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# Calculations of boron trifluoride catalyzed 1,3-dipolar additions of azide ion to organic nitriles

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## Abstract

The boron trifluoride catalyzed 1,3-polar cycloaddition of azide anion to nitriles was studied by AM1 and ab initio methods. A stepwise mechanism was considered because the calculations show that the concerted transition state has a higher energy of activation. In order to determine the steric and inductive effects on the reaction, the calculations were performed with methyl and fluorine substituted acetonitriles. A small effect was detected only in the case of highly sterically demanding groups. On the other hand, the electronic effects of the fluorinated acetonitriles have a profound influence on the activation energy of the reaction. The boron trifluoride catalyst substantially decreases the energy of all molecular species in the reaction scheme. The major effect was calculated to be on the intermediate because the negative charge is mostly on the nitrile nitrogen, whereas the stabilization of the tetrazole anion product is negligible due to distribution of the negative charge over the aromatic tetrazole ring. In the case of the fluorinated acetonitrile a small or even negative activation energy was calculated, which can be explained by better  $\text{BF}_3$  stabilization of the first transition state than the starting nitriles and by the fact that calculations are performed in the gas phase. The calculated reactivity of the substituted benzonitriles show good correlation with the electron withdrawing ability of the substituents.

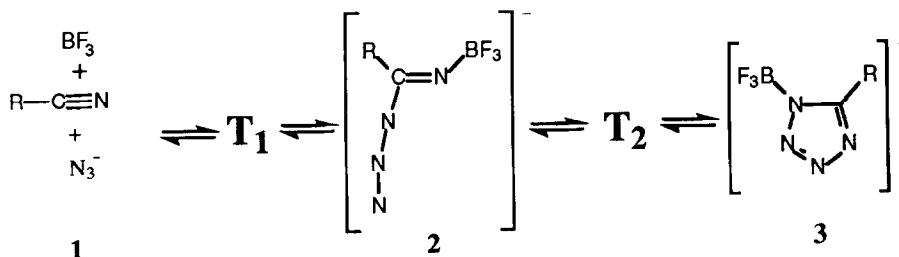
## 1. Introduction

The addition of the azide anion to nitriles is the most widely used route to 5-substituted tetrazoles [1]. The success in the preparation of the tetrazoles in this way strongly depends on the nature of the organic cyanide. The addition of sodium azide to trifluoroacetonitrile is an exothermic reaction while acetonitrile does not react at all and in fact acetonitrile is used as a solvent in the polar addition of

the azide to trifluoroacetonitrile [2]. While benzonitrile reacts with azide anion very slowly and product yield is low, electron withdrawing substituents on the aromatic ring substantially increase both the rate and the yield of the reaction [3]. To facilitate the addition of azide ion to unactivated azides many variations of the reaction conditions have been explored. More acidic sources than sodium azide have been used. When aluminum azide was used in reaction with aliphatic nitriles the yields are relatively high, but only one-third of the available azide is utilized [4]. Ammonium azide seems to be the synthetic source of the azide ion in polar cycloaddition to aliphatic nitriles [2]. Treatment of nitrilium salt with sodium azide ion

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Scheme 1. Proposed mechanism of the azide addition to the nitrile-boron trifluoride complex.

allows for the synthesis of a range of 1,5-disubstituted tetrazoles [5].

It is generally accepted that the stereochemistry of pericyclic reactions can be explained by orbital symmetry [6,7]. They are commonly believed to proceed through a concerted transition state [8]. There is considerable body of evidence that points out that the concerted transition state is not synchronous and has a biradical nature [9]. For polar cycloaddition reactions the stepwise mechanism is common [10].

Recently we initiated a theoretical study of the addition of the azide ion to organic nitriles [11]. This paper reports our theoretical study of addition of azide ion to organic nitrile-boron trifluoride complexes.

## 2. Procedures and methods

The semiempirical calculations were performed on an IBM compatible 486 DX/2 66 MHz computer and on a DEC 7620, while the ab initio calculations were performed with GAUSSIAN 92 [12] on a Silicon Graphics Personal Iris. CHEM-X [13] was used as a graphical interface for drawing and visualizing all structures and for preparing input files for MOPAC 6.0 [14].

The reactants were optimized together at an intermolecular distance of more than 10 Å. The search for the transition states was performed with MOPAC using the SADDLE search routine as described previously [15]. Vibrational and thermal analyses were performed on all optimized structures. All transition states had only one imaginary vibration corresponding to the mode along the new forming bond.

