Efficient Parameterization of Torsional Terms for Force Fields

Steven K. Burger, Paul W. Ayers,* and Jeremy Schofield

A novel method is presented for fitting force-field dihedral angles using an ensemble of structures generated from an *ab initio* Monte Carlo simulation. Importance sampling is used to achieve an efficient algorithm using a low level of theory to minimize the system at each step with the dihedral angles constrained, followed by dihedral fitting using the single point energies at a higher level of theory. The resulting method is an order of magnitude more efficient than the traditional method of doing a constrained scan over each dihedral independently. Also as the sampling is more uniformly distributed, the full surface is approximated to a greater accuracy. The dihedral fitting is done with a nonlinear optimization method to vary the phase as well as the force constant. The utility of the method is demonstrated by fitting dihedrals of methyl L-lactate, diisopropyl fluorophosphate, isopentenyl phosphate, a leucine dipeptide, and two inhibitors of Signal Transducer and Activator of Transcription 5. The results show that the Monte Carlo scheme is more efficient than constrained scans and is particularly effective at approximating the underlying potential energy surface when the dihedral degrees are coupled. © 2014 Wiley Periodicals, Inc.

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Introduction

To achieve long-time dynamics of large molecular systems molecular mechanic (MM) force fields (FF) are used to approximate what might otherwise be done with *ab initio* simulations. A FF may consist of any number of terms which attempt to mimic the potential energy surface (PES) of the molecular system. Often the most popular FF are those with the simplest structure since they can provide the longest-time scales.[1,2] The results of any such simulation are, of course, sensitive to the parameterization of the individual terms involved. The success of many FFs comes from the fact that many of the terms involved are transferable between systems.[3–7] For example, the force constants and equilibrium values for a hydroxyl group tend to be same regardless of the composition of the rest of the molecule.

Most FF consist of harmonic bonded terms that involve bonds, angles, dihedrals along with nonbonded terms to describe the Coulomb and Van der Waals interactions. Generally harmonic bonds and angles which do not have metal centers associated with them can be assigned based on the atom type. Such terms have high frequencies associated with them, and the simulation results tend not to be sensitive to differences between compounds. Van der Waal terms are also often transferable, being derived from bulk properties such as density and heat of vaporization.[8–10] When partial charges (monopoles) are used for the Coulombic term, the results are not as transferable although averaging over multiple conformations helps.[11–13] Also augmenting the FF with multipoles and polarizable terms improves the transferability but at a considerable computational cost.[14,15]

Dihedral terms are perhaps the most problematic term for a FF. Some values can be highly transferable for very simple systems such as the torsional profile of methylene groups. For more complex systems, torsional terms can be difficult to assign due to unexpected hyperconjugation effects[16,17] and interactions between substitutes over the course of the profile. When parameterized for individual systems torsions end up as catch-all terms for the differences between MM and quantum mechanical (QM) energies. Getting such terms correct for amino acids is known to be critically important for protein simulations as they can affect the rotamer populations of side-chain conformations.[18,19] For ligands, dihedrals can be automatically assigned based on atom type,[20] but often these results in profiles that differ dramatically from torsional terms derived using *ab initio* methods.[21]

A number of software packages, such as paramfit in AmberTools,[22] ForceFit,[23] Automated Frequency Matching Method,[24] and JavaGenes[25] have been developed to assign dihedral terms based on a set of configurations from which the MM and QM energies can be compared. However, these programs generally focus on how the parameters are fit and not how the structures are obtained. There are two methods that are often used to generate structures: (1) using the ensemble generated with molecular dynamics (MD) or (2) doing a scan of each dihedral coordinate of interest, minimizing over all the other degrees of freedom. Generally option (2) is preferred when developing terms as the effects from other dihedrals, which are not of interest, can be averaged out in the minimization. However, constrained optimization scans have problems associated with them. (1) The energy can change dramatically if a substituent group falls into a different configuration. This sudden change may happen at one level of theory but not at another, causing

