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OPTIMIZATION OF PARAMETERS OF NONBONDED INTERACTIONS IN A SPECTROSCOPICALLY DETERMINED FORCE FIELD

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Abstract—A procedure is given by which parameters of nonbonded interactions in a molecular mechanics energy function can be optimized for maximum compatibility with *ab initio* force fields and structures. The method is based on a previously derived transformation of *ab initio* valence parameters to the molecular mechanics formalism. Explicit analytical expressions for the derivatives of the molecular mechanics force constants and reference geometry parameters with respect to the parameters of the nonbonded interactions are derived. The form of the goodness-of-fit function is discussed. A first application to a set of alanine dipeptides is described.

INTRODUCTION

In our efforts to facilitate the utilization of *ab initio* results in the construction of molecular mechanics potential energy functions, we have previously developed a method by which scaled *ab initio* force fields and structures can be directly transformed into molecular mechanics force constants and reference geometry parameters, provided that reasonable parameters for the nonbonded interactions are known (Palmö *et al.*, 1991a, b). We call the resulting molecular mechanics force field a Spectroscopically Determined Force Field (SDFF), since it retains the *ab initio* vibrational frequencies. In the molecular mechanics model, the force constants and the reference geometry parameters are in general assumed to be independent of conformation. The *ab initio* force constants, on the other hand, may depend quite significantly on conformation, since the nonbonded interactions are very sensitive to the different interatomic distances in different conformations. In the transformation from *ab initio* (Palmö *et al.*, 1991a, b), the contribution of the nonbonded interactions is removed from the potential energy and its derivatives, and thus the van der Waals parameters determine, to some extent, the values of the computed molecular mechanics force constants and the reference geometry. This provides a means to adjust the van der Waals parameters towards better consistency with the *ab initio* force field and the molecular mechanics model. In the present work this goal has been implemented in the SDFF procedure to allow for optimization of van der Waals parameters using the criterion that, after being transformed, certain force constants and (possibly) geometry parameters should have values close to one another. In order to take full advantage of the procedure, *ab initio* results for several conformations of groups of related molecules should be available, and among them should preferably be molecules that are sterically strained. Relative energies of different conformations of a molecule can then also be used in the optimization, although this is associated with certain complications. The method is meant to be used as "fine tuning" of the parameters, and cannot replace techniques that utilize, for example, structures and spectroscopic data of molecular crystals and complexes. However, in order to reduce correlations between the parameters, the use of our method in combination with other techniques certainly would be advantageous.

A simple algorithm for adjusting van der Waals parameters towards better consistency with *ab initio* force fields and structures has already been outlined (Palmö *et al.*, 1991a). This algorithm involved fitting to Cartesian second derivatives obtained by subtracting the contribution of the quadratic part of the energy function from the *ab initio* Hessian. A major disadvantage of such an optimization procedure is that it does not provide direct information about which valence force constants and geometry parameters are sensitive to which parameters of the nonbonded interactions. A more traditional approach to the optimization problem is therefore preferable, especially since it turns out that the derivatives of most of the relevant quantities with respect to the nonbonded parameters can be computed analytically. Technically, this solves the optimization problem, since to carry out a nonlinear least squares fit, using for example Marquardt's method (Marquardt, 1963;

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Bevington, 1969), all that is needed in addition to the readily available software (Press *et al.*, 1987) is a subroutine that computes the value of the fitting function and its derivatives for given values of the fitting parameters.

