INTERFACIAL INTERACTIONS OF Fe^{3+} WITH PAMAM DENDRIMER IN DIFFERENT PRESSURE CONDITIONS. MOLECULAR DYNAMICS

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In the present paper, the interfacial interactions between carboxyl groups of a G2 PAMAM dendrimer and Fe^{3+} ions of Fe$_2$O$_3$ are studied using Molecular Dynamics simulation. As a novelty, these interactions have been simulated in two different conditions of pressure (20 atm and 80 atm, respectively). 7 ns simulation was done at neutral pH in explicit solvent (water) using an isothermal-isobaric (NPT) ensemble. In condition of high pressure the PAMAM dendrimer becomes more compacted and the branches negatively charged get closer to the dendrimer's core. At lower pressure, instead, the dimension of dendrimer increases. The radial distribution function of Fe^{3+} ions and the one of oxygens of PAMAM termination group have been calculated. The compaction of dendrimer at high pressure leads to less movement of chains. The structure at 20 atm is more open so that each ion can be bound to more than one charged residue.

INTRODUCTION

During the past two decades dendrimers have been widely developed and used successfully in the field of biomedicine because of their three dimensional, highly branched structures with a large number of reactive functional groups on the surface.[1-11]

The unique properties of dendrimers as well as their excellent biocompatibility and non-immunogenicity[5, 6] lead to the synthesis of various dendrimer-based organic/inorganic hybrid composite nanoparticles (NPs) for a wide range of biomedical applications. The major advantage of using dendrimers to generate organic/inorganic hybrid NPs is their tunable surface chemistry, providing many opportunities for the functionalization of the NP surfaces.[12] For example, through electrostatic interaction, dendrimers can be assembled onto magnetic iron oxide NPs to stabilize or functionalize the NPs for biomedical applications.[11,13] Iron oxide NPs have been also synthesized in the presence of carboxylated G4.5 PAMAM dendrimers. The electrostatic interaction of negatively charged carboxylated PAMAM dendrimers with positively charged iron oxide NPs is considered to play an important role for the stabilization of the NPs.[11] PAMAM dendrimers with other different functionalities (–NH2, –OH) cannot stabilize iron oxide NPs, indicating the role of electrostatic interaction for the NP stabilization.

The aim of the present paper was to study the interfacial interactions of PAMAM dendrimer with Fe^{3+} ions under high pressure conditions, using molecular dynamics (MD) simulation method. This serves as a complement to conventional experiments, enabling us to obtain some information about microscopic interactions and individual particle motions as a function of time that cannot be found in other ways.[14-18] Thus, they can be used to address specific questions about the behavior of the model system under high pressure conditions, often more easily than real experiments. As a novelty, MD simulation was developed to study the bonding between Fe^{3+} and COO$^-$ ions taking

into account the pressure that will be applied during hydrothermal synthesis of iron-dendrimers based nanostructured composites in real laboratory conditions.

EXPERIMENTAL

Simulation of Fe^{3+} interactions with PAMAM G2 with COO- terminal groups

In order to run a classical Molecular Dynamics (MD) simulation, the initial structure of PAMAM-COO⁻ (G2) dendrimer was generated using Materials Studio. The atomistic model of PAMAM-COO⁻ (G2) dendrimer was parameterized for the AMBER calculation using Antechamber suite. 16 Fe^{3+} cations were added as well as 32 Cl⁻ anions to ensure neutrality of the whole system. General Amber Force Field (GAFF) was used to asign all the relevant bond, nonbond parameters.[19] The weak-coupling algorithm was used to ensure constant temperature.[20] Pressure coupling algorithm as also described in [20] was used as the barostat. Simulation was done at neutral pH in explicit solvent (water). The results of 7 nanoseconds simulation in isothermal-isobaric (NPT) ensemble are presented below. In the isothermal-isobaric ensemble, moles (N), pressure (P) and temperature (T) are conserved. It corresponds most closely to laboratory conditions.

RESULTS AND DISCUSSION

In order to see the effect of high pressure on PAMAM interactions with Fe^{3+}, molecular dynamics simulations were performed using AMBER 10 software.

The interaction between Fe^{3+} ions and PAMAM dendrimers has been simulated at two different conditions of pressure (20 atm and 80 atm, respectively). The simulation has been carried out for a period of time equivalent to 7 ns before they clearly reach energetic equilibrium. The final frame of the dynamics is shown in Fig. 1.