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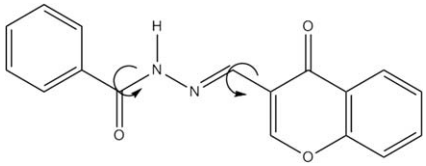
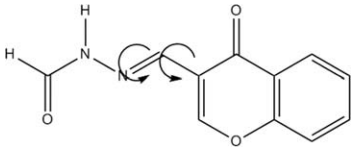
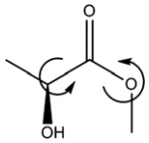
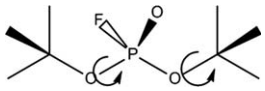
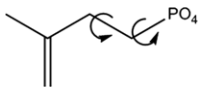
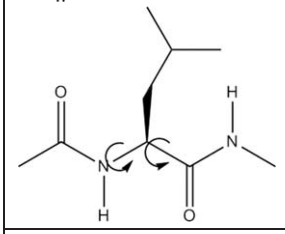
Table 1. Structures used to test various dihedral fitting methods.

Structure	Name
	STAT5 ligand 1
	STAT5 ligand 2
	(S)-Methyl L-lactate methyl ester
	Diisopropyl fluorophosphate
	Isopentenyl phosphate
	Leucine dipeptide

Varied dihedrals shown with arrows.

discontinuities in the profiles at different points. (2) If there are significant cross-terms between dihedrals, then the full potential will not be well described.

In this method, we propose to deal with these problems by taking an intermediate approach between purely sampling with dynamics and doing a constrained scan over each coordinate separately. This is done by sampling on the reduced PES[26,27] of the dihedral angles of interest, using the Monte Carlo (MC) method to generate the ensemble, while minimizing all other degrees of freedom. To avoid the high cost of minimizing the system at each step, importance sampling[28] is used. This involves doing the sampling at a low level of theory, while using a higher level of theory for accepting or rejecting points used in the dihedral fitting.[29] This gives an efficient algorithm that scales well with dimensionality as the MC method scales approximately linearly rather than the exponential scaling of doing a full scan.

The method was tested on the compounds: methyl L-lactate, diisopropyl fluorophosphate, isopentenyl phosphate, a leucine dipeptide, and two inhibitors of Signal Transducer and Activator of Transcription 5 (STAT5) shown in Table 1. Methyl L-lactate, diisopropyl fluorophosphate, isopentenyl phosphate, and a leucine dipeptide were chosen as they are small and their dihedral angles are not completely independent of one another. The STAT5 ligands were chosen to see how effective the MC method would be for larger ligands relevant for medicinal purposes. These ligands in particular are part of a larger set which has recently proved of interest in developing anticancer treatments.[30–32] Being able to assign better dihedral terms for these ligands would allow one to achieve much better results for free energy of binding calculations.[33] The results here were done in the gas phase, but they could have just as easily been done with an implicit or explicit solvent if one wanted to account for some of the environmental effects.

The results of the tests show that using importance sampling in conjugation with the MC method is a particular effective way to generate an ensemble of structures for dihedral fitting. Ensembles generated in this way give a much better agreement on the full PES, and computationally these ensembles are significantly more efficient than performing constrained scans.

Method

Force-field terms

While there are a wide range of FF we focused on the traditional AMBER[6] FF which has a potential of the form,

$$V=\sum_{\text{bonds}} k_b(r-r_0)^2+\sum_{\text{angles}} k_a(\theta-\theta_0)^2+\sum_{\text{dihedrals}} \frac{1}{2}V_d[1+\cos(n\phi-\psi_d)] + \sum_{i,j}\frac{A_{ij}}{r_{ij}^{12}}-\frac{B_{ij}}{r_{ij}^{6}}+\sum_{i,j}\frac{q_iq_j}{4\pi\varepsilon_0 r_{ij}} \quad (1)$$

where r_{ij} is the internuclear distance between atoms and the last two terms are the vdW and Coulombic terms. For the purposes of this work, we are primarily interested in the dihedral term, which when written out fully is,

$$V(\phi)=\sum_{i=1}^{\text{dihedrals}}\sum_{n=1}^{N_i}\frac{1}{2}V_{i,n}[1+\cos(n\phi_i-\psi_i)] \quad (2)$$

where the index i runs over all the dihedral angles in the system and N_i is the number of coefficients used with each dihedral. As eq. (2) is a Fourier expansion, with sufficiently large N_i a perfect agreement can be made between the QM and MM potential profile. However, usually for sp^3 bonded centers N_i is set no larger than 3 and for sp^2 hybridized orbitals N_i is set to 2.