## 3. Results and discussion

The computational study is divided into three parts according to the nature of the organic nitriles: the addition of azide anion to the boron trifluoride complex with aliphatic nitriles, fluorinated acetonitriles, and substituted benzonitriles. The most reasonable mechanism for the addition is outlined in Scheme 1.

A concerted mechanism for the azide addition was ruled out by our previous computational study of azide addition to organic nitriles [11]. The search for a synchronous transition state structure is unreasonable because the C–N bond of the nitrile-BF<sub>3</sub> complex is much more polarized than in the free nitrile. Thus, the polar addition, in this case, should proceed even easier through a stepwise mechanism. The other fact that prompted us to reject the consideration of a synchronous transition state is the fact that the BF<sub>3</sub> catalyst should stabilize all polar species in the reaction course, and consequently further decrease the activation energy in the stepwise mechanism.

### 3.1. Azide addition to boron trifluoride complexes with aliphatic nitriles

The activation energies of azide anion additions to the boron complexes are presented in Table 1. From the results generated by the AM1 it can be seen that the first activation energy increases very modestly with the size of the alkyl group attached to C–N. This behavior is in full agreement with the known influence of the steric effect on the rate of the reaction [16]. The second activation energy, as well as the energy difference between the second transition state and the reactants is almost the

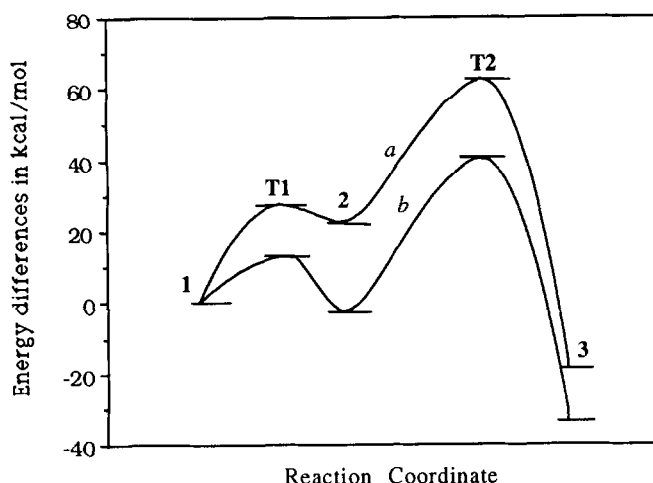


Fig. 1. Graphical presentation of the reaction path of azide addition to pivalonitrile (a) without and (b) with boron trifluoride.

same for all compounds, except for pivalonitrile which has a large sterically demanding tertiary butyl group (Table 1). This effect is pronounced in the second transition state that represents transformation of intermediate **2** into tetrazolium product **3**. Inspection of the generated structures of the pivalonitrile, corresponding to intermediate **2**, and tetrazolium product **3** shows that the steric interactions between the boron trifluoride and *tert*-butyl group increases during the course of the reaction. For example, the CCN angle involving the nitrile group changes from  $180^\circ$  to  $136^\circ$  from the reactant to the product. This is fully supported by the energy changes presented in Table 1. The differences between *iso*-butyronitrile and pivalonitrile are higher when the second transition state energy is compared to the reactant ( $6 \text{ kcal mol}^{-1}$ ) than with the intermediate ( $1.5 \text{ kcal mol}^{-1}$ ). In the

other cases the second activation barrier is almost the same. This can be explained by the fact that the alkyl group can adapt a conformation with minimal interactions with the boron trifluoride group in the second transition state.

To demonstrate the effect of the boron trifluoride catalyst on the activation energies the azide addition to pivalonitrile was chosen. A comparison of the activation energies calculated by AM1 for the uncatalyzed and catalyzed reactions are presented in Fig. 1. The highest stabilization is observed when ionic species are involved in the reaction course. The most stabilized species is the ionic intermediate (stabilized by  $34.1 \text{ kcal mol}^{-1}$ ). The stabilization of the tetrazolium product **3** is not so pronounced (stabilization by  $14.2 \text{ kcal mol}^{-1}$ ) due to the aromaticity of the newly formed tetrazolium ring. The decrease of the activation energy is  $15.1$  for  $T_1-1$  and  $22.1 \text{ kcal mol}^{-1}$  for  $T_2-1$  which is somewhere between the two values mentioned above and should considerably accelerate the rate of the reaction. A comparison of the structural features of the two transition state structures in the case of pivalonitrile with and without boron trifluoride reveals some interesting features (Figs. 2 and 3). The newly formed carbon–nitrogen bond in the first transition state is considerably longer (by  $0.218 \text{ \AA}$ ) in the case of the catalyzed (case A) than in the noncatalyzed reaction (case B). A similar effect can be seen in the comparison of N–C–C angles ( $152^\circ$  and  $141^\circ$ , respectively). All structural