It can be seen that there is a different behavior in terms of structure's conformations: at high pressure conditions the PAMAM dendrimer becomes more compacted and the negatively charged branches get closer to the dendrimer's core. Instead, at lower pressure, the dimension of dendrimer increases. These qualitative observations of the behavior are confirmed by the calculation of the radius of gyration of the molecule in the two cases (Fig. 2).
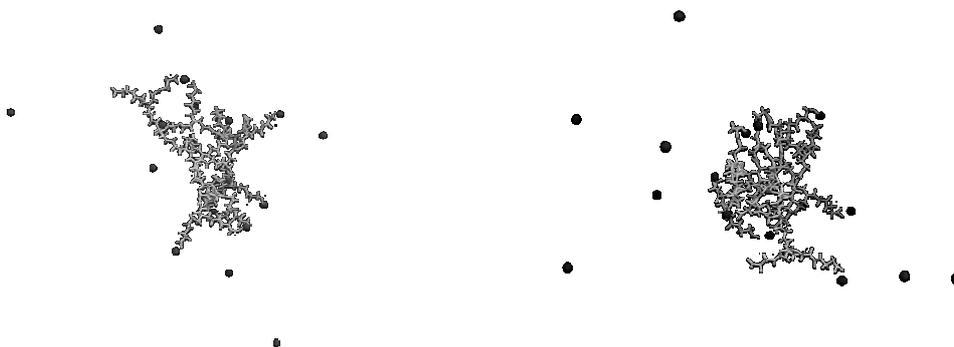

Fig. 1 – MD simulation of the Fe^{3+}-PAMAM structure at 20 atm (on the left side) and 80 atm (on the right side).
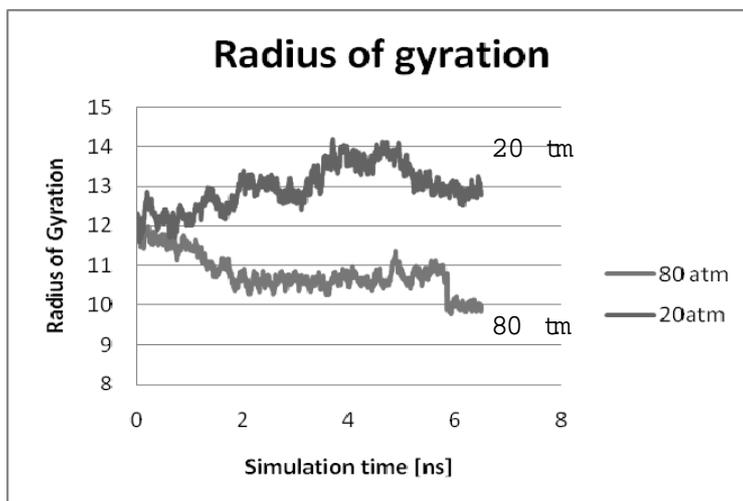

Fig. 2 – Radius of gyration calculated using molecular dynamics at 20atm and 80 atm.

The radius of gyration is a measure of the molecule size. During the simulation process it was revealed that radius of gyration value is influenced by the pressure conditions: at low pressure increases and at high pressure decreases. Also, the radius of gyration tends to stabilize and reaches a plateau after a short period of simulation at 80 atm. Pressure influences the spatial arrangement of the dendrimers and their structure becomes more compact with increasing pressure. Considering Fe^{3+} ions, most of them are bound to dendritic structure through COO⁻ groups in both cases (20 atm and 80 atm, respectively). However, some of them are still free in the aqueous solvent. This remark helps us in hydrothermal synthesis of Fe_2O_3-PAMAM composites using proper Fe^{3+}: PAMAM ratio and high pressure.

The radial distribution functions of Fe^{3+} ions and of oxygen from surface carboxylic groups have been calculated (Figs. 3 and 4). They represent the mean distribution of atoms around the center of mass, taking in consideration the final trajectories of the simulations.

The end groups (COO⁻), or better, the negative charges associated with the oxygens of the polymer are located at the different distance. There is an evident shift of the profile of about 5 Ångström, meaning that actually the structures have different dimensions. Comparing with the results presented for the radius of gyration, the consistency is reliable.