Parameter optimization

For a given ensemble of conformations, the parameters can be optimized to minimize the norm of the residual between the MM and QM energies. The residual takes the following form,

$$f(x)=\boldsymbol{E}^{\text{MM}}_{\text{dihedral}}(\{V_{i,n},\psi_i\};\phi_i)-\boldsymbol{E}^{\text{MM}}-\boldsymbol{E}^{\text{QM}}+\boldsymbol{I}c \quad (3)$$

where the vectors **E**, are the energies of each conformation and c is an adjustable constant. In this case, E^{MM} are the MM energies excluding the dihedral angles of interest. The extra adjustable constant c can simply be chosen as the difference in the QM and MM global minimum energies, however, usually significant better results are obtained by letting it vary. For the residue, the independent variable is $x=\{V_{i,n},\psi_i,c\}$. This is a nonlinear equation that can be solved with Levenberg–Marquardt method or with a least-square minimization.[34,35] Many authors take a further step of simplifying the optimization by constraining the phase factor to a fraction of the multiplicity (0°, 120°, or 180°). This reduces eq. (3) to a linear equation which may be trivially solved. While this is sometimes helpful in preserving symmetry, usually it is an unnecessary constraint that can dramatically reduce the quality of the fit.

A further constraint which is often added to eq. (3) is to require that the force constants, $V_{i,n}$, remain positive. While this seems physically reasonable, we have not included such a constraint as it also unnecessarily reduces the quality of the fit.

The derivative of eq. (3) with respect to the independent variables is the Jacobian matrix, $J=\nabla f(x)$. This can be used to solve the nonlinear equation with the Levenberg–Marquardt method, details of which can be found in Ref. [35]. Here, we follow the approach of solving eq. (3) as a least-square minimization with the function, $g(x)=\frac{1}{2}\sum_{i=1}^{N} f_i(x)\cdot f_i(x)$. The resulting Newton equations are,

$$J^TJ\Delta x=-J^Tf \quad (4)$$

which can be used to generate a sequence of steps terminating when either $\|\Delta x\|<TOL$ or $\|\nabla g(x)\|<\text{TOL2}$, where $\nabla g(x)=J(x)^Tf(x)$.

Importance sampling

The scheme used here is similar to that used in Ref. [29], and so we only briefly review the details. The idea is that statistically independent states can be drawn from a Markov chain generated with an approximation to the true function. In Ref. [29], a classical potential was used to generate the states, with sampling done at the DFT level after every 1000 MC steps. For the compounds considered here, a good description of MM function is generally unknown *a priori*, and MM tends to be a poor approximation. Instead, we either use a semiempirical method or a low-level QM method for the optimization with single point (SP) calculations done on the minimized structure at a higher level of theory. The QM MC steps are accepted based on the energy difference given by,

$$\Delta\Delta E=\Big(E_{\text{high}}(X_{\text{new}})-E_{\text{low}}(X_{\text{new}})\Big)-\Big(E_{\text{high}}(X_{\text{old}})-E_{\text{low}}(X_{\text{old}})\Big) \quad (5)$$

where the configurations X_{new}, are generated on the reduced PES using the Metropolis–Hastings MC method.[36] In the approach used in Ref. [29], a sufficient large number of steps at the lower level of theory are taken to ensure that the configurations are statically independent. Here, we are less concerned with achieving a Markov chain that has a Boltzmann distribution (although in the limit this is certainly true), so sampling is done at every step. Using importance sampling with MC there end up being three principle parameters which control the resulting ensemble of structures generated: M, the number of steps, S, the step-size of the dihedrals, and T, the temperature.

Computational Details

For an initial guess of the dihedral parameters, the general AMBER force field (GAFF)[37] was used, with atom types and other FF terms being assigned with the AmberTools software LEaP and antechamber.[22] AMBER 11 was used for the MM calculations and Gaussian09[38] for the QM calculations. The high-level QM calculations were done with MP2/cc-pVTZ for methyl L-lactate and HF/6-31G(d) for all other systems. The partial charges were assigned to atoms with a restrained electrostatic potential fit[39] using the electrostatic potential from the HF/6-31G(d) density and a 0.0005 a.u. restraint on the charges. The full and partial scans of the PES were done from the global minimum using a fixed step-size of 10° for the dihedral angles. The full scan involves freezing two dihedrals and minimizing over all the other degrees of freedom to get the energy, while for the partial scan each dihedral is frozen separately. The full