Table 1  
Activation energies in the addition of azide ion to the boron trifluoride complex with alkyl cyanides ( $R-CN-BF_3-N_3$ , **1**) generated by AM1

Reactants ( <b>1</b> )	Energies ( $\text{kcal mol}^{-1}$ )		
	$T_1-1$	$T_2-1$	$T_2-2$
Acetonitrile $-BF_3-N_3$	9.4	34.3	50.6
Propionitrile $-BF_3-N_3$	10.3	34.0	50.9
<i>iso</i> -Butyronitrile $-BF_3-N_3$	11.5	34.0	50.6
Pivalonitrile $-BF_3-N_3$	11.8	40.0	52.1
Pivalonitrile $-N_3$	26.9	62.1	39.6

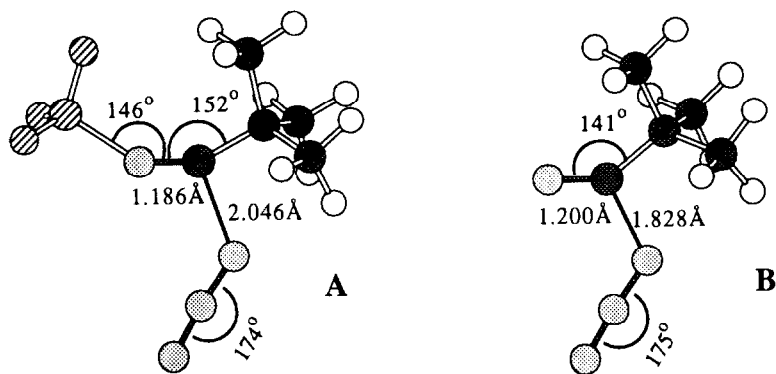


Fig. 2. AM1 generated structures of the first transition state ( $T_1$ ) in the azide anion addition to pivalonitrile with (A) and without (B) boron trifluoride.

parameters show that the first transition state in the complex with boron trifluoride is more similar to the reactants, and consequently should have a lower activation energy than the other which is more similar to the intermediate. The structural differences of the second transition states are not so obvious. Because of steric repulsion between boron trifluoride and the *tert*-butyl group the transition state C (Fig. 3) tends to keep the CCN angle as large as possible. In fact, the energy differences between the second transition state and the corresponding intermediate is much larger in the case of the boron complex (52.1 vs. 39.6, Table 1) due to the greater stabilization of the ionic intermediate. We have shown previously that in azide addition to organic nitriles the energy difference between the second transition state and the reactant correlate well with the experimental results [11].

Because experimental data for these kinds of 1,3-

polar azide reactions are not available we have compared the structural features of the two transition states generated by AM1 with one generated by different levels of ab initio calculations (Figs. 4 and 5). The closest correlation of the structural parameters are obtained between the AM1 and the RHF/6-311G structures for the first transition state ( $T_1$ ). The length of the C–C bond in formation is a little shorter in AM1 than in any obtained by Gaussian methods. Following the correlation of the C–C bond distance at different levels of ab initio calculations it can be concluded that the higher levels of Gaussian calculations produce a structure that is quite similar to the one generated by AM1. The comparison of the AM1 and ab initio generated structures of the second transition state (Fig. 5) shows the same pattern determined in the case of the first transition state. The AM1 structure is closest to the higher levels of ab initio calculations. The same applies for the predicted

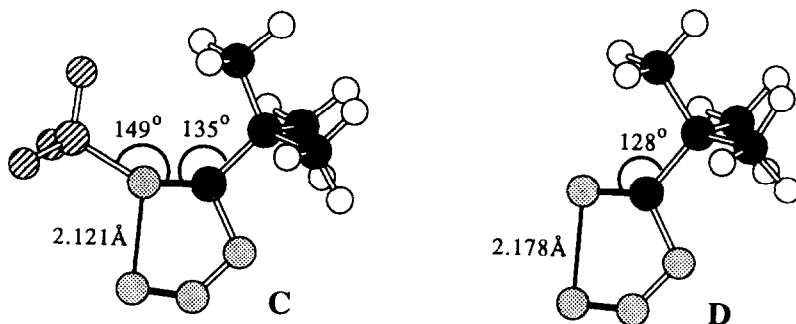


Fig. 3. AM1 structures of the second transition state of the addition of azide anion to pivalonitrile.

