Available online at www.sciencedirect.com
SCIENCE DIRECT®
Chemical Physics Letters 401 (2005) 1–6
CHEMICAL PHYSICS LETTERS
www.elsevier.com/locate/cplett

# Monte Carlo simulations of flexible molecules in a static electric field: electric dipole and conformation

P. Poulain, R. Antoine, M. Broyer, P. Dugourd *

*Laboratoire de Spectrométrie Ionique et Moléculaire, UMR No. 5579, Université Lyon I et CNRS, Bat. A. Kastler, 43 Bd du 11 Novembre 1918, 69622 Villeurbanne Cedex, France*

Received 12 October 2004; in final form 2 November 2004
Available online 23 November 2004

**Abstract**

We have performed Monte Carlo replica-exchange method calculations on the gas phase tryptophan-glycine dipeptide in a static electric field. At low electric field, the average dipole of the molecule follows the Langevin–Debye equation. At high electric field, a deviation from this law is observed and the analysis of the results shows that the external field modifies the conformation of the molecules. This opens the way to a possible control of the conformation of gas phase biomolecules with static electric fields.


## 1. Introduction

Electrostatic forces are long range interactions, which play a crucial role in defining the structure and properties of biomolecules [1–5]. Among others, they are involved in protein folding, molecular recognition processes, binding of proteins to other molecules, etc. The protein response to an external field, in particular orientational and structural relaxations, is involved in most of these phenomena. One of the difficulties to study, in solution, the protein response to an external field is that it happens concurrently with a significant reorganization of the solvent, which may hide the response of the molecule and which implies, on the theoretical point of view, a description of the protein and of the solvent [6–8]. The study of the electric response of unsolvated proteins is an alternative to solution experiments and has been recently developed by Antoine et al. [9]. The experiments consist in deflecting a molecular beam in a static and inhomogeneous electric field (see, for example [10,11]). The average dipole of the molecule in the external electric field is deduced from the deflection of the beam. In the low field limit, when the linear response theory applies [12], this average dipole is proportional to the external field and is given by the Langevin–Debye formula [13,14]:

$$\langle \mu_z \rangle = \chi F_z = \left( \frac{\langle \mu^2 \rangle_{0,T}}{3k_B T} + \alpha_e \right) F_z, \tag{1}$$

where $\chi$ is defined as the electric susceptibility of the gas phase molecule, $F_z$ is the applied electric field, $\alpha_e$ is the static electronic polarizability, $\langle \mu^2 \rangle_{0,T}$ the average value of the square dipole of the molecule calculated without electric field at temperature $T$, $\langle \mu_z \rangle$ the average value of the component of the dipole on the electric field axis and $k_B$ the Boltzmann's constant.

In high electric field, a significant orientation of the molecule occurs and this formula is no longer valid. Moreover, proteins are non-rigid molecules and the electric field may induce important structural reorganizations. The objective of this Letter is to provide a direct calculation of the average dipole of a non-rigid molecule

* Corresponding author.
*E-mail address:* dugourd@lasim.univ-lyon1.fr (P. Dugourd).

0009-2614/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.cplett.2004.11.025

in a static electric field. In particular, we want to investigate the region beyond the low field limit and to evaluate the possibility of using a static electric field to control the conformation of an unsolvated molecule in its electronic ground state. Monte Carlo simulations with a replica-exchange method (REM) [15–17,20–22] were performed for a dipeptide in presence of a static electric field. Calculations were performed for tryptophan-glycine (Trp-Gly, $C_{13}H_{15}O_3N_3$) for which experimental results are available [9]. At room temperature, this molecule is floppy [18], the side chain length of the tryptophan residue leads to a competition between a large variety of structures.

