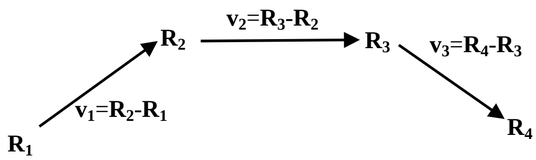
Supplementary Material

First and Second Cartesian Derivatives of Internal Coordinates

This section includes complete parameter derivatives (see Eqs. 4-5 of the paper) for the three main internal coordinates, derived in a form suitable for computer implementation. The distances, angles and torsional angles are defined for the corresponding sequence of 2-4 atoms:



The only non-zero derivatives of the vectors $\mathbf{v_i}$ pointing along the bonds are

$$\frac{\partial \mathbf{v_1}}{\partial \mathbf{R_2}} = \frac{\partial \mathbf{v}_2}{\partial \mathbf{R}_3} = \frac{\partial \mathbf{v}_3}{\partial \mathbf{R}_4} = -\frac{\partial \mathbf{v_1}}{\partial \mathbf{R}_1} = -\frac{\partial \mathbf{v}_2}{\partial \mathbf{R}_2} = -\frac{\partial \mathbf{v}_3}{\partial \mathbf{R}_3} = \mathbf{E}\,, \qquad (1S)$$

with $\mathbf{E}$ is a 3×3 unit matrix ($E_{\alpha\beta} = \delta_{\alpha\beta}$), while the second derivatives vanish completely, $\frac{\partial \mathbf{v_j}}{\partial \mathbf{R}_k \partial \mathbf{R}_l} = 0$, for any $\{j,k,l\}$. Thus it appears convenient to break down the expressions to the derivatives of the vectors $\mathbf{v_1}$-$\mathbf{v_4}$.

For the **distance** between atoms 1, 2,

$$p = (\mathbf{v_1}^2)^{\frac{1}{2}} = v_1\,, \qquad (2S)$$

we get immediately the first and second derivatives,

$$\frac{\partial p}{\partial R_{\lambda\alpha}} = \frac{1}{p}\mathbf{v_1}\boldsymbol{\cdot}\frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}}, \tag{3S}$$

$$\frac{\partial p}{\partial R_{\lambda\alpha}\partial R_{\mu\beta}} = \frac{1}{p}\frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}}\boldsymbol{\cdot}\frac{\partial \mathbf{v_1}}{\partial R_{\mu\beta}} - \frac{1}{p^3}\mathbf{v_1}\boldsymbol{\cdot}\frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}}\mathbf{v_1}\boldsymbol{\cdot}\frac{\partial \mathbf{v_1}}{\partial R_{\mu\beta}}. \tag{4S}$$

For the **bond angle** $\angle(1,2,3)$,

$$p = \arccos(o);\, o = -\frac{\mathbf{v_1}.\mathbf{v_2}}{v_1 v_2}, \tag{5S}$$

the derivatives are

$$\frac{\partial p}{\partial R_{\lambda\alpha}} = -\frac{1}{\sqrt{1-o^2}}\frac{\partial o}{\partial R_{\lambda\alpha}}, \tag{6S}$$

$$\frac{\partial^2 p}{\partial R_{\lambda\alpha}\partial R_{\mu\beta}} = -\frac{1}{\sqrt{1-o^2}}\frac{\partial^2 o}{\partial R_{\lambda\alpha}\partial R_{\mu\beta}} - o\left(1-o^2\right)^{-\frac{3}{2}}\frac{\partial o}{\partial R_{\mu\alpha}}\frac{\partial o}{\partial R_{\mu\beta}}. \tag{7S}$$

