Conformational Analysis of Free and Bound Retinoic Acid

*Zheng Fu, Xue Li and Kenneth M. Merz, Jr.**

Abstract

The conformational profiles of unbound all-*trans* and 9-*cis* retinoic acid (RA) have been determined using classical and quantum mechanical calculations. Sixty-six all-*trans*-RA (ATRA) and forty-eight *9-cis*-RA energy minimum conformers were identified via HF/6-31G* geometry optimizations *in vacuo*. Their relative conformational energies were estimated utilizing the M06, M062x and MP2 methods combined with the 6-311+G(d,p), aug-cc-pVDZ and aug-cc-pVTZ basis sets, as well as complete basis set MP2 extrapolations using the latter two basis sets. Single-point energy calculations performed with the M062x density functional were found to yield similar results to MP2/CBS for the low-energy retinoic acid conformations. Not unexpectedly, the conformational propensities of retinoic acid were governed by the orientation and arrangement of the torsion angles associated with the polyene tail. We also used previously reported QM/MM X-ray refinement results on four ATRA-protein crystal structures plus one newly refined 9-*cis*-RA complex (PDB ID 1XDK) in order to investigate the conformational preferences of bound retinoic acid. In the re-refined RA conformers the conjugated double bonds are nearly coplanar, which is consistent with the global minimum identified by the Omega/QM method rather than the corresponding crystallographically determined conformations given in the PDB. Consequently, a 91.3% average reduction of the local strain energy in the gas phase, as well as 92.1% in PCM solvent, was observed using the QM/MM refined structures *versus* the PDB deposited RA conformations. These results thus demonstrate that our QM/MM X-ray refinement approach can significantly enhance the quality of X-ray crystal structures refined by conventional refinement protocols, thereby providing reliable drug-target structural information for use in structure-based drug discovery applications.