

Electronic Supporting Information:
Force Field Simulations of a Hydrated
Lanreotide-based derivative: Hydration,
Dynamics and Numerical Evidence of
Self-Assembly in Dimer

Florian Pinzan , Franck Artzner , and Aziz Ghoufi *

*Institut de Physique de Rennes, UMR 6251 CNRS, Université de Rennes 1, 263 avenue
Général Leclerc, 35042 Rennes, France.*

E-mail: aziz.ghoufi@univ-rennes1.fr

1 Models and Computational Details

Intramolecular contribution is based on stretching, angle and dihedral potentials while the intermolecular interactions were modeled from the electrostatic potential between partial charges and from the Lennard-Jones potential allowing us to take into account of the van der Waals interactions. The total configurational energy U is defined by

$$U = U_{\text{INTRA}} + U_{\text{INTER}} \quad (\text{S1})$$

where U_{INTRA} , U_{INTER} are the intramolecular and intermolecular energy contributions, respectively. U_{INTRA} is expressed as

$$U_{\text{INTRA}} = U_{\text{BONDS}} + U_{\text{ANGLES}} + U_{\text{DIHEDRALS}} + U_{\text{NON-BONDED}} \quad (\text{S2})$$

such that

$$U_{\text{BONDS}} = k_r(r - r_0)^2, \quad U_{\text{ANGLES}} = k_{\Theta}(\Theta - \Theta_0)^2 \quad (\text{S3})$$

where r is the distance between two atoms, Θ is the valence angle between three atoms, k_r and k_{Θ} are the strengths of the bonds and valence angle, r_0 and Θ_0 are the equilibrium distance and angle. The dihedral potential is expressed from a triple cosinus potential

$$U_{\text{DIHEDRALS}} = A_0(1 + \cos(m\Phi - \delta)) \quad (\text{S4})$$

where A_0 is the strength of the dihedral force, Φ the dihedral angle, m the periodicity and δ the equilibrium angle. The non-bonded terms are evaluated from the electrostatic and Lennard-Jones potential described such that the intermolecular interactions are composed of repulsion-dispersion and electrostatic contributions that are represented by Lennard-Jones (LJ) and Coulombic (ELEC) potentials, respectively:

$$U_{\text{INTER}} = U_{\text{LJ}} + U_{\text{ELEC}} \quad (\text{S5})$$

$$\begin{aligned}
U_{\text{LJ}} &= \sum_{i=1}^{N-1} \sum_{j>i}^N \sum_{a=1}^{N_i} \sum_{b=1}^{N_j} u_{\text{LJ}}(r_{iajb}) \\
&= \sum_{i=1}^{N-1} \sum_{j>i}^N \sum_{a=1}^{N_i} \sum_{b=1}^{N_j} 4\epsilon_{ab} \left[\left(\frac{\sigma_{ab}}{r_{iajb}} \right)^{12} - \left(\frac{\sigma_{ab}}{r_{iajb}} \right)^6 \right]
\end{aligned} \tag{S6}$$

where r_{iajb} is the distance between force center a in molecule i and force center b in molecule j , ϵ_{ab} is the energy parameter of the interaction and σ_{ab} is the Lennard-Jones core diameter. N_i is the number of force centers in the molecule i . The LJ parameters for the interactions between unlike sites were calculated using the Lorentz-Berthelot combining rules

$$\epsilon_{ab} = (\epsilon_{aa}\epsilon_{bb})^{1/2} \quad \sigma_{ab} = \frac{1}{2}(\sigma_{aa} + \sigma_{bb}) \tag{S7}$$

The electrostatic interactions were calculated using the Ewald sum (EW) method from

$$\begin{aligned}
U_{\text{ELEC, EW}} &= \frac{1}{2\epsilon_o V} \sum_{\mathbf{k} \neq 0} Q(\mathbf{k}) S(\mathbf{h}) S(-\mathbf{h}) \\
&+ \frac{1}{8\pi\epsilon_o} \sum_i \sum_a \sum_{j \neq i} q_{ia} \sum_b q_{jb} \operatorname{erfc}(\alpha r_{iajb}) / r_{iajb} \\
&- \frac{\alpha}{4\pi^{3/2}\epsilon_o} \sum_i \sum_a q_{ia}^2 \\
&- \frac{1}{8\pi\epsilon_o} \sum_i \sum_a \sum_{b \neq a} \frac{q_{ia} q_{ib}}{r_{iaib}} \operatorname{erf}(\alpha r_{iaib})
\end{aligned} \tag{S8}$$