Introducing new symbols $o_u = \mathbf{v_1}.\mathbf{v_2}$ and $o_d = v_1 v_2$, so that $o = -\frac{o_u}{o_d}$, we can elaborate

$$\frac{\partial o}{\partial R_{\lambda\alpha}} = -\frac{1}{o_d}\frac{\partial o_u}{\partial R_{\lambda\alpha}} + \frac{o_u}{o_d^2}\frac{\partial o_d}{\partial R_{\lambda\alpha}}, \tag{8S}$$

$$\frac{\partial^2 o}{\partial R_{\lambda\alpha}\partial R_{\mu\beta}} = -\frac{1}{o_d}\frac{\partial^2 o_u}{\partial R_{\lambda\alpha}\partial R_{\mu\beta}} + \frac{1}{o_d^2}\left(\frac{\partial o_u}{\partial R_{\lambda\alpha}}\frac{\partial o_d}{\partial R_{\mu\beta}} + \frac{\partial o_d}{\partial R_{\lambda\alpha}}\frac{\partial o_u}{\partial R_{\mu\beta}}\right) - 2\frac{o_u}{o_d^3}\frac{\partial o_d}{\partial R_{\lambda\alpha}}\frac{\partial o_d}{\partial R_{\mu\beta}} + \frac{o_u}{o_d^2}\frac{\partial^2 o_d}{\partial R_{\lambda\alpha}\partial R_{\mu\beta}}, \tag{9S}$$

where

$$\frac{\partial o_u}{\partial R_{\lambda\alpha}} = \frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}} . \mathbf{v_2} + \mathbf{v_1} . \frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}} , \tag{10S}$$

$$\frac{\partial^2 o_u}{\partial R_{\lambda\alpha} \partial R_{\mu\beta}} = \frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}} . \frac{\partial \mathbf{v_2}}{\partial R_{\mu\beta}} + \frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}} . \frac{\partial \mathbf{v_1}}{\partial R_{\mu\beta}} , \tag{11S}$$

$$\frac{\partial o_d}{\partial R_{\lambda\alpha}} = v_2 \frac{\mathbf{v_1}}{v_1} . \frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}} + v_1 \frac{\mathbf{v}_2}{v_2} . \frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}} , \tag{12S}$$

$$\begin{aligned} \frac{\partial^2 o_d}{\partial R_{\lambda\alpha} \partial R_{\mu\beta}} = & \frac{\mathbf{v_1}}{v_1} . \frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}} \frac{\mathbf{v}_2}{v_2} . \frac{\partial \mathbf{v_2}}{\partial R_{\mu\beta}} + \frac{\mathbf{v}_2}{v_2} . \frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}} \frac{\mathbf{v_1}}{v_1} . \frac{\partial \mathbf{v_1}}{\partial R_{\mu\beta}} + \frac{v_2}{v_1} \frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}} . \frac{\partial \mathbf{v_1}}{\partial R_{\mu\beta}} \\ & + \frac{v_1}{v_2} \frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}} . \frac{\partial \mathbf{v_2}}{\partial R_{\mu\beta}} - \frac{v_1}{v_2^3} \mathbf{v}_2 . \frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}} \mathbf{v}_2 . \frac{\partial \mathbf{v_2}}{\partial R_{\mu\beta}} - \frac{v_2}{v_1^3} \mathbf{v_1} . \frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}} \mathbf{v_1} . \frac{\partial \mathbf{v_1}}{\partial R_{\mu\beta}} \end{aligned} . \tag{13S}$$

Finally, we want the derivatives for the **torsion angle** $\angle(1,2,3,4)$, defined as

$$p = \mathrm{sign} \, . \arccos\left(\frac{\mathbf{a.b}}{ab} \right) = \mathrm{sign} \, . \arccos(o) , \tag{14S}$$

with vector products $\mathbf{a} = \mathbf{v_1} \times \mathbf{v_2}$ and $\mathbf{b} = \mathbf{v_2} \times \mathbf{v_3}$. The sign $\mathrm{sign} = -1$ for $\mathbf{a.v_3} < 0$, else $\mathrm{sign} = 1$.

