Theoretical Studies on the Thermodynamics and Kinetics of the Lysine-Arginine Cross-Links Derived from α-Oxoaldehydes: A New Mechanism for Glucosepane Formation

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Abstract*:* Experimental results have previously shown that glucosepane is formed through an intermediate compound of lysine linked α-dicarbonyl under non physiological levels of glucose. But degradation of this intermediate in the glycation of human serum albumin under physiological conditions is supporting existence of another route in the formation of this cross link. Using wB97XD dispersion-corrected functional, a new mechanism for glucosepane formation through reaction of free α-oxoaldehydes with lysine and arginine residues has been proposed. This non enzymatic process can be described in three main steps, namely: (1) Schiff base formation from methyl amine, methyl glyoxal (MGO) and one water molecule, (2) addition of methyl guanidine and (3) addition of glyceraldehyde. We show that this mechanism is thermodynamically possible and presents a rate-determining step with a reasonable free energy barrier equal to 37.8 kcal/mol in water solvent. Comparisons were done with the mechanism formation of GODIC (glyoxal-derived imidazolium cross-link) and MODIC (methyl glyoxal-derived imidazolium cross-link), two other important cross-links in vivo. Our results show that glucosepane formation is more exothermic than others while its formation kinetics is slower.

Key words: Glucosepane; cross-link; physiological glucose levels; density functional theory; free α-oxoaldehydes; GODIC; MODIC and wB97XD functional.