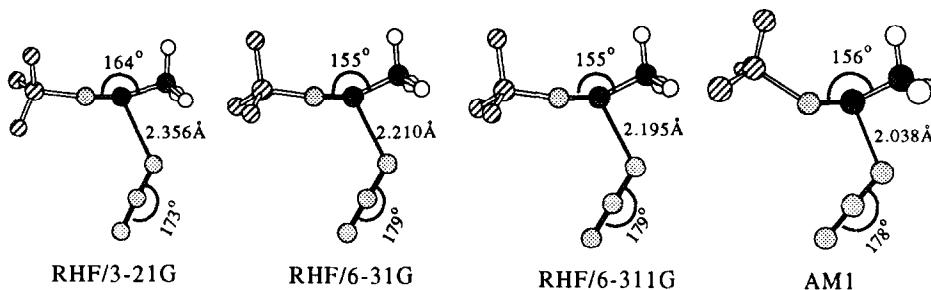


Fig. 4. *ab initio* and AM1 structures of the first transition state in the azide addition to the boron trifluoride-acetonitrile complex.

energy difference. It can be concluded that AM1 is as reliable as the applied level of *ab initio* calculations for studying the 1,3-polar cycloaddition of azide anion to organic nitriles.

### 3.2. Azide addition to the boron trifluoride complex with fluorinated acetonitriles

It is well known [17] that the fluorinated acetonitriles can react with azide anion without a catalyst. The reaction is particularly fast in the case of the trifluoroacetonitrile, and the rate of the reaction is controlled by the rate of bubbling of the trifluoroacetonitrile gas in the reaction mixture. From a mechanistic point of view it is interesting to determine the influence of the acid catalyst which can substantially stabilize all species involved in the reaction. The energy profile of the two step addition of the azide anion to trifluoroacetonitrile is shown in Fig. 6. Although the reaction has relatively low activation energy by itself, the presence of catalyst further decreases the activation energies of both transition states. Maximal stabilization is achieved with intermediate **2**. The first step in the noncatalyzed reaction proceeds

with a minimal barrier ( $2.5 \text{ kcal mol}^{-1}$ ) while the catalyzed reaction has a negative activation energy ( $-0.7 \text{ kcal mol}^{-1}$ ). Because the calculations simulate the gas phase the first step is without activation energy due to solvation. The results can be compared to the ones obtained by AM1 calculation of anion addition to carboxylic acid derivatives which is very exothermic ( $\Delta H = 20\text{--}30 \text{ kcal mol}^{-1}$ ) and is without activation [18]. The effect is also confirmed with *ab initio* calculations [19] and has been speculated to be the same for enzyme catalyzed reactions [20]. The energy differences for the fluorinated acetonitriles are presented in Table 2. It is obvious that by increasing the number of fluorine atoms in the acetonitrile molecule the reactivity of the corresponding boron complex drastically increases. The first activation barrier is negligible in the case of the acetonitrile and diminishes or is even negative in the case of fluorinated acetonitriles.<sup>2</sup> The activation energies for the second transition states are considerable, decreasing with the number of the

<sup>2</sup> It is surprising that the first activation energy in the case of difluoroacetonitrile is lower than for trifluoroacetonitrile. We do not have a satisfactory explanation for this fact at this time.

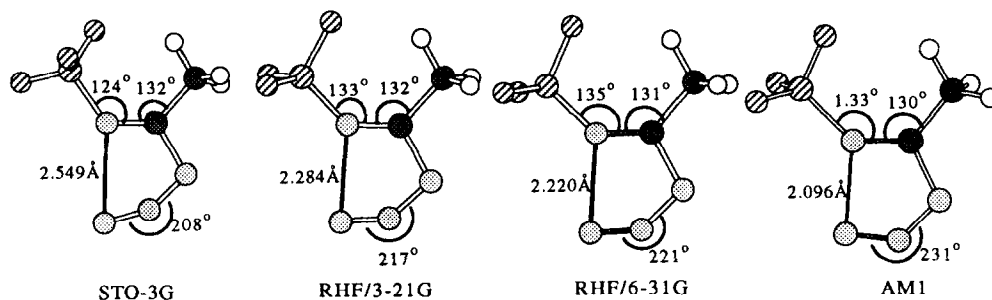


Fig. 5. *ab initio* and AM1 structures of the second transition state of the azide addition to the boron trifluoride-nitrile complex.