We can proceed analogously as for the bond angle, so that

$$\frac{\partial p}{\partial R_{\lambda\alpha}} = -\frac{\mathrm{sign}}{\sqrt{1-o^2}} \frac{\partial o}{\partial R_{\lambda\alpha}} , \tag{15S}$$

$$\frac{\partial^2 p}{\partial R_{\lambda\alpha}\partial R_{\mu\beta}} = -\frac{\text{sign}}{\sqrt{1-o^2}}\frac{\partial^2 o}{\partial R_{\lambda\alpha}\partial R_{\mu\beta}} - \text{sign}\left(1-o^2\right)^{-\frac{3}{2}} o \frac{\partial o}{\partial R_{\mu\alpha}}\frac{\partial o}{\partial R_{\mu\beta}} . \qquad (16S)$$

For the derivatives of o, introducing $o = -\frac{o_u}{o_d}$, with $o_u = -\mathbf{a}.\mathbf{b}$ and $o_d = ab$, we can use the formulae 13-14 given above. In addition, we need to know

$$\begin{aligned}\frac{\partial o_u}{\partial R_{\lambda\alpha}} &= \frac{\partial\left(v_2^2\mathbf{v_1}.\mathbf{v_3} - \mathbf{v_1}.\mathbf{v_2}\mathbf{v_2}.\mathbf{v_3}\right)}{\partial R_{\lambda\alpha}} = 2\mathbf{v_2}.\frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}}\mathbf{v_1}.\mathbf{v_3} + v_2^2\left(\frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}}.\mathbf{v_3} + \frac{\partial \mathbf{v_3}}{\partial R_{\lambda\alpha}}.\mathbf{v_1}\right) \\ &-\left(\frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}}.\mathbf{v_2} + \mathbf{v_1}.\frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}}\right)\mathbf{v_2}.\mathbf{v_3} - \mathbf{v_1}.\mathbf{v_2}\left(\frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}}.\mathbf{v_3} + \mathbf{v_2}.\frac{\partial \mathbf{v_3}}{\partial R_{\lambda\alpha}}\right),\end{aligned} \qquad (17S)$$

$$\begin{aligned}\frac{\partial^2 o_u}{\partial R_{\lambda\alpha}\partial R_{\mu\beta}} &= 2\frac{\partial \mathbf{v_2}}{\partial R_{\mu\alpha}}.\frac{\partial \mathbf{v_2}}{\partial R_{\lambda\beta}}\mathbf{v_1}.\mathbf{v_3} + 2\mathbf{v_2}.\frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}}\left(\frac{\partial \mathbf{v_1}}{\partial R_{\mu\beta}}.\mathbf{v_3} + \mathbf{v_1}.\frac{\partial \mathbf{v_3}}{\partial R_{\mu\beta}}\right) + \\ &+ 2\left(\frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}}.\mathbf{v_3} + \frac{\partial \mathbf{v_3}}{\partial R_{\lambda\alpha}}.\mathbf{v_1}\right)\mathbf{v_2}.\frac{\partial \mathbf{v_2}}{\partial R_{\mu\beta}} + v_2^2\left(\frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}}.\frac{\partial \mathbf{v_3}}{\partial R_{\mu\beta}} + \frac{\partial \mathbf{v_3}}{\partial R_{\lambda\alpha}}.\frac{\partial \mathbf{v_1}}{\partial R_{\mu\beta}}\right) \\ &-\left(\frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}}.\frac{\partial \mathbf{v_2}}{\partial R_{\mu\beta}} + \frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}}.\frac{\partial \mathbf{v_1}}{\partial R_{\mu\beta}}\right)\mathbf{v_2}.\mathbf{v_3} - \left(\frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}}.\mathbf{v_2} + \mathbf{v_1}.\frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}}\right)\frac{\partial \mathbf{v_2}}{\partial R_{\mu\beta}}.\mathbf{v_3}, \\ &-\left(\frac{\partial \mathbf{v_1}}{\partial R_{\lambda\alpha}}.\mathbf{v_2} + \mathbf{v_1}.\frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}}\right)\mathbf{v_2}.\frac{\partial \mathbf{v_3}}{\partial R_{\mu\beta}} - \left(\frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}}.\mathbf{v_3} + \mathbf{v_2}.\frac{\partial \mathbf{v_3}}{\partial R_{\lambda\alpha}}\right)\frac{\partial \mathbf{v_1}}{\partial R_{\mu\beta}}.\mathbf{v_2} \\ &-\left(\frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}}.\mathbf{v_3} + \mathbf{v_2}.\frac{\partial \mathbf{v_3}}{\partial R_{\lambda\alpha}}\right)\mathbf{v_1}.\frac{\partial \mathbf{v_2}}{\partial R_{\mu\beta}} - \mathbf{v_1}.\mathbf{v_2}\left(\frac{\partial \mathbf{v_2}}{\partial R_{\lambda\alpha}}.\frac{\partial \mathbf{v_3}}{\partial R_{\mu\beta}} + \frac{\partial \mathbf{v_3}}{\partial R_{\lambda\alpha}}.\frac{\partial \mathbf{v_2}}{\partial R_{\mu\beta}}\right)\end{aligned} \qquad (18S)$$

