Comparisons of Different Force Fields in Conformational Analysis and Searching of Organic Molecules: A Review

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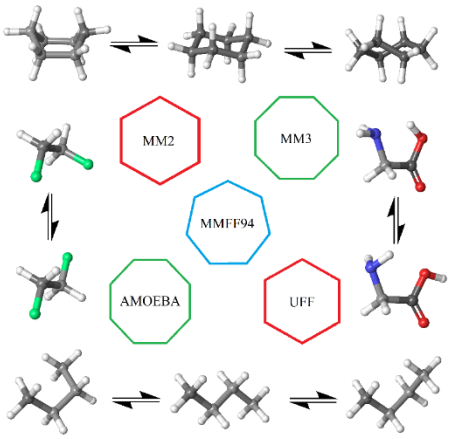
Abstract

This review aims to examine literature where different force fields are compared by their performances in conformational analysis and searching of organic molecules. Conformational analysis studies are those where energies and/or geometries of conformers are evaluated with force fields; the closer the values are to experiment or *ab initio* calculations, the better the force field performance. In conformational searching, an algorithm alters the geometry of a chemical system, followed by force field energy minimisation, then the process repeats, ideally until all conformations of the system are found. For conformational analysis, MM2, MM3 and MMFF94 often showed strong performances and their use is recommended. The polarisable AMOEBA force field consistently had strong performance and further comparisons with AMOEBA are advised. UFF showed very weak performance and is not recommended. For conformational searching, a distinct lack of comparisons were found, and the need for more work is emphasised.



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1. Introduction

In computational chemistry, force fields are theoretical constructs that aim to calculate the energies and geometries of chemical systems without the direct treatment of electrons. *Ab initio* (or quantum mechanical (QM)) methods solve approximate forms of the electronic Schrödinger wave equation for a chemical system, considering the electrons as individual wave particles. Force fields, instead, are composed of explicit energy functions that describe the potential energies of the interactions in the chemical system, i.e. bond stretching, bond angle bending, dihedral rotations (torsions), and the non-bonded van der Waals and electrostatic interactions (Figure 1).[1-3] This is often referred to as molecular mechanics, a "ball and spring" model where atoms are treated as hard spheres and bonds are described by equations similar to those from

Hooke's law. Force fields have an advantage over *ab initio* methods of having a significantly lower computational cost. However, their accuracies are more substantially more limited than those of more advanced *ab initio* electronic structure methods. Therefore, the ideal force field would be one that gives results close to, or the same as a QM method. This would mean a significant reduction in calculation time while maintaining the accuracy of the results.

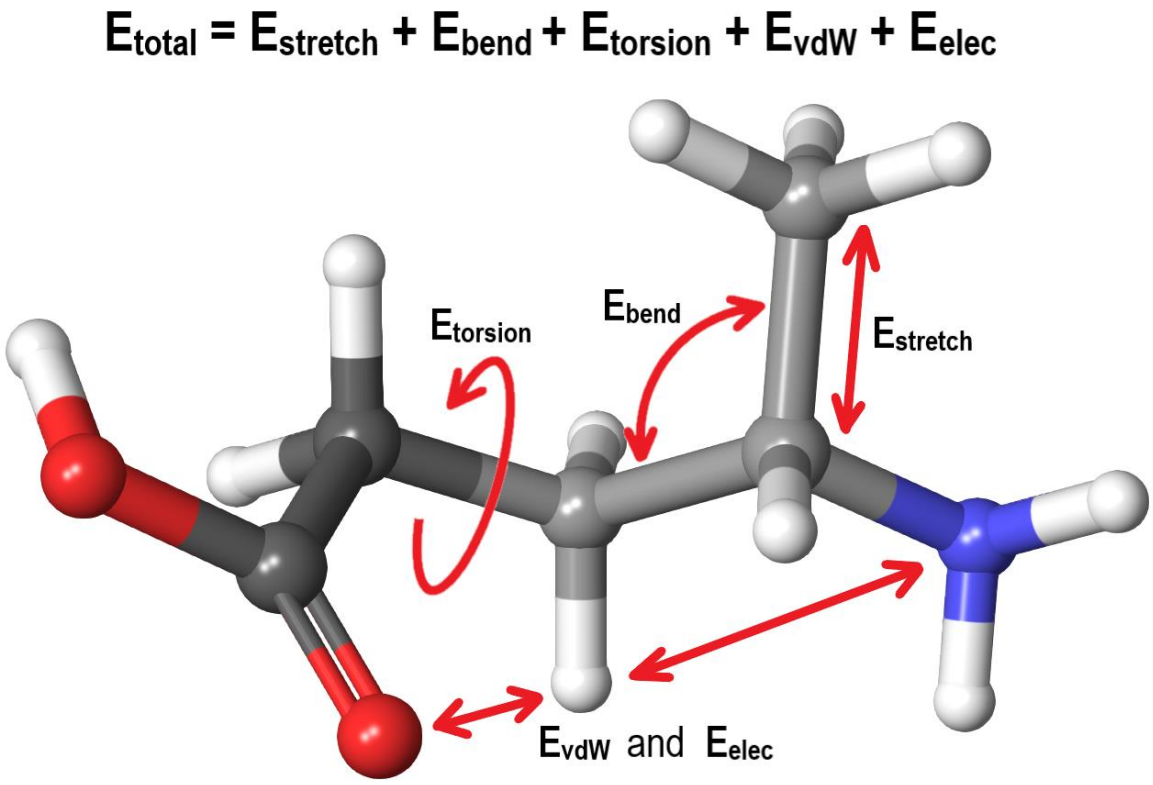

Figure 1. Illustration of the potential energy terms that make up the force field expression and the interactions they correspond to. The total force field energy is given by the sum of these terms.

The energy expressions that make up different force fields are not all identical, and the potential energy terms vary largely in complexity and accuracy. For example, the functions that describe bonded interactions can be truncated at the second order (harmonic), or can be extended with more complex higher order terms (anharmonic). The non-bonded terms can also vary largely in accuracy. They can include functions that are more accurate but more computationally costly e.g. higher order electric moments, or polarizability. To ensure usability, force fields must be parameterised against experimental or accurate *ab initio* data so they can accurately predict the properties of chemical systems. The data used for parameterisation also creates differences between the various force fields; a force field parameterised for proteins may give very different results from one intended for small organic molecules, depending on the system to which they are applied.

Larger chemical systems can be very flexible, and thus, conformational flexibility can be critical in understanding the mechanisms of organic reactions.[4-10] Therefore, a force field with low computational costs and a strong performance in conformational analysis[11, 12] would be a very useful tool in the understanding of complex organic reaction mechanisms. There is a large amount of literature concerning the comparisons of different force fields for the modelling of

macromolecular systems including proteins,[13-21] oligosaccharides,[22] enzymes,[23] lipid membranes,[24, 25] liquids,[26-28] microporous materials[29] and even protein-carbon nanotube complexes.[30] However, this review will focus exclusively on conformational analysis and searching in small/medium organic molecules.

