

The Selectivity of the *O*-/*N*-Nitroso Aldol Reactions

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Abstract: Nitrosoarenes (Ar-N=O) and related species have a rich history in organic synthesis [1]. For example, the nitroso aldol (NA) reaction is one of the most powerful tools to introduce hydroxy or amino groups at the α -position of the carbonyl group [2]. Over the past few decades several experimental investigations (with several setups and conditions) have been performed to understand how to control selectivity of the *O*-/*N*-NA reactions [1]. This has occurred because, in light of the opposite behavior often exhibited by convectional chemistry, the greater electrophilicity of oxygen than that of nitrogen in some NA reactions is unclear until now. Lewis *et al.* reported the reaction of nitrosobenzene with 1-morpholin-1-ylcyclohexene followed by simple hydrolysis to give the hydroxyamino ketone (*N*-NA reaction) as the major product. Surprisingly, Yamamoto *et al.* found that the similar reaction of nitrosobenzene with 1-pyrrolidin-1-ylcyclohexene gave rise to the aminoxy ketone (*O*-NA reaction) almost exclusively [3]. Indeed, these are few computational studies exploring the control and origin of the selectivity of the *O*-/*N*-NA reaction [4,5]. In this context, we have performed a quantum mechanical computational study to understand the selectivity of these reactions of nitrosobenzene with enamines (1-morpholin-1- and 1-pyrrolidin-1-ylcyclohexene). For such, the DFT methods were used to obtain the energy profiles that included the energetic and structural characterization of the stationary minimum points (reagents, products and intermediates) and maximum (TS). All calculations were performed in benzene (PCM, implicit solvation model) with the Gaussian09 program. Three important mechanistic steps have been observed in the energy profiles. First, the enamine attack on the oxygen or nitrogen of the nitrosobenzene. After, the formed intermediate changes its conformation with a subsequent intramolecular proton transfer (prototropy). Then, from the results obtained has been possible to indentify that the stability of the intermediate and the prototropy are key points for understanding of the selectivity of this *O*-/*N*-NA reaction.

Key-words: *O*-/*N*-NA reaction, selectivity, DFT

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