Semiempirical and ab initio study of 1,3-dipolar addition of azide anion to organic cyanides

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Abstract

The 1,3-polar azide anion cyloaddition to nitriles was studied by semiempirical and ab initio methods. Two mechanisms were considered: a concerted and a two-step mechanism. AM1 strongly supports the two-step mechanism that involves a nucleophilic attack of the azide ion on the carbon of the nitrile group (formation of iminoazide intermediate) followed by tetrazole ring closure. The calculated activation energies are in good agreement with the experimentally obtained reactivity of the nitriles. The calculations agree with the fact that electron-withdrawing substituents on the nitrile group decrease the activation barrier and facilitate the reaction. Although RHF/3-21G was unable to locate the first transition state in all cases of the two-step mechanism, its concerted transition state structures are very unsymmetrical. The distortion depends much more on the polarity of the substituents than on their size.

1. Introduction

In view of its synthetic value, the azide anion 1,3-dipolar addition to nitriles continues to be the method of choice for the preparation of a variety of tetrazole derivatives (see, for example, Ref. 1). However, there have been quite divergent opinions on the reaction mechanism of cycloaddition reactions even when simple non-polar dienes and dienophiles are involved [2]. Orbital symmetry rules allow a concerted path [3]. Other criteria, for example the stability of possible intermediates for 1,3-dipolar cycloadditions, mostly discussed in terms of diradicals [4], certainly support a stepwise mechanism. Houk et al. [5] studied the origin of regioselectivity in 1,3-dipolar cycloadditions including the addition of hydrazoic acid to the various classes of dipolarophiles by frontier orbital theory.

To the best of our knowledge there are no computational studies on the addition of the azide anion to organic cyanides. In this paper, we would like to present transition state calculations for the addition of the azide anion to nitriles using semiempirical and ab initio methods.

2. Computational methods

The structures of the starting components, intermediates and products were built with the CHEM-X computational package on an IBM compatible 486/66 PC or with CHEM3D PLUS on a Macintosh computer [6].

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The MOPAC [7] calculations were done with the AM1 method on the PC or on a DEC 7620 computer. The search for the transition state in MOPAC was performed with the SADDLE option and then the structure obtained was subjected to optimization by NLLSQ, followed by thermodynamic and vibrational analysis [8].

The ab initio calculations were performed at the RHF/STO-3G, RHF/3-21G and RHF/6-31 + G* levels with GAUSSIAN 92 [9]. Vibrational frequencies were calculated at the RHF/3-21G level for fluorine, hydrogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl and phenyl derivatives for the reactants and the transition states. For the fluoro derivatives vibrational frequencies were calculated for the reactants and the transition state at the RHF/6-31 + G* level.

3. Results and discussion

The reactants and the products considered in this study are presented in Fig. 1. For simplicity of the discussion, the results are divided into four groups according to their chemical similarity. They include azide addition to fluorocyanide, alkylcyanides, fluorinated acetonitriles and para-substituted benzonitriles. In all cases two separate mechanisms were considered (Fig. 2). One is concerted, in which two bonds (N—N and C—N) are formed almost at the same time with only one transition state (concerted transition state, CTS), and the other includes two steps and, consequently, two transition states (first transition state, TS1; second transition state, TS2). Because of chemical logic we
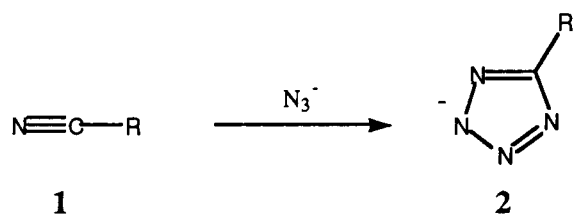
did not study the two-step mechanism that involves an N—N bond formation in the first step.

3.1. Addition of azide anion to fluorocyanide

To the best of our knowledge this reaction has not been performed experimentally. The model was chosen for study because of the low number of molecular orbitals and high polarization of the nitrile bonds. As such, it is a good starting point for the discussion of all other reactions that are experimentally supported by others and by us.