A wide range of force fields are available, and as we shall see, there can be wide variations between the performances of different force fields in different systems. Furthermore, without the knowledge of which force fields will perform best for a given system, the choice of force field can seem an arbitrary decision.[31-35] Here we review the works where different force fields have been compared by their performances in predicting the relative energies and/or geometries of different conformations of organic molecules. Our aim is to identify any trends in force field performances in the literature and make recommendations for the use of particular force fields in reaction modelling, should they show consistently good performance.

In the earlier years of computational chemistry, the expense of methods such as Hartree-Fock (HF), density functional theory (DFT), Møller-Plesset perturbation theory at the second order or above (MP2, MP3, MP4, etc.) or coupled cluster methods (e.g. CCSD(T)) was far too great, and force fields were required for calculating conformational energies. Nowadays, energies can be readily calculated by *ab initio* methods. However, force fields are currently the only methods which can perform conformational searches within a practical timeframe.[36, 37] Alongside conformational analysis, conformational searching is a key step in modelling organic reaction mechanisms.[31-34, 38-44] Therefore we have also reviewed the performance of different force fields in conformational searching.

2. Comparing Different Force Fields for Conformational Analysis

2.1. The "MM" Force Fields

The "MM" force fields, i.e. Allinger's MM2[45] and MM3[46] and Halgren's MMFF94[47-51] in particular are well established and widely used force fields for organic molecules. Here we review the literature comparing other force fields to the "MM" force fields for studies involving conformational analysis.

In the context of this review, conformational analysis studies are works that evaluate the energies and/or geometries of different conformations of organic molecules with different force fields, and compare the force field results to "reference" values, either from experiment or *ab initio* calculations. The closer the force field values are to those of the reference, determined by the difference or error between the two values, the better the performance of the force field. In this section, we consider the works where organic molecule conformations are obtained without a conformational searching algorithm, and the energies and/or geometries are evaluated with the force fields and reference method. In section 3, comparisons involving conformational searching algorithms are discussed further.

Due to the large number of "MM" force fields available, and their reputation for strong performance, it is first worth exploring if these force fields do indeed show a history of high performance for organic molecules. A review by Pettersson and Liljefors covered the comparison of different force fields for calculating conformational energies of organic molecules prior to the year 1996.[2] Not wanting to repeat that which has already been reviewed,

we direct the reader to their work for the detail of these earlier studies. In this section, all reviewed studies consider at least one "MM" force field but for the earliest studies, MM3 and MMFF94 were yet to be developed and compared to other force fields. However, MM2 and its derivatives (MM2(85), MMX from PCMODEL,[52] MM2(87) and "MM2" from Chem3D Plus[53]) would reliably show either good[54] (but not quite best) or the best performances[55-59] for reproducing the experimental relative energy values of small organic conformers considered in each study.

A 1994 study[60] by Hwang et al. showed that MM3 (and CFF93[60]) was better than the AMBER[61] and CVFF[62] force fields at predicting the experimental and HF/6-31G* structures, conformational energy differences and rotational barriers. However, a limited dataset of six hydrocarbons was used in this study.

The studies by Gundertofte et al,[56, 63] compared a large number of force fields from various software packages including: MMFF93 from Cerius[2] (pronounced "Cerius squared");[64] MM2* and MM3* from MacroModel;[65] "MM2" from Chem3D Plus; MMX from PCMODEL; MM2(85), MM2(91) and MM3(92); as well the UFF,[66] AMBER*, TRIPOS,[55] DREIDING,[67] CFF91[68] and CVFF force fields. This work found that the MM2 and MM3 force fields generally perform best for predicting reference energies and geometries. For all molecule types considered (including cyclic and acyclic hydrocarbons, and nitrogen, oxygen and halogen containing compounds), the best force fields were consistently MM2* and MMFF93. Again, a more detailed discussion of these studies can be found in the review by Pettersson and Liljefors.[2]

Gundertofte et al. would update their comparisons of force fields as part of a second review in 2003.[3] This work changes the Cerius[2] MMFF93 to Halgren's MMFF94 force field and adds the CHARMm2.3,[57] CFF99[68] and OPLS_AA[69] force fields to the comparison to experimental conformational energy differences, as well as the PM3 semiempirical and HF/6-31G* and B3LYP/6-31G* QM methods. MMFF94 and MM2* remained the best force fields, followed closely by MM2(91), MM3(92) and MM3*. MMFF94 and MM2* notably would outperform HF/6-31G* and have comparable accuracy to B3LYP/6-31G*.

In conjunction with the parameterisation of MMFF94, Halgren tested the abilities of the MMFF94, MM3, UFF and CHARMm[70] force fields to reproduce experimental geometries (bond lengths and angles from 30 organic molecules).[49] MMFF94 and MM3 were best and showed roughly the same performance, with MM3 being slightly better for bond lengths and equal to MMFF94 for angles. CHARMm was close to MMFF94 for bond lengths but was the worst of the two for angles.

Halgren would later provide a larger-scale comparison of nine force fields for their abilities to calculate conformational energy differences with both experimental and high-quality *ab initio* data as reference, and also to reproduce the energies and geometries (bond distances and angles) of intermolecular hydrogen-bonding interactions.[71] Among the force fields were MMFF94, MMFF94s[72] (a slight variation of MMFF94 that differs only in its treatment of trigonal delocalised nitrogen), MM2* and MM3* from MacroModel. There were two reference datasets of conformer energy differences from experiment: one that was used during the characterisation of MMFF94 (37 molecules with conformational energy differences) and a second (19 molecules) that was not. The theoretical reference dataset consisted of 147 MP4SDQ/TZP calculated conformational energy differences. For the intermolecular

hydrogen-bonding interactions test, 66 complexes were optimised at the HF/6-31G* level of theory and the energies and geometries were scaled to attempt to make these values more accurate. MMFF94 and MMFF94s performed best for calculating conformational energy differences relative to the reference values, including the systems that were not considered during the initial parameterisation of MMFF94, and they were also the only force fields that adequately described the interaction energies and geometries. MM3* had the narrowest range of molecules out of all the force fields for which it was parameterised, but still showed acceptable performance for conformational energy differences for those it could perform calculations on. However, its interaction energies were deemed too small for the force field to be useful for molecular dynamics simulations in high-dielectric solutions. MM2* showed both large errors in the conformational energy differences and its interaction energies were also deemed to be too small.

Perez et al.[73] used principal component analysis (PCA),[74] a type of statistical analysis that, sparing the technical detail, in this context gives a two-dimensional representation of how similarly the chosen force fields perform i.e. the more closely the points corresponding to different force fields sit, the closer the performance of those force fields. Twenty force fields were chosen (including MM3(92), MM3(96) from Tripos Associates, and MM3* from MacroModel with dielectric constant set at both $\varepsilon = 1$ and $\varepsilon = 80$), and the PCA compared their performances using geometric and energetic properties of seven carbohydrate molecules optimised by the force fields. Unfortunately, Perez et al.'s PCA assessment did not include reference data, either from *ab initio* calculations or experiment. Therefore, the force fields could only be compared relative to each other and it was not possible to determine which of the force fields performed best. Although, the PCA assessment did show that the points corresponding to different variants of the same force field, i.e. those of AMBER and MM3, would cluster together, indicating that the variants tended to produce similar results for the energies and geometries of the carbohydrates, despite the alterations made to the force fields.