## 2. Simulations

The energy of a peptide in an homogeneous electric field is the sum of the conformational energy $E_0$ of the peptide and of the interaction energy with the electric field:

$$E = E_0 - \vec{\mu} \cdot \vec{F}. \tag{2}$$

The conformational energy $E_0$ is obtained from the all-atom Amber force field with Amber96 [19] parameters set. $\vec{F}$ is the applied electric field and $\vec{\mu}$ the dipole of the molecule calculated from:

$$\vec{\mu} = \sum_{i=1}^{N} q_i \vec{r}_i + \alpha_e \vec{F}, \tag{3}$$

where $q_i$ are the partial charges and $r_i$ the position of each atom. Partial charges from Amber96 parameters set are used. They are kept constant during the simulation: there is no possible charge transfer due to conformation modifications or induced by the external field. The electronic polarizability $\alpha_e$ (28.4 Å$^3$ for Trp-Gly) is obtained from an additive model [9]. It does not depend on the conformation and on the orientation of the molecule. For simplicity, it will not be included in the following.

Simulations are Monte Carlo calculations implemented with a REM [15–17,20–22], also known as parallel tempering or multiple Markov chain method. In the REM, a number of non-interacting copies (replicas) of the original system are simulated independently and simultaneously at different temperatures by a Monte Carlo or molecular dynamics method. Pairs of replicas are regularly exchanged with a specified transition probability [21].

Originally build up for spin glass simulations [15], it is now commonly used for protein folding [20–22]. Its strength lies in the sampling enhancement of conformational space. Low temperature replicas explore potential energy minima while high temperature replicas broadly browse the conformational space.

Practically, REM samples $n$ independent copies (replicas) of the system in the canonical ensemble, each at different temperature, $T_i$, with $T_1 < T_2 < \cdots < T_{n-1} < T_n$. Exchange of temperature between two replicas $i$ and $j = i + 1$ is accepted with the probability

$$p = \min(1, \exp[-(\beta_i - \beta_j)(E_j - E_i)]), \tag{4}$$

where $\beta_i$ is the reciprocal temperature $1/k_B T_i$ of system $i$, with $k_B$ the Boltzmann's constant and $E_i$ the potential energy of the system $i$.

We performed REM simulations of 100 000 000 Monte Carlo sweeps with five replicas at temperatures 200, 269, 354, 463 and 600 K. The temperature distribution follows the annealing schedule used in simulated annealing simulations [22]. Our simulations are initiated with a random conformation and the first 20 000 Monte Carlo sweeps are used for thermalization and are not included in statistics. During each Monte Carlo sweep, we updated every dihedral angles in the peptide backbone (including $\phi$ and $\psi$ angles) as well as those in the tryptophan side chain. This represents a total of eight dihedral angles. Bond lengths and angles are kept constant. A replica-exchange was attempted after every period of 100 Monte Carlo sweeps.

Simulations were performed at seven different electric field values from 0 to $10^9$ V/m. The electric field axis is along the $\vec{Z}$ axis The physical quantities $\mu^2$, $\mu_x$, $\mu_y$, $\mu_z$ and $E$ are monitored after each Monte Carlo step and stored in multidimensional histograms. The average value of the physical observable $\mathscr{A}$ at temperature $T_i$ is obtained from:

$$\langle \mathscr{A} \rangle_{T_i} = \frac{\sum p_i(\mathscr{A}) \cdot \mathscr{A}}{\sum p_i p_i(\mathscr{A})}, \tag{5}$$

where $p_i(\mathscr{A})$ is the probability distribution of $\mathscr{A}$ at temperature $T_i$.

Average at any temperature between $T_{min}$ and $T_{max}$ can be obtained using the weighted histogram analysis method (WHAM) [23,24].

Simulations were performed on a 1.5 GHz Xeon double processor personal computer.

## 3. Results and discussion

Fig. 1 displays time series [20,22] of temperatures, energies and square dipoles that are visited during the simulation. Figs. 1a, b are obtained for a simulation without external electric field. Figs. 1d, e are obtained with a field of $10^8$ V/m. In Figs. 1a, d, the continuous and random swap of the conformation between high and low temperatures guarantees a random walk in 'energy space' (Figs. 1b, e). Figs. 1c, f show the evolution of the dipole during the simulation. The square dipole oscillates between 0.2 and 70 D$^2$.

