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PM3 Calculations of Diels-Alder Reactions of "Pull-Push" Activated Isoprenes with Aceto- and Acrylonitrile

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Abstract: *PM3 calculations of the pull-push dienes in the Diels-Alder reactions with acetonitrile and acrylonitrile are presented. Two of the pull-push dienes, 1-dimethylamino-1-iodoisoprene and 1-fluoro-1-dimethylaminoisoprene where studied. In the iodo isomer the C-I bond can be easily broken and the actual species considered in the calculation is the corresponding cation 3. Frontier orbitals and the energy barriers in the reactions were considered for all possible cases in the two step, as well as in the concerted mechanism. The frontier orbital calculations of the reactants correctly predict the products of the reactions. According to the calculated energy barriers for the CN addition of acrylonitrile to cation 3 the two step addition is preferred over the concerted mechanism. In the case of the Diels-Alder reaction of fluoroisoprene and acrylonitrile the concerted mechanism was favored. The PM3 energy barriers of all possible cases suggest that in the endo acrylonitrile addition, the CC double bond rather than the CN triple bond is added to the diene. The predicted PM3 products of the reactions are in full agreement with ones obtained experimentally.*

Introduction

The hetero Diels-Alder reactions as part of the family of Diels-Alder reactions[1] are a very powerful method for the preparation of a wide variety of heterocyclic compounds.[2] There is a large number of both experimental[1] and theoretical[3] studies of the all-carbon Diels-Alder reactions. The hetero Diels-Alder reactions have been studied less, both experimentally[2] and even less theoretically.[4,5]

The ability of nitriles to act as Diels-Alder dienophiles has been known since 1935 when Filthy and co-workers discovered that tetracyclone reacts with nitriles at

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high temperatures giving rise to substituted pyridines.[6] One of the features of the Diels-Alder reactions with most alkyl and aryl nitriles, as well as cyanides, that has made them rather unattractive as heterodienophiles is that very high reaction temperatures are required for the cycloadditions.[7] To make the reaction feasible at less rigorous conditions either the nitrile or the diene can be activated with different substituents. Because the dienophiles are usually the electron acceptors in the Diels-Alder reactions, the most effective derivatives of nitriles are the sulfonyl cyanides.[8] They react with dienes at reasonably low temperatures and afford 3,6-dihydropyridines which under the reaction conditions are oxidized to the corresponding 2-sulfonylpyridines or if hydrolyzed *in situ* give rise to 2-pyridones.[9]

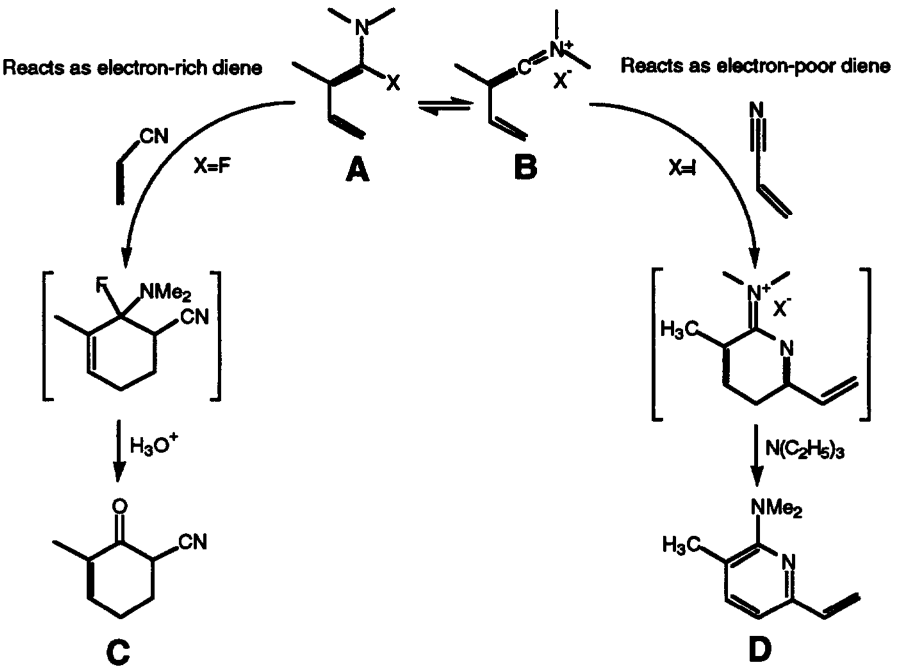
On the other hand, the use of a wide variety of nitriles in hetero Diels-Alder reactions can be facilitated if very reactive dienes are used. In this way, almost any organic nitrile can react with so called push-pull dienes.[10] These dienes are sufficiently electrophilic to react at relatively low temperatures with inactivated, electron-rich nitriles, affording initial [4 + 2] adducts which tautomerize to 2-aminopyridines. There are no theoretical studies of the push-pull dienophiles for nitrile Diels-Alder reactions. Herein we would like to present our PM3 studies of these reactions.