Hemmingsen et al.[75] continued the work of Perez et al. with the same force fields and a reduced set of molecules, but also optimised the carbohydrate molecule conformers at the B3LYP/aug-cc-pVDZ//B3LYP/6-31G(d) level of theory. While the accuracy of the B3LYP density functional, especially without dispersion correction, can be disputed,[76-78] the authors provided a validation of their *ab initio* method as suitably accurate and estimated the B3LYP/aug-cc-pVDZ energies to be correct within 1 kcal / mol. With the QM reference data, the performance quality of the force fields could be analysed using the PCA assessment, i.e. the closer a point corresponding to a force field on the PCA plot sits to the QM point, the more accurate the force field. The force field closest in performance to the QM method was CHEAT(95),[79] followed by AMBER(94), then Glennon's parameterisation of AMBER,[80] MM3(92) and MM3(96).

Arnason et al. performed calculations on 1,3,5-trisilacyclohexane with the MM2 and MM3 force fields and three semiempirical methods AM1, MNDO and PM3.[81] It was shown that the HF/6-31G* values for the geometric parameters of the ring compared favourably with experimental values, and thus, the HF/6-31G* geometries and relative energies of the conformers were chosen as references. Both MM2 and MM3 were found to perform closely to HF for geometries and conformational relative energies, with MM3 being slightly better than MM2. Interestingly, the three semiempirical methods performed much more poorly than either of the force fields. Arnason et al. do not propose an explanation as to why the semiempirical methods performed much worse than the force fields, but since both force fields and

semiempirical methods rely heavily on their parameterisation for accurate results, we speculate that the force fields simply happened to have better parameterisation for the silacyclohexane than the semiempirical methods.

Grůza et al. tested the abilities of MM3 and four different parameterisations of the AMBER force field to predict the geometries and relative energies of the conformations of two ribofuranoside molecules.[82] X-ray crystal geometries and HF/6-31G** conformer energies and geometries were used as reference. MM3 was found to produce geometries close to those from experiment and *ab initio* calculations, as well as good relative energies for the conformers. Only one of the AMBER parameterisations was able to obtain results reasonably close to those of MM3, and all the other parameterisations showed problems with either incorrect geometries or being unable to correctly predict the relative energies and energy ordering of the conformers.

So far, it is clear that the "MM" force fields often outperform others where their abilities to predict properties of organic conformers are compared. However, there are a few studies[83-86] that show reduced performance in the "MM" force fields.

The first of these comes from Barrows et al., where the conformational properties of glucopyranose were examined.[83] The relative energies of eleven conformers of glucopyranose were calculated with 10 force fields (including MM3 and MMFF94). The reference values came from a linear combination of MP2, CCSD and HF energies calculated with larger and smaller basis sets on MP2/cc-pVDZ optimised geometries; a so-called "composite" QM method. Of the ten force fields compared, MM3 and MMFF94 were the 3rd and 5th worst respectively at calculating the glucose conformer relative energies with reference to the composite QM energies. However, despite the poor performance of MM3 at predicting conformer energies, the rotational-vibrational thermal contributions to the free energy calculated with this force field did show a fairly strong agreement with those calculated at the HF/cc-pVDZ level of theory. Barrows et al. stated that MM3, while not correctly determining their relative depths, was able to predict the shapes of the minima on the glucose potential energy surface very well. The reason why force fields such as MM3 and MMFF94 may not perform so well for carbohydrate molecules, is that these systems are highly polar, flexible and their conformational properties strongly depend on stereoelectronic effects such as the anomeric (Figure 2) and exo-anomeric effects.[87-89] Since the "MM" force fields do not have functionality for polarisation, and force fields in general have no direct treatment of electrons, it is clear why carbohydrates may be a challenge for them.

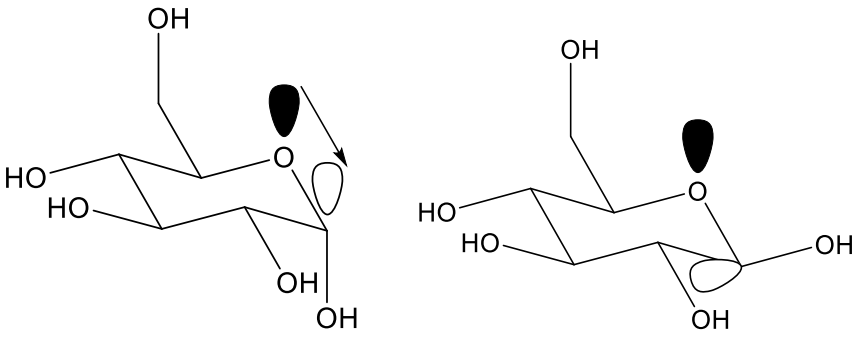

Figure 2. The anomeric effect in the α-anomer of D-glucose (left) and its absence in the β-anomer (right). Any direct treatment of electrons, including molecular orbitals, is neglected by force fields. Hence, stereoelectronic effects such as this are generally quite problematic for force fields, unless extra care is taken during their parameterisation.[87, 88, 90-92]

Rasmussen et al. demonstrated the importance of the inclusion of higher order electric multipoles and polarisability in a force field,[84] particularly for more polar systems, by comparing three parameterisations of the AMOEBA[93, 94] force field and five other force fields, including MM2*, MM3* and MMFF from MacroModel. Seven organic molecules were chosen, in increasing polarity ranging from an alkane to a zwitterion (Figure 3). Conformations of each molecule were found at the MP2/cc-pVDZ level of theory and the relative energies of the conformers, which served as the reference values, were calculated at the LMP2/cc-pVTZ level of theory. The force field qualities were compared by plotting the force field energies (of all the conformers of each molecule) against the LMP2/cc-pVTZ energies of the same conformers. Then, the gradients of the lines of best fit and correlation coefficients (R^2) were obtained. In theory, values for these which are closer to unity indicate a stronger force field. For the "MM" force fields, and the other two fixed partial charge force fields, AMBER94 and OPLS, their gradients and R^2 values tended to worsen significantly as the polarity of the molecules increased, which was attributed to their simple treatment of electrostatic interactions. However, this variability was less extreme for MMFF than MM2* and MM3*. Other workers would use this method of examining the correlation between force field and reference energies to analyse force field performance in later studies we also cover.[86, 95, 96] However, we are unable to find any further discussion on whether this is a wholly reliable way of determining performance, for example, what is the likelihood of a force field finding the correct energies for the wrong conformers and showing a misleadingly good correlation?