OPTIMIZATION TO FORCE CONSTANTS

A molecular mechanics potential energy function generally has the following basic form (Lifson and Warshel, 1968; Pietilä, 1989)

$$V = \tfrac{1}{2}\sum F_{ij}(R_i - R_{i0})(R_j - R_{j0}) + \sum V_{\text{torsion}} + \sum V_{\text{nonbonded}} \quad (1)$$

where the F_{ij}s are molecular mechanics force constants defined in terms of the internal coordinates R_i, and their intrinsic equilibrium values R_{i0}. The last two sums in equation (1) account for the potential energy due to periodic torsions and nonbonded interactions, respectively. In addition, cubic and quartic terms are sometimes used in connection with heavily deformed valence coordinates, but in the present application we mainly consider cases where the deformations are due to steric strain, and the significance of the higher order terms is then not crucial. In the optimization of the parameters of the nonbonded interactions, repeated use is made of the transformation from *ab initio* to molecular mechanics (Palmö *et al.*, 1991a, b). Unlike standard CFF calculations, the mathematics involved here requires that the set of internal coordinates used be nonredundant. This is no serious restriction, however, since the force field may afterwards easily be transformed into a conventional molecular mechanics coordinate basis (Palmö *et al.*, 1992). To make the transformation of an *ab initio* force field into molecular mechanics energy parameters we divide the energy function into quadratic and nonquadratic terms,

$$V = V_q + V_{nq}. \quad (2)$$

At this stage the periodic torsions may also be considered to be quadratic if they are only moderately deformed from their respective local intrinsic minima. Assuming that the nonquadratic interactions are known, it is then possible to compute values for the force constants and the reference geometry parameters, such that, together with the nonquadratic interactions, they exactly reproduce the *ab initio* equilibrium geometry and vibrational frequencies. The molecular mechanics force constants were found to be (Palmö *et al.*, 1991a)

$$F_{ij} = \sum_\alpha \left[Q_{\alpha,ij}\frac{\partial V_q}{\partial x_\alpha} + \sum_\beta P_{\alpha i}P_{\beta j}\frac{\partial^2 V_q}{\partial x_\alpha \partial x_\beta}\right] \quad (3)$$

where x_α and x_β run over the Cartesian coordinates, and

$$P_{\alpha i} = \frac{\partial x_\alpha}{\partial R_i} \quad (4)$$

and

$$Q_{\alpha,ij} = \frac{\partial^2 x_\alpha}{\partial R_i \partial R_j}. \quad (5)$$

The inverse derivatives $P_{\alpha i}$ and $Q_{\alpha,ij}$ can be computed using the method described previously (Palmö *et al.*, 1991a). At an energy minimum we also have

$$\frac{\partial V_q}{\partial x_\alpha} = -\frac{\partial V_{nq}}{\partial x_\alpha} \quad (6)$$

and

$$\frac{\partial^2 V_q}{\partial x_\alpha \partial x_\beta} = H_{\alpha\beta} - \frac{\partial^2 V_{nq}}{\partial x_\alpha \partial x_\beta} \quad (7)$$

where the Hessian elements $H_{\alpha\beta}$ represent the *ab initio* force field in Cartesian coordinates. To optimize the parameters of V_{nq} using the criterion that certain force constants should be close to each other, we need to compute the derivatives of the force constants with respect to these parameters. Introducing the notations

$$v_\alpha = \frac{\partial V_{nq}}{\partial x_\alpha} \quad (8)$$

and

$$w_{\alpha\beta} = \frac{\partial^2 V_{nq}}{\partial x_\alpha \partial x_\beta} \quad (9)$$

we can write the force constants as

$$F_{ij} = \sum_\alpha \left[-v_\alpha Q_{\alpha,ij} + P_{\alpha i}\sum_\beta P_{\beta j}(H_{\alpha\beta} - w_{\alpha\beta})\right]. \quad (10)$$

Of the quantities in equation (10), only v_α and $w_{\alpha\beta}$ depend on the nonquadratic interactions. If the parameters of these are denoted by $a_1, \ldots, a_M$, the derivatives of the force constants are

$$\frac{\partial F_{ij}}{\partial a_s} = \sum_\alpha \left[-Q_{\alpha,ij}\frac{\partial v_\alpha}{\partial a_s} - P_{\alpha i}\sum_\beta P_{\beta j}\frac{\partial w_{\alpha\beta}}{\partial a_s}\right] \quad (11)$$

