Title: **Theoretical study of the mechanism of the Cope rearrangement in 2,5-substituted 1,5-hexadiene: the role of cyano and phenyl substituents**
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The study of the Cope rearrangement arises high interest, due to its application in organic synthesis of natural products, flavors and fragrances, both at the laboratory and industry scales. One must emphasize its importance in the pharmaceutical industry. In fact, this mechanism is part of the reaction sequence of the synthesis of some drugs, such as licoramina and mesembrina. The licoramina is used as a drug to combat the Alzeimer disease, and the mesembrina acts as antidepressant.

Previous experimental and theoretical studies have shown that the Cope rearrangement of 1,5-hexadiene can occur through three possible transition states (Fig. 1): an aromatic transition state (Fig. 1, middle), and two radical structures, the cyclohexane-1,4-diil (Fig. 1, top) and bis al.lil (Fig. 1, bottom).

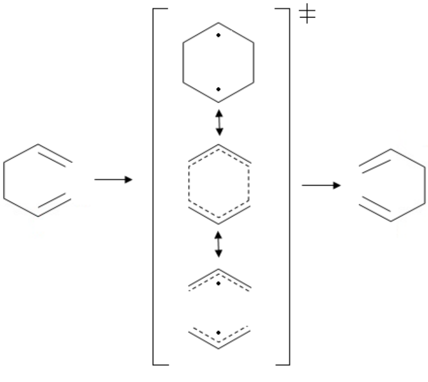

Fig. 1. Cope rearrangement and transition states

According to the literature, the most favorable path is concerted through an aromatic transition state. Note that the formation energies of bis-allyl and cyclohexane-1,4-diyl radicals are 11 kcal/mol and 26 kcal/mol, respectively, higher than the formation energy of the aromatic transition state. These data indicate that the aromatic transition state is the most favorable structure through which the Cope rearrangement of 1,5-hexadiene takes place. With the introduction of both cyano and phenyl substituents in positions C2 and C5, the radical transition states are stabilized, although being more energetic than the aromatic one.

In this work, the main objective is to study the mechanisms of the Cope rearrangement of 1,5-hexadiene and its derivatives with cyano and phenyl substituents at positions C2 and C5. The goal is, then, to locate all the basic structures and transition states that characterize them. As a result, we obtain three reaction profiles corresponding to the mechanism of the Cope rearrangement of 1,5-hexadiene, 2,5-diphenyl-1,5-hexadiene and 2,5-dicyano-1,5-hexadiene.

It can be anticipated that we are able to characterize radical structures that are consistent with those suggested in the literature. However, although they are present in the reaction profile, these radical transition states are not involved in the mechanism of the Cope rearrangement of any of the three species analyzed in this study. The reason that justifies this is that the minima can evolve towards an alternative pathway to other transition states, which are energetically more favorable than the radical ones. The structures that give rise to the less energy pathway are the result of rotations of single bonds instead of cyclization of the skeleton or breaking bonds.

As mentioned before, according to the literature, both cyano groups (electron attracting groups) and phenyl groups (electron donor groups) cause the same effect in reducing the energy barrier of the Cope rearrangement. This work corroborates this fact by comparing the energy differences corresponding to the same structures of the 1,5-hexadiene parent and its cyano and phenyl derivatives. Finally, the geometry of the structures that are found in all three reaction profiles has been analyzed. Similar structures are observed in the Cope rearrangement profile of 2,5-diphenyl-1,5-hexadiene and 2,5-dicyano-1,5-hexadiene. This latter contribution corroborates the fact that the two cyano and phenyl substituents cause the same effect on the mechanism of the Cope rearrangement of the 1,5-hexadiene