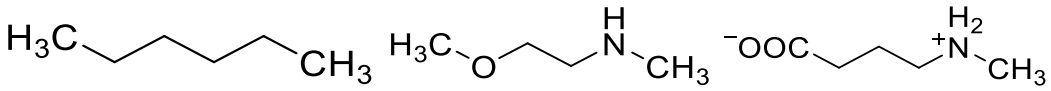

Figure 3. A selection of the molecules in the study by Rasmussen et al. to illustrate the range of polarity in the molecules. From left to right: lowest polarity, intermediate polarity, highest polarity.

Kaminský and Jensen analysed the conformational behaviour of four amino acids: glycine, alanine, serine and cysteine.[85] For each amino acid, a set of trial structures were made by altering the torsion angles along the amino acid backbone, and then optimising all of the resulting conformations at MP2/6-31G(d,p), followed by the more advanced MP2/aug-cc-pVDZ level of theory. The relative energies of the optimised conformers used as reference were obtained by calculating HF, MP2 and CCSD(T) energies, extrapolating the HF and MP2 results to the basis set limit and adding the difference between the CCSD(T) and MP2 energies. Conformational relative energies and geometry optimisations were also performed using a set of eight force fields including MM2*, MM3* and MMFFs from MacroModel and the polarisable AMOEBA force field. The performances of the force fields were assessed by three approaches: how well the force fields were able to find, accurately reproduce and not obtain false conformations relative to the MP2 level of theory; how well the force fields reproduced the torsional angles of the amino acids; and how closely the force fields predicted the conformational relative energies to the QM values. For the first of these quality tests, for each force field, all the conformers of all four amino acids were labelled one of: "good" if the force field geometry had torsional angles with root mean square deviation (RMSD) from the MP2 torsional angles less than 40°; "poor" if the torsional angle RMSD was greater than 40°; "missing" if the MP2 conformation was not a minimum on the force field's potential energy surface; "artificial" if the force field found a conformation that did not correspond to a minimum on the MP2 potential energy surface. Mean absolute deviations (MADs) for the RMSDs between MP2 and force field torsional angles and conformer relative energies were

given as measures for the other two quality tests. MM2* and MM3* were the two worst force fields for finding the MP2 conformers and obtaining the correct relative energies, with the lowest numbers of "good" conformers, the highest numbers of "missing" conformers and the highest relative energy MADs. MM2* also had the highest torsional angle RMSD MAD. Therefore overall, MM2* and MM3* both showed a very poor performance for the conformations of these amino acids. However, MMFFs was able to redeem the "MM" force fields. Of the non-polarisable, fixed partial charge force fields, MMFFs showed the largest number of "good" and the lowest number of "missing" conformations, as well as the lowest torsional angle RMSD MAD (joint with the CHARMM27[97] force field) and the second lowest relative energy MAD.

Later, Kaminský and Jensen would undertake another study with the same four amino acids, but this time they would attempt the more challenging task of trying to find the energies of the conformational interconversion transition states (TSs) and subsequently comparing the accuracies of eight force fields for this task.[86] The same three "MM" force fields were included in this study (MM2*, MM3* and MMFFs) and the reference relative energies were obtained by the same extrapolated and corrected QM method. The TSs were found by varying torsional angles in steps between the values corresponding to the conformers being interconverted and calculating the energy at each point at the MP2/6-31G** level of theory. The energies of geometries that corresponded to TSs at the MP2/6-31G** level of theory were recalculated with each force field. The TS relative energies from the force fields were plotted against those of the extrapolated and corrected QM method, and the correlation coefficients, gradients of the line of best fit, as well as the RMSD between the force field and QM TS relative energies, were used to assess the accuracies of the force fields. No force field performed exceptionally well in this study, with overall error from all force fields being in the ~10 kJ / mol range. In fact, most often the force fields show roughly similar performance. However, as in the previous work, MM2* and MM3* were generally among the worst of the force fields and showed higher errors, while MMFFs was slightly better but still very far from perfect.

We now return to studies where the "MM" force fields have been found to be superior to other force fields. In 2009, Stortz et al. undertook a comparison of sixteen force fields using three disaccharide molecules: β-cellobiose, α-maltose and α-galabiose.[98] The force field set included MM2, MM3 and MM4[99] each at two dielectric constants of 1.5 and 4, and the MM2 variants MMX and MM+.[100] 54 conformers of each disaccharide were generated and optimised by each force field. For β-cellobiose, DFT conformational relative energies and geometries were available at the B3LYP/6-311++G** level of theory; for α-maltose, B3LYP/6-311++G** geometries, but not energies, were available; for α-galabiose, a crystal structure was available for one conformer only. Thus, with these overall limited sets of reference data, most of the comparisons in this work were between the geometries produced by the force fields, relative to each other. For β-cellobiose, MM4 showed the closest agreement with DFT for the relative energy of the most stable conformer, followed by three other force fields then MM3 then MM2. Although, MM4 did show a problem, in that it predicted a "flipped" conformer of β-cellobiose that was more stable than a "normal" one. For the geometries of β-cellobiose and α-maltose, MM3 and MM4 both showed very good agreement with those from DFT, with MM3 showing one of the strongest performances of all the force fields in the test. For α-galabiose, the best matches of force field geometry with the crystal structure came from MM2 and MM4 (the MM3 structures were not as good, but still close). The overall conclusion was that MM3 was

one of the strongest force fields, with MM4 being a close alternative and MM2 and its variants being weaker.

Finally, two studies by Hutchinson et al. contain brief comparisons of the performances of MMFF94, GAFF[101] and UFF. The earlier study attempts to assess the general ability of force fields for applications such as conformational searching.[95] From a dataset of 700 small organic molecules, 250 conformations of each molecule were generated. MMFF94, GAFF, UFF and semiempirical PM7 single-point energies were calculated for each conformation of each molecule and the force field conformer energies were plotted against the PM7 energies. Correlation coefficients (R^2) and Spearman rank correlation coefficients[102] were obtained from the plots for each molecule, and both the mean and median values of each were calculated from the full molecule set. Out of the three force fields, MMFF94 had the best R^2 and Spearman coefficient values and was thus chosen for further study, although MMFF94 (and as Hutchinson et al. infer, all classical force fields) was demonstrated to be exceptionally poor for obtaining both conformational energies and geometries.

The later study by Hutchinson et al. expands the comparison of computational methods to include more QM methods, especially DFT functionals, and modern machine learning potentials as well as the original three force fields.[96] From the same set of 700 molecules, 10 conformations of each molecule were chosen and optimised at B3LYP-D3BJ/def2-SVP level of theory followed by single-point energy calculations at the "gold standard" DLPNO-CCSD(T)/cc-pVTZ level of theory. As before, the DLPNO-CCSD(T)/cc-pVTZ conformational energies were plotted against the energies of each method and R^2 and Spearman coefficients were found. Also, the mean absolute relative error (MARE) for the relative energies of the conformers compared to DLPNO-CCSD(T)/cc-pVTZ were calculated for all molecules. Of the three force fields MMFF94 had by far the lowest median MARE, however the median R^2 and Spearman coefficients of MMFF94 and GAFF were very close, with those of MMFF94 being slightly lower. Therefore, MMFF94 was the best of the force fields for predicting the relative energies of the conformers but was very slightly worse than GAFF for a reliable energetic ordering of the conformers.

