

Molecular Simulations of dendrimeric Porphyrins

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Abstract

A series of iron (II) porphyrin-based aryl ether dendrimers and the corresponding dioxygen complexes are simulated via computer experiments based on molecular mechanics/ molecular dynamics techniques. The results obtained are in agreement with the available experimental data and reveal that generation 5 can give the more stable oxygen adducts, even in the presence of water.

Introduction

Dendritic macromolecules are hyperbranched polymers that emanate from a central core, have a defined number of generations and functional end groups, and are synthesized in a stepwise process by a repetitive reaction sequence. This hyperbranched topology results in a unique series of physical and chemical properties exhibited by these molecules which, in turn, could be exploited in a number of diverse possible applications, such as nanoscale catalysis, micelle mimics, immuno-diagnostic and NMR imaging agents, chemical sensors and molecular antennae, just to name a few.

In mimicking biological functions of hem proteins, one of the attractive targets is to realize the reversible dioxygen binding activities of hemoglobin and myoglobin. To this purpose, a variety of sterically hindered iron porphyrins have been synthesized (Almong et al., 1975; Collman et al., 1975 and 1983; Ward et al., 1981; Momemteau and Reed, 1994), some of which indeed form stable dioxygen adducts but only under anhydrous conditions. On the other hand, in aqueous media, successful examples have been limited to only iron picket-fence porphyrin embedded within a synthetic bilayer membrane (Tsuchida et al., 1993). Quite recently, Jin et al. (1993) have synthesized a series of aryl ether dendrimers bearing porphyrin functionality as a core. Their experimental

characterization has shown that the interior porphyrin functionality is almost encapsulated when the number of aromatic layer in the dendrimer framework is higher than 4. Due to the steric and hydrophobic protection around the active site, a large dendrimer iron porphyrin has been verified to show a dioxygen binding activity, similar to hemoglobin (Jiang and Aida, 1996). In this study we report the results obtained from an extensive series of molecular simulations performed on 5 successive generations of these iron porphyrin-based dendrimers, with the intent of verifying the stability of these monomolecular models of dioxygen-carrying hem proteins in the aqueous environment.

Computational details

All simulations were run on a Silicon Graphics Origin 200 and performed by using the commercial software *Cerius²* (v. 4.2) and *Materials Studio*, both from Molecular Simulation Inc.. The generation of accurate model structures of the dendrimer series was conducted as follows. For each dendrimer, the molecule was built and its geometry optimized *via* energy minimization using the COMPASS force field (Sun, 1998). The molecules were modeled to have a total charge equal to zero, and the distribution of the partial charge within each molecule was determined by the charge equilibration method of Rappé and Goddard (1991). Energy was minimized by up to 5000 Newton–Raphson iterations. Following this procedure, the root-mean-square (rms) atomic derivatives in the low energy regions were smaller than 0.05 kcal/mole Å. Long-range nonbonded interactions were treated by applying suitable cutoff distances, and to avoid the discontinuities caused by direct cutoffs, the cubic spline switching method was used. van der Waals distances and energy parameters for nonbonded interactions between

heteronuclear atoms were obtained by the 6th-power combination rule proposed by Waldman and Hagler (1993).

The details of the isolated molecular structures at 298 K were obtained by performing MD simulations under NVT conditions. For the calculation of the dendrimer energetics in the aqueous environment, a suitable number of water molecules were confined, together with a dendrimeric molecule, in a cubic box with periodic boundary conditions (PBC). The number of water molecules within each box was fixed to 100, and each water molecule was modeled by a simple 3-point charge (SPC) model, which satisfactorily describes the properties of bulk water at ordinary temperatures (Berendsen et al., 1981). In order to minimize the artifact of periodicity, a cutoff distance was set equal to half the box length. The resultant structures were relaxed *via* MM, again using the COMPASS FF; in this case, the Ewald technique was employed in handling nonbonded interactions. Such a straightforward molecular mechanics scheme is likely to trap the simulated system in metastable local high-energy minima. To prevent the system from such entrapments, the relaxed structures were subjected simulated annealing (5 repeated cycles from 298 K to 1000 K and back) using constant volume/constant temperature (NVT) MD conditions. At the end of each annealing cycle, the structures were again relaxed *via* FF, using a rms force less than 0.1 kcal/mole Å for the molecule and 0.1 kcal/mole Å³ for the stresses on the periodic boxes as convergence criteria. Both convergence criteria were simultaneously satisfied for the system to be relaxed completely. The simulation box was allowed to vary in size and shape during energy minimization, in order to find the equilibrium density for each structure. Each molecular dynamics run was started by assigning initial velocity for the atoms according to a Boltzmann distribution at $2 \times T$.