$$\frac{\partial o_d}{\partial R_{\lambda\alpha}} = \frac{\partial(ab)}{\partial R_{\lambda\alpha}} = b\frac{\partial a}{\partial R_{\lambda\alpha}} + a\frac{\partial b}{\partial R_{\lambda\alpha}}, \qquad (19S)$$

$$\frac{\partial^2 o_d}{\partial R_{\lambda\alpha}\partial R_{\mu\beta}} = \frac{\partial a}{\partial R_{\lambda\alpha}}\frac{\partial b}{\partial R_{\mu\beta}} + b\frac{\partial^2 a}{\partial R_{\lambda\alpha}\partial R_{\mu\beta}} + \frac{\partial b}{\partial R_{\lambda\alpha}}\frac{\partial a}{\partial R_{\mu\beta}} + a\frac{\partial^2 b}{\partial R_{\lambda\alpha}\partial R_{\mu\beta}}, \qquad (20S)$$

$$\frac{\partial x}{\partial R_{\lambda\alpha}} = \frac{\mathbf{x}}{x} \cdot \frac{\partial \mathbf{x}}{\partial R_{\lambda\alpha}} \quad (\text{for } \mathbf{x} = \mathbf{a}, \mathbf{b}), \tag{21S, 22S}$$

$$\frac{\partial^2 x}{\partial R_{\lambda\alpha} \partial R_{\mu\beta}} = \frac{1}{x} \frac{\partial \mathbf{x}}{\partial R_{\lambda\alpha}} \cdot \frac{\partial \mathbf{x}}{\partial R_{\mu\beta}} + \frac{\mathbf{x}}{x} \cdot \frac{\partial^2 \mathbf{x}}{\partial R_{\lambda\alpha} \partial R_{\mu\beta}} - \frac{\mathbf{x}}{x^3} \cdot \frac{\partial \mathbf{x}}{\partial R_{\lambda\alpha}} \mathbf{x} . \frac{\partial \mathbf{x}}{\partial R_{\mu\beta}} \quad (\mathbf{x} = \mathbf{a}, \mathbf{b}), \tag{23S, 24S}$$

$$\frac{\partial \mathbf{a}}{\partial R_{\lambda\alpha}} = \frac{\partial \mathbf{v}_1}{\partial R_{\lambda\alpha}} \times \mathbf{v}_2 + \mathbf{v}_1 \times \frac{\partial \mathbf{v}_2}{\partial R_{\lambda\alpha}}, \quad \frac{\partial \mathbf{b}}{\partial R_{\lambda\alpha}} = \frac{\partial \mathbf{v}_2}{\partial R_{\lambda\alpha}} \times \mathbf{v}_3 + \mathbf{v}_2 \times \frac{\partial \mathbf{v}_3}{\partial R_{\lambda\alpha}}, \tag{25S, 26S}$$

