

# Evaluation and Reparametrization of the OPLS-AA Force Field for Proteins via Comparison with Accurate Quantum Chemical Calculations on Peptides<sup>†</sup>

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We present results of improving the OPLS-AA force field for peptides by means of refitting the key Fourier torsional coefficients. The fitting technique combines using accurate ab initio data as the target, choosing an efficient fitting subspace of the whole potential-energy surface, and determining weights for each of the fitting points based on magnitudes of the potential-energy gradient. The average energy RMS deviation from the LMP2/cc-pVTZ(-f)/HF/6-31G\*\* data is reduced by ca. 40% from 0.81 to 0.47 kcal/mol as a result of the fitting for the electrostatically uncharged dipeptides. Transferability of the parameters is demonstrated by using the same alanine dipeptide-fitted backbone torsional parameters for all of the other dipeptides (with the appropriate side-chain refitting) and the alanine tetrapeptide. Parameters of nonbonded interactions have also been refitted for the sulfur-containing dipeptides (cysteine and methionine), and the validity of the new Coulombic charges and the van der Waals  $\sigma$ 's and  $\epsilon$ 's is proved through reproducing gas-phase energies of complex formation heats of vaporization and densities of pure model liquids. Moreover, a novel approach to fitting torsional parameters for electrostatically charged molecular systems has been presented and successfully tested on five dipeptides with charged side chains.

## I. Introduction

The development of an accurate molecular modeling force field for proteins is a central task of biomolecular modeling. Over the past 20 years, intensive efforts have been devoted to this task in a substantial number of research groups.<sup>1</sup> Although there has been significant improvement in the quality of force fields during this time, it is not yet the case that uniformly high accuracy has been achieved. Consequently, efforts are ongoing to produce the next generation of force fields which will remedy many of the deficiencies that have been detected in presently available methods.

A major problem with all widely used protein force fields is the functional form of the potential energy. At present, this functional form has significant restrictions, for example the use of atom-centered charges (as opposed to a more accurate description of the molecular charge distribution, as might be achieved by explicitly representing lone pairs on electronegative acceptors such as oxygen) and the failure to treat electronic polarization explicitly. We and others have shown that, unless the functional form is modified to be more realistic, some errors in energetics cannot be overcome.<sup>2,3</sup> However, it is still useful to ask how accurate one can make the standard functional form simply by adjusting parameters. This is a useful direction to pursue for three reasons. First, fixed charge, atom-centered force fields are very fast to evaluate computationally and, even when superior functional forms are developed, will often be the method of choice for rapid screening of large systems (alter-

natively, one might represent a small part of a large system with the more accurate functional form and the remainder of the system with the simpler form). Second, the process of refitting the parameters is a good way to develop automated and improved fitting technology, which can then be applied to the more complex representations needed to achieve the highest accuracy. Third, the overwhelming majority of applications are currently being run with force fields of standard functional form; an assessment of how accurate such calculations are is of interest to those carrying them out.

Force fields based on liquid-state simulations, the OPLS series of force fields, have been under development in one of our laboratories for almost 20 years.<sup>1d</sup> These force fields have proved to be highly successful in computing liquid state thermodynamic properties<sup>4</sup> and more recently in protein and protein–ligand modeling.<sup>5</sup> Although nonbonded interactions (charge–charge and van der Waals terms) can be obtained from liquid state calculations, parameters such as stretching, bending, and torsional terms are generally fit to quantum chemical calculations. Over the years, the quality of these calculations has been systematically upgraded, with the most recent OPLS-AA force field being fit to 6-31G\*/HF torsional energetics obtained from small molecule side chain analogues.<sup>1d,6</sup> At the time that OPLS-AA was parametrized, limitations on quantum chemical technology precluded the use of a more accurate level of theory or the examination of larger molecular representations of the amino acid side chains and backbone. Over the past 5 years, improvements in both computational hardware performance and quantum chemical software have qualitatively altered this situation. In particular, the development of pseudospectral local MP2 (LMP2)

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methods with large basis sets in the Jaguar suite of ab initio programs<sup>7</sup> provides a demonstrably improved, yet readily accessible, methodology for computing conformational energy differences. Furthermore, Jaguar allows significantly larger system to be investigated along with the substantial upgrade in the quality of the quantum chemical energetics.

The present paper reports our initial effort to utilize these new available quantum chemical capabilities to evaluate and improve the OPLS-AA force field with regard to its performance for the intramolecular conformational energy surface. To do this, we generate a large data set, more than 2000 data points, of energies for the 20 amino acids based on geometry optimization at the HF/6-31G\*\* level followed by single-point LMP2/cc-pVTZ(-f) calculations. This level of theory has previously been shown to yield average deviations for conformational energy differences of 0.25 kcal/mol from carefully calibrated experimental data, a value that is likely close to the experimental error bars for this test suite.<sup>8a</sup> The data encompasses a complete two-dimensional surface for backbone torsions of the alanine dipeptide, along with ~300 rotamer states generated initially via OPLS-AA and then minimized and evaluated via the quantum chemical protocol described above. Around each minimum, restrained torsional surfaces are obtained for each torsion to be parametrized, yielding a robust fitting protocol for all cases studied here. The fitting protocol has been automated using the insights gained in studying this large dataset and can now be employed in the parametrization of other organic molecules.

The quantum chemical data is first used to evaluate the performance of the current OPLS-AA force field. Additionally, we include comparisons with the MMFF94 force field of Halgren.<sup>1c</sup> These two force fields displayed the best performance in our previous evaluation of alanine tetrapeptide conformational energetics using the same level of quantum chemical theory.<sup>8b</sup> In the present case, where a wide range of side chain energetics is examined, OPLS-AA displays a significant, although not overwhelming, advantage. Then, backbone and side chain torsional parameters are refit to the quantum chemical data; in one case, which we discuss in detail, van der Waals and charge parameters are also modified, on the basis of new liquid-state simulation data. The resulting force field, which we designate OPLS-AA/L (the L for LMP2), has an RMSD from the quantum chemical data that is less than half of the value obtained from either OPLS-AA or MMFF, a very substantial improvement which one would expect to see have a significant impact on protein and protein–ligand modeling efforts. On the other hand, certain types of errors are not reparable by refitting; these will require alteration of the form of the potential function to address. We have already published a paper, demonstrating that the problem of over-polarizing protein-related molecular systems in gas-phase can be successfully resolved by use of a polarizable force field,<sup>3</sup> but each type of the errors will have to be examined in detail when the new functional form results are generally available.

The evaluation and parametrization of charged residues constitutes a special case in that the effects of solvation here are sufficiently large that simply fitting to the gas phase surface is not likely to produce the most meaningful set of results. Therefore, we have devised a new protocol in which the rotamer state minima for charged side chains are determined using a solvated conformational search, and the torsional profiles are similarly mapped out in a continuum solvent environment. To avoid having to make detailed comparisons between the QM and MM versions of our continuum solvation methodology, we

use the solvation term to define the region of phase space for which fitting is to be carried out; this for example eliminates regions in which the side chain is directly bonded to the backbone, a conformation that is never seen in real proteins but appears routinely if one carries out a gas phase conformational search. Once a reasonable set of solution phase geometries is defined, fitting can be done in the gas phase under the assumption that the solvation models themselves need to be fit independently to reproduce experimental free energies of solvation of the relevant functional groups. To our knowledge, this is the first time that an extensive set of protein force field parameters has been developed using continuum solvent models to define the relevant phase space.

The remainder of the paper is organized as follows. In section II, we discuss the quantum and molecular mechanics computational methodology, including the functional form of the OPLS-AA force field. Section III presents our approach to generating quantum chemical data that covers the relevant conformational space and describes the other aspects of the torsional fitting. Section IV discusses the refitting of OPLS-AA, including both torsional refitting to the quantum chemical data and refitting of the parameters of the sulfur-containing side-chain groups of cysteine and methionine via new gas- and liquid-state simulations. A detailed analysis of each amino acid side chain is presented here, discussing where errors are occurring and which errors are intractable to the current refitting efforts. This section also summarizes the results and compares them with OPLS-AA and with MMFF. Finally, section V, the conclusion, discusses new directions.

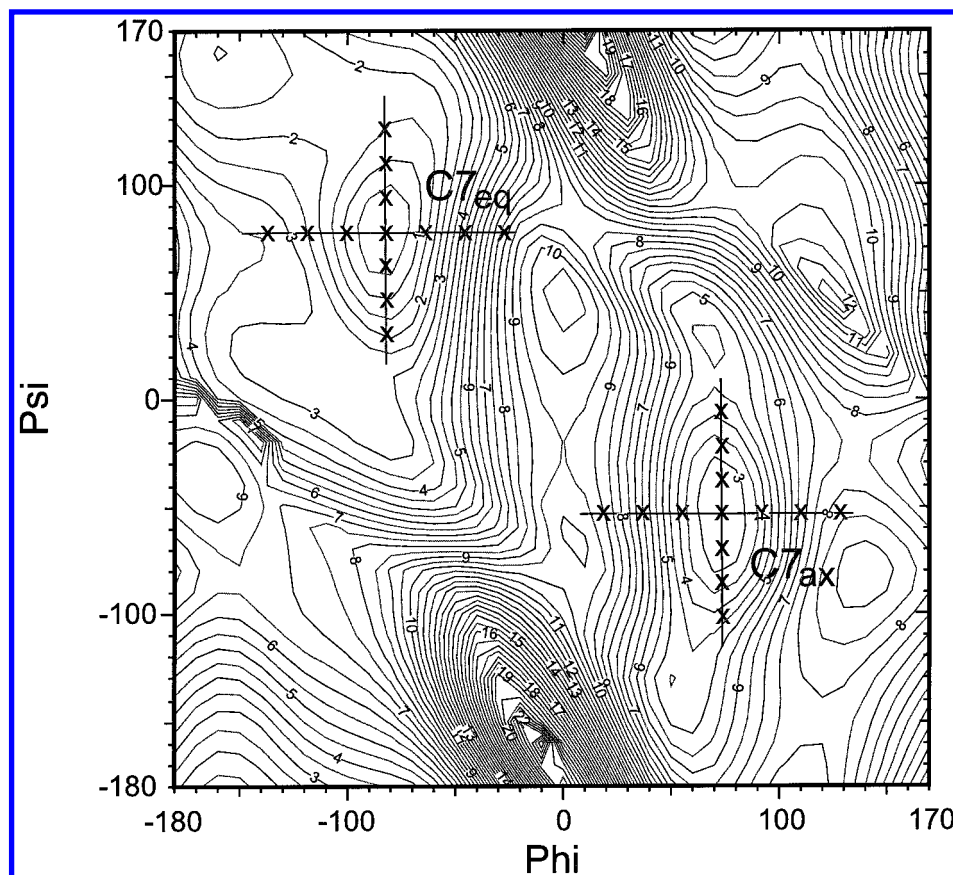
## II. Ab Initio and Molecular Mechanics Calculations