Temperature was controlled *via* weak coupling to a temperature bath (Berendsen et al., 1984) with coupling constant $\tau_T=0.01$ ps. The Newton molecular equations of motion were solved by the Verlet leapfrog algorithm (Verlet, 1967), using an integration step of 1 fs. Since the partial charges assigned by the charge equilibration method are dependent on structure geometry, they were updated regularly every 100 MD steps during the entire MD runs. Each MD simulation consisted in a system equilibration phase, during which the equilibration process was followed by monitoring the behavior of both kinetic and potential energy, and a data collection phase. Almost in all cases, the energy components have ceased to show a systematic drift and have started to oscillate about steady mean values around 30 ps. Accordingly, equilibration phases longer than 100 ps (*i.e.*, 1000,000 MD steps with time step =1 fs) and data acquisition runs longer than 300 ps were judged not necessary to enhance data accuracy.

Results and Discussion

Figure 1 show the wireframe structures of generation 1 and 5 for the iron porphyrin-based dendrimers obtained as a result of the first structural investigations performed with MD simulations under NVT conditions.

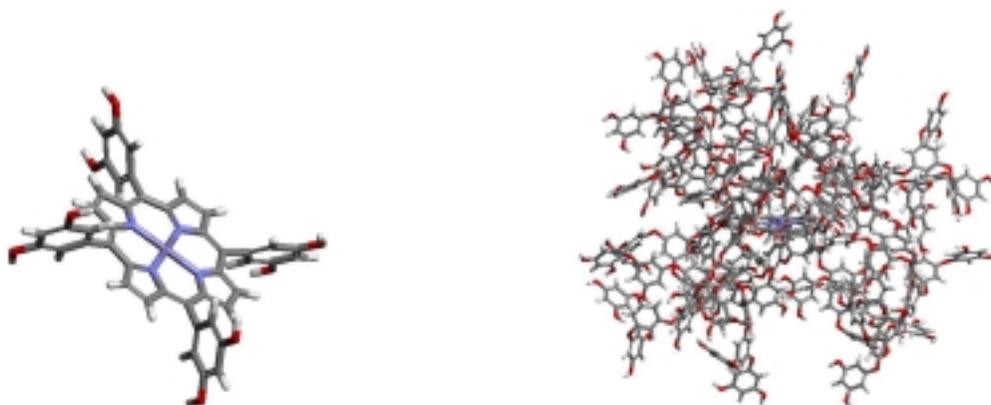


Figure 1. Wireframe structures of generation 1 (left) and generation 5 (right) of the iron porphyrin-based dendrimers.

According to the NMR evidences of Jiang and Aida (1996), the analysis of computer simulations reveals that, in generation 5, the porphyrinic core is well embedded into the dendrimeric shell, which can act as a steric and hydrophobic protection for dioxygen binding activity. This is well evident also from the trends in the values of the potential energy obtained for the different dendrimer generations with bounded oxygen (see Figure 2).