Two reaction mechanisms of the polar addition were considered: the synchronous (Path A, Fig. 2) and the one with two steps (Path B, Fig. 2). The saddle point of the CTS structure was calculated by AM1. The two newly formed bonds have similar lengths. The saddle-point structure was then optimized with both semiempirical and ab initio methods. They both tend to force the molecule to be similar to transition state TS2 (Fig. 2). We were able to obtain a concerted "transition state" (Fig. 3) with AM1 but two imaginary vibrations were present [10]. The number of imaginary vibrations is a good test for the validity of the transition state. A saddle point has to have one, and only one, negative second derivative; the remaining $3N - 7$ second derivatives should be positive. The negative second derivative corresponds to a force constant for the motion along the reaction coordinate, referred to as an "imaginary vibration frequency", since the vibration frequency is proportional to the square root of the force constant [11]. However, because this was the best structure that was obtained either with MOPAC or with GAUSSIAN calculations as a concerted transition state structure, we will use it in the comparison with the other transition states.

In the second mechanism (Path B, Fig. 2), one can propose two kinds of polar intermediates: a polar intermediate where the negative charge is on the former nitrile nitrogen, or a biradical anion intermediate. The polar anion intermediate is 6.1 kcal mol^{-1} more stable than the biradical anion intermediate according to AM1 calculations. Consequently, in our discussion only the polar anion intermediate will be considered. The energy
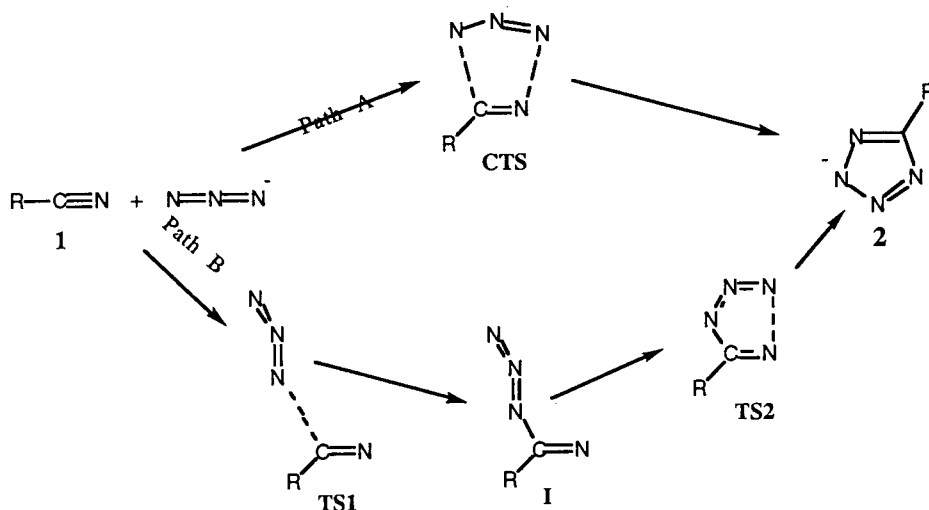
Fig. 1. Structures of studied compounds. R = (a)F; (b) CH$_3$; (c) CH$_2$CH$_3$; (d) CH(CH$_3$)$_2$; (e) C(CH$_3$)$_3$; (f) CFH$_2$; (g) CF$_2$H; (h) CF$_3$; (i) p-O$_2$NC$_6$H$_4$; (j) p-NCC$_6$H$_4$; (k) p-F$_3$C$_6$H$_4$; (l) C$_6$H$_5$; (m) p-H$_3$CC$_6$H$_4$; (n) p-H$_3$COC$_6$H$_4$.

Fig. 2. Two alternative mechanisms of polar 1,3-addition of azide anion to organic cyanides.

profile of the azide anion addition to the fluoro-cyanide calculated with AM1 is presented in Fig. 4. If we accept the CTS as energetically valid for comparison with the alternative one, we can see that it is energetically unfavorable. According to AM1, and in view of transition state theory [12], the two-step mechanism is favored by $12.0 \, \text{kcal} \, \text{mol}^{-1}$ over the concerted mechanism. The molecular structures of the species involved in the two-step mechanism of this reaction are presented in Fig. 5.

Besides the energy, the entropy change in the transition structures is also lower for the stepwise mechanism. If the entropy is considered as a measure of disorder, then by following the structures along the reaction coordinate, the entropy has to decrease with every step, because first one, and then another bond forms. The formation of the two bonds of the tetrazole ring drastically increases

Fig. 3. The concerted mechanism "transition state" structure obtained by AM1 calculations with two imaginary vibrations.

the order of the system reflected by a decrease in its entropy. The entropy changes for the two proposed mechanisms are presented in Fig. 4.