where $s = 1, \ldots, M$. This is easy to compute for any functional form of V_{nq}. For example, for nonbonded interactions described by Lennard–Jones potentials, we have

$$V_{nq} = \sum_{(k,l)} \left[\frac{a_k a_l}{r_{kl}^m} - \frac{b_k b_l}{r_{kl}^n}\right], \quad (12)$$

where a_k and b_k are adjustable parameters specific to atom k, r_{kl} is the distance between atoms k and l, and m and n are integers (usually $m = 12$ or 9, and $n = 6$). The summation is over nonbonded atom pairs, usually 1–4 and higher. The functions v_α and $w_{\alpha\beta}$ then come out as

$$v_\alpha = \sum_{(kl)} [-a_k a_l C_\alpha^{(m)}(k,l) + b_k b_l C_\alpha^{(n)}(k,l)] \quad (13)$$

and

$$w_{\alpha\beta} = \sum_{(kl)} [-a_k a_l D_{\alpha\beta}^{(m)}(k,l) - b_k b_l D_{\alpha\beta}^{(n)}(k,l)], \quad (14)$$

where

$$C_\alpha^{(m)}(k,l) = \frac{m}{r_{kl}^{m+1}}\frac{\partial r_{kl}}{\partial x_\alpha} \quad (15)$$

and

$$D^{(m)}_{\alpha\beta}(k,l) = \frac{m(m+1)}{r_{kl}^{m+2}} \frac{\partial r_{kl}}{\partial x_\alpha} \frac{\partial r_{kl}}{\partial x_\beta} - \frac{m}{r_{kl}^{m+1}} \frac{\partial^2 r_{kl}}{\partial x_\alpha \partial x_\beta}. \quad (16)$$

The derivatives of v_α and $w_{\alpha\beta}$ with respect to the adjustable parameters a_k and b_k follow immediately from equations (13) and (14).

OPTIMIZATION TO REFERENCE GEOMETRY PARAMETERS

Once the molecular mechanics force constants have been determined, the intrinsic equilibrium geometry may be computed from (Palmö *et al.*, 1991a)

$$\sum_j F_{ij}(R_j - R_{j0}) = -\sum_\alpha v_\alpha P_{\alpha i}, \quad (17)$$

where $i = 1, \ldots, 3N-6$ (N is the number of atoms). Taking the derivative of equation (17) with respect to a parameter a_s, we get

$$\sum_j F_{ij} \frac{\partial R_{j0}}{\partial a_s} = \sum_j \frac{\partial F_{ij}}{\partial a_s}(R_j - R_{j0}) + \sum_\alpha P_{\alpha i} \frac{\partial v_\alpha}{\partial a_s}. \quad (18)$$

For $i = 1, \ldots, 3N-6$ this forms a complete set of linear equations with respect to the unknowns $\partial R_{j0}/\partial a_s$, $j = 1, \ldots, 3N-6$. However, before these quantities can be computed, the derivative of every force constant F_{ij} with respect to the parameter a_s must first be derived. This could be excessively computationally intensive, and may not be necessary if the force constant optimization gives acceptably close geometry parameters.

GOODNESS-OF-FIT FUNCTION

When optimizing parameters of a certain model, there is normally a set of known data points which one wants the model to reproduce as accurately as possible. This is always assumed in standard χ^2 minimization software. However, in the transformation from *ab initio* to molecular mechanics we do not have any fixed set of force constants or reference geometry parameters to which we could fit the nonbonded interactions. The force constant values and derivatives are therefore not suitable for use as such in the minimization software, but have to be slightly modified. The same is true of the reference geometry parameters, for which the situation is analogous. Since we want transformed force constants of the same type to be close to one another in different conformations and molecules, we define the goodness-of-fit function in the following way:

$$\chi^2 = \sum_{i=1}^{N} \chi_i^2 \quad (19)$$

where

$$\chi_i^2 = W_i \sum_{j=1}^{n_i} (F_i^j - F_i^{ave})^2. \quad (20)$$

Here F_i^j denotes a force constant of type F_i, obtained in the transformation from *ab initio*, and

