell when convergence has been reached. About the only diagnostic elements available are the penalty function values from preceding steps. When no improvement has been obtained for a specified number of steps, or when variation in penalty function values is decreased, the refinement cycle may be stopped. For methods with an updating step size, another convergence criterion may be that the total step is below the expected accuracy of the parameters.

Employing gradient-based techniques gives a distinct advantage in detecting convergence. First of all, the penalty function derivatives are available. If, for one parameter, the second derivative is positive and large compared to the first derivative, no further modification of only that parameter will improve the penalty function. For dependent parameters, it is still possible that a simultaneous change can improve the penalty function, even though each parameter is stable to isolated modification. Such situations can be detected from the SVD, the determinant of the Hessian, and/or the covariance matrix. A pragmatic method is to consider convergence to be achieved when no Hessian-based step results in improvement (within a specified threshold), and all single parameters are stable.

4. Validating parameters

At the end of the parameter refinement, it is necessary to evaluate if the goals have been achieved. First of all, it must be ascertained that the accuracy within the training set is sufficient. Second, the predictivity of the final force field must be validated. If the final force field fails to meet the expectations, it may be necessary to modify the functional form, augment the training set with better or more varied data, or change the intended use of the force field.

4.1. Internal validation

Several ways of validating the performance with respect to the training set have already been covered as part of the convergence criteria. The penalty function and other global diagnostics like MAD (Eq. (16)) will give information about the average performance of the force field. At this point, it may also be relevant to examine the data points by type. Single large errors should be identified and examined individually. It should always be kept in mind that there can be different reasons for a strong training set deviation in a final force field: deficiencies in either the functional form or the refinement procedure, or errors in the data. The former are probably more common, but in some cases it is possible to identify erroneous reference data by a failure to fit a proper functional form.

If possible, the quality of the final fit should be examined for each parameter. In any gradient-based refinement, the first and second derivatives of the penalty function will be available [76,78]. Employing a truncated Taylor expansion, an estimate of the expected penalty function change upon small variations of one parameter at a time can be calculated from Eq. (20). By specifying an arbitrary allowed change of the penalty function, it is now possible to calculate the maximum change in the parameter that can be accommodated. This value will be a measure of the precision of each parameter within the specified training set [56]. Note that this treatment ignores dependencies between parameters and any errors in the data. To calculate a true confidence interval, both these factors must be considered.

$$\Delta\chi^2(p_i) \approx \frac{\partial\chi^2}{\partial p_i}\Delta p_i + \frac{\partial^2\chi^2}{\partial p_i^2}\frac{(\Delta p_i)^2}{2} \tag{20}$$

4.1.1. Cross-validation

The predictivity of a force field may be estimated within the training set by cross-validation techniques [113]. However, this methodology is only feasible if the refinement cycle is very rapid. The training set is divided into several groups. Each group in turn is excluded from the training set, whereupon the entire parameter set is fully optimized and the excluded data points predicted by the resulting force field. This procedure will yield the *internal predictivity* of the force field. It is important that the data is divided in such a way that all parameters are well defined by the remaining data.

The internal predictivity cannot fully reflect the performance of the force field in real applications. The training set will have influenced the selection of the final functional form. Before a cross-validation, the ability of the chosen force field to fit the entire data set will have been verified. A full test of the predictive ability of a force field must always include an external test set of data.

4.2. External validation

The best measure of the predictivity of a force field is to apply it to a test set of data points that has not been involved in any way in the parameterization. Such a data set should ideally be selected to test all possible situations where the force field might be applied. Apart from this, application of external validation is straightforward. However, it should be noted that reoptimization of a force field based on a failure to achieve acceptable external predictivity will introduce a dependence. For a completely unbiased validation in such a situation, a new test set should be defined.

5. Concluding remarks

Force field modeling of organic structures is a mature science today. A conformational energy accuracy around 2 kJ mol^{-1} for a large set of molecules, sufficient for most applications, was attained already in the mid 1980s [114]. In the last decade, development has mainly been towards extending the scope, not increasing the quality [12,115]. Parameterization is increasingly based on accurate QM results [13], obviating the need for predetermined experimental results. The QM-guided force field methodology can now give true predictions [100,101], and should no longer be seen merely as an interpolation method.

For coordination complexes, the higher requirements in force field flexibility and the much larger diversity in structural motifs has hampered the development of molecular mechanics methodology. Development of a traditional force field including parameters for all possible coordination complexes is truly daunting. However, recent progress in at least three separate areas has widened the applicability of force field methods considerably. The development of generalized force fields has already been mentioned [26–28,103]. Even though current implementations sometimes lack in accuracy [12], it is definitely possible to develop rule sets that allow derivation of entire force fields based only on atomic parameters. The research in this area is mainly focused on finding proper functional forms that allow separation into atomic parameters. In particular for bond angles, astounding correlation with 'strange' coordination types has been obtained using a truly predictive methodology [64].

A second general type of force field application is the QM/MM methodology, which was mentioned briefly in Section 1. In this type of calculation, no new parameters are needed. A QM method is used for the parts of the molecule where the force field is undefined (e.g. metal centers [116] and/or breaking bonds in a transition state [117]). The time required for a QM/MM calculation is in the order of that for a single model system, making QM/MM the preferred choice for situations where only a few forms of each type of complex are needed. However, for any situation where a large number of structurally similar systems must be treated (e.g. in conformational searches), pure force field applications still have a distinct time advantage, even if much QM reference data is needed in the parameterization [100]. A so far unexplored opportunity is to utilize QM/MM calculations for large model systems as a source of parameterization data, thus including environmental effects on the wave function into the target force field.

The third general type of force field applications to coordination complexes has been detailed here, development of specialized force fields for each system to be studied. So far, this choice has only been open to experts willing to spend substantial time in force field development. However, force field estimation and refinement is becoming increasingly more rapid and automated [76]. With a well-defined methodology largely based on QM reference data, truly predictive force fields for coordination complexes can now be obtained within a reasonable time frame [78].

To conclude, we live in interesting times with rapid development in several diverse areas of inorganic and organometallic modeling. The future looks bright for Coordination Complex Computational Chemistry.

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