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The activation of phosphoramide mustard anticancer drugs from ab initio simulations. MARKUS ALLESCH, Graz University of Technology, Austria, and Lawrence Livermore National Laboratory, ERIC SCHWEGLER, Lawrence Livermore National Laboratory, MIKE COLVIN, University of California, Merced, FRANCOIS GYGI, GIULIA GALLI, Lawrence Livermore National Laboratory and University of California, Davis — The nitrogen mustard based DNA alkylating agents were the first nonhormonal drugs to be used effectively in the treatment of cancer and remain one of the most important drugs for the chemotherapeutic management of many common malignancies today. An understanding of the activation of these compounds is, in itself, of scientific interest, but also critical in designing improved analogs of greater selectivity and efficacy. We have investigated the activation pathways of one of the most active metabolites, phosphoramide mustard (PM), and its methylated ester (PMME). In particular, we have examined the activation barrier and reaction free energy for the intramolecular cyclization reaction using first principles molecular dynamics simulations with explicit and continuum solvation models. Structural, dynamical and electronic properties along the reaction path have been computed mainly to address the question why de-esterification is required to activate these drugs. This work was performed under the auspices of the U.S. Dept. of Energy at the University of California/Lawrence Livermore National Laboratory under contract no. W-7405-Eng-48.

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