Molecular Modeling and Computational Study of Tyrosine-Derived Polyarylates

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Statement of Purpose:
Previously, a semi-empirical model to predict bioresponse (i.e., fibrinogen adsorption) for the entire combinatorial library of L-tyrosine-derived polyarylates was developed by Smith et al. [1-3]. The model was based on molecular descriptors obtained from non–relaxed two dimensional polymer structures. Better descriptors can be derived from relaxed 3D polymeric structures, which are calculated from molecular dynamics simulations (MD).

Methods:
The following commercial simulation packages were used sequentially: MacroModel vs 5.1 (Schrodinger [4]) and DRAGON (Milano Chemometrics and QSAR Research Group [5]). The OPLS–all atom force field (by W. Jorgensen, Yale University) was used. All energy minimizations were carried out in a stepwise manner using the Polak–Ribiere Conjugate Gradient algorithm. Convergence was achieved during 2500-5000 iterations with a threshold of 0.05. MD simulations were performed for each polymer, in vacuum and implicit water with canonical (NVT) statistical ensemble. The SHAKE algorithm was applied to constrain bonds to hydrogen.

Results / Discussion:
MacroModel 5.1 was utilized in all MD simulations because of the quality of its molecular builder, format compatibility with DRAGON, availability of an implicit solvent model, and excellent tools to perform conformational analysis. From all force fields available in MacroModel, OPLS–all atom force field has proven to be one of the best for condensed-phase simulations of peptides. It also gives comparable results for a wide variety of organic systems. We chose a time step of 1.0 fs at 298K. Reduction of the time step down to 0.5 fs only slightly reduced the size of energy fluctuations but noticeably increased the total simulation time.
The computational challenge of this project is to build conformationally realistic structures that are relaxed to the lowest energy state for the polymers of interest. An additional challenge was posed by the need to ensure the compatibility of input and output file formats when using different software packages sequentially. In our MD simulations we were limited to the use of tetramers because of the limited system size of DRAGON which allows for a total of 300 atoms only. We found that the equilibration time required to obtain converged energies for systems containing on average 300 atoms varies from 0.4 ns (in vacuum) to 1.0 ns (in implicit solvent). Based on these observations, we selected 0.5 ns for all production runs. Total energies (Figure 1), average enthalpies, the key bond and torsion angles were monitored during production runs and configurations were sampled every 50 ps. Detailed structural analysis allowed us to capture the most important packing and local conformational trends, which indicated that the conformational behavior of the short-chain tetramers resemble to a large extent those observed for longer (20-unit) polyarylate segments.

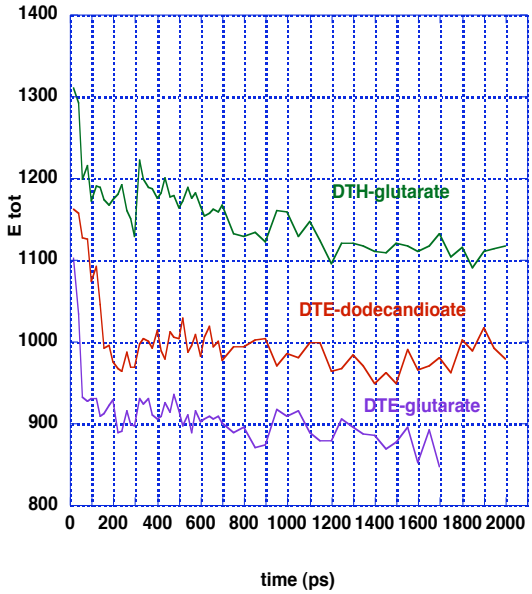

Figure 1. Tetramers of representative polyarylates simulated in aqueous environment (equilibration time: 0.9 ns; production time: 1.0 ns).

Conclusions:
To our knowledge this is the first time a Molecular Dynamics-based conformational study was carried out for a library consisting of 45 structurally related polymeric biomaterials. The computational protocol described above allowed us to build and minimize 3D molecular structures of polyarylates, carry out MD simulations, and obtain low energy conformations. These results provided us with the necessary input for the computational prediction of fibrinogen adsorption for the entire library of polyarylates. We anticipate that the use of descriptors obtained from the relaxed 3D polymer structures will improve the accuracy of the predictions of our model of protein adsorption on polymer surfaces.

References:
[1] Smith, J. Polymer, 2005 (46: 4296-4306).
[2] Smith, J. Macromolecular Rapid Communications, 2004 (25: 127-140).
[3] Smith, J. Journal of Chemical Information and Computer Science, 2004 (44: 1088-1097).
[4] www.schrodinger.com/ProductDescription.php ?mID=&sID=8&cID=0
[5] www.talete.mi.it/products/dragon_all_about.htm