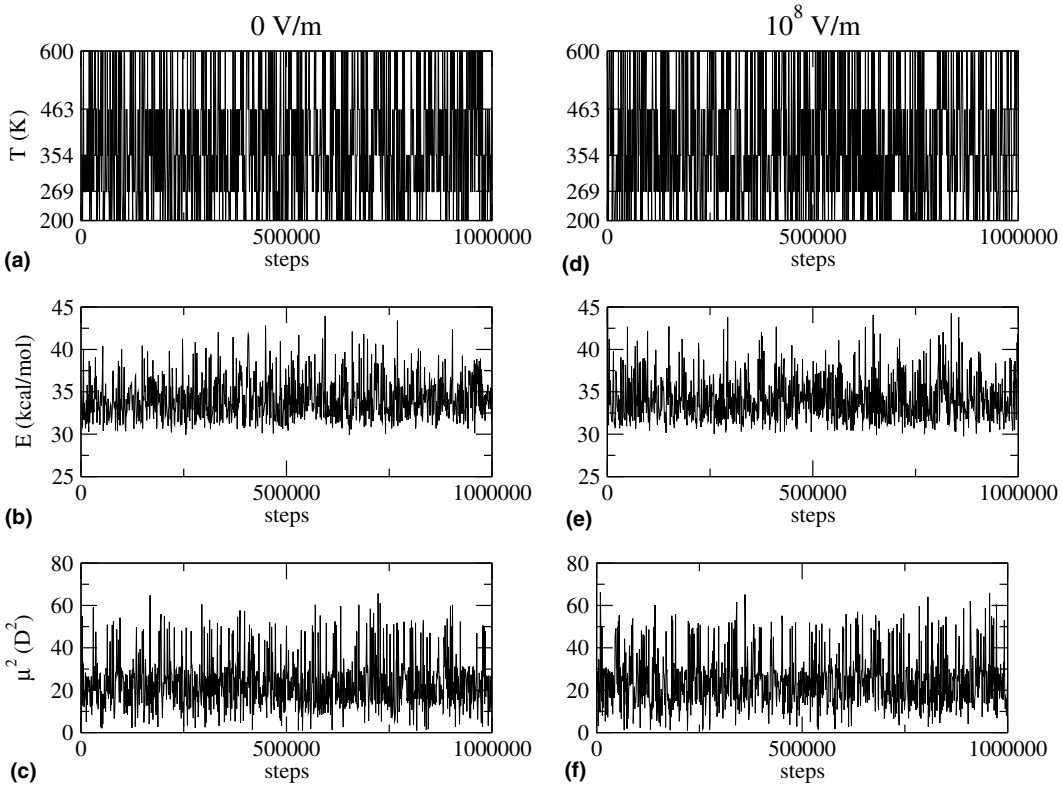


Fig. 1. (a) Temperature, (b) potential energy and (c) square dipole timeseries obtained at $F = 0$ V/m. (d), (e) and (f) idem at $F = 10^8$ V/m. These figures were obtained for replica 1.

Table 1
Acceptance ratios of temperature update

| Pair of temperatures (K) | Acceptance ratio | |
|---|---|---|
| | $F = 0.0$ V/m | $F = 10^8$ V/m |
| 200 ↔ 269 K | 0.59 | 0.59 |
| 269 ↔ 354 K | 0.61 | 0.60 |
| 354 ↔ 463 K | 0.63 | 0.63 |
| 463 ↔ 600 K | 0.65 | 0.65 |

For optimal performances of REM, acceptance ratio of replica exchange should be uniform and large enough [21]. Table 1 reproduces these acceptance ratio without and with an electric field of $10^8$ V/m. Values vary between 59% and 65%.

The random walk in temperature and the values in Table 1 confirm that the simulation has performed properly and has converged. Convergence for a protein or in solution would be drastically more challenging.

### 3.1. Average dipole value

In Fig. 2, we plot the average square dipole calculated without external electric field as a function of the temperature. $\langle\mu^2\rangle$ varies from 25.29 to 22.26 $D^2$ as the temperature increases from $T = 200$ to 600 K. The increase in temperature increases the conformational landscape that is explored by the peptide. At high temperature, the decrease in average square dipole is due to the apparition of elongated structures with low dipole value. The calculated average values $\mu_x$, $\mu_y$ and $\mu_z$ without electric field are null.