$$F_i^{ave} = \frac{1}{n_i} \sum_{j=1}^{n_i} F_i^j \quad (21)$$

is the mean of the n_i force constants of type F_i. N denotes the number of different types of force constants, and the W_is are weighting factors. If, in each iteration, we assume that the force constants are linear functions of the parameters of the nonbonded interactions, i.e. that incrementation of the parameters by Δa_p, $p = 1, \ldots, M$, causes the force constants to change from F_{j0}^i to

$$F_i^j = F_{i0}^j + \sum_p \frac{\partial F_i^j}{\partial a_p} \Delta a_p, \quad (22)$$

we obtain for the first derivative of χ^2 with respect to a parameter a_s:

$$\frac{\partial}{\partial a_s}\chi^2 = 2\sum_{ij} W_i \left[(F_{i0}^j - F_{i0}^{ave}) + \sum_p \left(\frac{\partial F_i^j}{\partial a_p} - \left(\frac{\partial F_i}{\partial a_p}\right)^{ave} \right) \Delta a_p \right] \cdot \left(\frac{\partial F_i^j}{\partial a_s} - \left(\frac{\partial F_i}{\partial a_s}\right)^{ave} \right) \quad (23)$$

where

$$F_{i0}^{ave} = \frac{1}{n_i} \sum_j F_{i0}^j \quad (24)$$

and

$$\left(\frac{\partial F_i}{\partial a_s}\right)^{ave} = \frac{1}{n_i} \sum_j \frac{\partial F_i^j}{\partial a_s}. \quad (25)$$

At the minimum of χ^2 the first derivatives are all zero, i.e.

$$\frac{\partial}{\partial a_s}\chi^2 = 0, \quad s = 1, \ldots, M. \quad (26)$$

If we denote

$$\beta_s = -\sum_{ij} W_i (F_{i0}^j - F_{i0}^{ave}) \left[\frac{\partial F_i^j}{\partial a_s} - \left(\frac{\partial F_i}{\partial a_s}\right)^{ave} \right] \quad (27)$$

and

$$A_{sp} = \sum_{ij} W_i \left[\frac{\partial F_i^j}{\partial a_s} - \left(\frac{\partial F_i}{\partial a_s}\right)^{ave} \right] \cdot \left[\frac{\partial F_i^j}{\partial a_p} - \left(\frac{\partial F_i}{\partial a_p}\right)^{ave} \right], \quad (28)$$

the equations that yield the parameter increments Δa_s needed to reach the minimum (in each iteration) can be written in the following standard form:

$$\sum_{p=1}^{M} A_{sp} \Delta a_p = \beta_s, \quad s = 1, \ldots, M. \quad (29)$$

These equations are the same as those obtained for a fixed data set (Bevington, 1969; Press *et al.*, 1987). Thus, standard software can be used in the calculation of the parameter values that minimize the χ^2-function of equation (19), provided that the subroutine that computes the value of the fitting function and its derivatives takes the definitions (27) and (28) of the quantities A_{sp} and β_s into account. Specifically, this means that the fixed data points must all be set equal to zero, the computed data points be replaced by $F_{i0} - F_{i0}^{ave}$, and the derivatives be replaced by

$\partial F_i^l/\partial a_s - (\partial F_i/\partial a_s)^{ave}$. This increases the programming and computational effort somewhat, since every included force constant and its derivatives have to be either stored or computed twice in each iteration. It could therefore be tempting to use a "changing data set", i.e. to use the standard definitions of A_{sp} and β_s, and recompute the "data points" F_i^{ave} in each iteration [cf. equation (20)]. In principle this also works but leads to very slow convergence.