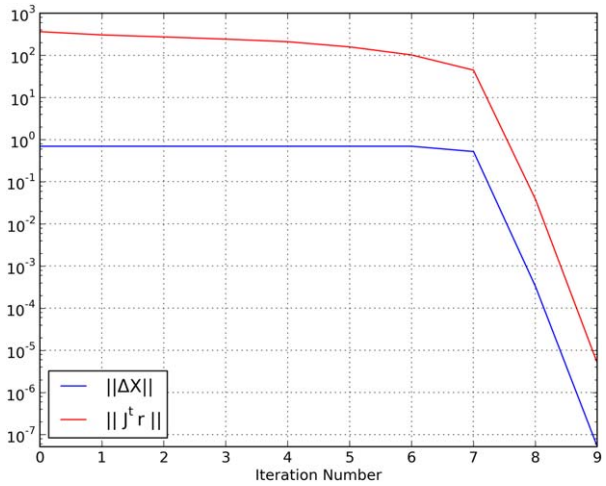


Figure 1. Convergence plot of the dihedral parameters of methyl L-lactate. The step-size is restricted so that $\|x\| \leq 0.7$. When this constraint is not active (after iteration 6) then convergence is superlinear.

scan involved 36^2 minimizations while the partial scan 2×36-1 minimizations.

The nonlinear optimization detailed in the Parameter optimization section was implemented with a python program. To make sure the parameters converged, the step-size was scaled when necessary so that $\| \Delta x \| \leq 0.7$, where x includes both the barrier heights (kcal/mol) and the phase (in radians). Also the constant c was set initially to the average difference between the QM and MM energy values. Convergence was defined with TOL=10^{-3}. Only two dihedrals were fit for each compound to make the comparison to the reduced PES scan tractable. For methyl L-lactate, diisopropyl fluorophosphate, and isopentenyl phosphate, the multiplicity was set to 3 which resulted in 13 parameters being optimized while for the rest of the molecules the multiplicity was set to 2 giving nine adjustable parameters.

The MC algorithm was changed slightly by adding in an attempt to rotate the dihedral by a factor of 360° divided by the multiplicity, if a random number is less than 0.05. This was found to significantly improve the sampling (results not shown).

Parallel tempering (PT)[40] was also attempted. This was done with a second MC simulation running at twice the temperature of the first with an exchange frequency of ½. The standard Metropolis–Hastings criterion was used to determine the acceptance of an exchange.

The quality of the fits was determined by the root mean square deviation (RMSD), which can be written in terms of the least-squares function $g(x)$ as, RMSD=$\sqrt{g(x)/n}$. Error estimates for the MC runs were determined by doing 15 separate runs using a different initial structure each time and taking the standard deviation of the results.

Results and Discussion

(S)-Methyl L-lactate methyl ester

Methyl L-lactate was used as a benchmark to study how the various different sampling methods and levels of theory would influence the quality of the fit. The parameters were fit using nonlinear least-square optimization. As part of the second derivative term is used in eq. (4) for the optimization, the parameters converge superlinearly. This is shown in Figure 1. The initial flat part of the graph is due to the step-size being scaled to ensure that final solution is close to the initial guess. Once the parameters are closer to the solution, superlinear convergence sets in. Of note is that the solution is not always unique and the results can vary depending on the initial guess. In this regard, methods that use a global optimizer such as a genetic algorithm[41] may produce a better solution. However, we tried using different initial parameters for many of the compounds and did not find any solutions which gave better RMSD values compared to those starting with the GAFF parameters (results not shown).

The various methods tested are shown in Table 2. The best possible results for the full surface are obtained with an exhaustive, full two-dimensional (2D) scan in increments of 30° for each dihedral. This plots out the PES from which the dihedral angles can be fit. While this gives the best fit to the entire surface as we have not weighted the points by their energy, it does not always give impressive results for the most relevant region of the PES which we have defined as those points which are within 5 kcal/mol of the minimum.

For methyl L-lactate, the parameters from GAFF and from a partial scan of the surface are significantly worse than the ideal ones from a full scan, with the error being almost twice as large. This is likely due to the fact that the dihedrals are more strongly coupled for this compound than for many others. The 2D PES at the MP2/cc-pVTZ level is shown in Figure 2. The GAFF and partial scan derived parameters give good qualitative agreement with the surface, partly due to the

Table 2. RMSD (kcal/mol) of various methods used to fit the dihedrals terms compared to a 2D scan using MP2/cc-pVTZ.