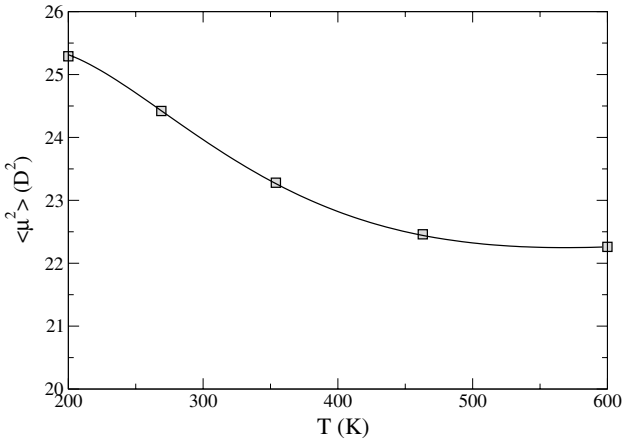


Fig. 2. Evolution of the average square dipole as a function of temperature without external electric field. The squares correspond to the temperature of the different replica used for the simulation. The line corresponds to the WHAM calculations.

At 300 K, the average square dipole obtained by WHAM calculations is 24.08 $D^2$. Using Eq. (1) and $\alpha = 28.4$ Å$^3$, we get a susceptibility of 222 Å$^3$ that is consistent with the experimental susceptibility obtained by Antoine et al. [9] ($214 \pm 27$ Å$^3$). The calculated value obtained by Antoine et al. [9] (240.4 Å$^3$) using CHARMM force field and an additive model to compute the dipole is in agreement with this work.

Fig. 3 shows the calculated average value of the $z$ component of the dipole as a function of the external electric field (the average values of the $x$ and $y$ components of the dipole were also calculated and are in absolute value inferior to $1 \times 10^{-2}$ D). The expected values calculated from the linear response theory (Langevin–Debye formula, Eq. (1)) with $\mu^2$ taken from simulations without electric field (25.29, 24.42 and 22.26 $D^2$ for $T = 200$, 269 and 600 K) are also plotted in Fig. 3. The results of the Monte Carlo simulation at $T = 600$ K are in agreement with the linear response theory. At $T = 200$ and 269 K, two domains can be distinguished. First, at low electric field, the calculated dipole is proportional to the external field and in agreement with the Langevin–Debye formula. This is true for $\mu F/k_B T \ll 1$. Using $\mu^2 \sim 25$ $D^2$, this corresponds to $F \ll 1.7 \times 10^8$ V/m at $T = 200$ K and $F \ll 2.2 \times 10^8$ V/m at $T = 269$ K. One can note that, in [9,25], electric deflection experiments were performed with $F \leqslant 1.5 \times 10^7$ V/m where Eq. (1) is valid.

Beyond the low field limit, saturation clearly occurs and the average dipole is no longer given by the linear response theory. For example, a rigid molecule with a dipole of $\mu_0$, $\langle \mu_z \rangle$ would tend toward $\mu_0$ which corresponds to an alignment of the molecule on the electric field. For a linear molecule, the evolution of the average dipole with the value of the external field is given by the well-known Langevin function ($\mathscr{L}(x) = \coth(x) - 1/x$) [13]. For a floppy molecule, the situation is more complex as not only rotational orientation but also changes in the conformation may occur in the electric field. The effect of the electric field on the conformation is an important issue and it is discussed in the next paragraph.

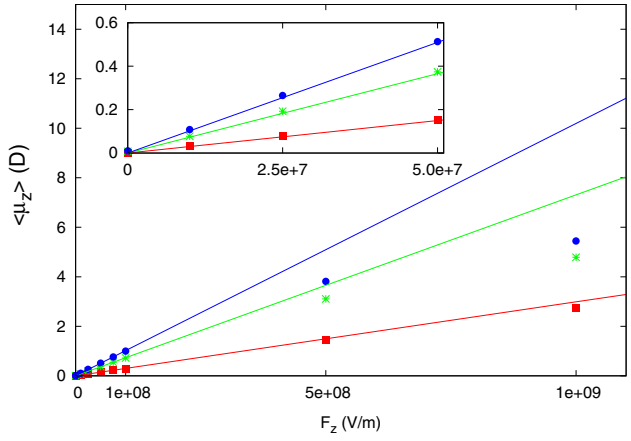


Fig. 3. Average value of the projection of the electric dipole along the electric field axis at different temperatures. Red squares correspond to $T = 600$ K, green stars to $T = 269$ K and blue circles to $T = 200$ K. The lines correspond to the values given by the Langevin–Debye formula. A zoom between $F = 0$ and $F = 5 \times 10^7$ V/m is shown in the inset. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