**Quantum Mechanical Methods.** All of the ab initio calculations were run with Jaguar software.<sup>7</sup> The pseudospectral generalized valence bond (PSGVB) electronic structure code was used. It has already been established and reported that the PSGVB technique allows high accuracy, while considerably increasing calculation speed for large molecular systems.<sup>8b</sup> Geometry optimizations of large structures are carried out 5–10 times faster than with Gaussian 92.<sup>9,10</sup> All of the final single-point calculations were done with the cc-pVTZ(-f) basis set and local MP2 (LMP2). In this case, time scaling of  $N^{2.5}$  for the basis set size  $N$  is observed, whereas the Gaussian MP2 gives  $N^5$  time dependence.<sup>11</sup> The computational efficiency of the quantum mechanical methods employed has allowed us to obtain the extensive set of data needed for the torsional refitting. Geometry optimizations were done at the HF/6-31G\*\* level. Where noted, ab initio data were taken from previously published papers.

**OPLS-AA Force Field.** The total energy  $E_{\text{tot}}$  of a molecular system was evaluated as a sum of the following components: the nonbonded energy  $E_{\text{nb}}$ , bond stretching and angle bending terms  $E_{\text{bond}}$  and  $E_{\text{angle}}$ , and the torsional energy  $E_{\text{torsion}}$ . The nonbonded part was computed as a sum of the Coulomb and Lennard-Jones contributions for pairwise intra- and intermolecular interactions:

$$E_{\text{nb}} = \sum_{i < j} [q_i q_j e^2 / r_{ij} + 4\epsilon_{ij} (\sigma_{ij}^{12} / r_{ij}^{12} - \sigma_{ij}^6 / r_{ij}^6)] f_{ij} \quad (1)$$

Geometric combining rules for the Lennard-Jones coefficients were employed:  $\sigma_{ij} = (\sigma_{ii} \sigma_{jj})^{1/2}$  and  $\epsilon_{ij} = (\epsilon_{ii} \epsilon_{jj})^{1/2}$ . The summation runs over all of the pairs of atoms  $i < j$  on molecules A and B or A and A for the intramolecular interactions. Moreover, in the latter case, the coefficient  $f_{ij}$  is equal to 0.0



**Figure 1.** Cross-like torsional fitting subspace, exemplified on the alanine dipeptide  $\phi/\psi$  potential-energy surface. The crosses were placed at each minima, and each arm contained four fitting points. Some crosses and points are omitted for clarity on this figure.

for any  $i$ - $j$  pairs connected by a valence bond (1-2 pairs) or a valence bond angle (1-3 pairs).  $f_{ij} = 0.5$  for 1,4 interactions (atoms separated by exactly three bonds) and  $f_{ij} = 1.0$  for all of the other cases.

The bond stretching and angle bending energies were obtained in accordance with eqs 2 and 3:

$$E_{\text{bond}} = \sum_{\text{bonds}} K_r (r - r_{\text{eq}})^2 \quad (2)$$

$$E_{\text{angle}} = \sum_{\text{angles}} K_{\Theta} (\Theta - \Theta_{\text{eq}})^2 \quad (3)$$

Here the subscripts eq are used to denote the equilibrium values of the bond length  $r$  and angle  $\Theta$ .

Finally, the torsional term was computed as follows:

$$E_{\text{torsion}} = \sum_i \frac{V_1^i}{2} [1 + \cos(\phi_i)] + \frac{V_2^i}{2} [1 - \cos(2\phi_i)] + \frac{V_3^i}{2} [1 + \cos(3\phi_i)] \quad (4)$$

with the summation performed over all of the dihedral angles  $i$ .

Values of all of the parameters were taken directly from the standard OPLS-AA,<sup>1d</sup> with the exception of those torsional energy Fourier coefficients which have been refitted in this work. There were also cases when protein side chains had new values of some nonbonded parameters, and those cases are described in detail below.

**Gas-Phase Geometry Optimizations.** OPLS-AA gas-phase geometry optimizations were run for all of the points for which the ab initio calculations described above had been carried out. Exactly the same restrictions were imposed, that is, the dihedral angles defining the potential surface to be fitted were frozen, whereas all of the other degrees of freedom were left completely unconstrained. The minimizations were done with BOSS38 program,<sup>12</sup> and the convergence criterion for the calculations was set to  $10^{-6}$  kcal/mol.

**Liquid-State Simulations for Methanethiol and Ethane-thiol.** Liquid-phase Monte Carlo calculations were also carried out with BOSS38, in NPT ensemble, at  $5.96^\circ$  for the methanethiol and  $25^\circ$  for the ethanethiol at 1 atm. The setup included 267 molecules in a cubic box with periodic boundary conditions. In each case, we carried out  $2 \times 10^6$  Monte Carlo configurations of equilibration followed by  $8 \times 10^6$  configurations of averaging. Gas-phase runs necessary for computing the heats of vaporization consisted of  $2 \times 10^5$  configurations of equilibration and  $2 \times 10^6$  configurations of averaging. Volume moves were attempted every 600 configurations. Intermolecular interactions were truncated at 11 Å, with the standard correction for the interactions beyond that radius.<sup>13</sup> The electrostatic interactions were quadratically feathered to zero over the last 0.5 Å before the cutoff distance. Ranges of molecular and volume moves were adjusted to yield ca. 40% acceptance ratio. The solvent molecules were considered completely flexible.

### III. Torsional Fitting Technique

**Choosing the Fitting Subspace.** The least-squares fitting method was employed to obtain the improved torsional Fourier coefficients. Figure 1 illustrates the scheme we used for



generating the fitting data sets. One-dimensional sections cutting through minima on the dihedral potential-energy surface were employed. The cuts were oriented along the axis of the dihedral space, so that two adjacent points on the “cross”-like fitting subspace correspond to one and the same molecule with only one dihedral angle value different. The points were positioned 20° apart, four on each arm of the cross. Thus, each arm was extended over 80°, and so although only the potential minima were “sliced”, the resultant subspace presented a good sampling of the whole potential-energy surface.

A comparison of performance of torsional Fourier coefficients for the alanine dipeptide backbone obtained on the fitting subspace described in this section and on the whole  $\phi/\psi$  potential surface is given in the Results and Discussion section below.

The dipeptide conformers geometries were obtained as follows. For the alanine dipeptide, they were a result of study of the whole  $\phi/\psi$  map. All of the alanine dipeptide and tetrapeptide minima are described in ref 8b. For all of the other dipeptides, conformational search was performed with the BOSS program, followed by further geometry optimization with Jaguar at the HF/6-31G\*\* level. It should be pointed out that the number of the conformers used in this work is lower than the total number of all of the torsional potential-energy surface minima. However, we believe that the chosen subset of all of the minima is extensive enough, because our aim is to make sure that all biophysically relevant local configurations, especially those with hydrogen bonds, are represented, and not to check how well does the method perform on every single gas-phase dipeptide minimum.

At each of the points chosen for the fitting subset, a constrained minimization was run with the LMP2/cc-pVTZ(-f)/HF6-31G\*\* level. Only the dihedral angles involved in building the torsional space “crosses” were restrained; the rest of each system was completely flexible. Then the restrained minimizations were repeated with the molecular mechanics force field. Weighting of the points used in the fitting of the Fourier coefficients was done as described in the subsection below.

**Weighting of the Fitting Points.** The highest weight was given to those of the fitting set points located at or near the bottom of the torsional potential surface minima. This means that not only the global minimum but also the local ones were given higher weight; thus, the procedure was fundamentally different from a simple Boltzmann weighting. This is why we utilized the potential-energy surface gradient as the criterion. Areas with high magnitudes of the gradient correspond to steep parts of wells; low-gradient ones have to be closer to the bottom. Points close to the maxima would also have low magnitudes of the gradient, but they are less likely to be included in our sampling subsets because the base points for the crosses are the potential surface minima. Weighting was computed according to eq 5:

$$W_i = \exp(-A \cdot G_i) \quad (5)$$

where  $G_i$  denotes the absolute value of the gradient at the fitting point  $i$ , for which the weight  $W_i$  is computed, and  $A$  stands for a parameter defining the ratio of the maximum and minimum weights for the particular molecular system. In calculations presented in this work, the values of the parameter  $A$  were chosen for each system individually to achieve the best fit and fell into the range from 1.0 to 1000.0. The gradients were estimated on the basis of the values of the ab initio potential energy at the closest neighboring points of the subset (finite difference approach).