Procedures and Methods

All calculations were performed on a DEC 7620 computer. Chem-3D Plus on a Macintosh IIfx was used as a graphical interface for drawing and visualizing all structures and for preparing input files for MOPAC 6.0.[11] The search for the transition states and their verification[12] was performed as described previously.[13] Vibrational and thermal analyses were performed for all optimized structures.

Results and Discussion

The theoretical study of push-pull dienes was chosen not only because there are no available theoretical studies of their reactivity but also because they are synthetic equivalents to vinylketenes, extremely important intermediates. The possibility of adjusting the reactivity of the diene and the pathway of the reaction by changing the equilibrium between 1-dimethylaminoisoprene (**A**) and vinylketeniminium salt (**B**) make these dienes highly versatile for the preparation of 2-cyclohexenone (**C**) and 2-dimethylaminopyridne (**D**) derivatives (Scheme 1). The reactivity of the diene can be adjusted through the anion-counterion salt **B** (X=Cl, I, or OTs). Furthermore, having all experimental data and reaction conditions necessary for effecting the reactions in both ways,[10] makes this system highly suitable for theoretical studies.



Scheme 1. Diels-Alder Reactions with "Push-Pull" Dienes.[10]

The system of interest is computationally complex and for proper ab initio calculations requires large basis sets which would include not only polarization but also diffuse functions and a level of theory that would account for the electron correlations. Despite its known limitations, especially in calculating the energy barriers, a semiempirical approach was chosen instead, in order to compare its findings to the experimentally obtained data. PM3[14] was used because it was shown[15,16] in the case of 1,3-dipolar cycloaddition of the methylsulfonyl azide to nucleophilic 1,3-dipolarophiles, that the PM3 structure of the reactive intermediate is almost superimposable with the one obtained by X-ray analysis.[17]

The Diels-Alder reaction between 1-chloro-1-dimethylaminoisoprene and the unactivated nitriles is catalyzed by sodium iodide.[10] It is reasonable that actually the corresponding cation which is formed from 1-dimethylamino-1-iodoisoprene, rather than from the original chloro derivative, is involved in the reaction. We have optimized the structures of both the *cis-* (**1**) and the *trans-* (**2**) isomers of 1-dimethylamino-1-iodoisoprene as well as the corresponding cation (**3**). According to PM3 the isomer **1** has 2.8 kcal/mol lower energy than the isomer **2**. It is interesting that in both isomers the two CC double bonds are not in one plane. The dihedral angles are 57.7° and 125.7°, respectively, due to steric interactions with the iodine atom.