We have seen the prominent use and notable performance of the "MM" force fields, MM2, MM3 and MMFF94, in numerous studies where different force fields have been compared by their capability to reproduce and predict the energies and geometries of conformations of organic molecules. Very often these "MM" force fields have been shown to be the best, or at least good, for the organic conformational tasks they are presented with. This seems likely due to their functional forms which, sparing detail, contain anharmonic stretching, bending and torsional terms which allow for more flexible and accurate descriptions of molecules,[1] as well as the initial parameterisation of all three being strongly focused towards small organic molecules.[45-51] This is contrasted with force fields such as AMBER or OPLS, that only use more limited harmonic functions and were initially parameterised with a reduced focus on small organic molecules since they were also designed for the modelling of proteins.[61, 103] Hence the performance of the "MM" force fields is often seen to be better than other non-polarisable, fixed partial charge force fields. As seen in Table 1 the "MM" force fields generally outperformed the other very commonly used force fields: AMBER, OPLS and CHARMM. We also notice that the performance of the three force fields *almost* exclusively increases in the order: MM2, MM3 then MMFF94.[2, 3, 71, 81, 83-86, 98] Therefore, we recommend the use of these

"MM" force fields in applications where evaluating the conformational properties of organic molecules requires a force field.

Table 1. The overall performances of any variants of the most commonly used force fields in conformational analysis comparisons. The "good" columns indicate the references where that force field had one of the top three performances. The "best" columns indicate the references where that force field showed the best performance out of all force fields in the comparison. The "Any "MM"" columns combine the MM2, MM3 and MMFF columns. Note that the MMFF force field variant in reference [3] was MMFF94 and in [63] it was MMFF93. In both of these references, MM2 and MMFF had joint lowest errors. Also, in reference [86] the AMOEBA, AMBER and CHARMM variants showed roughly the same performance overall. The "Total" rows give the number of appearances of any variant of the corresponding force field. The "%" rows show the percentage of the studies with the corresponding force field performance out of the total number of studies with that force field.

	MM2 good	**MM2 best**	**MM3 good**	**MM3 best**
Refs.	3, 54-59, 63, 81	3, 55-59, 63	3, 49, 60, 63, 71, 75, 81, 82, 98	49, 60, 81, 82, 98
Total	14		14	
%	64%	50%	69%	36%

	MMFF good	**MMFF best**	**Any "MM" good**	**Any "MM" best**
Refs.	3, 49, 63, 71, 85, 95, 96	3, 63, 71, 95, 96	3, 49, 54-60, 63, 71, 75, 81, 82, 85, 95, 96, 98	3, 49, 55-60, 63, 71, 81, 82, 95, 96, 98
Total	10		21	
%	70%	50%	86%	71%

	AMBER good	**AMBER best**	**OPLS good**	**OPLS best**
Refs.	75, 83, 86, 96	86, 96	83, 85, 98	None
Total	12		6	
%	33%	17%	50%	0%

	CHARMM good	**CHARMM best**	**AMOEBA best**	**UFF good**
Refs.	57, 71, 86	57, 86	84-86, 104	None
Total	8		4	4
%	38%	25%	100%	0%

Table 2. Reference by reference list of the best, "good" and all other force fields within each study, along with a very brief description of what method or reference was used to determine force field performance. As above, a force field shall be considered "good" if it showed one of the top three performances in the study. Where only

four or fewer force fields are included only the top two are considered "good". Force fields in the "good" force fields column within ((double brackets)) had very poor performances and are within the top force fields either because only a few were tested, or most performed poorly. Note that the early force fields used in reference [54] are very obscure and not widely used today. Note that in reference [98] the MM3, GLYCAM and GROMOS force fields showed roughly the same performance overall, as did the OPLS, MM4 and CSFF force fields.

Reference	Best Force Field(s)	Good Force Fields	Other Force Fields	How Determined
[3]	MM2 and MMFF94	MM3	AMBER, CFF, CHARMM, CVFF, DREIDING, OPLS, TRIPOS, UFF	MAD between force field and experimental conformational energies
[49]	MM3	MMFF94	CHARMM, UFF	RMSD between force field and experimental conformational geometries
[54]	Boyd	MM2, White-Bovill	Ermer-Lifson, Rasmussen, Schleyer EAS, MUB2	Deviation between force field and experimental conformational energies
[55]	MM2	((TRIPOS))	-	Deviation between force field and experimental conformational energies
[56]	MM2	((TRIPOS))	ChemX[105]	Deviation between force field and experimental conformational energies
[57]	CHARMM	MM2	TRIPOS, DREIDING	Deviation between force field and experimental conformational energies and geometries
[58]	MM2	((TRIPOS))	-	RMSD between force field and experimental conformational energies
[59]	MM2	((UFF))	-	Deviation between force field and experimental conformational energies and geometries

[60]	MM3	CFF93	AMBER, CVFF	Deviation between force field and experimental and HF/6-31G* conformational energies and geometries
[63]	MM2 and MMFF93	MM3	AMBER, DREIDING, TRIPOS, CVFF, CFF, UFF	MAD between force field and experimental conformational energies
[71]	MMFF94	MM3, CHARMM	MM2, OPLS, AMBER, CFF, CVFF	RMSD between force field and experimental, MP4SDQ/TZP and HF/6-31G* conformational energies
[75]	CHEAT(95)	AMBER, MM3	CVFF, CFF, GROMOS, DREIDING, CHARMM, TRIPOS	Proximity to B3LYP/aug-cc-pVDZ//B3LYP/6-31G(d) reference on PCA plot
[81]	MM3	MM2	-	Deviation between force field and HF/6-31G* conformational energies and geometries
[82]	MM3	AMBER	-	Deviation between force field and HF/6-31G** conformational energies and geometries
[83]	CSK[106]	OPLS, AMBER	MMFF94, MM3, CHARMM, GROMOS, ChemX	MAD between force field and composite QM conformational energies
[84]	AMOEBA	((MMFF94, OPLS))	MM2, MM3, AMBER	Slopes and R^2 between force field and LMP2/cc-pVTZ //MP2/cc-pVDZ conformer energies
[85]	AMOEBA	MMFF94, OPLS	MM2, MM3, AMBER, CHARMM	Number of MP2/aug-cc-pVTZ found and MAD and RMSD between

				force field and MP2/aug-cc-pVTZ conformer energies
[86]	AMOEBA, AMBER, CHARMM	((MMFF94s))	OPLS, MM2, MM3	R^2 and RMSD between force field and MP2/6-31G** energies of conformational interconversion TSs
[95]	MMFF94	((GAFF))	UFF	R^2 and Spearman coefficient between force field and PM7 conformer energies
[96]	GAFF and MMFF94	((UFF))	-	MARE, R^2 and Spearman coefficient between force field and DLPNO-CCSD(T)/cc-pVTZ//B3LYP-D3BJ/def2-SVP conformer energies
[98]	MM3, GLYCAM, GROMOS	OPLS, MM4, CSFF	MM2, AMBER, CHARMM, MM+	MAD between force field and B3LYP/6-311++G** or experimental energies or geometries
[104]	AMOEBA	((AMBER))	-	Deviation between force field and M05-2X/6-31G(d,p) conformer energies

2.2. The Polarisable AMOEBA Force Field

One limitation of classical force fields commonly used for the study of organic molecules is their simple treatment of electrostatic interactions. The AMOEBA force field aims to address this issue by including functionality to account for electric monopoles, dipoles and quadrupoles as well as polarisation induced by neighbouring atoms and groups.[93, 94, 107] We previously noted the standout performance of the AMOEBA force field in the literature (also see Table 1). Thus, in this section, we cover the work we were able to find where AMOEBA was compared to other force fields for their proficiency in conformational analysis. We have already covered the first three studies of this area in the "MM" force fields section,[84-86] and rather than repeating ourselves, details can be found in section 2.1.