OPTIMIZATION TO ENERGY DIFFERENCES

In our approach, optimization of the parameters of the nonbonded interactions to relative energies of different conformations is less than straightforward. This is because the quadratic energy terms and the torsions depend on the parameters $a_1, \ldots, a_M$ if full (or near) compatibility with the *ab initio* potential energy surfaces is to be retained at all times. This causes particular problems as regards torsions. For the quadratic part of the potential the derivative with respect to a parameter a_s is

$$\frac{\partial V_q}{\partial a_s} = \sum_{i \leqslant j} \left[\frac{\partial F_{ij}}{\partial a_s}(R_i - R_{i0})(R_j - R_{j0}) - F_{ij}\frac{\partial R_{i0}}{\partial a_s}(R_j - R_{j0}) - F_{ij}(R_i - R_{i0})\frac{\partial R_{j0}}{\partial a_s} \right]. \quad (30)$$

For internal coordinates other than torsions there are no further complications. For the torsions, however, even if they are considered to be quadratic near their intrinsic minima, their full contribution to the derivative of the energy difference between two conformations is not given by equation (30). In addition we need to take into account the energy difference between the intrinsic torsion minima in question. This energy difference also depends on the parameters of the nonbonded interactions, and to compute it the parameters of the torsion potentials first have to be determined so as to be in agreement with the intrinsic torsion minima and curvatures (force constants) obtained in the transformation from *ab initio* to molecular mechanics. This requires, of course, that the functional forms of the torsions be known. Even then, the derivatives of the energy differences between torsion minima would have to be calculated numerically.

Another approach may be used if both the functional form and some fairly reliable initial parameters for a torsion are known. Such parameters may be obtained relatively easily by using the normal CFF procedure (Lifson and Warshel, 1958; Pietilä, 1989; Mannfors *et al.*, 1991). In this case the torsion can be treated as a nonbonded interaction and the optimization of its parameters to the relative energies and other data is then, at least in principle, less problematic. For such a torsion the quadratic force constant value computed in the transformation from *ab initio* should be small, a fact that possibly could be used in the optimization. If all the interaction force constants with this torsion are also small, the corresponding line and column should be deleted when solving for the intrinsic equilibrium geometry and its derivatives [equations (17) and (18)]. In general, however, part of these interaction force constants will remain significant, and can be used to derive the real interactions between the torsion and the neighboring internal coordinates.

EXAMPLE

As a first application we have investigated a few sets of existing van der Waals parameters, using *ab initio* force fields and structures of four conformations of the alanine dipeptide (Cheam and Krimm, 1990). Out of the available *ab initio* conformations we used the β_2-, α_R-, α_L-, and α'-structures, none of which contains any hydrogen bonds. The sets of van der Waals parameters that we tested pertain to Lennard–Jones 12-6 functions, and are shown in Table 1. Each set was combined with the recommended atomic charges, though the charges turned out not to have a crucial effect on the computed SDFF parameters. The Chem-X set of van der Waals parameters was combined with atomic charges from the CVFF force field in Discover (Version 2.7.0, Biosym Technologies Inc., March 1991). As is seen in Table 1, there are large differences between the respective sets. The molecular mechanics force constants that they yield are also very different. For example, the C–N–C$^\alpha$ angle bending force constant is very sensitive to the nonbonded interactions, and in the transformation from *ab initio* it took the following values in the β_2-conformer (in units of kcal

Table 1. Comparison of one-atom Lennard–Jones 12-6 parameters*

	CHARMm†		DISCOVER‡		CHEM-X§		AMBER¶	
	a	*b*	*a*	*b*	*a*	*b*	*a*	*b*
H (on N)	3.7	1.3	0.0	0.0	57.6	3.2	9.0	1.6
H (on C)	135.9	7.6	84.3	5.7	57.6	3.2	85.4	4.1
C (sp^2)	1027.6	27.8	1723.0	36.4	653.0	19.8	888.8	24.8
C (sp^3)	654.1	19.8	1338.0	23.0	653.0	19.8	533.2	16.1
O	412.5	19.2	522.4	22.3	118.6	8.7	480.2	20.7
N	721.1	20.8	1505.6	35.1	300.6	13.0	735.3	24.2

* Units: energy in kcal/mol; length in Å.
† Momany *et al.* (1990).
‡ The CVFF force field in Discover (Version 2.70, Biosym Technologies Inc., March 1991).
§ Davies and Murall (1989).
¶ Scott *et al.* (1986).

