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Theoretical Investigation of the Biginelli Reaction Mechanism: When Knoevenagel is a Possible Mechanism Pathway

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Abstract: Multicomponent reactions (MCR) have received great attention in organic synthesis and medicinal chemistry, since they allow the design of new molecules and pharmaceuticals, in special, with great structural complexity and excellent yields. [1] In the Biginelli reaction, the reactants are an aldehyde, a β-ketoester and urea or thiourea leading to a myriad of dihydropyrimidinones/thiones. From the possible combinations of the reactants, three reaction pathways can be expected: the Knoevenagel pathway, the iminium ion pathway and the enamine pathway, being the second pointed out, from both experimental and theoretical works with common aromatic and aliphatic β-ketoesters, as the most probable initiation route. [2] However, if a coumarin β-ketoester derivative is used, the Knovenagel pathway seems to prevail. [3] In order to understand the differences between these reaction pathways, this work has been proposed aiming to the calculations of the possible reaction paths in the coumarin β-ketoester + benzaldehyde + urea MCR and to the understanding of the contribution of the coumarin nucleus in the β-ketoester moiety for the changes in the reaction mechanism. Calculations have been performed at different theoretical levels. First, the semiempirical PM6 method has been adopted and stationary points, including saddle points and several proposed intermediates, have been located. Geometry optimizations have been then performed at the Density Functional Theory (DFT) level, adopting the M06-2X, B3LYP and BHandHLYP fuctionals and the 6-31+G(d,p) basis set. The former has been chosen, since literature points out this functional as the most suitable for describing reaction thermochemistry and kinetics of organic species, [4] whereas the B3LYP and BHandHLYP functionals have been chosen for comparison (B3LYP is still the most used functional worldwide and the BHandHLYP functional is similar, differing in the coefficients of the exchange terms). Based on the initial guess, provided from the PM6 calculations, stationary points have been located for the three reaction channels at the different DFT levels. From our calculations, the stationary points with lower relative energies belong to the Knoevenagel reaction path. All reaction pathways are initiated with the formation of an ion-dipole pre-barrier complex, stabilized by 27 – 35 kcal mol^{-1} (relative to the isolated protonated reactants). The calculated barrier height for the reaction between the coumarin β-ketoester + benzaldehyde (which initiates the Knoevenagel channel) is -18.10 kcal mol^{-1} (relative to the isolated protonated reactants). For the enamine and iminium ion pathways, barrier heights are 6.21 kcal mol-1 and -16.27 kcal mol^{-1}, respectively (the enamine pathway is initiated from the coumarin β-

ketoester + urea reaction and the iminium ion is initiated form the urea + benzaldehyde reaction). Therefore, the barrier height of the first step in the Knoevenagel pathway is *ca.* 24 and 2 kcal mol^{-1} lower than the barrier heights of the first step in the enamine and iminium ion pathways, respectively. The reaction product in the Knoevenagel pathway is also the most stabilized (30.63 kcal mol^{-1} below the isolated protonated reactants, while the products in the enamine and iminium ion pathways are located, with respect the isolated reactants, at 5.85 and -25.04 kcal mol^{-1}, respectively). The second step in all pathways is the dehydration, and barrier heights and reaction energy differences are -12.36 and -20.46, 23.93 and 3.10 and -2.77 and -12.21 kcal mol^{-1} (Knoevenagel, enamine and iminium ion, respectively). The final steps concern the addition of the third reactant, and the intermediates and transition states belonging to the Knoevenagel pathway remain the lowest energy structures. Thus the Knoevenagel pathway is finally attributed as the lowest energy pathway in this complex mechanism for the coumarin β-ketoester + benzaldehyde + urea MCR. No great differences in these trends or conclusions have been observed by changing the theoretical level. The Knoevenagel intermediate has been experimentally detected, [3] and such previous observation can be justified from our theoretical calculations. As compared to other intermediates, the Knoevenagel intermediate is the most stabilized, being ca. 25 and 10 kcal mol^{-1} below the enamine and iminium ion intermediates, respectively. Similar calculations have been performed for the β-ketoester + benzaldehyde + urea MCR, where the β-ketoester nucleus is either a methyl, a phenyl or a 4-OH-phenyl group. For all these reactions, the iminium ion channel has been shown to prevail from all other channels, as previous described in the literature, indicating that the coumarin group plays a distinct role. These results satisfactorily compare to the experimental observations and demonstrate that the coumarin nucleus in the β-ketoester moiety promotes the change of the mechanism initiation from the iminium ion to the Knoevenagel pathway.

Key-words: Multicomponent Reaction, Biginelli Reaction, Knoevenagel intermediate
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