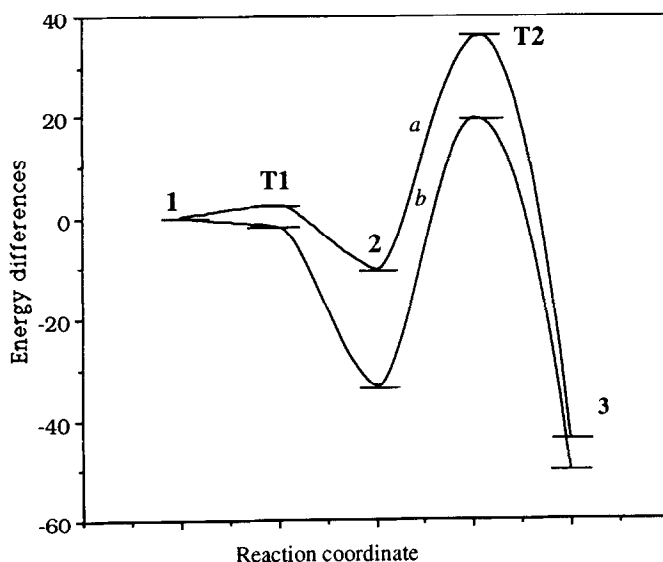


Fig. 6. Energy profile of the azide addition to (a) trifluoronitrile and (b) boron trifluoride-trifluoronitrile complex.

fluorine atoms (Table 2). The energy differences between the second transition state and the intermediate actually increases with the number of fluorine atoms. This supports our assumption that the intermediate is the most stabilized species by boron trifluoride catalyst in the reaction scheme.

### 3.3. Azide addition to the boron trifluoride complex with substituted benzonitriles

The purpose of this study was to determine the influence of the substituents on the activation energy of the reaction with and without the catalyst. The energy profile for the two benzonitrile derivatives with an activating group (methoxy) and one with a deactivating group (nitro) with and without catalyst is presented in Fig. 7. As in the case of aliphatic nitriles the catalyst substantially decreases the second activation energy. The catalytic effect of stabilization of the first transition state is much more pronounced for benzonitriles with electron donating substituents. Again, greater stabilization is achieved with the intermediate because the negative charge is partially located on the nitrile nitrogen which makes a bond with the boron trifluoride catalyst. The values of the change of the activation energy for the transition states of benzonitriles are presented

in Table 3. The activation energies correlate with electron donating-withdrawing abilities of the substituent (Fig. 8) [21]. This again confirms the fact that a certain amount of positive charge has to be located on the nitrile carbon to facilitate the reaction. Both the electron withdrawing substituent and the boron trifluoride catalyst generate a considerable amount of positive charge on the nitrile carbon and thus increase the probability of formation of the new C–N bond in the first reaction step. The only reasonable energy values are obtained when the difference between the second transition state and the starting components are compared. The energy differences between the intermediate and the second transition state ( $T_2-2$ , Table 1, 2, and 3) are around  $50 \text{ kcal mol}^{-1}$  and do not follow common reactivity patterns.

Table 2  
Activation energies in the addition of azide ion to boron trifluoride complexes with alkyl cyanides

Reactants (1)	Energy ( $\text{kcal mol}^{-1}$ )		
	$T_1-1$	$T_2-1$	$T_2-2$
Acetonitrile– $\text{BF}_3\text{--N}_3^-$	9.4	34.3	50.6
Fluoroacetonitrile– $\text{BF}_3\text{--N}_3^-$	6.6	27.9	50.9
Difluoroacetonitrile– $\text{BF}_3\text{--N}_3^-$	–7.0	21.5	53.1
Trifluoroacetonitrile– $\text{BF}_3\text{--N}_3^-$	–0.7	19.4	52.9