In some cases, weights of points around a certain minimum had to be uniformly adjusted in order to compensate for high ab initio gradients around it. Such cases are noted in the Results and Discussion section below. We also added artificial barriers to the ab initio energies around minima in certain cases to “wall in” the conformers and prevent them from disappearing when the energy wells were too shallow and happened to be lost in the fitting. This was done by manually modifying ab initio target data, so that the shallow minima appeared to be deeper to the fitting program. The resulting refitted torsional potential displayed minima that would not be present otherwise, and their depths were not as great as those of the modified data. Finally, our aim was to change as few of the OPLS-AA torsional Fourier coefficients as possible. This was especially important when dealing with such widely used dihedrals as, for example, the alkane-like C—C—C—C one, because we tried to avoid introducing new special torsion parameters types whenever possible. Sometimes this meant that we only performed a one-dimensional refitting for a particular dipeptide side chain. Details about fitting each particular molecular system are presented in the section below.

**Generating Data for the Charged Dipeptides.** A special technique was employed to deal with the five charged residues: aspartic and glutamic acid, lysine, protonated histidine, and arginine. Gas-phase optimizations could not be used to obtain the structures, because a geometry with a favorable gas-phase energy could have a significantly higher relative energy in aqueous solution. For example, conformers with internal hydrogen bonds represent one such case. So, liquid-phase SCRF runs at the HF/6-31G\*\* level were used to find the solvated energy minimum structures. Then liquid-phase restrained ab initio geometry optimizations were carried out, in the same way as for the uncharged dipeptides, to obtain the data for the cross-shaped fitting subspaces. Gas-phase single-point LMP2/cc-pVTZ(-f) calculations were carried out to find the final target energies. Molecular mechanics OPLS-AA and OPLS-AA/L runs were also performed in the gas phase, with all of the principal dihedral angles restrained to their positions found in the hydrated ab initio minimizations. This way we did not have to worry about the differences in simulating the liquid environment which would be present in parallel liquid-state molecular mechanics and quantum mechanics runs. On the other hand, it has been ensured that the relevant part of the conformational space has been sampled.

#### IV. Results and Discussion

**Alanine.** Alanine has a special place in this work. The backbone parameters obtained for the alanine dipeptide were used in all of the other peptide backbones. A number of sets of fitting points on the dihedral energy map to be used in the subsequent torsional refitting have been tested. The most suitable has been found to be the cross-like one described above, because it allows the best quality in reproducing the ab initio conformational energies. Each of the dipeptide minima had a cross associated with it. Each arm of the cross had four points, separated by 20°. Neither the standard OPLS-AA nor the OPLS-AA/L were able to reproduce all of the six ab initio alanine dipeptide minima, so we assigned a higher weighting factor to the  $C7_{eq}$ ,  $C5$ ,  $C7_{ax}$ , and  $\alpha'$  minima in the torsional fitting. Minimizations with the  $\phi$  and  $\psi$  angles constrained at their ab initio values were also performed. Although the  $\beta_2$  minimum is reproduced better with the new parameter set, the opposite is true for the  $\alpha_L$  one.

Table 1 shows the conformational energies for the alanine dipeptide obtained with the standard OPLS-AA, OPLS-AA/L,

**TABLE 1: Alanine Dipeptide, Energy of the Conformers, RMS Deviations in  $\phi$ ,  $\psi$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L
C7 <sub>eq</sub>	0.00	-0.31/7.5	-0.11/9.1
C5	0.95	1.01/8.7	0.82/4.5
C7 <sub>ax</sub>	2.67	2.24/4.5	2.46/0.5
$\beta_2$	2.75	7.90 <sup>c</sup>	6.57 <sup>c</sup>
$\alpha_L$	4.31	4.55 <sup>c</sup>	3.16 <sup>c</sup>
$\alpha'$	5.51	6.19/16.5	5.97/8.0
RMS error <sup>d</sup>		0.43/10.3	0.27/6.5

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF/6-31G\*\*, ref 8b. <sup>c</sup> Results of constrained minimizations,  $\phi$  and  $\psi$  angles kept fixed, no true minima. <sup>d</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results. The RMS computed for the C7, C5, and  $\alpha'$  minima only.

and LMP2/cc-pVTZ(-f)//HF/6-31G\*\*. Positions of all of the minima were shifted uniformly to achieve the smallest possible RMS energy error with respect to the quantum mechanics. To assess the accuracy of reproducing the conformer structures, we are also presenting RMS deviations from ab initio for the key dihedral angles. Those angles are  $\phi$  and  $\psi$  in the alanine dipeptide case, but the same method of checking the structural behavior was also employed for all of the other dipeptides, with both of the backbone angles  $\phi$  and  $\psi$  and the side chain dihedrals  $\chi$  contributing into this RMS. Such a method of judging the quality of our calculations is justified in the case of such molecules as di- and tetrapeptides, because we are using all of the key dihedral angles, and the rest of the molecular degrees of freedom cannot result in significant Cartesian geometry RMS deviations because of the fact of the thorough fitting of the bond stretching, angle bending, and methyl-like torsions parameters.

It can be seen from the results presented in Table 1 that both the energy RMS error and the dihedral RMS deviation from the ab initio data dropped after the refitting of the backbone torsions (which are the only difference between the standard OPLS-AA and OPLS-AA/L parameters yielding the results in Table 1). The RMS errors dropped from 0.43 to 0.27 kcal/mol and from 10.3° to 6.5°, respectively. At the same time, the energy difference between the lowest minima became 0.93 kcal/mol after refitting, which is much closer to the quantum chemical 0.95 kcal/mol than the standard OPLS-AA result of 1.31 kcal/mol.

Moreover, to test the transferability of the new alanine backbone parameters, we also used them to compute conformational energies of the alanine tetrapeptide, using the ab initio data from ref 8b. It should be emphasized that no refitting was done for the tetrapeptide, and we used exactly the same parameters as for the alanine dipeptide. Table 2 displays the tetrapeptide results, and one can see that here the advantage of using the refitted Fourier coefficients is even more profound, with the RMS energy deviation from the LMP2/cc-pVTZ(-f)//HF/6-31G\*\* data reduced from 1.47 to 0.56 kcal/mol, which is probably the best result one might need to obtain for such calculations, given the accuracy of the ab initio results themselves.<sup>8b</sup>

To assess the efficiency of our choice of the cross-like fitting subspace, we also carried out the alanine dipeptide torsional parameters fitting utilizing the full  $\phi/\psi$  dihedral space with 10° spacing between the adjacent points (full 360° × 360° map). The resulting dipeptide RMS conformational energy error was 0.69 kcal/mol, with the tetrapeptide RMS deviation of 0.50 kcal/mol. Thus, on one hand, both of the fitting subsets granted an improvement compared with the standard OPLS-AA results. On the other hand, using the whole map with a finer spacing

**TABLE 2: Alanine Tetrapeptide, Energy of the Conformers, RMS Deviations in  $\phi_{1-3}$ ,  $\psi_{1-3}$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L
1	2.71	2.56/9.4	3.19/4.4
2	2.84	2.20/8.6	3.19/6.5
3	0.00	-1.57/8.1	-0.32/8.4
4	4.13	3.33/11.0	4.40/5.8
5	3.88	4.32/8.6	3.14/9.3
6	2.20	2.94/6.4	0.96/12.7
7	5.77	3.85/6.8	5.82/6.6
8	4.16	6.79/10.3	4.83/18.8
9	6.92	5.82/6.0	7.14/8.2
10	6.99	9.35/11.6	7.25/14.2
RMS error <sup>c</sup>		1.47/8.9	0.56/10.4

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF/6-31G\*\*, ref 8b. <sup>c</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

**TABLE 3: Refitted Backbone Torsional Fourier Coefficients, kcal/mol**

type	$V_1$	$V_2$	$V_3$	torsion
36	-0.596	0.279	-4.913	C(O)-N-C-C(O), $\phi$ in peptides
37	0.743	2.508	-0.805	N-C-C(O)-N, $\psi$ in peptides
38	0.519	0.877	5.233	C(O)-N-C-C, $\phi'$ in peptides
39	1.865	0.089	0.351	C-C-C(O)-N, $\psi'$ in peptides

**TABLE 4: Serine Dipeptide, Energy of the Conformers, RMS Deviations in  $\phi$ ,  $\psi$ ,  $\chi_1$ , and  $\chi_2$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L 1	OPLS-AA/L 2
1	0.00	0.23/6.3	0.49/7.9	0.30/7.8
2	2.76	3.16/3.6	3.30/1.3	2.83/1.6
3	3.75	2.75/4.6	3.08/1.7	3.45/2.2
4	3.95	3.96/8.7	4.12/6.7	3.69/6.7
5	5.13	5.38/1.7	4.90/4.0	4.76/3.7
6	7.43	7.54/3.2	7.13/4.2	7.98/4.0
RMS error <sup>c</sup>		0.47/5.2	0.44/4.9	0.34/4.9

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF/6-31G\*\*. <sup>c</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

between the grid points (1296 points) yields no better results that utilization of only 95 points in cross-like subspaces. The fact that the dipeptide behavior is worsened by the whole-map fitting can be explained by noting that the latter enforces sampling of not only areas of the potential surface around the minima but the other parts of the map as well. This leads to some improvement in the tetrapeptide results, because the tetrapeptide conformers may have  $\phi$  and  $\psi$  values not pertaining to the dipeptide, but the dipeptide results themselves get worse because of the fitting that tries to take care of areas of the potential surface, which are not relevant.

The alanine parameters thus obtained were used for all of the other dipeptide backbones without exception. The new torsional parameters for the alanine dipeptide are given in Table 3.