	All	<5 kcal/mol
Full 2D scan	0.54	0.46
Partial scan	1.16	1.22
GAFF	1.24	0.82
HF/3-21G		
S = 20	1.00 +/− 0.10	0.72 +/− 0.08
S = 40	1.63 +/− 0.42	2.06 +/− 0.53
S = 60	0.74 +/− 0.09	0.46 +/− 0.11
S = 20 T = 1000K	1.14 +/− 0.11	1.09 +/− 0.15
S = 20 (PT)	1.11 +/− 0.23	1.73 +/− 0.41
S = 100	0.89 +/− 0.27	0.94 +/− 0.27
S = 60 T = 4000K	0.67 +/− 0.26	0.74 +/− 0.23
S = 40 M = 400	0.75 +/− 0.07	0.52 +/− 0.18
S = 40 (Constrained bonds)	2.34 +/− 0.18	1.85 +/− 0.52
S = 40 (Constrained bonds and angles)	3.93 +/− 1.05	2.91 +/− 1.07
Semi empirical		
S = 20 (AM1)	1.32 +/− 0.08	2.16 +/− 0.82
S = 20 (PM3)	1.78 +/− 0.17	1.14 +/− 0.25
S = 60 (AM1)	1.35 +/− 0.29	2.13 +/− 0.48

Comparison is made either with all the points on the PES or only using points that are within 5 kcal/mol of the global minimum. The MC runs were done with T = 2000 K and M = 200 unless otherwise indicated. Error estimates were obtained by performing 15 independent runs using different initial structures for each run.

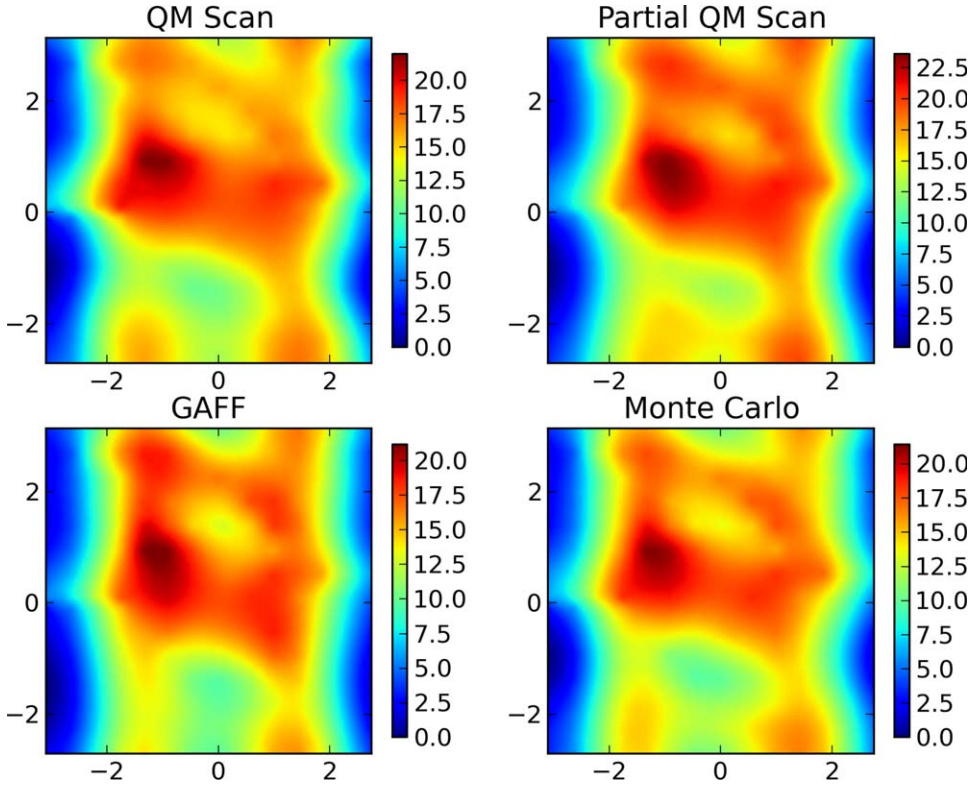


Figure 2. 2D PES (in kcal/mol) of the dihedral angles (in radians) of methyl L-lactate at the MP2/cc-pVTZ level. "QM Scan" is the exact surface while the other three are the MM surfaces. The Monte Carlo method uses $S = 60$ and $T = 2000$ K. Energy is in kcal/mol.

steric interactions being well-described. However, reducing the error by accounting for more of the fine features of the PES requires methods which give a more representative sample of the entire surface.