The three parameterisations of AMOEBA that Rasmussen et al. examined[84] were the only three force fields that maintained slopes and R^2 values around unity as the polarity of the molecules

increased. However, the slopes and R^2 values of the AMOEBA parameterisations were not the closest to unity for the less polar molecules. Therefore, according to these values, AMOEBA likely represents the best force field overall, given its reasonably consistent performance over the whole set of molecules.

In Kaminský and Jensen's first comparison of force fields for the energies and geometries of the conformations of four amino acids,[85] AMOEBA outperformed other force fields (which all used fixed partial charges) by every measurement considered. AMOEBA found the greatest number of "good" conformations and the lowest number of "missing" conformations, although it was third best for the number of "poor" conformations and in fact, found the largest number of "artificial" conformations. AMOEBA also had the lowest torsional angle RMSD and relative energy difference MADs of all the force fields in the study.

In Kaminský and Jensen's later study considering TS interconversions between the amino acid conformations,[86] all of the force fields had higher and closer errors. However, AMOEBAPRO13[108] (a 2013 version of AMOEBA used in this work) and the AMBER and CHARMM22[109] variants (AMBER14SB and CHARMM22_CMAP) showed marginally lower RMSDs for the relative energies of the conformational TSs and tended to show slightly better correlations (slopes and R^2 values closer to unity).

The final study of this section comes from Doemer et al.[104] when they attempted to ascertain which of the three AMBER parameterisations and AMOEBA would best reproduce the relative energies and energy ordering of conformers of a protonated cyclic decapeptide gramicidin S. Nine conformations of the decapeptide were optimised at the M05-2X/6-31G(d,p) level of theory, and cold ion spectroscopy revealed that the lowest energy conformer calculated by the M05-2X functional was the same as the experimental conformation. The energies of the nine conformers were also calculated with the four force fields, and AMOEBA showed the lowest RMSD in the relative energies and the best energy ordering of the conformers out of all the force fields, when compared to the reference M05-2X results. All three AMBER variants were deemed unsuitable for the task of describing the conformational energy surface of this decapeptide.

So far, we have not seen many comparisons of AMOEBA's conformational performance with that of other force fields. However, given its good performance in all the studies comparing it to other force fields (Table 1), perhaps further investigation is warranted. In the future, it may be interesting to comparatively assess AMOEBA's ability in conformational searching applications, and whether its increased accuracy is worth the increased computational cost introduced by the force field's improved treatment of electrostatics and polarisation.

2.3. The Universal Force Field

UFF aims to calculate energies for molecules and complexes containing any element on the periodic table, using general rules and formulae, rather than specific parameterisation.[66] However, this flexibility and generality engenders a large reduction in the accuracy of UFF, even for common organic molecules, and the comparisons in conformational analysis of UFF with other force fields illustrates this quite clearly (Table 1). As with the AMOEBA section, some of the presented studies have previously been discussed[49, 63, 95, 96] and further information on these can be found in the "MM" force fields section.

Soon after the initial creation of UFF, Casewit et al. carried out an evaluation of UFF's aptitude for computing bond lengths, bond angles and energy differences between conformers of common small organic molecules, relative to the values obtained from MM2 and experiment.[59] For hydrocarbons only, UFF would achieve good agreement with the energies and geometries from experiment and MM2, but UFF's performance became very poor for any molecule containing one or more heteroatoms.

In three works concerning Gundertofte et al.'s comparison of force fields in conformational analysis,[2, 3, 63] UFF would consistently show the highest (or close to the highest) errors in the conformational energy differences of all the molecules examined. Hence, by a long stretch, UFF showed the greatest compiled error of any of the force fields. Halgren also found the errors (relative to experiment) in UFF's calculated bond lengths and bond angles to be the greatest of all four force fields.[49] Finally, in Hutchinson et al.'s assessments with force fields,[95, 96] UFF had the worst correlations with the conformational energy reference methods (PM7 and DLPNO-CCSD(T)/cc-pVTZ) of the three force fields.

To conclude this brief section, we have found a few studies illustrating that UFF is an unreliable force field, and we would not make any recommendation to use UFF unless absolutely required. It could almost seem that general force fields are, by their nature, fairly untrustworthy for producing accurate results. However, a recent and very promising general force field from Grimme et al.[110] (GFN-FF) definitely warrants comparisons with other, established force fields in conformational analysis of organic molecules.

3. Comparing Force Fields in Conformational Searching

As computing power increases, more advanced quantum chemical methods have become easier and cheaper to perform. Therefore, evaluating conformational energies with more accurate methods has become much more tractable and conformational analysis of organic molecules no longer needs to be done with force fields. Now, however, one niche for force fields in organic chemistry is conformational searching. In order to fully explore the conformational space of a flexible chemical system, upwards of thousands of energy minimisations need to be done. Figure 4 illustrates this shift in the focus of force fields in organic chemistry. The left-hand graph shows the number of papers, by each year range, comparing force fields in the area of conformational analysis, and the right side shows the numbers of papers comparing force fields for conformational searching. As clearly illustrated, the number of papers for conformational analysis tends to decrease with time, and the number of papers concerning conformational searching increases in the later years. Also apparent from Figure 4 is the much lower number of force field comparison studies concerning conformational searching. Given that conformational searching is a critical part of studying and understanding reaction mechanisms[31-34, 38-44] (Figure 5), there is drastic need for more work evaluating force fields and their performance in conformational searching. Many conformational searching programs are available, and commercial software such as Schrödinger's MacroModel[65] and ConfGen[111] or Chemical Computing Group's MOE[112] will likely have access to a range of common force fields (for example, variants of the MMFF94, MM2, MM3, OPLS and AMBER force fields are available in MacroModel). However, if restricted to open-source software, for example, RDKit,[113] Open Babel[114] or Balloon,[115] then the user may be restricted to a very limited number

of force fields and often only MMFF94 is available (RDKit and Open Babel do have the UFF force field, but as seen earlier, this force field is not likely to show great performances).