**Serine.** Results for the serine dipeptide are given in Table 4. The standard OPLS-AA force field produces the serine dipeptide conformational energies in a wrong order, with the second minimum having a higher energy than the third one. This discrepancy cannot be patched by fitting only the  $\chi_1$ -related torsional coefficients (for N-C-C-O and C(O)C-C-O), because the only significant geometrical difference between those two conformers is in the  $\chi_2$  angle (C-C-O-H(O)), which is 82.5° for the second conformer and 167.9° for the third one. On the other hand, the standard OPLS-AA uses the all-atom alcohol C-C-O-H(O) torsional parameters for  $\chi_2$ , and we did

**TABLE 5: Phenylalanine Dipeptide, Energy of the Conformers, RMS Deviations in  $\phi$ ,  $\psi$ ,  $\chi_1$ , and  $\chi_2$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L
1	0.00	-0.08/8.2	-0.19/6.2
2	0.88	0.50/7.0	0.90/10.6
3	1.65	2.11/4.0	1.82/3.8
RMS error <sup>c</sup>		0.35/6.6	0.15/7.5

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF6-31G\*\*. <sup>c</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

**TABLE 6: Gas-Phase Binding Energies (kcal/mol), S-S or S-O Distances (Å) for CH<sub>3</sub>SH**

system	ab initio <sup>a</sup>	OPLS-AA	OPLS-AA/L
CH <sub>3</sub> SH-CH <sub>3</sub> SH	-1.56/4.27	-3.88/3.38	-2.31/3.74
CH <sub>3</sub> SH-CH <sub>3</sub> OH	-2.37/3.68	-6.25/2.97	-3.23/3.25

<sup>a</sup> Reference 14.

**TABLE 7: Heats of Vaporization (kcal/mol) and Molecular Volumes (Å<sup>3</sup>) for CH<sub>3</sub>SH and CH<sub>3</sub>CH<sub>2</sub>SH**

system/property	experiment <sup>a</sup>	OPLS-AA	OPLS-AA/L
CH <sub>3</sub> SH, $\Delta H_{\text{vap}}$	5.87	6.05 ± 0.02	5.74 ± 0.02
CH <sub>3</sub> SH, V	90.0	89.5 ± 0.2	89.7 ± 0.1
CH <sub>3</sub> CH <sub>2</sub> SH, $\Delta H_{\text{vap}}$	6.58	6.79 ± 0.04	6.57 ± 0.04
CH <sub>3</sub> CH <sub>2</sub> SH, V	123.8	120.7 ± 0.2	120.1 ± 0.2

<sup>a</sup> Reference 1d.

not want to produce new torsion types unnecessarily. This is why we made two sets of the torsional parameters. One involved refitting the N-C-C-O and C(O)-C-C-O Fourier coefficients only, thus preserving the default C-C-O-H(O) one, at a cost of still having the second conformer higher than the third one. Fitting this set involved setting the value of parameter A in eq 5 to yield the maximum/minimum weights ratio of 1000.0 and additional manual reweighting of the lowest minimum. This set is denoted as OPLS-AA/L 1 in Table 4, and it allows a very slight improvement of the total energetical and geometrical RMS errors.

The second refitted set for the serine dipeptide case involved changing the  $\chi_2$  parameters as well, with no reweighting and with the maximum/minimum weights ratio equal to 1.0. It allowed reproduction of the correct order of the conformer energies and further improved the energetic results.

**Phenylalanine.** No changes were introduced in the case of phenylalanine dipeptide (except for changing the backbone torsions). As can be seen from Table 5, just introducing the modified  $\phi$  and  $\psi$  torsional parameters was enough to reduce the energy RMS error by more than a factor of 2. The standard OPLS-AA parameters themselves worked very well in this case, too. The results indicate transferability of the backbone parameters, at least for the nonpolar side chains.

**Cysteine.** Cysteine dipeptide was one of the few cases when we had to modify the OPLS-AA nonbonded parameters. By looking at the data in Tables 6 and 7, one can see that the standard OPLS-AA charges on the sulfur atom and the adjacent hydrogen are probably too high in magnitude for the R-SH systems. Indeed, although the liquid-state properties of the CH<sub>3</sub>-SH and C<sub>2</sub>H<sub>5</sub>SH are in very good agreement with the experimental results (Table 7), the gas-phase dimerization energies are greatly overestimated. To a certain degree, such a behavior can be expected because the OPLS-AA force field does not include any explicit treatment of the electrostatic polarizability. To correctly reproduce the condensed phase properties, the

**TABLE 8: Cysteine Dipeptide, Energy of the Conformers, RMS Deviations in  $\phi$ ,  $\psi$ ,  $\chi_1$ , and  $\chi_2$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L
1	0.00	-2.99/4.8	0.15/6.2
2	1.72	2.92/5.9	1.82/3.7
3	2.26	4.96/6.7	2.79/6.7
4	3.18	2.52/5.8	2.84/6.9
5	4.79	4.54/6.2	4.36/4.9
RMS error <sup>c</sup>		1.91/5.9	0.35/5.8

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF6-31G\*\*. <sup>c</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

**TABLE 9: New/Old Nonbonded Parameters for the Cysteine Side Chain**

OPLS						
type	symbol	$q$ , electron	$\sigma$ , Å	$\epsilon$ , kcal/mol	atom	
200	SH	-0.335/-0.435	3.60/3.55	0.425/0.250	S, thiols	
204	HS	0.155/0.255	0.0/0.0	0.0/0.0	H(S), thiols	

induced polarization in the liquid state has to be included in the average sense, and thus, the point charges are overestimated in the gas phase, which leads to high absolute dimerization energies magnitudes. The problem here, however, is that not only the absolute but also relative gas-phase association energetics is overestimated. Indeed, the OPLS-AA CH<sub>3</sub>OH-CH<sub>3</sub>SH energy is 2.36 kcal/mol lower than the CH<sub>3</sub>SH-CH<sub>3</sub>-SH one, whereas the ab initio difference is only 0.81 kcal/mol. One might suggest that explicit treatment of polarization effects could help here, but we were able to improve the model by simply decreasing the S and H(S) permanent electrostatic charges and adjusting the sulfur van der Waals parameters. The latter was done by performing molecular dynamics simulations for CH<sub>3</sub>SH in the liquid state utilizing a polarizable force field, in which the Lennard-Jones parameters were adjusted every several steps in order to correctly reproduce the condensed-phase thermodynamic properties. The resultant van der Waals parameter values were adapted for the current work with slight changes to account for the different way of representing the electrostatic interaction. A more detailed description of the procedure will be given in a separate paper describing development of a polarizable protein force field. Tables 6 and 7 show that we succeeded in building a less polarized set of S-H pair parameters, which allowed us to adequately reproduce both the gas-phase and liquid state properties. Moreover, the new model was shown to work not only for the CH<sub>3</sub>SH but also for the C<sub>2</sub>H<sub>5</sub>SH system. The gas-phase complex formation energies were computed as the difference between the optimized dimer energies and energies of the optimized monomers.

With the new nonbonded parameters, we were able to obtain a very good fit for the cysteine dipeptide side chain by refitting the  $\chi_1$  parameters only (N-C-C-S and C(O)-C-C-S) and not changing the  $\chi_2$  part (C-C-S-H(S)). Shown in Table 8 are the dipeptide conformational energies. It can be easily seen that, although the standard OPLS-AA is able of reproducing the geometry of the conformers rather well with the RMS deviation from the ab initio of less than 6° for the  $\phi$ ,  $\psi$ ,  $\chi_1$ , and  $\chi_2$  angles, the energies are very wrong with a huge RMS deviation of 1.91 kcal/mol and incorrect order of the minima. A refitting of the  $\chi_1$  with the backbone parameters from the alanine dipeptide allowed a very good set of both geometries and energies of the conformers, with the correct order of the conformers and the RMS energy deviation of only 0.35 kcal/mol. The parameters for the S and H(S) are given in Table 9.



**TABLE 10: Asparagine Dipeptide, Energy of the Conformers, RMS Deviations in  $\phi$ ,  $\psi$ ,  $\chi_1$ , and  $\chi_2$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L
1	0.00	-1.30/48.0	-0.16/8.8
2	3.49	4.79/17.9	3.64/26.2
RMS error <sup>c</sup>		1.30/36.2	0.16/19.5

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF6-31G\*\*. <sup>c</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

**TABLE 11: Glutamine Dipeptide, Energy of the Conformers, RMS Deviations in  $\phi$ ,  $\psi$ ,  $\chi_1$ ,  $\chi_2$ , and  $\chi_3$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L	raw alanine OPLS-AA/L
1	0.19	0.29/3.0	0.30/6.1	0.12/2.5
2	0.46	0.93/3.9	0.73/9.7	0.69/2.7
3	0.00	-1.32/13.0	-0.60/10.4	-1.02/12.9
4	1.07	-0.08/6.5	0.52/9.0	0.02/11.7
5	0.92	-0.27/11.9	0.16/21.7	-0.12/29.7
6	1.80	0.85/6.5	1.29/9.8	1.06/10.0
7	2.83	4.26/9.7	3.91/8.8	3.79/7.8
8	4.02	5.53/6.0	5.90/8.8	6.16/8.0
9	5.29	5.31/3.1	5.83/7.9	5.66/3.1
10	5.32	5.84/3.9	5.72/5.6	5.53/3.9
11	8.54	9.11/11.3	6.68/31.6	8.56/9.2
RMS error <sup>c</sup>		0.98/8.0	0.96/13.9 0.82/10.6 <sup>d</sup>	0.93/11.6

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF6-31G\*\*. <sup>c</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results. <sup>d</sup> Without the last conformer.

**Asparagine.** This is another case where a significantly better result than that allowed by the standard OPLS-AA can be achieved as shown in Table 10. The energy RMS deviation from the ab initio data dropped from 1.30 to 0.16 kcal/mol. Although the RMS deviation in dihedral angles at the minima was reduced from 36.2° to 19.5°, the high-energy conformer actually moved further away from the HF/6-31G\*\* counterpart than in the standard OPLS-AA case.