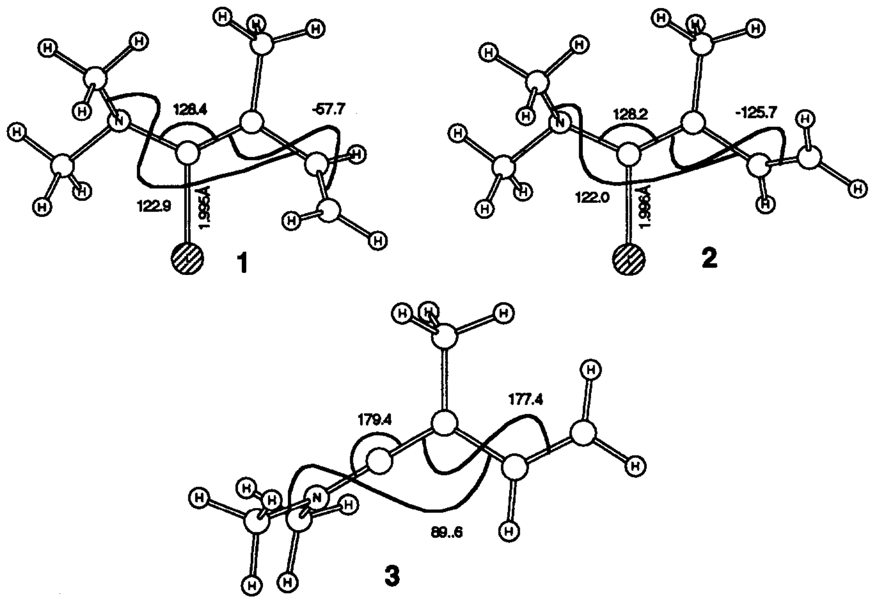


Figure 1. The isomeric reactants and the cationic product in reaction of C-I bond breaking.

The reactivity of 1-dimethylamino-1-iodoisoprene, or actually its cation 3, with acetonitrile can be studied in terms of the frontier orbitals.[13] According to the frontier orbital theory the reaction will be facilitated if the HOMO-LUMO energy gap between the reactants is smaller. In our model study of addition of acetonitrile to butadiene, a smaller HOMO-LUMO energy gap between the reactants is LUMO$_{acetonitrile}$ - HOMO$_{butadiene}$ = 10.87 eV. The energy gap between our studied reactants, acetonitrile and cation 3, is only 7.19 eV and it is a LUMO diene controlled reaction (LUMO$_{cation\ 3}$ - HOMO$_{acetonitrile}$). Thus, the addition of acetonitrile to cation 3 is preferred over the addition to butadiene. Frontier orbital theory can also predict the regioselectivity of the cycloaddition reactions from the atomic orbital contribution of the atoms that are making the bonds, the LUMO of cation 3 and the HOMO of acetonitrile. This is presented in Chart 1. However, even though frontier orbital theory correctly predicts the regioselectivity of the product of the reaction[10] it cannot tell anything about the activation barrier, the reaction mechanism and the stereoselectivity of the reaction.

Both the synchronous and stepwise mechanism of acetonitrile addition to cation 3 were considered. The transition structures for both mechanisms are presented in Figure 2. In the two step mechanism we have also considered the case when a C-C bond forms first, but were unable to locate the corresponding transition structure. The formation of the C-N bond first should be more predominant than the C-C bond

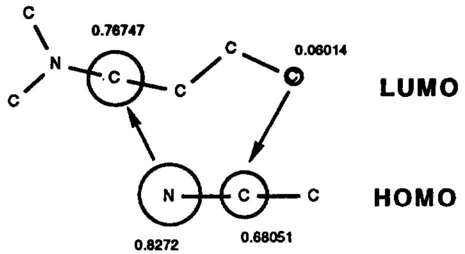


Chart 1. Atomic orbital contributions to frontier orbitals of cation 3 and acetonitrile.

formation, anyway. The energetic profiles for both mechanisms are presented in Chart 2. According to PM3 the two step mechanism is energetically greatly favored over the concerted mechanism. Experimentally 2-dimethylaminopyridine was obtained under mild reaction conditions, so an activation energy of 21.1 kcal/mol doesn't seem to be an unreasonable value.