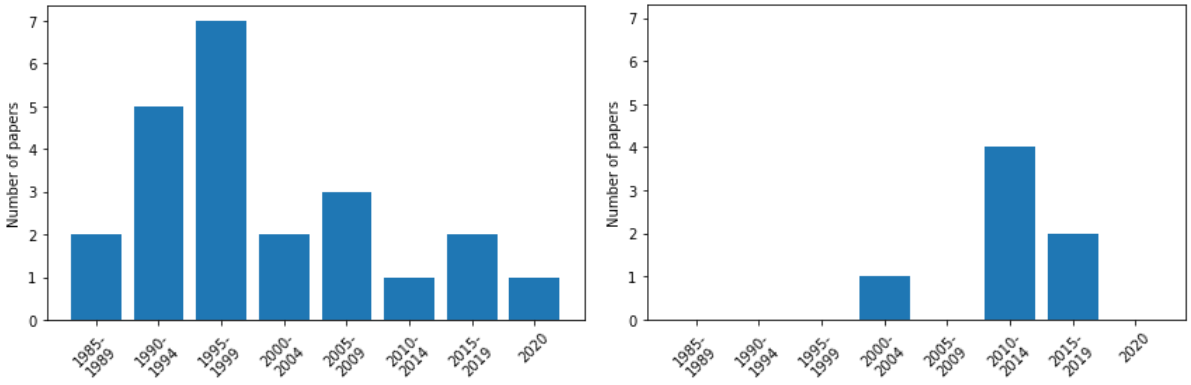

Figure 4. The numbers of papers found comparing different force fields for "conformational analysis" (left) and conformational searching (right) within each 5-year range.

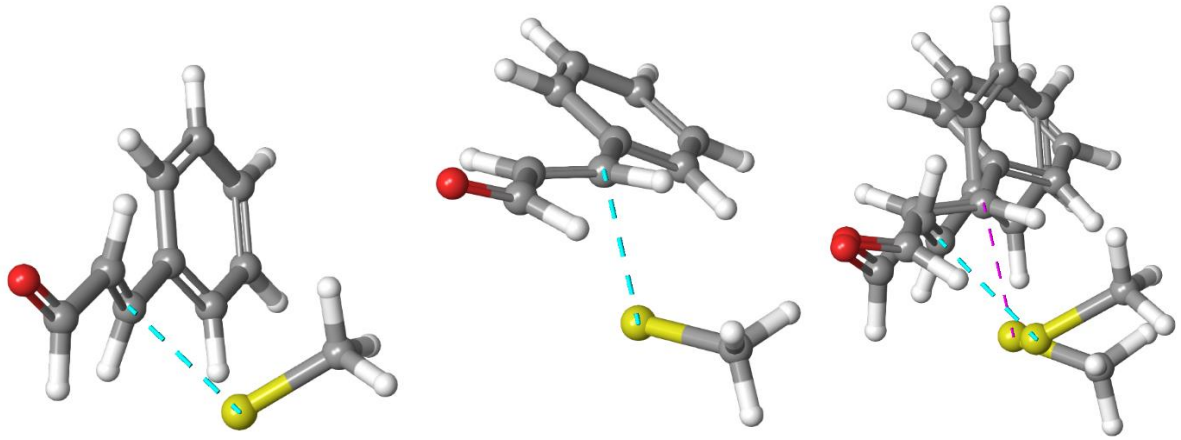

Figure 5. Two different conformations of the transition state in the reaction between the Michael acceptor cinnamaldehyde and methanethiolate (left and middle) along with the two conformations superimposed (right). One of the conformations will be lower in energy, and thus, the reaction mechanism will more likely follow the lowest energy pathway corresponding to that transition state.

Despite the relative lack of studies in this area, those found seem to fall into one of three types: where force field conformers are optimised at a higher level QM method; where a larger study briefly mentions a comparison of force fields in one search method; and where the force field conformers are assessed by their similarities to bioactive conformations. However, each area consists of only two to three papers. Therefore, concluding which force field(s) are generally best for conformational searching is difficult to establish.

3.1. Conformational Searching Comparisons with *Ab Initio* Optimisation

Here we review comparisons where conformational searches are performed with multiple force fields, and the resulting conformers are optimised with a higher-level QM method. The conformers are compared before and after optimisation, and closer agreement between the force field and QM method indicates a better performing force field. This would appear to be the most thorough way of evaluating a force field for conformational searching, given that it is experimentally unfeasible to determine the relative energies of all possible conformations of a

system. A sufficiently accurate QM method is the only way to fully evaluate conformational searching with different force fields.

Castillo et al. performed conformational searches[116] on six diastereomers of a cyclic urea HIV inhibitor molecule with the Low Mode/Monte Carlo (LM:MC) combination search method and MacroModel force fields OPLS-AA and AMBER* in the GBSA(water) solvent model. It was stated that, from previous work, the HF/6-311G**-SCRF(water) level of theory was able to give reliable descriptions of conformational properties and solvation respectively, and the lowest energy conformer of each diastereomer from both force fields were optimised at the HF/6-311G**-SCRF(water) level of theory. The relative energies of the six diastereomers (lowest energy conformer of each) and the RMSDs between the force field and optimised conformers were determined. The ordering of the diastereomer relative energies from OPLS-AA were in much better agreement, and closer in value to those of HF/6-311G** than those from AMBER*. The RMSDs between the OPLS-AA and HF/6-311G** optimised conformers were also much lower for all the diastereomers than those for AMBER*. Therefore, Castillo et al. concluded that OPLS-AA provided a better representation of the cyclic urea molecule's potential energy surface than AMBER*.

Dong et al. carried out conformational searches on five forms of the dipeptide glycylglycine[117] (GlyGly): unaltered GlyGly, deprotonated ($GlyGly^-$), complexed with a chloride anion ($GlyGly{\bullet}Cl^-$), complexed with a sodium cation ($GlyGly{\bullet}Na^+$) and the dihydrate ($GlyGly{\bullet}(H_2O)_2$). All conformational searches used the Monte-Carlo Multiple Minimum (MCMM) method and either the AMBER94, MM3*, MMFFs and OPLS-2005 force fields in MacroModel with an energy cutoff set to 50 kJ mol^{-1}. All conformers from all force fields were pre-optimised at the HF/6-31G(d) level of theory. Then, all conformers within 40 kJ mol^{-1} of the minimum energy conformer for that force field were optimised at the MP2/6-311++G(d,p) level of theory and all conformers within 20 kJ mol^{-1} of the minimum were analysed in detail. No geometric or energetic comparisons between the force field and optimised conformations were made. Instead, the only assessment of the force fields was how many of the low energy conformers they were able to find after optimisation. Overall, MMFFs was able to find the greatest number of conformers after optimisation out of all the force fields, despite, in fact, finding the lowest total number of conformers over all five systems. Dong et al. determined that this was due to MMFFs having good treatment of: hydrogen bonding in GlyGly; electrostatics in $GlyGly^-$ and the two ion complexes; and the dihydrate, for which MMFFs was unable to find only one conformation. It was also discussed that AMBER94 had a good description of the hydrogen bonding in GlyGly and that OPLS-2005 was similar in performance to MMFFs for the ion complexes and had good handling of the electrostatics. MM3* was the worst force field for finding the optimised conformers; it consistently found the lowest numbers of conformations for all five systems and did not have non-bonded parameters for the lone sodium ion in $GlyGly{\bullet}Na^+$.