Both  $\chi_1$  and  $\chi_2$  torsional parameters were refitted in this case. A value of  $A$  was chosen for the maximum/minimum weights ratio equal to 1000.0. An artificial barrier mentioned in the last subsection of the previous section was created in the ab initio data input around the lower minimum.

**Glutamine.** Results of the final geometry minimizations are presented in Table 11. Both side chain dihedral angles were scanned for refitting the Fourier coefficients. Manual reweighting of the minima was utilized. No gradient dependence of the weights was used here. It should be pointed out that, although the energetic results for the glutamine dipeptide are only slightly better than those produced by the standard OPLS-AA and the geometries are even slightly worse, the overall result here is a success, because it once again proves that the new backbone parameters derived for the alanine case are transferable to the other peptides. Moreover, excluding the highest energy conformer (more than 8.5 kcal/mol) from the comparison (Table 11) leaves the rest of the conformational energies more improved with respect to the standard OPLS-AA. Another proof of that is the column of the Table 11 with the "raw alanine" results, this means that only the new backbone parameters were adopted, with no side chain fitting. The average results are even better than after the refitting, but some individual conformers deviate

**TABLE 12: Histidine Dipeptide, Energy of the Conformers, RMS Deviations in  $\phi$ ,  $\psi$ ,  $\chi_1$ , and  $\chi_2$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L
1	0.00	-0.35/5.2	-0.63/5.0
2	0.19	0.43/9.6	0.31/4.1
3	2.41	1.83/8.9	0.77/7.3
4	2.95	3.89/4.6	4.18/10.7
5	3.26	3.89/14.3	4.18/3.9
6	3.45	4.50/8.3	3.88/10.4
7	4.90	4.22/2.3	4.48/49.6
8	5.48	4.22/3.3	5.45/4.3
RMS error <sup>c</sup>		0.79/8.0	0.85/18.7

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF6-31G\*\*. <sup>c</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

**TABLE 13: Leucine Dipeptide, Energy of the Conformers, RMS Deviations in  $\phi$ ,  $\psi$ ,  $\chi_1$ , and  $\chi_2$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L 1	OPLS-AA/L 3
1	0.00	0.40/1.7	0.41/2.5	0.53/2.5
2	0.81	0.08/8.5	0.15/10.8	0.25/10.5
3	0.77	0.30/7.6	0.38/6.2	0.14/6.0
4	1.23	1.07/4.2	1.33/5.1	1.32/4.1
5	1.28	1.30/4.3	1.00/3.4	1.23/2.7
6	2.01	2.06/7.8	2.05/4.6	1.83/4.5
7	2.91	3.10/9.2	3.16/8.8	2.95/8.8
8	3.27	3.62/3.4	3.60/2.5	3.70/1.4
9	3.63	3.96/4.6	3.80/5.6	3.93/5.6
RMS error <sup>c</sup>		0.37/6.2	0.34/6.1	0.38/5.9

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF6-31G\*\*. <sup>c</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

**TABLE 14: Valine Dipeptide, Energy of the Conformers, RMS Deviations in  $\phi$ ,  $\psi$ , and  $\chi_1$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L 2	OPLS-AA/L 3
1	0.00	-0.45/2.3	0.06/6.2	-0.20/6.5
2	0.35	0.28/5.4	0.24/3.2	0.36/3.3
3	0.69	1.20/8.9	0.74/12.8	0.87/12.9
RMS error <sup>c</sup>		0.39/6.1	0.08/8.4	0.16/8.6

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF6-31G\*\*. <sup>c</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

tions are greater. To decrease those errors, we performed the fitting with the minima reweighting.

**Histidine.** Table 12 presents results of the histidine geometry optimizations with the ab initio, standard, and OPLS-AA/L. The gradient weighting parameter was adjusted to produce 1000.0 ratio between the heaviest and the lightest points. Minima 1, 2, 3, and 7 were weighted heavier than the others, and some artificial minima walling was employed. The resulting conformational energies RMS deviation of 0.85 kcal/mol is comparable with the original OPLS-AA 0.79 kcal/mol.

**Leucine and Valine.** These were the case when we did not fit the  $\chi_2$  torsional parameters in order to preserve the C—C—C—C constants in the form used in all other alkane-like OPLS-AA molecular fragments.

There are three sets of new torsional parameters here. The first one allows the best results for the leucine dipeptide conformational analysis. The second set works best for the valine dipeptide. The last one is a common one, producing decent conformational data for the both. Tables 13 and 14 show the results of the conformational analysis. It can be seen that, first of all, all of the molecular mechanics results were very good,

**TABLE 15: Isoleucine Dipeptide, Energy of the Conformers, RMS Deviations in  $\phi$ ,  $\psi$ ,  $\chi_1$ , and  $\chi_2$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L
1	0.00	1.72/5.5	0.26/4.9
2	0.69	-0.21/1.7	0.58/5.7
3	0.88	0.30/4.6	0.75/2.8
4	1.00	2.11/4.8	0.40/8.8
5	1.11	0.38/4.4	0.80/3.0
6	1.80	1.66/3.2	2.19/6.6
7	2.18	2.22/5.2	2.84/6.0
8	3.49	2.97/5.4	3.32/3.6
RMS error <sup>c</sup>		0.88/4.5	0.38/5.5

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF6-31G\*\*. <sup>c</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

**TABLE 16: New/Old Nonbonded Parameters for the Methionine Side-Chain**

OPLS					
type	symbol	Q, electrons	$\sigma$ , Å	$\epsilon$ , kcal/mol	atom
202	S	-0.335/-0.435	3.60/3.55	0.355/0.250	S, sulfides
209 and 210	CT	old-0.05e/old <sup>a</sup>	3.50/3.50	0.066/0.066	C, sulfides

<sup>a</sup> The old values for the carbon atom types 209 and 210 are 0.0375e and 0.0975e, respectively.

**TABLE 17: Heat of Vaporization (kcal/mol) and Molecular Volume (Å<sup>3</sup>) for CH<sub>3</sub>SCH<sub>3</sub>**

property	experiment <sup>a</sup>	OPLS-AA	OPLS-AA/L
$\Delta H_{\text{vap}}$	6.61	7.05 $\pm$ 0.03	6.97 $\pm$ 0.03
V	122.5	124.5 $\pm$ 0.2	123.9 $\pm$ 0.4

<sup>a</sup> Reference 1d.

including the standard OPLS-AA itself, and application of the torsional fitting allowed us to improve even those good results.

In fitting the leucine parameters, the weights ran from 1.0 to 1000.0 and, for the valine, from 1.0 to 1.0. The common set of parameters was sought as a linear combination of the both.

**Isoleucine.** We could not produce a set of torsional parameters which would work well for all of the three hydrocarbon side-chain dipeptides: leucine, valine, and isoleucine. In the case of isoleucine, we had to introduce a new type. However, we were able to keep the  $\chi_2$  C-C-C-C torsion constants unchanged, and a dramatic improvement was achieved in the conformational energies compared with the standard OPLS-AA (Table 15), with the energy RMS error decreased from 0.88 to 0.38 kcal/mol. The molecular mechanics geometries were close to the ab initio ones in both cases. No gradient weighting was done in this case, whereas the lowest energy conformer had to be manually given a higher weight.

**Methionine.** This is another dipeptide containing sulfur, and we refitted the nonbonded parameters for the sulfur and adjacent atoms for the same reason as in the case of cysteine above. The parameters and results of their testing on the pure liquid CH<sub>3</sub>SCH<sub>3</sub> are shown in Tables 16 and 17.

Table 18 presents results of the methionine dipeptide minimizations done with the LMP2-level ab initio, standard OPLS-AA, and the OPLS-AA/L. We refitted only the  $\chi_1$  Fourier coefficients, with maximum weight/minimum weight = 1000.0 gradient-based weighting and no other special tricks. As can be seen from Table 17, significant improvement compared with the standard OPLS-AA has been achieved.

**Proline.** Proline dipeptide is a special case, because there are no  $\chi_1$  or  $\chi_2$  angles to do the usual scans here. We performed

**TABLE 18: Methionine Dipeptide, Energy of the Conformers, RMS Deviations in  $\phi$ ,  $\psi$ ,  $\chi_1$ ,  $\chi_2$ , and  $\chi_3$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L
1	0.00	1.05/5.6	0.64/3.5
2	2.95	2.92/4.7	2.26/5.1
3	2.49	2.60/0.9	2.47/3.9
4	1.88	-0.31/6.6	1.28/3.9
5	3.06	2.74/2.6	2.64/4.3
6	2.07	2.68/5.8	2.17/3.1
7	3.56	4.33/5.7	4.55/5.3
RMS error <sup>c</sup>		1.00/4.9	0.59/5.2

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF6-31G\*\*. <sup>c</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

**TABLE 19: Tryptophan Dipeptide, Energy of the Conformers, RMS Deviations in  $\phi$ ,  $\psi$ ,  $\chi_1$ , and  $\chi_2$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L
1	0.00	-0.80/8.5	-0.01/7.2
2	0.15	-0.43/7.7	0.38/6.5
3	1.30	1.70/7.3	2.16/11.6
4	1.65	1.58/8.2	1.72/4.7
5	2.18	1.88/8.4	2.56/9.8
6	2.22	1.98/2.5	2.05/5.2
7	3.26	4.20/5.0	2.19/49.0
8	2.91	3.68/2.7	2.56/48.2
9	3.41	3.29/4.4	3.48/13.7
RMS error <sup>c</sup>		0.56/6.5	0.50/24.2

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF6-31G\*\*. <sup>c</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