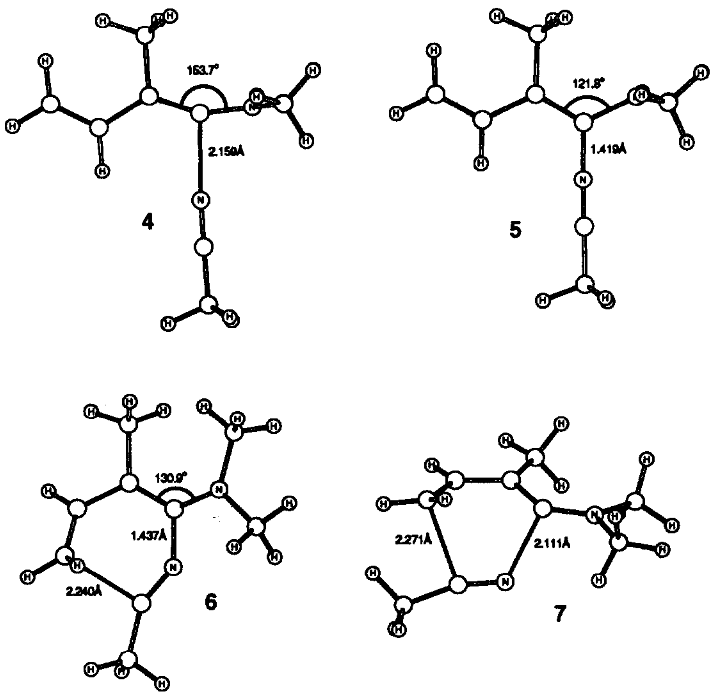


Figure 2. Geometries of the transition structures and intermediate in both stepwise and concerted mechanism of acetonitrile addition to cation 3.

The second part of the pull-push diene study was the acrylonitrile addition to 1-dimethylamino-1-iodoisoprene and 1-dimethylamino-1-fluoroisoprene (Scheme 1). Two different products were observed, one that originates from CN and the other from CC bond addition to the diene. All possible structures involved in the stepwise mechanism of acrylonitrile addition to cation **3** are presented in Figure 3. The reaction coordinate is presented in Chart 3. Again, as in the case of the acetonitrile addition, the two step mechanism is favored by 31.5 kcal/mol compared to the concerted mechanism. The first and second reaction barrier, as well as the barrier for the concerted transition structure, are somewhat lower than in the case of the acetonitrile addition. That is in agreement with the experimental observations and can be explained by the ability of the π-orbitals of acrolein to partially delocalize the positive charge in the transition state, in the intermediate, and in the product.

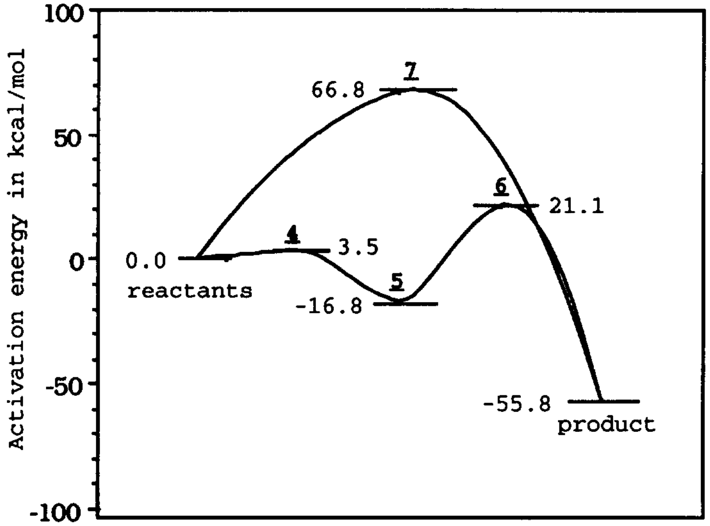


Chart 2. Graphical presentation of the relative energies of the transition structures and the intermediate involved in both the two step and concerted mechanism of the reaction.

