Formation mechanism of glyoxal-DNA adduct, a DNA cross-link precursor

Vilanova B.

Fernández D.

Casasnovas R.

Pomar A.M.

Alvarez-Idaboy J.R.

Hernández-Haro N.

Grand A.

Adrover M.

Donoso J.

Frau J.

Muñoz F.

Ortega-Castro J.

DNA nucleobases undergo non-enzymatic glycation to nucleobase adducts which can play important roles in vivo. In this work, we conducted a comprehensive experimental and theoretical kinetic study of the mechanisms of formation of glyoxal?guanine adducts over a wide pH range in order to elucidate the molecular basis for the glycation process. Also, we performed molecular dynamics simulations to investigate how open or cyclic glyoxal?guanine adducts can cause structural changes in an oligonucleotide model. A thermodynamic study of other glycating agents including methylglyoxal, acrolein, crotonaldehyde, 4-hydroxynonenal and 3-deoxyglucosone revealed that, at neutral pH, cyclic adducts were more stable than open adducts; at basic pH, however, the open adducts of 3-deoxyglucosone, methylglyoxal and glyoxal were more stable than their cyclic counterparts. This result can be ascribed to the ability of the adducts to cross-link DNA. The new insights may contribute to improve our understanding of the connection between glycation and DNA cross-linking.