### 3.2. Effect of the electric field on the conformation

Fig. 4 shows the distribution of average square dipole obtained at different values of electric field and different temperatures. At $F = 0$ V/m, $T = 200$ and 269 K, three main peaks can be distinguished in the distribution. They are centered around 15, 27 and 50 $D^2$. These peaks can be assigned to four families of structures. Representative conformations of these four families are shown in Fig. 5. The first peak in Fig. 4 is due to two families of structures (structures (a) and (a′) in Fig. 5). These two structures are stabilized by favorable interactions between the hydrogen atom of the carboxylic group and the oxygen of the peptide bond and between the oxygen of the carboxylic group and the hydrogen bound to the nitrogen atom of the indole res-

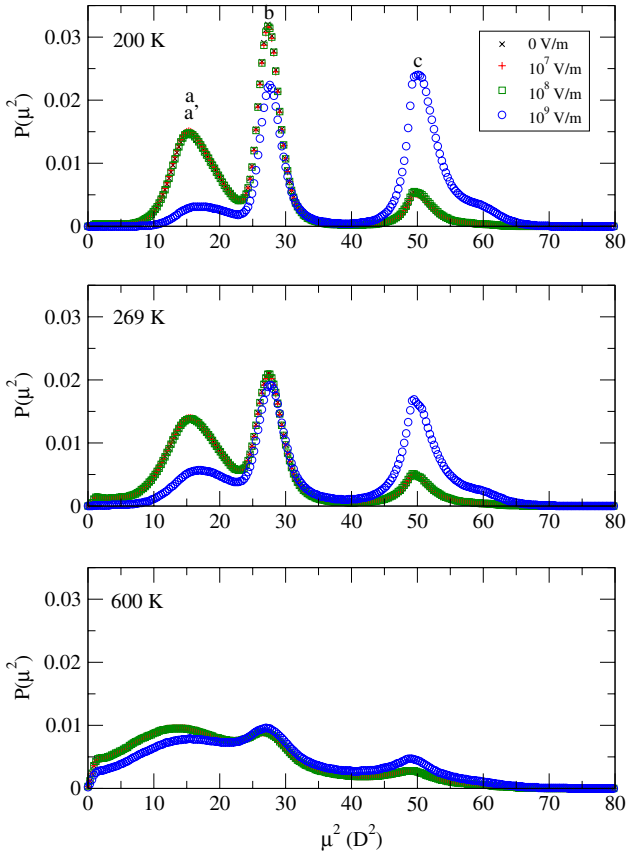


Fig. 4. Probability distribution of $\mu^2$ for different external electric fields at $T = 200$, 269 and 600 K. a, a′, b and c correspond to the square dipole values of the structure shown in Fig. 5.