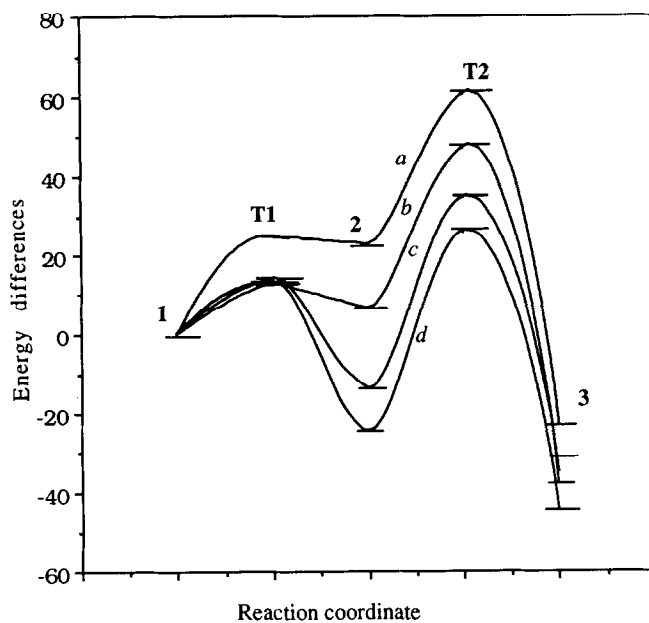


Fig. 7. Energy profile of the azide addition to (a) 4-methoxybenzonitrile (b) 4-nitrobenzonitrile (c) boron trifluoride complex with (c) 4-methoxybenzonitrile and (d) 4-nitrobenzonitrile.

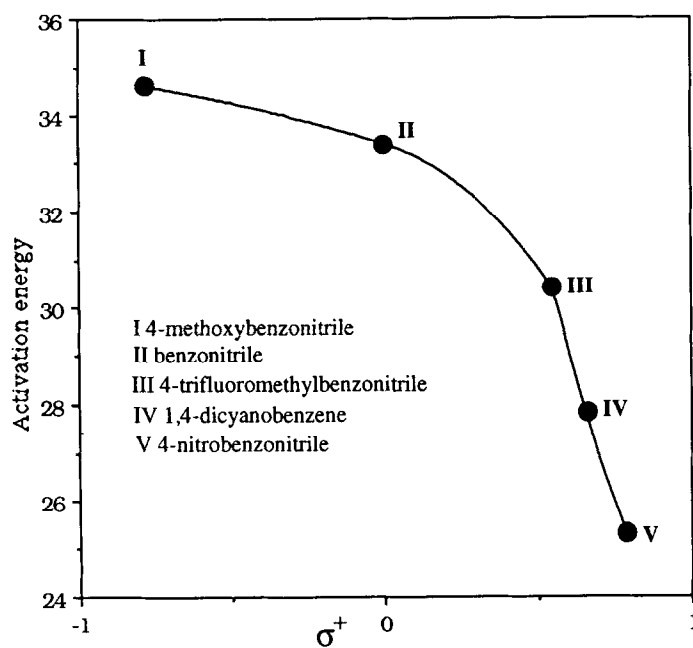
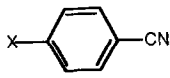


Fig. 8. Correlation of AM1 calculated second energy barrier in the addition of azide anion to  $\text{BF}_3$  activated benzonitriles with the  $\sigma^+$ .

Table 3

Activation energies of the addition of the azide anion to substituted boron trifluoride-benzonitrile complexes

	Energy (kcal mol <sup>-1</sup> )		
	T <sub>2</sub> -1	T <sub>2</sub> -1	T <sub>2</sub> -2
X = OCH <sub>3</sub>	14.0	34.6	48.0
X = H	12.5	33.4	51.2
X = CF <sub>3</sub>	9.6	30.4	51.1
X = CN	8.5	27.8	49.0
X = NO <sub>2</sub>	6.6	25.3	50.0

The structural features of the two transition states are very similar to the transition states of the aliphatic nitriles. The bond distances of the new bonds and angles are in the same range. For example, the newly formed C–C bonds and NCC angles for the 4-trifluorobenzonitrile transition states are 2.093 Å and 149° for the first transition state and 2.085 Å and 131° for the second transition state. The values are very similar in all other benzonitrile transition states and are comparable with those of trifluoroacetonitrile (Figs. 4 and 5).

#### 4. Conclusion

Because of the large polarization of the nitrile bond in the nitrile-boron trifluoride complex only the two step mechanism of 1,3-dipolar azide addition was examined. Comparison of the structural features of the transition states and their activation energies for the acetonitrile-BF<sub>3</sub> complex between different levels of ab initio and AM1 methods reveals that AM1 calculations are as reliable as the RHF/6-311G. The BF<sub>3</sub> Lewis acid stabilizes all species in the reaction scheme but the largest effect is obtained in the stabilization of the anionic intermediate, and a lesser effect is observed in the product because a relatively stable aromatic tetrazole ring is formed. The enhancement of the reactivity is usually more than 10 kcal mol<sup>-1</sup>. The rate of the reaction strongly depends on the nature of the nitriles as lower activation energy was calculated for nitriles with electron withdrawing groups than with electron donating groups.

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