MMFFs still follows the trend of good performance as seen in the conformational analysis section above, thus lending further weight to our recommendation for its use. Other than this, unfortunately, it is difficult to draw any strong conclusions from only these two studies, due to the small numbers of types of system and force fields. Clearly, a greater number of force field conformational search comparisons, evaluated with *ab initio* optimisation, should be done in order to verify which force field will produce the best results.

3.2. Brief Comparisons as Part of a Larger Study

Some larger studies that compare different search methods or different searching programs also make brief mentions of using two or three force fields for conformational searching. Here we will review these studies.

Firstly, Bai et al. performed a comparison of 'normal' conformational search methods, based purely on using force fields, versus a search method based on multiple empirical criteria.[118] They compared the MacroModel force fields MMFFs and OPLS-2005 as three 'pure' force field methods, and also compared MMFF94 and TRIPOS for the empirical criteria method. Throughout the study, performances were measured by the retrieval rates of bioactive conformations from crystal structures of 742 protein ligands. The retrieval rate was determined by the proportion of ligands for which at least one of the conformations found has RMSD from the bioactive conformation in a given range (e.g. proportion of ligands where at least one force field found conformation had RMSD lower than 0.5 Å, or between 0.5 Å and 1.0 Å, etc.). For both comparisons (MMFFs vs OPLS-2005 and MMFF94 vs TRIPOS), both force fields would show very similar retrieval rates no matter the search method. Thus, Bai et al. concluded that force field choice does not strongly affect the ability of the conformational search algorithm to reproduce bioactive conformations.

While comparing some freely available conformational searching tools,[119] Ebejer et al. also evaluated the UFF and MMFF94 force fields from RDKit[113] using the (minimum) RMSDs between the force field generated conformers and crystal structures of 708 drug-like molecules. The molecules in the dataset were grouped by the number of rotatable bonds. For molecules with zero or one rotatable bonds, MMFF94 showed slightly lower mean RMSDs, but for molecules with two or more rotatable bonds UFF had slightly lower mean RMSDs, although the RMSD ranges for both force fields were often very similar and always strongly overlapped.

Watts et al. assessed their newly developed conformational searching method for macrocyclic molecules in MacroModel against other established methods.[120] They used experimental crystal structures from 50 macrocycles as reference, and measured performance by calculating RMSD between the found and experimental structures. Results were not shown for the force field comparison, but it was stated that the MacroModel force fields MMFFs, OPLS-2005 and OPLS2.1 all showed similar performances in reproducing the experimental structures of the macrocycle test set.

It is interesting that all three studies report little or no difference in the performance of any of the force fields they test. A possible explanation for this could lie in the fact that there may be changes in the geometry of a molecule upon becoming its bioactive conformation[121-123] or entering the solid state.[124-128] Since force fields are normally parameterised to predict the energy minima of unconstrained molecules, there will likely be a small difference between force field and experimental structures. A force field will be unable to predict the direction or magnitude of this structural deviation, and therefore, there may be a small random error on each RMSD between the experimental and force field structure. Over a large enough dataset, as used in these three studies, these errors may cancel out for each force field, making their performances seem roughly equal.

3.3. Bioactive Conformation Searching Comparisons

This final section concerns studies where the conformational search performance of different force fields is assessed by comparison of conformations found by the force field, with the bioactive conformation of ligands as determined by crystallography of ligand-protein complexes. However, these works provide much more detail on the comparisons, and were able to identify the best performing force fields in this type of comparison.

Gürsoy and Smieško compared the abilities of the OPLS3, OPLS-2005, MMFFs and AMBER* force fields from MacroModel to reproduce the experimental bioactive conformations of protein ligands from a conformational search,[129] using the same RMSD retrieval rate assessment as Bai et al.[118] (see above). Two-step conformational searches were performed on the set of 809 ligands. The first step used the MCMM/Low-Mode search method and the OPLS-2005 force field in the GBSA(water) solvent model, and retained all conformers up to 50 kcal mol^{-1} above the minimum energy conformation. The second step took the conformer with greatest RMSD from the crystal structure of the ligand, and from this structure, searched with each of the four force fields, whilst only retaining conformers up to 5 kcal mol^{-1} above the minimum. Results for the four force fields were similar, however OPLS3 showed calculated vs experimental RMSDs to be slightly lower than the other force fields.

As part of a reparameterisation of MMFF94s,[130] Wahl et al. compared MMFF94s (before and after reparameterisation) against OPLS3 and MM2. The same validation method of RMSD retrieval rates of bioactive conformations was used with a set of 2912 ligands. An actual searching algorithm was not used, but 1000 random conformations of each ligand were generated and optimised to an energy minimum by each force field. Before the reparameterisation of MMFF94s (by fitting inaccurate torsional profiles to those calculated at the MP2/cc-pVTZ level of theory), OPLS3 was the best force field for reproducing the bioactive conformations of the ligands, with MMFF94s being close but slightly poorer, and MM2 having distinctly worse performance. However, after reparameterisation, MMFF94s was able to match OPLS3's ability to find the bioactive conformations.

These two studies have shown that OPLS3 is an acceptable force field for finding bioactive conformations of protein-binding ligands from conformational searching. This directly contrasts with studies from the previous section, where no force field was found to be better than any others for reproducing experimental structures. OPLS3 appears to have a slight advantage in this area, which likely arises since it was initially parameterised with experimental crystal data.[131]

4. Conclusion

To conclude, we have reviewed a large number of papers where the "MM" force fields (MM2, MM3 and MMFF94) show strong performances in the conformational analysis of organic molecules. The conformational analysis studies were those that determined the energies and geometries of small organic molecule conformers with different force fields and compared them to a reference method (from experiment or QM method). The closer the force field calculated properties were to the reference, the better the performance of the force field was stated to be. Thus, we believe we are able to make a recommendation for their use in this area, particularly MMFF94, with the caveat that a few systems may be better suited to a different

force field. From papers that included comparison of other force fields with the polarisable AMOEBA force field, we found that it consistently showed the strongest results and we suggest further studies where comparisons with AMOEBA are carried out, particularly for conformational searching. On the other hand, UFF always showed the worst performance of any of the force fields it was tested against, and so we do not recommend the use of UFF for studying the conformational properties of organic molecules.

In more recent years, as computing power has increased and conformational energies are more readily evaluated with advanced QM methods, force fields have become more useful for conformational searching. However, there is an unfortunate lack of studies comparing the performances of different force fields in conformational searching, especially with *ab initio* optimisation as the measure of their abilities. Conformational search comparisons where the different force fields are assessed by how well they reproduce experimental conformations find that: either there is little difference between force fields for this type of study, or, a force field parameterised with crystal data (OPLS3) may show slightly better performance. Whatever the case may be, it is clear that more work is needed to find the best performing force field for the conformational searching of organic molecules.

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