**TABLE 20: Threonine Dipeptide, Energy of the Conformers, RMS Deviations in  $\phi$ ,  $\psi$ ,  $\chi_1$ , and  $\chi_2$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L 1 <sup>c</sup>	OPLS-AA/L 2 <sup>c</sup>
1	0.00	-0.27/6.7	-0.22/8.1	0.20/8.2
2	2.81	2.60/6.3	2.46/3.1	2.48/3.5
3	3.72	2.09/6.0	2.05/2.7	2.00/3.3
4	5.25	5.95/7.0	6.64/11.5	6.26/11.5
5	5.45	5.59/6.4	5.69/4.0	5.82/4.2
6	5.99	6.49/3.0	6.03/6.4	5.49/6.1
7	7.52	8.29/4.8	8.10/7.7	8.60/8.7
RMS error <sup>d</sup>		0.77/5.9	0.87/6.9	0.87/7.1

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF6-31G\*\*. <sup>c</sup> Same as for the serine dipeptide. <sup>d</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

**TABLE 21: Tyrosine Dipeptide, Energy of the Conformers, RMS Deviations in  $\phi$ ,  $\psi$ ,  $\chi_1$ ,  $\chi_2$ , and  $\chi_6$  from the ab Initio Data<sup>a</sup>**

conformer	ab initio <sup>b</sup>	OPLS-AA	OPLS-AA/L
1	0.00	-0.20/5.7	-0.09/4.4
2	0.34	0.49/7.3	1.13/5.7
3	0.39	-0.02/6.3	0.07/9.2
4	1.67	1.79/2.1	1.73/3.2
5	2.17	1.87/5.5	1.78/5.5
6	2.64	3.27/14.9	2.30/14.9
RMS error <sup>c</sup>		0.35/8.0	0.39/8.1

<sup>a</sup> Energies in kcal/mol; angles in degrees. <sup>b</sup> LMP2 cc-pVTZ(-f)//HF6-31G\*\*. <sup>c</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

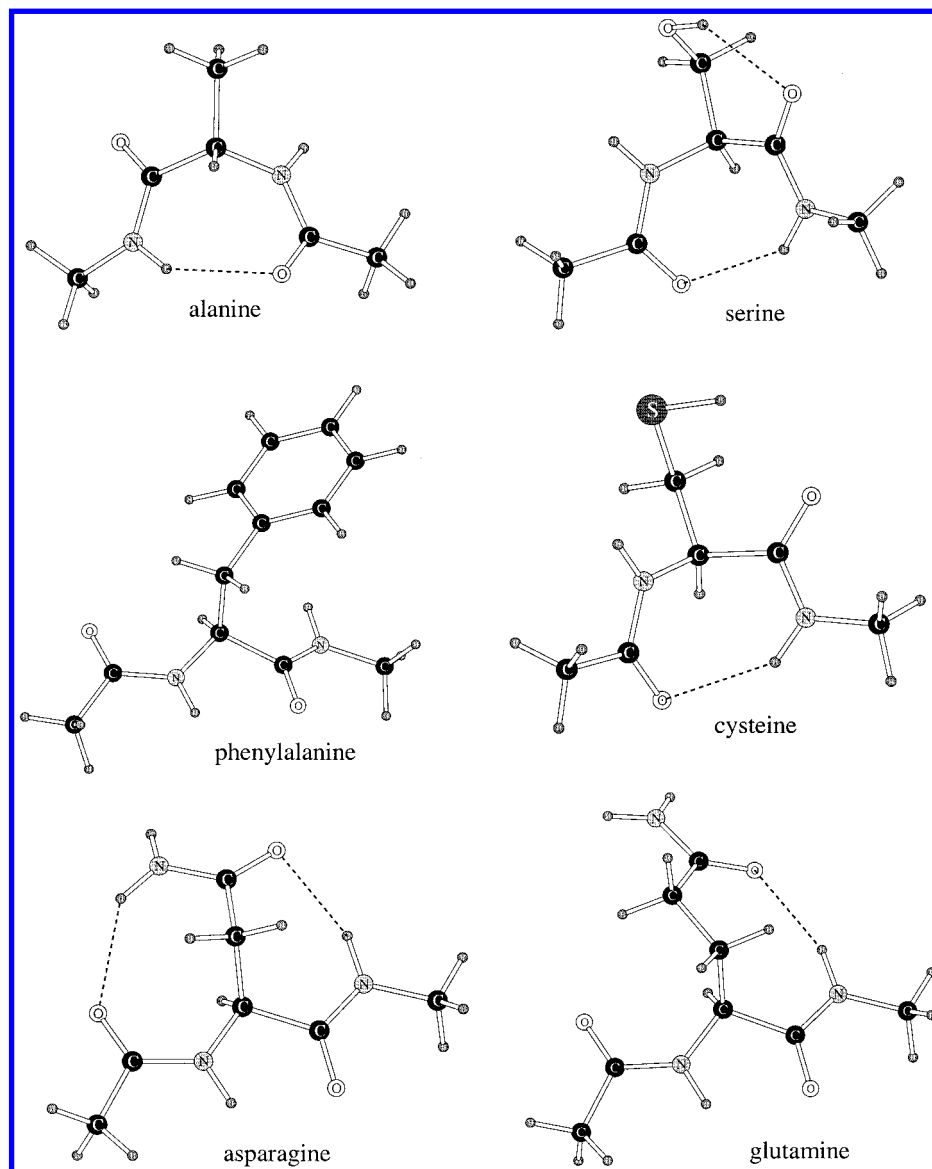
a series of restrained geometry optimizations with the N-C-C(O)-N angles constrained to be at 0°, +60°, -60°, and 180° from the energy minimum. The only nonstandard parameters



**TABLE 22: Aspartic Acid Dipeptide, Energies of the Restrained Conformers Compared with the ab Initio Data, kcal/mol**

conformer	ab initio <sup>a</sup>	OPLS-AA	new backbone only	OPLS-AA/L, ver. 1	OPLS-AA/L, ver. 2
1	5.40	8.04	7.55	5.63	7.74
2	0.00	-5.86	-5.13	-0.08	2.43
3	3.72	6.93	6.70	3.57	3.80
RMS error <sup>b</sup>		4.15	3.65	0.16	1.95

<sup>a</sup> LMP2 cc-pVTZ(-f)/HF6-31G\*\*. <sup>b</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

**Figure 2.** Ab initio lowest energy conformers for dipeptides.

here were those for the backbone derived for the alanine dipeptide, and the results of the constrained optimizations show that the energy RMS deviations from ab initio are reduced from 2.25 to 1.54 kcal/mol by employing the new OPLS-AA/L Fourier coefficients.

**Tryptophan.** The new torsional parameters were obtained by refitting with the coefficient  $A$  to produce maximum weight/minimum weight = 1000.0 and no special tricks. Only the  $\chi_1$  Fourier coefficients were modified. The results of the conformational calculations are shown in Table 19.

It can be seen that, although the overall RMS error for the energies was decreased, the minima 7 and 8 clearly have different geometries than the ab initio conformers which served

as the starting points for the minimizations, and they also differ from the standard OPLS-AA results. No new artificial minima were introduced in this case. The minimization starting from the minimum 8 ends up in the conformer 5 well. As to the conformer 7, we carried out an ab initio minimization starting from the final OPLS-AA/L conformer 7 geometry and found an energy minimum nearby. Thus, no unrealistic wells on the potential-energy surface were produced.

**Threonine.** We did not derive any new parameters in this case. Instead, the OPLS-AA/L Fourier coefficients fitted for the serine dipeptide above were employed. Both sets worked reasonably well, as can be seen from Table 20. The performance of the set 1, which was derived by refitting only the  $\chi_1$ -related

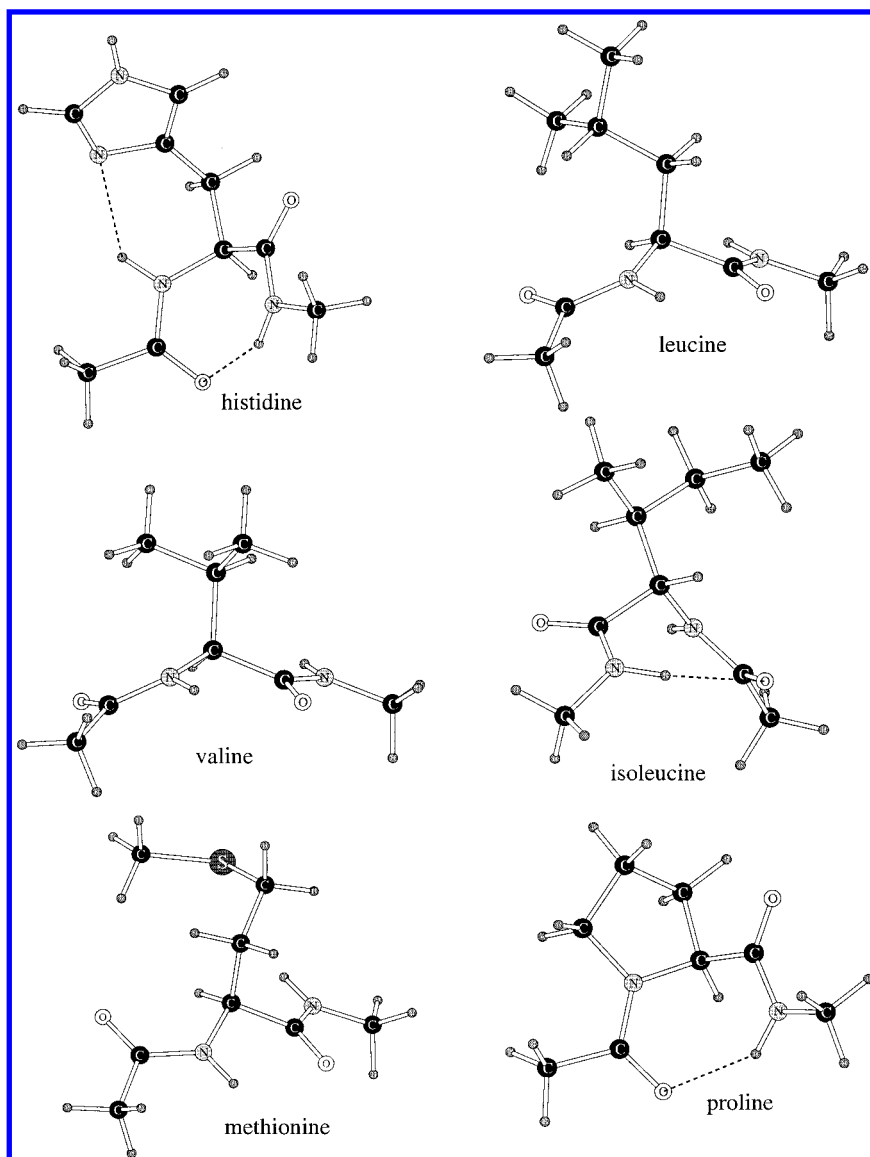


Figure 3. Ab initio lowest energy conformers for dipeptides.