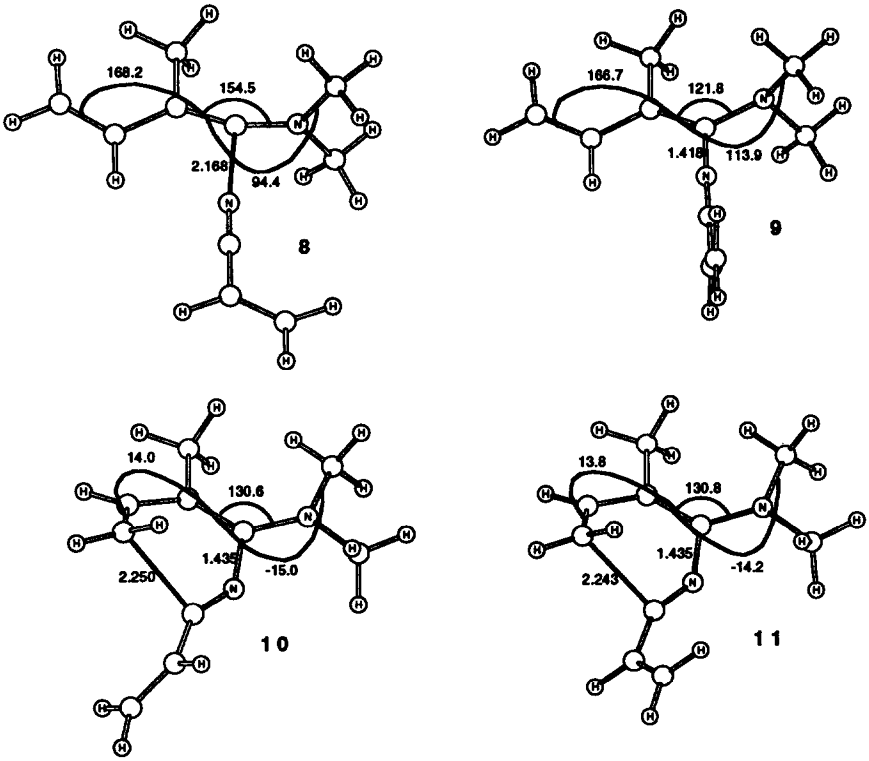


Figure 3. PM3 generated geometries of the first transition, intermediate, and the second transition structures in acrylonitrile addition to cation 3.

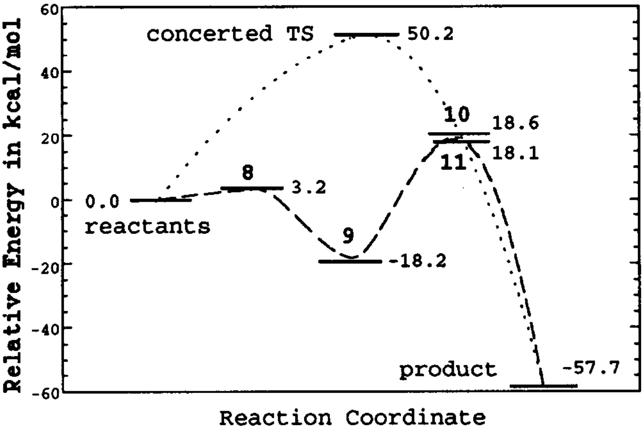


Chart 3. Graphical presentation of the relative energies of the reaction species in the addition of acrylonitrile to cation 3.

The addition of acrylonitrile to cation **3** through formation of two new CC bonds (addition of the double bond instead of the CN triple bond) was also studied, although experimentally this kind of product was not observed.[10] All four possible isomeric concerted transition structures were located, and they are presented in Figure 4. The activation energies for the concerted mechanism vary from 37.8-41.6 kcal/mol, which is around 20 kcal/mol higher than in the two step mechanism of the CN acrylonitrile addition to cation **3** (Chart 3). The Alder rule is preserved in the addition, presented by transition structures **12** and **13**, while in the formation of the other regioisomer, the calculation predicts that the nitrile would have added through transition structure **15** which leads to an anti-Alder product. Thus, according to energy barriers none of these transition states can be reached, and the corresponding products will not be formed, which is in agreement with the experiments.[10]