Table 2. Force constant and geometry parameters of alanine dipeptide[1]

	Ab Initio[3]				Transformed 1[7]				Transformed 2[8]			
Coordinate[2]	F[4]	$\delta(F)$[5]	R[6]	$\delta(R)$[5]	F	$\delta(F)$	R_0	$\delta(R_0)$	F	$\delta(F)$	R_0	$\delta(R_0)$
CN1 s	892.2	18.2	1.368	0.004	872.6	19.1	1.374	0.007	881.9	18.6	1.373	0.004
CN2 s	952.1	24.0	1.351	0.007	927.5	22.7	1.343	0.011	939.9	24.4	1.348	0.006
NC^{α} s	695.7	3.7	1.468	0.004	665.5	4.3	1.458	0.002	672.8	6.4	1.460	0.004
$NC(H_3)$ s	755.0	3.5	1.464	0.002	739.7	3.6	1.455	0.003	742.6	3.4	1.458	0.001
$C^{\alpha}C$ s	594.3	5.3	1.533	0.005	559.7	11.4	1.507	0.007	572.4	7.8	1.515	0.004
$C^{\alpha}C^{\beta}$ s	608.9	12.4	1.536	0.004	594.0	13.3	1.532	0.003	595.5	12.9	1.533	0.004
$NCC(H_3)$ d	212.2	1.9	114.6	0.2	196.1	1.6	114.4	0.4	212.6	1.6	115.0	0.2
NCC^{α} d	235.4	6.9	115.8	1.0	165.2	22.6	110.6	3.6	214.7	5.7	115.3	1.0
CNC^{α} d	202.5	7.9	121.1	0.5	168.6	8.3	121.0	0.4	172.7	9.1	120.4	0.4
$CNC(H_3)$ d	173.5	1.2	120.1	0.3	152.4	1.1	121.6	1.3	157.0	0.5	119.8	0.2
CO1 ib	333.5	5.2	0.6	0.1	332.6	3.6	0.6	0.2	332.6	3.6	0.5	0.2
CO2 ib	329.8	11.3	0.7	0.9	319.8	7.0	0.9	1.0	319.8	7.0	1.1	0.9
NH1 ib	170.7	1.6	−0.7	0.1	154.3	8.0	−1.6	1.6	171.3	2.7	−1.1	0.4
NH2 ib	165.1	2.2	−0.2	0.5	143.7	6.8	−1.5	3.4	162.3	3.1	1.8	0.4
CO1 ob	87.6	0.8	−0.2	0.6	92.4	0.4	0.0	0.6	92.1	0.4	−0.1	0.5
CO2 ob	108.0	6.6	−1.1	2.8	108.2	6.2	−0.4	1.8	107.7	5.6	−0.4	2.2
NH1 ob	28.7	1.8	−1.4	12.9	26.7	1.2	−4.8	14.5	28.5	1.7	−2.5	9.8
NH2 ob	20.9	1.5	2.6	7.1	19.2	1.3	2.3	4.4	20.8	1.2	0.9	4.1
CN1 t	61.9	3.6	0.5	0.4	62.6	4.0	0.8	1.2	61.8	4.0	0.5	0.6
CN2 t	58.5	2.0	−2.0	2.5	58.4	2.8	−2.6	0.8	57.0	1.2	−1.5	1.6

[1] $CH_3C(1)ONHC^{\alpha}H(C^{\beta}H_3)C(2)ONHCH_3$.
[2] s, Stretch; d, deformation; ib, in-plane bend; ob, out-of-plane bend; t, torsion.
[3] Cheam and Krimm (1990).
[4] Mean value for four conformers. Units: energy in kcal/mol; distance in Å; angle in radians.
[5] Standard deviation.
[6] Length in Å, angle in degrees. In-plane coordinate, $1/2(\varphi - \varphi')$; out-of-plane coordinate, deviation from planarity.
[7] Unoptimized Chem-X parameters.
[8] Optimized Chem-X parameters.