$$\frac{\partial^2 \mathbf{a}}{\partial R_{\lambda\alpha} \partial R_{\mu\beta}} = \frac{\partial \mathbf{v}_1}{\partial R_{\lambda\alpha}} \times \frac{\partial \mathbf{v}_2}{\partial R_{\mu\beta}} - \frac{\partial \mathbf{v}_2}{\partial R_{\lambda\alpha}} \times \frac{\partial \mathbf{v}_1}{\partial R_{\mu\beta}} \tag{27S}$$

and, finally,

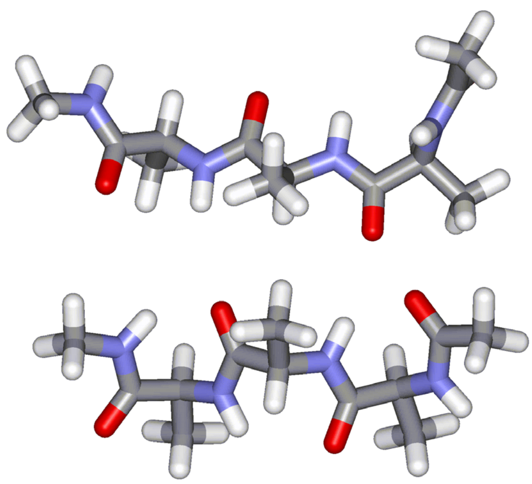
$$\frac{\partial^2 \mathbf{b}}{\partial R_{\lambda\alpha} \partial R_{\mu\beta}} = \frac{\partial \mathbf{v}_2}{\partial R_{\lambda\alpha}} \times \frac{\partial \mathbf{v}_3}{\partial R_{\mu\beta}} - \frac{\partial \mathbf{v}_3}{\partial R_{\lambda\alpha}} \times \frac{\partial \mathbf{v}_2}{\partial R_{\mu\beta}} . \tag{28S}$$

Restrained optimization with the Tinker program by the quasi-Newton routine.

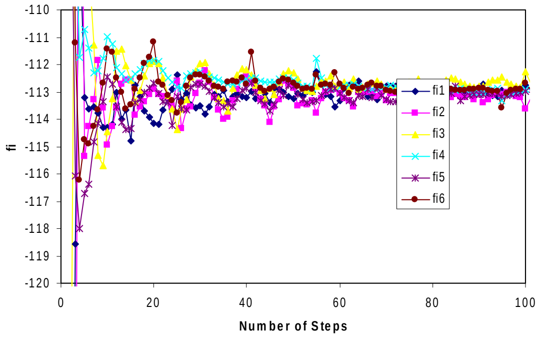
In order to compare the optimization documented in Figure 8 to independent optimizer, analogous constrained energy-minimization was performed in Tinker[1,2] (subroutine minimize) for the parallel β-sheet peptide. Note, that exactly the same procedure could not be used, since the optimization to "unknown" values is not implemented in Tinker. With the same starting geometry (displayed also in Fig. 7) as for the normal mode optimization, the (φ,ψ) angles were constrained to (-113,116°) *via* the Tinker RESTRAIN-DIHEDRAL routine and the energy minimized with the Amber molecular force field.

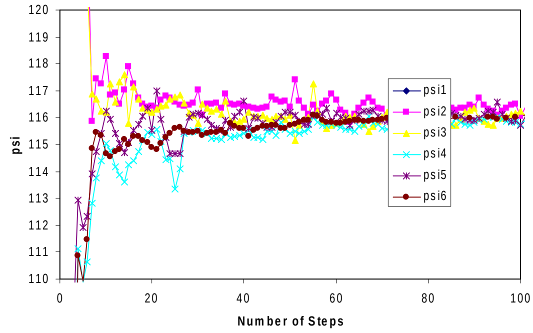
As can be seen below, 1) in the initial stages of optimization the values of the angles oscillates in a similar manner as for the normal mode method and 2) the convergence speed of the energy is also comparable. Thus we can conclude that the qualitative behavior of the convergence in both methods is similar and given by the anharmonic components in molecular force field.