where $\operatorname{erfc}(x)$ is the complementary error function and $\operatorname{erf}(x)$ is the error function. α is chosen so that interaction pairs only in the central cell need to be considered in evaluating the second term in eqn S8. The functions $S(\mathbf{h})$ and $Q(\mathbf{h})$ are defined using eqns S9 and S10, respectively

$$S(\mathbf{h}) = \sum_i \sum_a q_{ia} \exp(i\mathbf{h} \cdot \mathbf{r}_{i\mathbf{a}}) \quad (\text{S9})$$

$$Q(h) = \frac{1}{h^2} \exp\left(-\frac{h^2}{4\alpha^2}\right) \quad (\text{S10})$$

where the reciprocal lattice vector \mathbf{h} is defined as $\mathbf{h} = 2\pi(l/L_x \mathbf{u}, m/L_y \mathbf{v}, n/L_z \mathbf{w})$ where $\mathbf{u}, \mathbf{v}, \mathbf{w}$ are the reciprocal space basis vectors and l, m, n take values of $0, \pm 1, \pm 2, \dots, \pm \infty$. The reciprocal space sum is truncated at an ellipsoidal boundary at the vector $|\mathbf{h}^{max}|$. The convergence factor α is calculated from $\frac{2\pi}{L_x}$. The maximum reciprocal lattice vectors $|\mathbf{h}_x^{max}| = |\mathbf{h}_y^{max}| = |\mathbf{h}_z^{max}|$ are fixed to 64.

To decrease the computational time, electrostatic interactions can also be computed in the direct space by using the reaction field (RF) method developed by Neumann ^[S1] such that

$$U_{\text{ELEC, RF}} = \sum_{i=1}^{N-1} \sum_{j>i}^N \sum_{a=1}^{N_i} \sum_{b=1}^{N_j} q_{ia} q_{jb} \left[\frac{1}{r_{iajb}} + \frac{B_0 r_{iajb}^2}{2r_c^3} - \frac{1}{r_c} - \frac{B_0}{2r_c} \right] \quad (\text{S11})$$

with

$$B_0 = \frac{(\epsilon_I - 1)}{(2\epsilon_I + 1)} \quad (\text{S12})$$

with ϵ_I the dielectric constant outside the cavity that was taken to be equal to the water value i.e. $\epsilon_I = 78.5$. In this work both Ewald sum (EW) and reaction field (RF) methods have been then compared.

Table S1: Average distance between both M-Lanr monomers where the error bar is provided in subscript. d_i and d_f correspond to the initial and final (obtained from MD simulation of 100 ns) distances.

	$d_{i1} / \text{\AA}$	$d_{f1} / \text{\AA}$	$d_{i2} / \text{\AA}$	$d_{f2} / \text{\AA}$
MULLIKEN-EW	30	31.2_4	10	27.8_4
HIRSHFELD-EW	30	8.7_2	10	8.2_2
CHELPG-EW	30	9.1_2	10	8.5_2
ESP-EW	30	18.4_5	10	23.8_5

References

(S1) Neumann, M.; Steinhauser, O. The influence of boundary conditions used in machine simulations on the structure of polar systems. *Mol. Phys.* **1980**, *39*, 437.

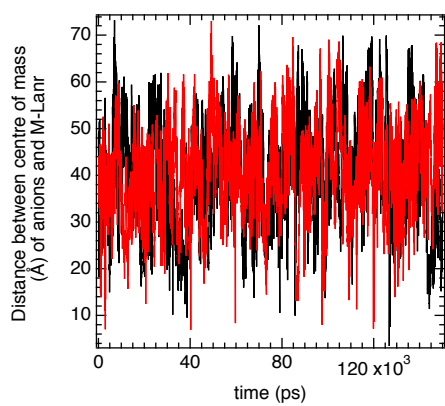


Figure S1: Average distance between both acetate ions and M-Lanr as a function of time. Distance was calculated by considering the centre of mass of ions and M-Lanr modeled from the combination of the CHELPG method and the Ewald sum.

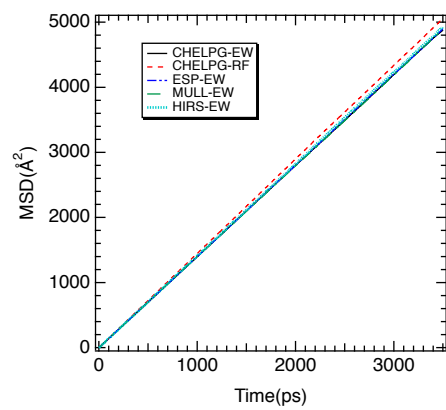


Figure S2: Mean square displacement of water molecules as a function of time for all methods of calculations of partial charges.