Abstract

Studying biochemical reactions at the molecular level is extremely important in connection to the understanding of human physiological processes, especially those connected to aging, diseases and cacinogenesis. Computationl chemistry is thereby becoming a more and more popular alternative to the classical experimental approach. It is especially appealing for studying extremely fast processes and isolating the unwanted factors, which can be impossible to achieve in a laboratory setting. An excellent example represent studies of structures of transition states as well as individual contributions of different inter-particle interactions to the thermodynamics and kinetics of chemical reactions, and to the stability of biomacromolecules. Acrylonitrile (AN) is a known carcinogen in rats and a suspected carcinogen in humans. In an oxidative cellular environment a part of AN can be converted via epoxidation on cytochrome P450 2E1 to an even more reactive cyanoethylene oxide (CEO). CEO is a mutagen and due to its high reacitvity towards DNA a potential carcinogen. Using quantum-chemical methodology we performed a broad and comprehensive analysis of the damage of DNA's double strand nucleobases via alkylation with the reactive species CEO and its precursor AN. The obtained results successfully reproduced experimentally determined activation barriers as well as relative reactivities of individual nucleobases. Furthermore, we delved into the individual contributions of nonbonding interactions of nucleobases with their immediate surroundings to the stability of the system. By examining 8 different reactions on dinucleosides we observed that neighbouring nucleobases can indirectly influence the stability and reactivity of the reacting nucleobase. Additionally, we assessed the efficacy of some of the natural scavengers of chemical carcinogens such as various members of the polyphenol group and capsaicin. Their calculated activation barriers were very similar to those obtained for nucleobase alkylations, in some cases even lower. Polyphenols resveratrol and delphinidine along with structurally similar capsaicin proved to be the most promising scavengers. Last but not least, we examined the effect of microwave catalysis on the alkylation as well as on the structures of biomacromolecules such as nucleic acids, peptides and proteins. In a modern society mankind is constantly exposed to microwave irradiation. The results of the latest studies have shown a connection between microwave radiation and the onset of carcinogenesis. Rotationally excited CEO molecule can indeed significantly decrease the activation barrier for nucleobase alkylation. Microwaves can even cause misfolding of peptides which has been attributed to the formation of insoluble aggregates and fibrillation – generally associated with neurodegenerative diseases.

Keywords: DNA alkylation, cyanoethylene oxide, microwave catalysis, biomacromolecular structure, computational chemistry