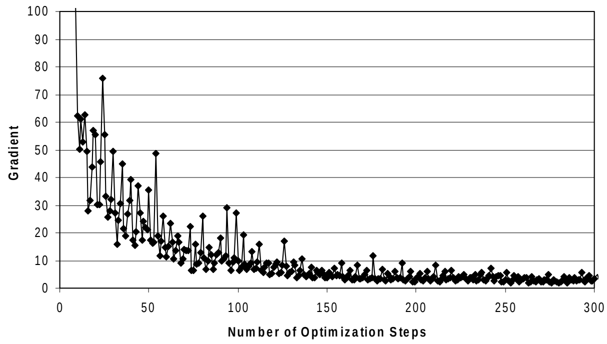
Structure of the parallel β-sheet

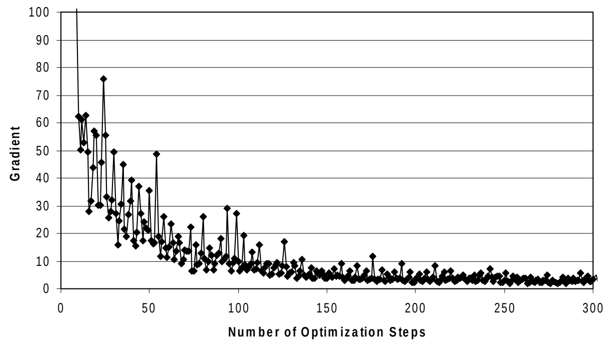


Convergence of the torsional angles (φ,ψ, initial optimization stages only), gradient and energy



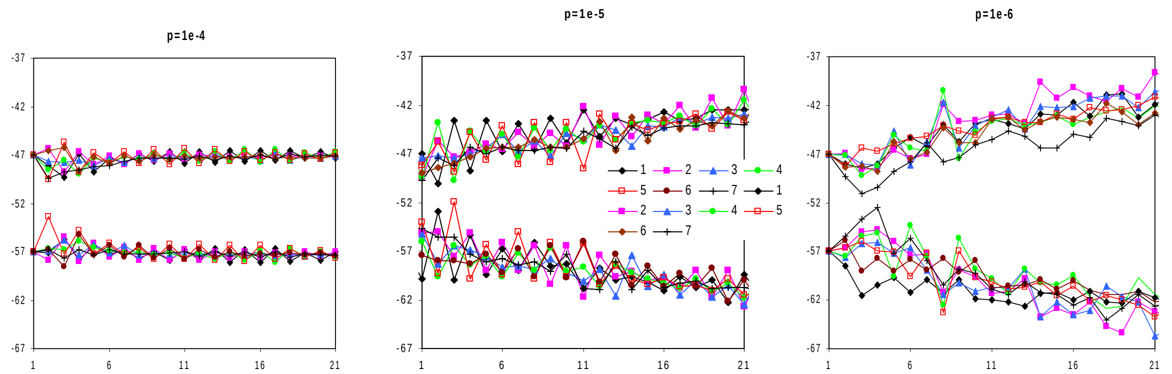






The Dependence of the Multiple Parameter Constrained Optimization (α-helical Peptide of Figure 9) on the Magnitude of the Penalty Parameter

Initial stages of the optimization are displayed only. Apparently, the parameter is too high (10^{-4}, on the left hand side) the constraint is too strict and the torsion angles do not change (i.e. change unacceptably slowly). For medium value of the parameter (10^{-5}, in the middle) reasonable convergence is achieved. The oscillations of the geometry parameters can be somewhat damped by further decrease of the parameter (10^{-6}, on the right), but in this case the constraint is not strong enough to keep the torsion angles oscillating around same value.



Number of the Optimization Steps

References

[1] Pappu R. V., Hart R. K., Ponder J. W.: *J. Phys. Chem. B* **1998,** *102*, 9725.

[2] Ponder J. W.: Tinker, version 3.8, **2000** (see also http://dasher.wustl.edu/tinker/).