For implementing importance sampling with the MC method, the two most important considerations were the level of theory for the approximate potential and the MC algorithm parameters. As it was desirable to explore a larger sample of the surface generally higher temperatures and larger than normal step-sizes were used.

For the level of theory, very quick methods such as MM or semiempirical will work for some cases but fail spectacularly for others. In general, the geometries were significantly different from *ab initio* calculations so that RMSD did not improve sufficiently even when using a longer MC run or larger step-sizes. For the higher-level MP2 or HF calculations, we found that HF/3-21G was sufficient for importance sampling.

For a relatively small sample of points, using a maximum number of iterations of 200 ($M = 200$) allowed a reasonable evaluation of the effectiveness of changing certain parameters. For $M > 500$, the results were less affected by changes in parameters. In general, using a large step-size ($S > 40^\circ$) and a higher temperature ($T > 1000$K) was particularly effective in obtaining a good ensemble of structures. Although clearly in Table 2, $S = 40$ is an anomaly which highlights the importance of doing more sampling for reliable results.

PT was used in an effort to improve the sampling. For some of the other compounds, this proved to be useful in reducing the RMSD, but generally the results were mixed. Increasing the step-size and temperature alone seemed to be sufficient to explore the surface.

In an effort to improve the correspondence between the levels of theory in the importance sampling, we attempted to constrain the bonds and angles of the structure to the values of the minimized structure from the higher level of theory. This significantly worsened the results either when just the bonds or when both bonds and angles were frozen.

In Table 3, a comparison of the number of higher level calculations is given. With importance sampling only SP calculations are done at the end of the MC run as the structures are minimized during the MC steps at the lower level of theory. As a result with an acceptance ratio of 0.63, only 126 calculations need to be performed. This is more than an order of magnitude more efficient either the full or partial scan. In both cases, the scans are done by minimizing the structures which require SP and gradient calculations for each step on the surface. Of course the GAFF assigns the dihedral terms based on the atom types and so does not require any further calculations to determine the dihedral parameters.

Table 3. Number of gradient plus the number of SP evaluations used by each method for determining the dihedral angles of methyl L-lactate.

Full scan	4640
Partial scan	1564
GAFF	0
MC $S = 60$	126

Table 4. Comparison of methods for all compounds.

Molecule	Method	RMSD (all)	RMSD (<5 kcal/mol)	Number of evaluations
Diisopropyl fluorophosphate	Full scan	0.46	0.45	6008
	Partial scan	0.62	0.54	2128
	GAFF	1.89	1.67	0
	MC ($S = 40$)	0.50	0.50	176
Isopentenyl phosphate	Full scan	1.92	4.78	6406
	Partial scan	3.51	3.00	3712
	GAFF	3.52	3.14	0
	MC ($S = 40$, $M = 400$)	3.33	2.68	250
Leucine dipeptide	Full scan	1.18	2.20	11172
	Partial scan	1.48	2.19	4304
	GAFF	2.72	1.01	0
	MC ($S = 40$, $M = 400$)	1.33	1.31	283
STAT5 ligand 1	Full scan	2.14	8.46	6954
	Partial scan	3.31	3.59	3658
	GAFF	3.03	3.20	0
	MC ($S = 40$, $M = 400$)	2.77	1.30	284
STAT5 ligand 2	Full scan	1.35	3.67	6892
	Partial scan	1.78	2.54	2226
	GAFF	3.64	3.11	0
	MC ($S = 40$)	2.0	1.90	180

Other compounds

A comparison for all other compounds excluding methyl L-lactate is made in Table 4 (the converged dihedral values can be found in Supplementary Table 1). For these compounds, the difference is less dramatic when compared against the traditional method of doing partial scans or a full scan of the surface. This is most likely due to the fact that the dihedral angles are less coupled, which can be seen in Figure 3, the PES scan of the STAT5 ligand (the PES scans of the other compounds in Table 1 is given in the Supplementary Information). However, in the most relevant regions of the PES (points less than 5 kcal/mol from the minimum) the improvement is much