The different height in profile can be interpreted in a more stable configuration, in terms of mean displacement from the average position of chains, suggesting that the compaction of dendrimer at high pressure lead to less movement of chains.
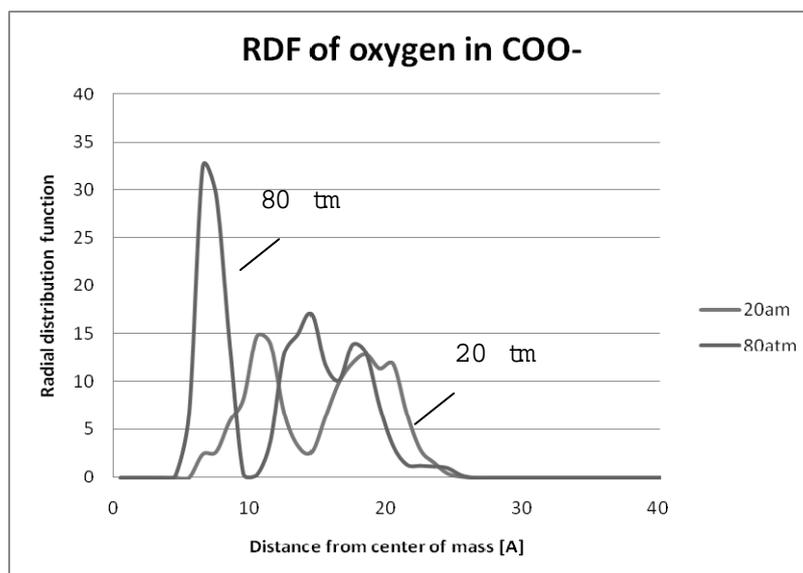

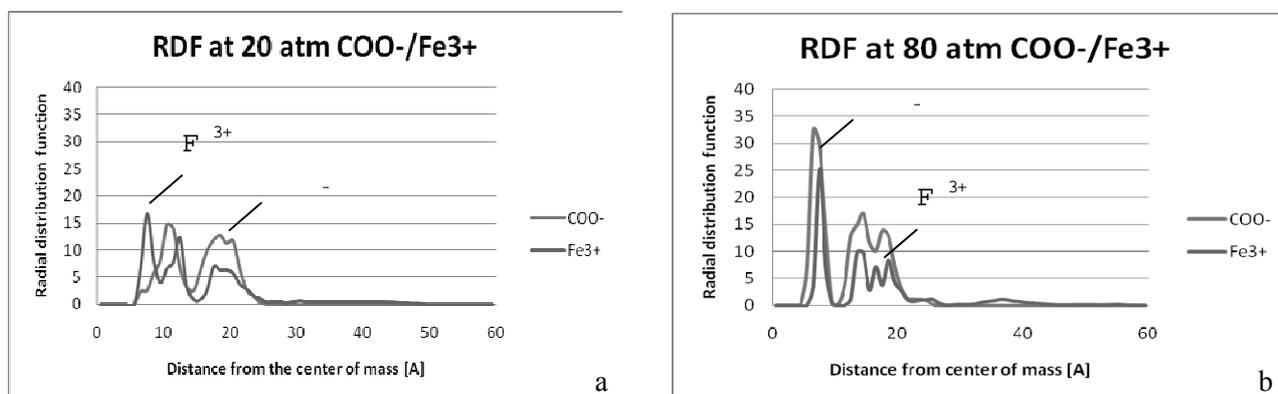Fig. 3 – The radial distribution function of oxygens of surface carboxyl groups.

Fig. 4 – The radial distribution function of Fe^{3+} ions: a) at 20 atm and b) at 80 atm.

It's reasonable that the binding effect can be seen in term of relative motion between iron ions and COO⁻ groups: the stronger it is, the more they will tend to move together as a single object; the radial distribution functions should therefore look in a similar fashion, both for Fe^{3+} and COO⁻ groups (Fig. 4b). This fact is actually evident at higher pressure. In the case of low pressure (20 atm) it can be noted a substantial difference: the closest peak to the center of mass for COO⁻ residue corresponds to two shifted peaks for the Fe^{3+} distribution (Fig. 4a). A possible explanation could be: at 20 atm the structure is more open and each ion can be bound to more than one charged functional group, consequently the correspondence in radial distribution function is different (Fig. 4a).

CONCLUSIONS

The influence of pressure on Fe^{3+}-PAMAM interactions through COO⁻ functional groups of polyamidoamine was studied using molecular dynamics method. It has been observed that pressure influences the spatial arrangement of the dendrimers and their structure becomes more compact with increasing pressure. In high pressure conditions (80 atm) the negatively charged branches of the PAMAM dendrimer get closer to its core. At lower pressure (20 atm), size of dendrimer increases. The structure is more open in this case and each Fe^{3+} ion can be bound to more than one surface charged group.

