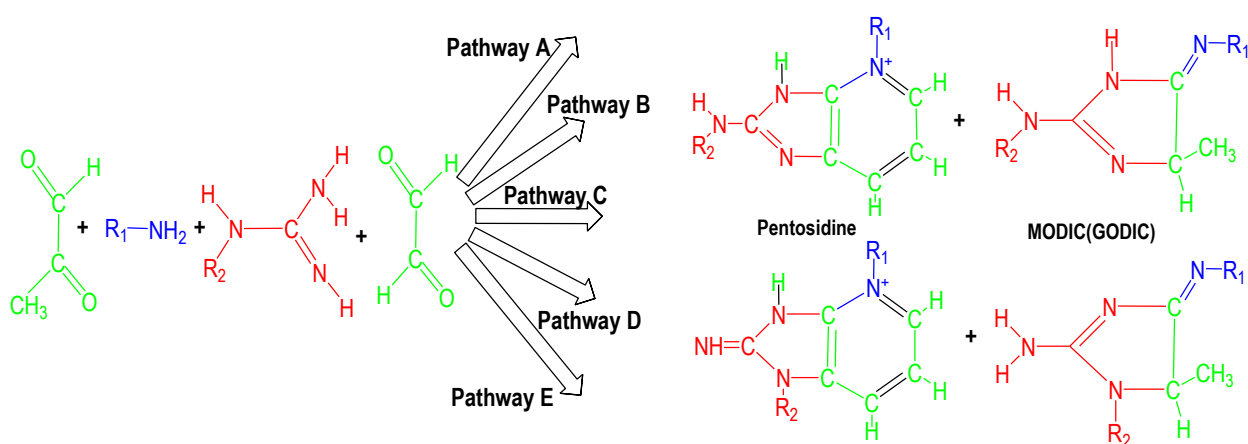


# Computational Studies on Cross-Linking Process: Evidence for Multiple-Novel Reaction Pathways in Pentosidine, MODIC and GODIC Formation

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Cross-linking in proteins by  $\alpha$ ,  $\beta$ -dicarbonyl compounds is one of the most damaging consequences of reactive carbonyl species *in vivo* and in foodstuffs. In this study, cross-linking of glyoxal and methyl glyoxal with lysine and arginine residues were investigated computationally using density functional theory and the wB97XD dispersion-corrected functional. Five pathways, A-E, for pentosidine [1], methyl glyoxal-derived imidazolium cross-linking (MODIC) [2] and glyoxal-derived imidazolium cross-linking (GODIC) [2] have been characterized. In pathways A and B, the reaction proceeds via formation of the Schiff base, aldimine, followed by addition of arginine for MODIC(GODIC) formation and also glyoxal (GO) in third stage of process for pentosidine. By contrast, in pathways C-E, direct addition of arginine to the dicarbonyl compounds occurs first, leading to a dihydroxyimidazolidine intermediate, which then reacts with lysine after dehydration and proton transfer reactions, resulting in the formation of MODIC (GODIC) and then reacts with GO to give pentosidine. The findings reveal that pathways A, C and E are competitive whereas reactions via pathways B and D are much less favorable. Inclusion of up to five explicit water molecules in the proton transfer and dehydration steps is found to lower the free energy barriers in the feasible pathways by about 5–20 kcal/mol.



Our calculations show that the reaction process for pentosidine is highly exergonic, and comparison of the mechanisms of MODIC and GODIC shows that the activation barriers are lower for GODIC than MODIC in agreement with experimental observations. These results served to underline the potentially important role that  $\alpha$ -oxoaldehydes play as precursors upon the aforementioned cross-links formation and provided new insights on how formation of cross-links by reactive carbonyl species occurs and should be useful in better understanding cross-linking processes in the complex field of glycation.

[1] Nasiri, R.; Field, J.M.; Zahedi, M. **J. Phys. Chem.** 2012, In Press.

[2] Nasiri, R.; Field, J.M.; Zahedi, M.; Moosavi-Movahedi, A.A. **J. Phys. Chem.** 2011, 115, 13542-13555.