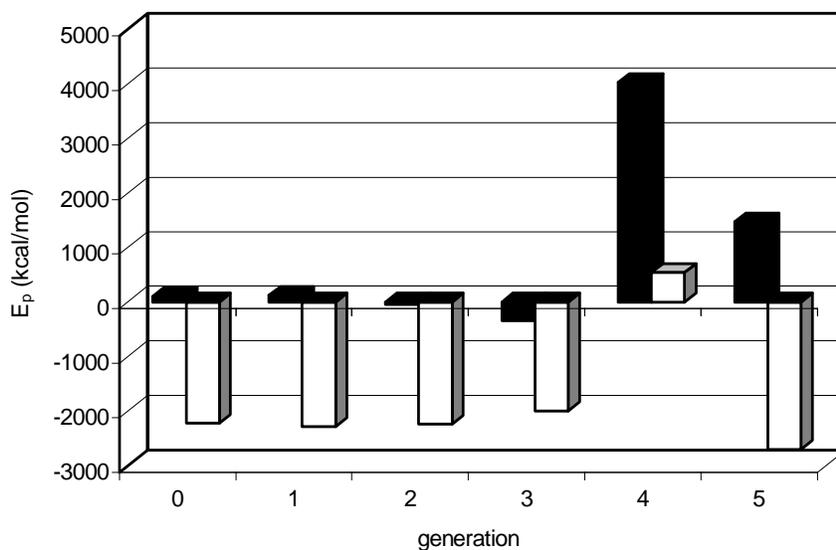


Figure 2. Potential energy as a function of dendrimer generation for oxygenated dendrimers in vacuo (black) and in the aqueous environment (white).

The anomalous behavior shown by generation 4 is a typical feature of starburst molecules, in particular of symmetrically branched dendrimers (Blasizza et al., 2000). As it is well evident from this Figure, the deoxy-bound dendrimer results to be stable in water; in particular, generation 5, which contains almost the same number of atoms of hemoglobin, seems to have the lowest energy content of the series analyzed.

The analysis of the radius of gyration (R_g) as a function of generation reveals that the relationship is linear for this series of dendrimers (see Figure 3), and the R_g value of the

5th generation (15.5 Å) is very close to the corresponding value for the isolated hemoglobin molecule (15.1 Å). The agreement of the simulated values with the corresponding available experimental data is also very good. Further, the linear regression of the data in Figure 3 indicate a fractal dimensionality of 2.46, which is very close to the values of the corresponding fractal dimensions of several proteins (Birdi, 1993).

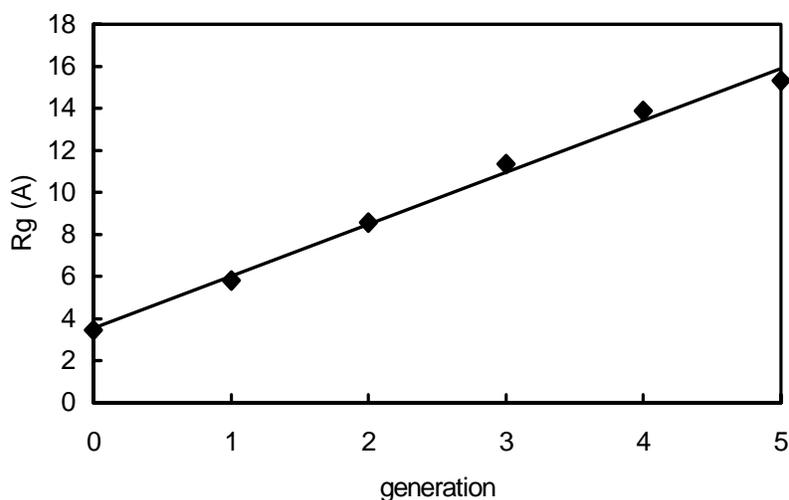


Figure 3. Radius of gyration as a function of isolated dendrimer generations.

Conclusions

This paper presents the preliminary results obtained from MM/MD simulations on a series of iron porphyrin-based dendrimers. From the structural point of view, the agreement between the results achieved from computer experiments and the relevant experimental observations is very good. The evidences obtained seem to indicate that generation 5 of this dendrimer series is the most suitable molecule to be used as a possible synthetic molecule able to display dioxygen binding activity, in which the dioxygen adduct survives in the presence of water. Further work is currently in progress

to confirm the results obtained and to expand the data series to higher dendrimer generations and to the binding of other biologically interesting metals.

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Acknowledgments

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