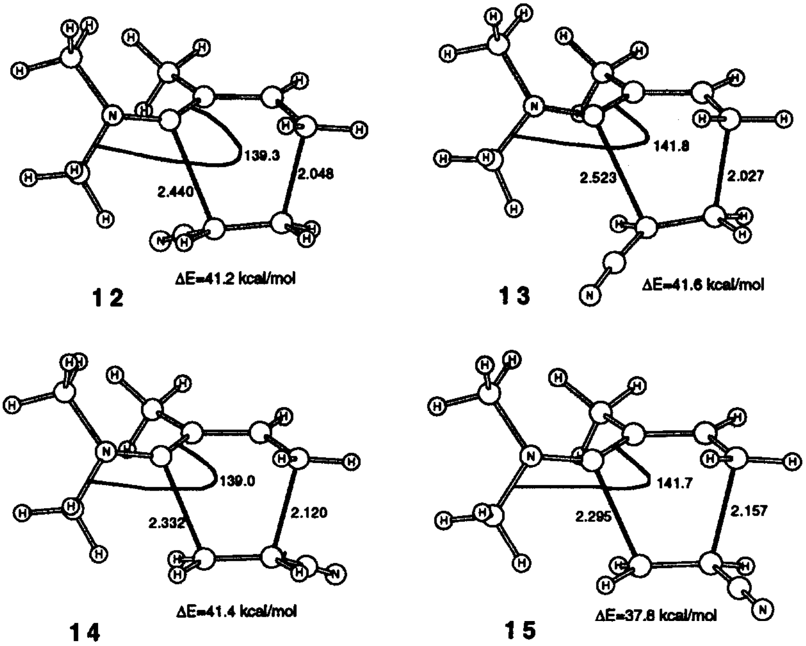


Figure 4. Isomeric transition structures in the CC addition of acrylonitrile to cation **3**.

Although the addition of acrylonitrile to 1-dimethylamino-1-iodoisoprene gives the product of the CN addition, the same reaction with 1-fluoro-1-dimethylaminoisoprene (**16**) leads to the CC bond adduct. Breaking the C-F bond requires much more energy than breaking the C-I bond, and it is reasonable to propose that the diene in the Diels-Alder reaction is neutral isoprene **16**, rather than cation **3**. In that case, the concerted mechanism is preferred over the stepwise as in the case of ordinary Diels-Alder reactions.[3] The addition of acrylonitrile can be explained by frontier orbitals.[18]

There are two possible adducts that can be formed: one involves the CC double bond and the other the CN triple bond of acrylonitrile. The energy gap between the HOMO of **16** and the LUMO of acrylonitrile (ΔE=8.54 eV) is lower than in the case of the other frontier orbital combination (ΔE=10.88 eV). Furthermore, because of better frontier orbital overlap, the addition of the CC double bond is preferred over the addition of CN triple bond with regioselectivity presented in Chart 4, case **A**. That is in full agreement with the experimental observations.