TABLE 23: Glutamic Acid Dipeptide, Energies of the Restrained Conformers Compared with the ab Initio Data, kcal/mol

conformer	ab initio <sup>a</sup>	new backbone		
		OPLS-AA	only	OPLS-AA/L
1	0.00	-2.19	-1.63	-1.28
2	7.89	8.48	9.04	7.89
3	3.68	6.04	5.78	3.19
4	14.09	12.38	12.67	13.62
5	7.20	4.95	5.22	6.05
6	12.79	12.04	11.66	12.60
7	10.95	14.91	13.86	14.55
RMS error <sup>b</sup>	-	2.24	1.85	1.53

<sup>a</sup> LMP2 cc-pVTZ(-f)//HF6-31G\*\*. <sup>b</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

parameters and the set 2, for which both of the side-chain dihedrals were used in refitting, is quite similar and comparable with that of the standard OPLS-AA.

**Tyrosine.** Presented in Table 21 are the results of the conformational analysis done for the tyrosine dipeptide. No side-chain parameters changes were done in this case, only the alanine-derived backbone parameters are different from the

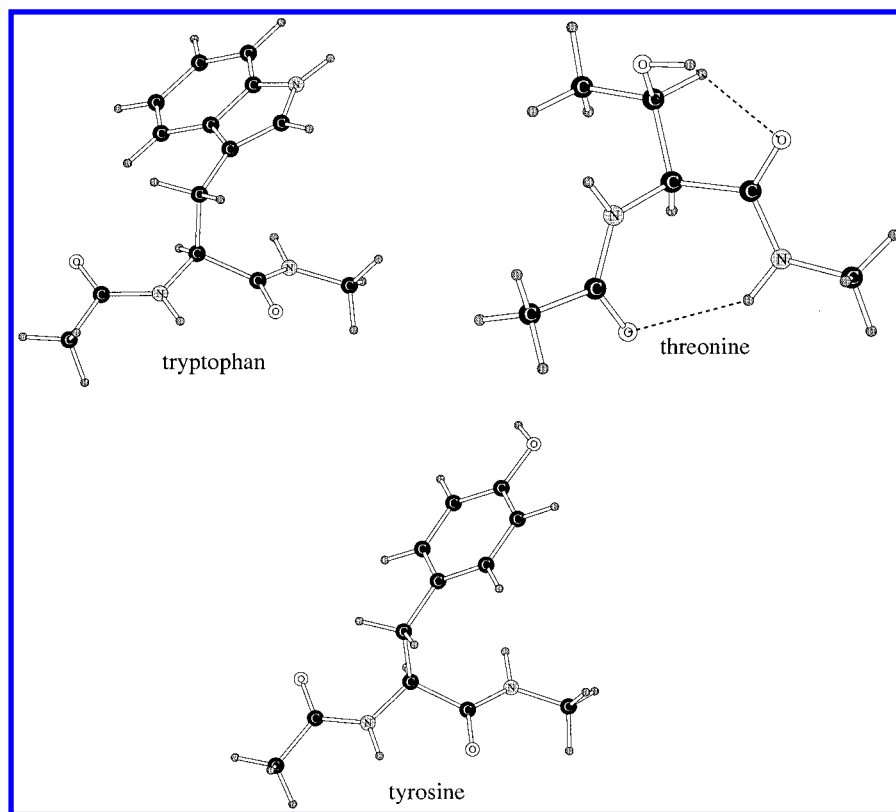
TABLE 24: Lysine Dipeptide, Energies of the Restrained Conformers Compared with the ab Initio Data, kcal/mol

conformer	ab initio <sup>a</sup>	new backbone		
		OPLS-AA	only	OPLS-AA/L
1	17.16	17.11	16.21	16.87
2	21.45	20.37	20.29	20.08
3	16.70	17.98	17.55	17.48
4	0.00	1.14	1.66	1.39
5	15.21	13.52	14.33	15.05
6	13.25	13.65	13.73	12.90
RMS error <sup>b</sup>		1.09	1.06	0.88

<sup>a</sup> LMP2 cc-pVTZ(-f)//HF6-31G\*\*. <sup>b</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

standard OPLS-AA, with the RMS results similar to the unchanged force field.

**Aspartic Acid.** Comparison of the computed conformational energies is given in Table 22. There are two resultant sets of the Fourier coefficients. The first one allows a much lower value of the energy RMS deviation from the ab initio results, as low as 0.16 kcal/mol. However, the  $V_1$  coefficient in this case has a large magnitude, hinting that such a success is probably a result of having only three conformers in the fitting. Another



**Figure 4.** Ab initio lowest energy conformers for dipeptides.

fitting (version 2) with the magnitude of the  $V_1$  restrained to be no more than 4.5 kcal/mol, produces the resultant minimized energies with the RMS deviation from the ab initio counterparts being more than two times smaller than the 4.15 of the original OPLS-AA. Only the Fourier coefficients for the  $\chi_1$  were refitted, with no gradient-based reweighting. It should also be noted that application of the new alanine-derived backbone parameters alone still allows an improvement over the original OPLS-AA.

**Glutamic Acid.** Optimization results are presented in Table 23. There is an adequate number of conformers in this case, so that no Fourier coefficients had to be constrained. Conformers 1 and 7 were manually reweighted to achieve a better fit. Both the alanine backbone only and the backbone plus  $\chi_1$  fitting parameter sets resulted in the energy RMS deviations (1.85 and 1.53 kcal/mol, respectively) lower than the standard OPLS-AA result of 2.24 kcal/mol.

**Lysine.** Optimizations results are presented in Table 24. Only  $\chi_1$ -related Fourier coefficients were refitted with no special reweighting employed. Although the resulting energies are not so much closer to the ab initio results as, for instance, in the aspartic acid case, there is still an improvement, because the energy RMS deviation is lowered below 1 kcal/mol.

**Protonated Histidine.** Only the  $\chi_1$  parameters were refitted. Conformational energies computed with the different methods are shown in Table 25. The  $\chi_1$  parameters were refitted. The energy RMS deviation from ab initio is reduced by more than a factor of 2, from 2.05 kcal/mol for the original OPLS-AA to 0.97 kcal/mol with the full refitting. Just replacing the backbone parameters allowed a slight improvement with the RMS deviation of 1.84 kcal/mol.

**Arginine.** The last residue to be presented is arginine. Table 26 shows the final conformational energies. No special reweighting was done. Although applying the new alanine-derived backbone parameters either alone or complemented by the new  $\chi_1$  coefficients both led to improved energy RMS deviations,

**TABLE 25: Protonated Histidine Dipeptide, Energies of the Restrained Conformers Compared with the ab Initio Data, kcal/mol**

conformer	ab initio <sup>a</sup>	OPLS-AA	new backbone	
			only	OPLS-AA/L
1	0.00	0.81	0.50	0.94
2	4.86	6.03	5.89	5.40
3	0.31	-0.12	0.13	0.56
4	7.20	4.96	5.52	6.92
5	4.48	7.80	6.68	5.03
6	4.67	2.04	1.80	2.68
RMS error <sup>b</sup>		2.05	1.84	0.97

<sup>a</sup> LMP2 cc-pVTZ(-f)/HF6-31G\*\*. <sup>b</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

**TABLE 26: Arginine Dipeptide, Energies of the Restrained Conformers Compared with the ab Initio Data, kcal/mol**

conformer	ab initio <sup>a</sup>	OPLS-AA	new backbone	
			only	OPLS-AA/L
1	0.00	-1.67	-1.85	-0.80
2	10.76	9.87	10.59	9.72
3	3.29	2.33	2.98	1.95
4	13.87	16.65	16.57	15.73
5	8.58	8.28	7.88	9.21
6	4.25	5.29	4.58	4.93
RMS error <sup>b</sup>		1.50	1.38	1.15

<sup>a</sup> LMP2 cc-pVTZ(-f)/HF6-31G\*\*. <sup>b</sup> Positions of the minima shifted uniformly to achieve the lowest RMS deviation from the ab initio results.

we have managed to achieve only a marginal decrease in the deviations, as can be seen from the Table 26. On the other hand, all of the deviations are reasonably low (for a charged dipeptide), and thus, an adequate force field for this residue is at our disposal now.