Considering Fe^{3+} ions, most of them are bound to dendritic structure through COO⁻ groups in both cases (20 atm and 80 atm). However, some of them are still free in the aqueous solvent.

The results obtained in this paper will be used for hydrothermal synthesis at high pressure of Fe_2O_3-PAMAM composites. The potential of this method regarding the formation of strong interactions between Fe^{3+} and COO⁻ ions will be studied. Also, specially designed dendrimers with carboxyl surface groups will be considered for the preparation of hybrid organic – inorganic dendrimer nanocomposites with improved properties.

REFERENCES

1. B. Klajnert, D. Appelhans, H. Komber, N. Morgner, S. Schwarz, S. Richter, B. Brutschy, M. Ionov, A.K. Tonkikh, M. Bryszewska and B. Voit, *Chem. Eur. J.*, **2008**, *14*, 7030-7041.
2. N. Sanvicens and M.P. Marco, *Trends Biotechnol.*, **2008**, *26*, 425-433.
3. D.J. Bharali, M. Khalil, M. Gurbuz, T.M. Simone and S.A. Mousa, *Int. J. Nanomedicine,* **2009**, *4*, 1-7.
4. W.H. Suh, K. S. Suslick, G.D. Stucky and Y.H. Suh, *Progr. Neurobiol.*, **2009**, *87*, 133-170.
5. F. Vögtle, G. Richardt and N. Werner, "Dendrimer Chemistry", WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, 2009, p.9-15, 50-61, 289-290.
6. S. Svenson and D. A. Tomalia, *Adv. Drug Deliv. Rev.*, **2005**, *57*, 2106-2129.
7. D. Appelhans, H.Komber, M.A. Quadir, S. Richter, S. Schwarz, J. van der Vlist, A. Aigner, M. Muller, K. Loos, J. Seidel, K-F. Arndt, R. Haag and B. Voit, *Biomacromoecules*, **2009**, *10*, 1114-1124.
8. S.R. Puniredd and M.P. Srinivasan, *Ind. Eng. Chem. Res.*, **2007**, *46*, 464-471.
9. J.M. Oliveira, A.J. Salgado, N. Sousa, J.F. Mano and R.L. Reis, *Progr. Polym. Sci.*, **2010**, *35*, 1163-1194.
10. L.M. Bronstein and Z.B. Shifrina, *Nanotechnol. Russia,* **2009**, *4*, 576-608.
11. W-D. Jang, K.M. Kamruzzaman Selim, C-H. Lee and I-K. Kang, *Progr. Polym. Sci.,* **2009**, *34*, 1-23.
12. M. Shen and X. Shi, *Nanoscale*, **2010**, *2*, 1596-1610.
13. T. Pietsch, D. Appelhans, N. Gindy, B. Voit and A. Fahmi, *Colloids Surf. A Physicochem. Eng. Asp.,* **2009**, *341*, 93-102.
14. H-P. Zhang, X. Lu, Y. Leng, L. Fan, S. Qu, B. Feng, J. Weng and J. Wang, *Acta Biomater.*, **2009**, *5*, 1169-1181.
15. G. Lamoureux, E. Harder, I.V. Vorobyov, B. Roux and A.D. MacKerell, *Chem. Phys. Lett.,* **2006**, *418*, 245-249.
16. M.P. Allen, "Computational Soft Matter: From Synthestic Polymers to Proteins, Lecture Notes", NIC Series, vol. 23, N. Attig, K. Binder, H. Grubmuller, K. Kremer (Eds.), John von Neumann Institute for Computing, Julich, 2004, 1-28.
17. X. Dong, Q. Wang, T. Wu and Haihua Pan, *Biophys. J.*, **2007**, *93*, 750-759.
18. M. Karplus and J.A. Mc Cammon, *Nat. Struct. Biol.*, **2002**, *9*, 646-652.
19. J. Wang, R.M. Wolf, J.W. Caldwell, P.A. Kollamn and D.A. Case, *J Comput Chem*, **2004**, *25*, 1157-1174.
20. H.J.C. Berendsen, J.P.M. Postma, W.F. van Gunsteren, A. DiNola and J.R. Haak, *J. Chem. Phys.*, **1984**, *81*, 3684-3690.