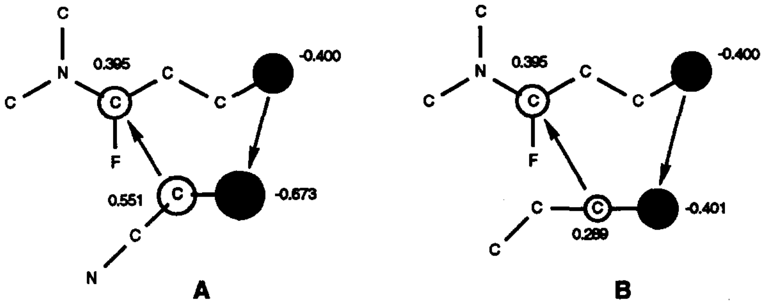
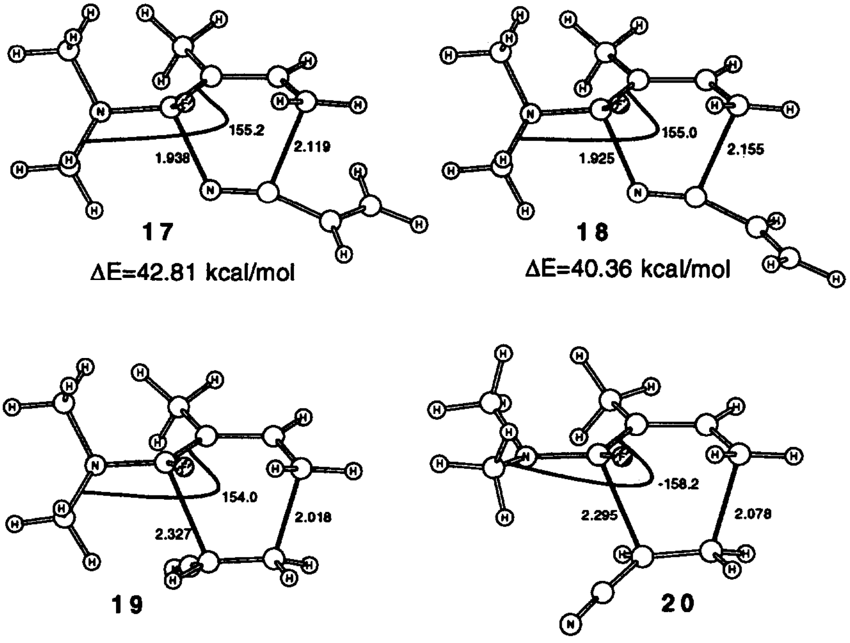


Chart 4. Frontier orbitals of diene **16** and acrylonitrile.

For the semiempirical calculations only the transition structures that lead to the observable products were considered. The PM3 generated transition structures are presented in Figure 5. All of these transition structures have higher activation barriers than the addition of acrylonitrile to cation **3** in the two step mechanism (Chart 3). In the concerted mechanism the CC endo addition of acrylonitrile (transition structure **19**) is the most energetically favored and is the one that produces the experimentally observable product. The energy barrier is by at least 7 kcal/mol lower than for the exo CN acrylonitrile addition to **16**. The most energetically favorable transition structure **19** is in agreement with the Alder rule of predominantly endo Diels-Alder adducts as well as with the experimental and frontier orbital results.

The present study was performed for species in the gas phase. Although ions are involved, it should be pointed out that for both the concerted and the stepwise addition reactions there is no net creation or elimination of charge. Therefore, the solvent effects should be limited to similar and rather delocalized ions and the preference for the stepwise over the concerted mechanism in solution, is not expected to be reversed.



17 ΔE=42.81 kcal/mol

18 ΔE=40.36 kcal/mol

19 ΔE=32.97 kcal/mol

20 ΔE=41.97 kcal/mol

Figure 5. Concerted transition structure of acrylonitrile addition to isoprene **16** generated by PM3.

Conclusion

Frontier orbital theory correctly predicts the experimentally obtained products in both cases of acrylonitrile addition to cation **3** and isoprene **16**. The relative energies obtained by the PM3 semiempirical method can be used to predict the reactivity and regioselectivity of the Diels-Alder reactions with "pull-push" dienes. In the case of aceto- and acrylonitrile addition to cation **3**, a two step addition mechanism is preferred over the synchronous by more than 30 kcal/mol. The CN triple bond two-step addition to cation **3**, is favored over the CC double bond of acrylonitrile addition. In the case when 1-fluoro-1-dimethylaminoisoprene (**16**) was used, the formation of cation **3** is not energetically favored, and the molecule behaves as an ordinary diene. In this case a concerted transition structure for acrylonitrile cycloaddition to isoprene **16** was generated. The calculation correctly predicts the CC addition with the endo nitrile group in the transition structure that leads to the experimentally obtained products. The theoretically obtained results with both frontier orbital and activation energy barrier are in full agreement with experimental results.

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