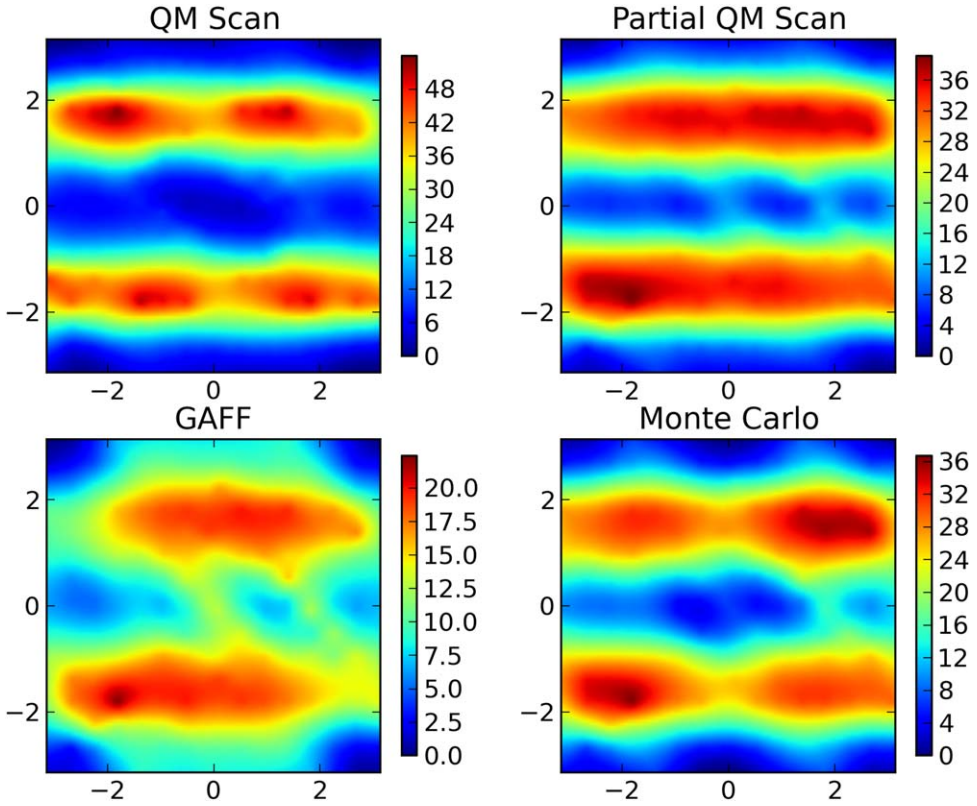


Figure 3. 2D PES (in kcal/mol) of the dihedral angles (in radians) of STAT5 ligand 2 at the HF/6-31G(d) level of theory. The two dihedrals are not strongly coupled in this case and the partial scan fitting gives a MM PES similar to the MC surface. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

more significant for the compounds. The difference between the full QM scan and the MC method is most significant for the higher energy regions which tends to make the plots appear visually to more different. If a higher temperature is used and much longer sampling, then the plots end up being quite similar.

For Table 4, we only show a single MC run using $T = 2000$ K. In most cases, 200 iterations were sufficient to obtain a good approximation to the full scan results, but for some systems more steps were needed. If a larger dataset were used, and the full scan QM results were not available to compare against, then it would be prudent to use $M = 400$ for all cases. In either case, the number of SP required at the higher level of theory is still more than order of magnitude less than using scans.

Conclusions

When building an ensemble of structures to use for dihedral fitting, the standard methods of doing a partial scan or using a MM trajectory often do not give good agreement with the QM derived terms that account for the full surface. Importance sampling using the MC method bridges the gap between the two approximations by doing sampling relatively quickly at the lower level while still retaining structures that are close the higher-level QM optimized ones. We have shown that MM and semiempirical functions are insufficient for the compounds we tested, but that a low-level *ab initio* calculations can give good results. To achieve a wide sampling of the ensemble high temperatures and larger step-sizes were used, along with occasional flips based on the multiplicity of the dihedrals. The number of higher-level QM calculations required was an order of magnitude lower than doing constrained scan, yet the results were better than doing partial constrained scans of the surface. This was particular true for the regions close to the minimum which would likely be the only parts visited during a simulation. We hope this method will be of use to other researchers as they develop FF for their own ligands.

Keywords: parameterization · force fields · dihedral angles · optimization · Monte Carlo

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