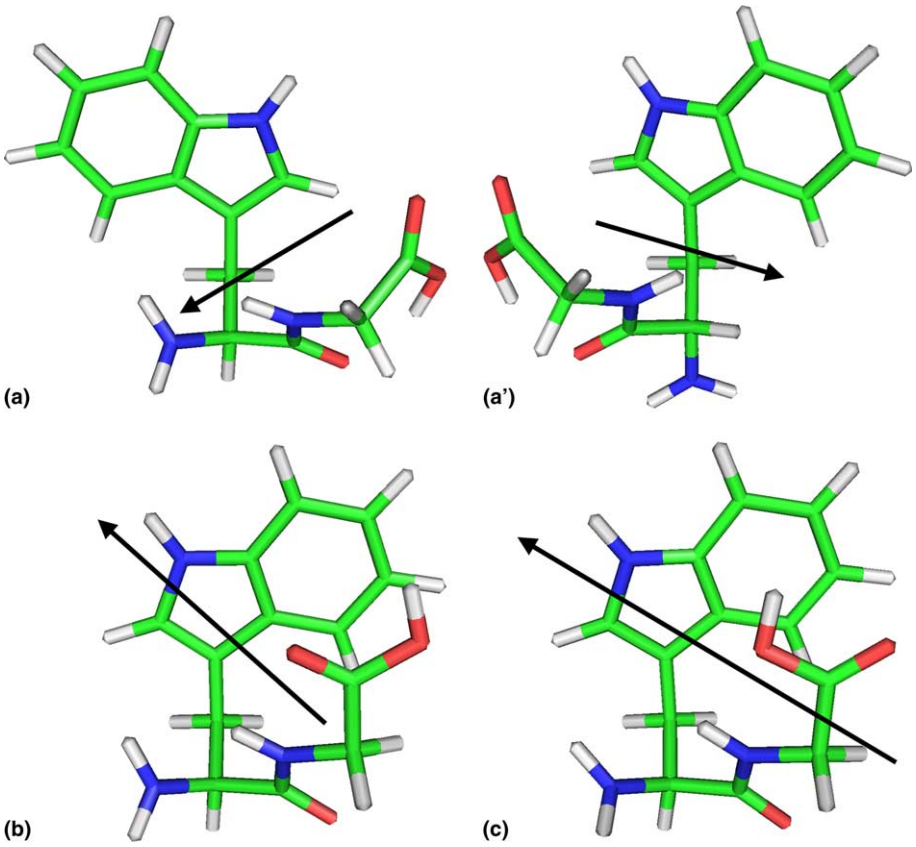


Fig. 5. Representative structures obtained during the simulation at $T = 269$ K and drawn with PyMOL [26]. In this figure, carbon atoms are in green, nitrogens are in blue, oxygens in red and hydrogens in grey. For molecule (a) $E = 29.56$ kcal/mol and $\mu^2 = 15.18$ D$^2$, for molecule (a′) $E = 29.95$ kcal/mol and $\mu^2 = 14.66$ D$^2$, for molecule (b) $E = 29.79$ kcal/mol and $\mu^2 = 27.12$ D$^2$ and for molecule (c) $E = 30.43$ kcal/mol and $\mu^2 = 51.52$ kcal/mol. The arrow shows the permanent dipole of the molecule. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

idue. The structure (a) is the most stable structure that was obtained during the simulation at $T = 200$ K and $F = 0$ V/m. This structure dominates in simulations performed at $T = 50$ K (not shown here). Structures (b) and (c) are stabilized by an interaction between the indole and the carboxylic group. They mainly differ by a flip of the carboxylic group. The large dipole value of the last family of structures is due to a constructive addition of the dipoles of the indole residue, of the peptide bond and of the carboxylic group. We want to outline that structures in Fig. 5 are representative of the peaks observed in Fig. 4 but Trp-Gly is a flexible molecule and a large variety of structure is explored during simulations. At $T = 600$ K, the peaks are less pronounced and the relative weight of low dipole structures is increased in agreement with Fig. 2.

Distributions at $F = 10^7$ and $10^8$ V/m are similar to the distribution obtained at $F = 0$ V/m. These values of electric field are not sufficient to induce significant changes in the conformation of the dipeptide. At $F = 10^9$ V/m, and $T = 200$ and 269 K, different distributions of dipoles are observed. The three former peaks are still present but with different relative weights. The interaction with the electric field is higher for structures with a large dipole, and high electric field clearly stabilizes these structures. For a given molecule, conformational changes can be enhanced by either increasing the value of the external field or by decreasing the temperature.

To get significant changes in conformation with the value of currently available electric fields in molecular beam deflection experiments (typically between $10^7$ and $10^8$ V/m), the best strategy is to choose a molecule for which there is a competition between low electric and high dipole structures. A designed peptide with a competition between a globular or a β-sheet which has a low electric dipole and an α-helix which has a macrodipole is a good candidate. In this case, structural control could be obtained with available static electric fields and one can hope to mimic structural changes driven by electrostatic forces in living organisms.