$mol^{-1}rad^{-2}$): 34 (AMBER), −21 (CHARMm), 159 (Chem-X), and −161 (DISCOVER). The scaled *ab initio* value is 202 kcal $mol^{-1}rad^{-2}$. Obviously, the value yielded by Chem-X is the only one that makes sense. The Chem-X van der Waals parameters were also the only ones that consistently gave reasonable although not perfect values for the SDFF force constants and reference geometry. We therefore decided to use the Chem-X parameters in the further investigations. In its original form, the Chem-X set of van der Waals parameters is very simple and involves only one atom type each for hydrogen, carbon, nitrogen, and oxygen (Davies and Murrall, 1989). However, it turned out that by optimizing a new separate value for the repulsive parameter of hydrogen attached to nitrogen, significantly better SDFF parameters could be obtained. In the optimization, the value of the repulsive parameter changed from 57.65 to 17.57 with a statistical error of 0.90. Altogether, 25 nonredundant force constants were used in the optimization. Not surprisingly, it turned out that the angle bending force constants were the most sensitive in the process. Some of them are given in Table 2, together with the corresponding geometry parameters. The latter were computed in the transformation from *ab initio* but were not used in the optimization. The numbers shown in the table are means and standard deviations for the four conformers. The clearest improvement of the SDFF parameters, achieved in the optimization, occurs in the α_R conformer, where the force constant of the C^{α}–C–N angle bending coordinate changed from 131.5 to 210.7 kcal $mol^{-1}rad^{-2}$. This should be compared with the mean value of the same force constant in the other conformers, which changed from 176.5 to 216.1 kcal $mol^{-1}rad^{-2}$. Similarly in α_R, the reference value of the C^{α}–C–N angle changed from the far too small value of 105.3 to 116.5°, while the mean value for the other conformers was 112.3 and 114.9° before and after optimization, respectively.

After optimization, the standard deviations of the transformed force constants and reference geometry parameters are quite reasonable, so using the mean values in the molecular mechanics force field should not cause any large deviations with regard to computed structures and vibrational frequencies, as compared to the *ab initio* results. However, further optimization of the SDFF parameters can and should be done using the usual CFF procedure (Lifson and Warshel, 1968; Pietilä, 1989). Such optimization is in general also necessary in order to compute the parameters of the periodic torsions, and to compensate for the many small interaction force constants that may be left out of the final force field (Palmö *et al.*, 1991a).

CONCLUSIONS

As demonstrated in the above example, the SDFF procedure makes it easy to adjust van der Waals parameters from reasonable initial values so that better correspondence between the molecular mechanics model and some specific *ab initio* force fields and structures is obtained. The simplest procedure is to use only force constants for this purpose since the derivatives of the reference geometry parameters are fairly costly to compute. Unfortunately, the energy differences are also complicated to use in this context.

If suggested by the circumstances though, it may well be worth while utilizing these additional properties.

Nonbonded interactions can of course also be optimized directly in standard CFF calculations, where *ab initio* or experimental structures and vibrational frequencies, as well as relative energies, are used in addition to intermolecular data. However, then the valence force constants and the reference geometry parameters either remain unchanged or have to be explicitly varied. The degrees of freedom are thereby quickly used up. In the SDFF procedure on the other hand, all the valence force constants and the reference geometry automatically respond to changes in the van der Waals parameters, so that full compatibility with the *ab initio* force fields and structures is retained at all times. Even the normal modes of the vibrations are preserved. Still, correlations between the parameters to be optimized is a problem also in this case and special care must be taken not to bring about incompatibility with crystal and other important data that are not explicitly used in the optimization. The combined use of our method and those that utilize intermolecular data thus appears to be an optimal way to compute van der Waals parameters of the best possible quality in the context of the functional form employed.

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