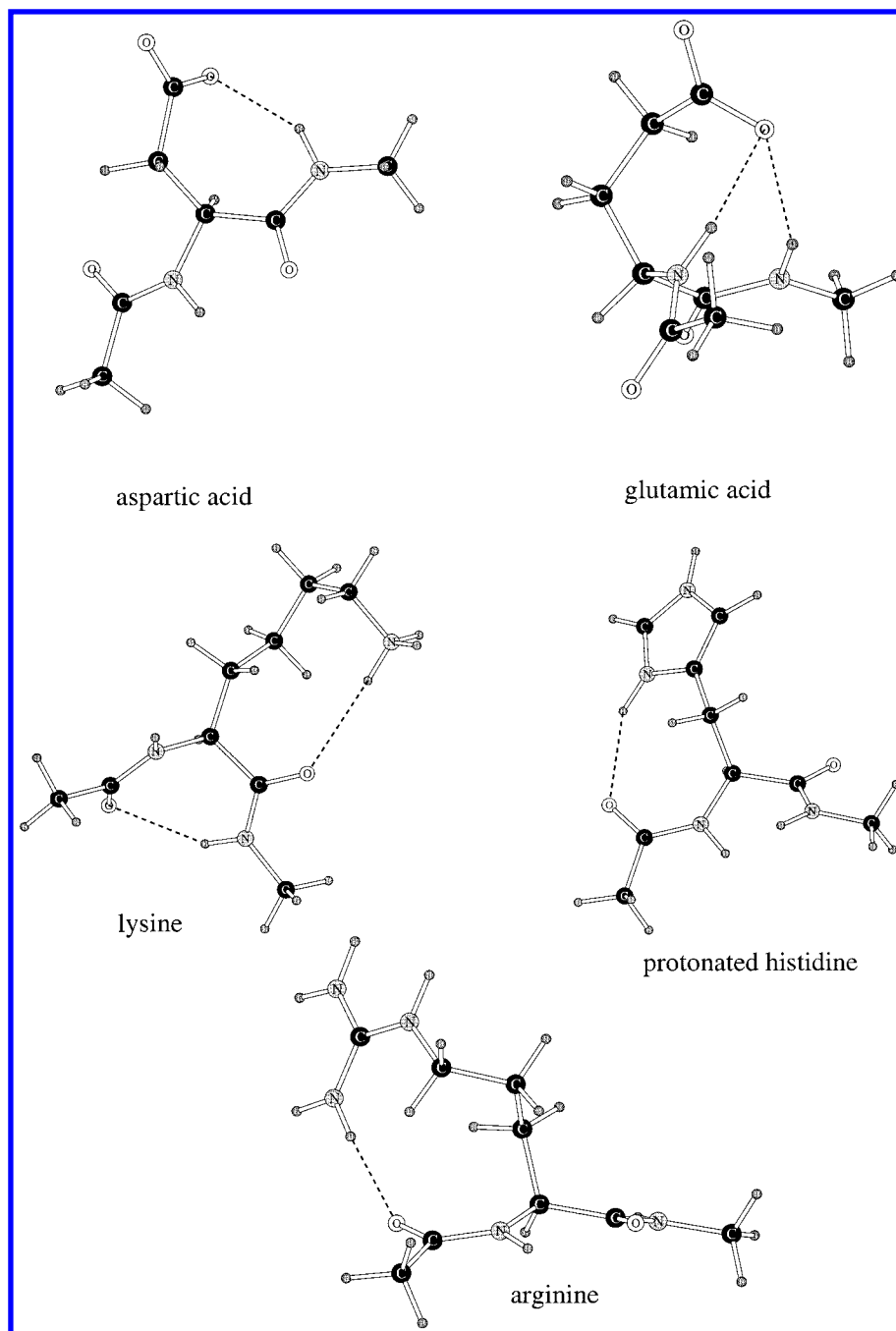


Figure 5. Ab initio lowest energy conformers for charged dipeptides.

**Summary and Comparison with the MMFF.** Figures 2–5 display the lowest energy HF/6-31G\*\* structures for all of the dipeptides studied in this work. Table 27 summarizes the energy RMS deviations from the LMP2 data for the standard OPLS-AA, the OPLS-AA/L, and the MMFF94 force field<sup>1c</sup> for the uncharged residues. Table 28 presents the same data for the charged ones. Let us deal with the results in Table 27 first. It should be mentioned that we did not include the proline data into the overall RMS shown. The reason for that is that the comparison for the proline, upon which the corresponding RMS deviation depends, was done not for energy minima but rather for relatively high-lying restrained conformers. As the energies themselves are greater in magnitude than for the most of the other dipeptide conformers so is the RMS, and thus it is reasonable to exclude the proline result from the overall average RMS computations.

Furthermore, one can see that the torsional fitting improves the overall average RMS deviation by about 40% compared with the standard OPLS-AA, the average deviation dropping from 0.89 to 0.53 kcal/mol. It is also interesting to note that the MMFF94 force field, which employs a similar choice of the torsional fitting subspace (although without the other parts of the fitting technique we are using, and also, with somewhat different functional form of the force field), yields the average RMS deviation from the LMP2 data of 1.04 kcal/mol or almost 100% greater than the OPLS-AA/L. However, it has to be noted that the MMFF94 parameters were not fitted to the ab initio data set employed in this work, and thus, the value of this particular comparison is somewhat limited.

Let us now consider the charged dipeptide results given in Table 28. Several general observations can be made. First, because the absolute values of the relative dipeptide energies

**TABLE 27: Summary of RMS Deviations of Energies from LMP2/cc-pVTZ(-f)//HF/6-31G\*\* for Peptides, kcal/mol**

peptide	OPLS-AA	OPLS-AA/L	MMFF94
Tetrapeptide			
alanine	1.47	0.56	
Dipeptides			
alanine	0.43	0.27	
serine	0.47	0.44/0.34	0.97
phenylalanine	0.35	0.15	0.21
cysteine	1.91	0.35	1.21
asparagine	1.30	0.16	2.25
glutamine	0.98	0.96	1.00
histidine	0.79	0.85	1.60
leucine	0.37	0.34/0.38	1.27
isoleucine	0.88	0.38	0.66
valine	0.39	0.08/0.16	1.01
methionine	1.00	0.59	1.05
proline	2.25	1.54	
tryptophan	0.56	0.50	0.83
threonine	0.77	0.87	1.15
tyrosine	0.35	0.39	0.28
average <sup>a</sup>	0.81	0.47	1.04

<sup>a</sup> Proline not included.**TABLE 28: Summary of RMS Deviations of Energies from LMP2/cc-pVTZ(-f)//HF/6-31G\*\* for Charged Dipeptides, kcal/mol**

peptide	OPLS-AA	new backbone	OPLS-AA/L
aspartic acid	4.15	3.65	0.16/1.95
glutamic acid	2.24	1.85	1.53
lysine	1.09	1.06	0.88
protonated his	2.05	1.84	0.97
arginine	1.50	1.38	1.15
average	2.20	1.96	0.94/1.29

are greater in the case of the charged residues, it makes sense perfectly that the RMS deviations of the molecular mechanics energies from their ab initio counterparts are greater here. Second, we have managed to improve the standard OPLS-AA results by refitting the torsional parameters, and in some cases, the errors in energy were reduced by more than a factor of 2. Finally, even just replacing the standard backbone parameters with those derived for the alanine dipeptide allows to improve the results in all of the cases.

The above observations allow us to conclude that we have managed to assemble all of the adequate components for producing a force field, which allows the resulting average deviations from the quantum chemical results to be within the accuracy of the ab initio calculations themselves.

## V. Conclusions

We have presented results of torsional refitting of the OPLS-AA force field for peptides. The overall average energy deviation from the LMP2/cc-pVTZ(-f)//HF/6-31G\*\* data has been reduced by ca. 40% from 0.81 to 0.47 kcal/mol as a result of the fitting for the uncharged residues. It has to be emphasized that, although in some cases the energetic and geometry results were comparable with the standard OPLS-AA or even slightly worse, we have nevertheless demonstrated good transferability of the Fourier coefficients obtained via the fitting procedure involved. This was done by using the dipeptides backbone torsional parameters derived for the alanine dipeptide for all of the other systems in the presented work. Moreover, applying these parameters to the alanine tetrapeptide energy minimizations allowed us to reduce the RMS energy deviation from the LMP2 data from 1.47 to 0.56 kcal/mol.

Although in the majority of the cases it was enough to refit the Fourier coefficients only, we have demonstrated that in the case of side chains containing sulfur, refitting of the nonbonded parameters was necessary as well. It was carried out via reproducing gas-phase dimerization energies and heats of vaporization and densities, computed for pure model liquids with the Monte Carlo technique.

For the charged dipeptides, the average energy RMS deviation decreased from 2.20 to 1.29 kcal/mol. Just using the alanine-derived backbone parameters here allowed us to reduce the average error to 1.96 kcal/mol. Furthermore, the novel protocol of torsional fitting for charged molecules, which takes into account effects of solvation, proved to be successful in developing adequate torsional parameter sets.

The success of our efforts to produce improved OPLS-AA parameters was ensured by combining a thoroughly developed and tested force field and a highly effective and efficient torsional fitting technique, which utilized high-level ab initio data as the target.

Further efforts will be in two directions. First, we have accumulated a large amount of data and experience in using the torsional fitting procedure involved. Thus, we will work toward making the fitting more automated, with a fully automated system as the strategic goal. Second, a force field with explicit treatment of the electrostatic polarization will be developed utilizing the described torsional fitting technique. This should allow us to overcome the natural limitations of the OPLS-AA and further improve the agreement between the molecular mechanics and ab initio results.

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**Supporting Information Available:** Tables containing all of the refitted Fourier coefficients, energies of restrained proline rotamers, and all of the key dihedral angles values ( $\phi$ ,  $\psi$ , and  $\chi$ 's) for the di- and tetrapeptides resulted from the HF/6-31G\*\* ab initio minimizations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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