## 4. Conclusion

In conclusion, we have performed Monte Carlo REM calculations on a floppy molecule in a static electric field. At low electric field, the average dipole of the molecule follows the Langevin–Debye equation. At high electric field, a deviation from this law is observed and result analysis shows that the electric field modifies the conformation of molecules. Experiments and simulations are in progress on larger peptides.

## References

[1] K.A Dill, Biochemistry 29 (1990) 7133.
[2] A. Warshel, J. Aqvist, Annu. Rev. Biophys. Biophys. Chem. 20 (1991) 267.
[3] M. Costabel, D.F. Vallejo, J.R. Grigera, Arch. Biochem. Biophys. 394 (2001) 161.
[4] W.G.J. Hol, Prog. Biophys. Molec. Biol. 45 (1985) 149.
[5] A. Wada, Adv. Biophys. 9 (1976) 1.
[6] C.N. Schutz, A. Warshel, Proteins 44 (2001) 400.
[7] T. Simonson, D. Perahia, G. Bricogne, J. Mol. Biol. 218 (1991) 859.
[8] T. Simonson, Int. J. Quantum. Chem. 73 (1999) 45.
[9] R. Antoine, I. Compagnon, D. Rayane, M. Broyer, P. Dugourd, G. Breaux, F.C. Hagemeister, D. Pippen, R.R. Hudgins, M.F. Jarrold, J. Am. Chem. Soc. 124 (2002) 6737.
[10] M. Broyer, R. Antoine, E. Benichou, I. Compagnon, P. Dugourd, D. Rayane, C.R. Physique 3 (2002) 301, and references therein.
[11] K.D. Bonin, V.V. Kresin, Electric-dipole Polarizabilities of Atoms, Molecules and Clusters, World Scientific, Singapore, 1997, and references therein.
[12] The Langevin–Debye formula (Eq. (1)) applies in molecular beam deflection experiments for an ensemble of molecules with a canonical distribution before they enter the electric field and if $\langle \mu_{z,(t=0)} \mu_{z,(t)} \rangle \to 0$ while the molecules go through the deflector (i.e. lost of memory of the initial rotational motion).
[13] P. Debye, Polar Molecules, Dover, New York, 1929.
[14] J.H. Van Vleck, Phys. Rev. 30 (1927) 31.
[15] R.H. Swendsen, J.S. Wang, Phys. Rev. Lett. 57 (1986) 2607.
[16] H. Hukushima, K. Nemoto, J. Phys. Soc. Jpn. 65 (1996) 1604.
[17] D. Gront, A. Kolinski, J. Skolnick, J. Chem. Phys. 113 (2000) 5065.
[18] R. Antoine, I. Compagnon, D. Rayane, M. Broyer, Ph. Dugourd, G. Breaux, F.C. Hagemeister, D. Pippen, R.R. Hudgins, M.F. Jarrold, Eur. Phys. J. D 20 (2002) 583.
[19] W.D. Cornell, P. Cieplack, C.I. Bayly, I.R. Gould, K.M. Merz, D.M. Ferguson, D.C. Spellmeyer, T. Fox, J.W. Caldwell, P.A. Kollman, J. Am. Chem. Soc. 117 (1995) 5179.
[20] U.H.E. Hansmann, Chem. Phys. Lett. 281 (1997) 140.
[21] A. Mitsutake, Y. Okamoto, Chem. Phys. Lett. 332 (2000) 131.
[22] A. Mitsutake, Y. Sugita, Y. Okamoto, Biopolymers 60 (2001) 96.
[23] A.M. Ferrenberg, R.H. Swendsen, Phys. Rev. Lett. 63 (1989) 1195.
[24] S. Kumar, D. Bouzida, R.H. Swendsen, P.A. Kollman, J.M. Rosenberg, J. Comput. Chem. 13 (1992) 1011.
[25] R. Antoine, I. Compagnon, D. Rayane, M. Broyer, P. Dugourd, N. Sommerer, M. Rossignol, D. Pippen, F.C. Hagemeister, M.F. Jarrold, Anal. Chem. 75 (2003) 5512.
[26] W.L. DeLano, The PyMOL Molecular Graphics System, DeLano Scientific, San Carlos, CA, USA, 2002.