Other interesting features are the changes in the bond distances and angles, particularly the ones close to the new bonds. Initially, when the two reactants are separated by more than 4 Å there are only negligible interactions between them and they preserve their individual structural properties. The bond angles in the azide anion and fluoro-cyanide are exactly 180° but as the reactants approach each other the bond angles change. Consequently, in the TS1 the first C–N bond formed is 1.9 Å and the bond angle for the azide moiety changes to 175.0° and for the fluorocyanide to 146.0°. In the transition state with the newly formed bond of 1.534 Å, the two angles are 171.1 and 129.9°, respectively. The azide angle in the intermediate (I) is very close to the one for alkyl azides obtained by microwave spectroscopy [13] (174° for methyl azide [14]) and obtained by high level ab initio calculations (for methyl azide with HF/6-311G** the angle is 175.3°) [15]. The angle around the carbon atom is close to the expected sp^3 hybridized atom. The TS2 that presents the transformation of the intermediate I into the tetrazolium anion P brings together the two nitrogens that will close the ring (2.17 Å) and further decreases the N_3 bond angle. The product, of course, has perfect ring bonds and distances (Fig. 5).
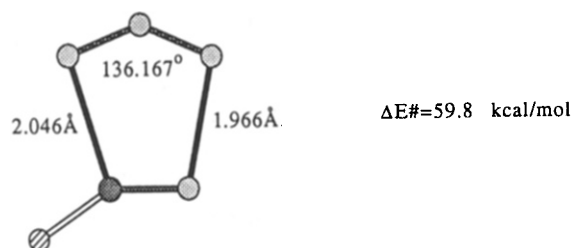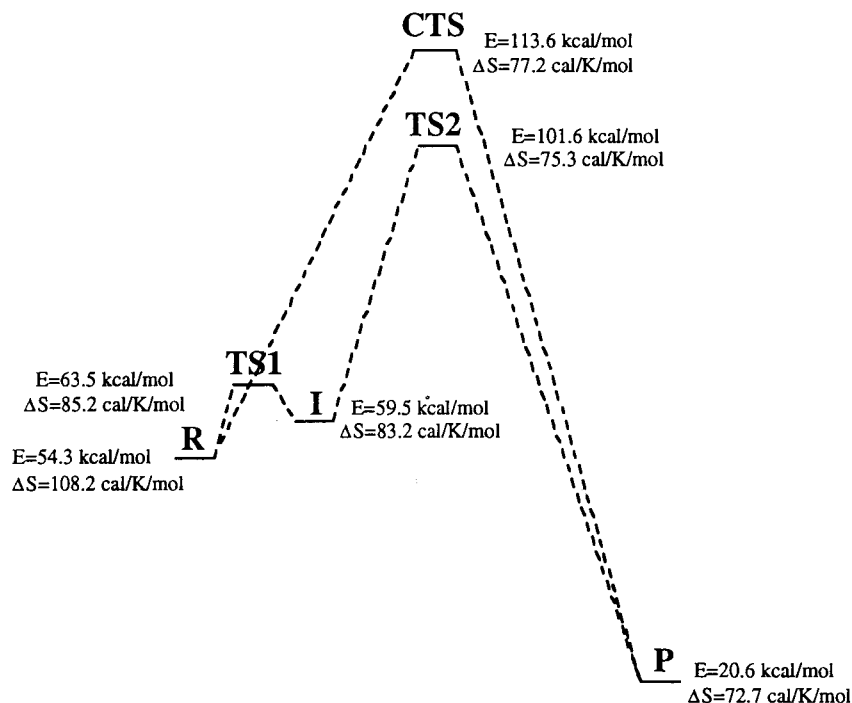
Fig. 4. The reaction diagram for the azide anion addition to fluorocyanide calculated by the AM1 method.

Our attempts to locate the first transition state as well as the CTS with RHF/STO-3G, RHF/3-21G and RHF/6-31G methods were unsuccessful. The optimization of the first transition state was interrupted because the only negative eigenvalue was transformed into positive. When the optimization was continued from that point but not as a transition state optimization, the structure of intermediate I was obtained. The second transition state was optimized without any problem and the structures obtained are presented in Fig. 6. The structure of the second transition state calculated by AM1 is much closer to the higher theoretical ab initio model RHF/6-31 + G* than to the lower
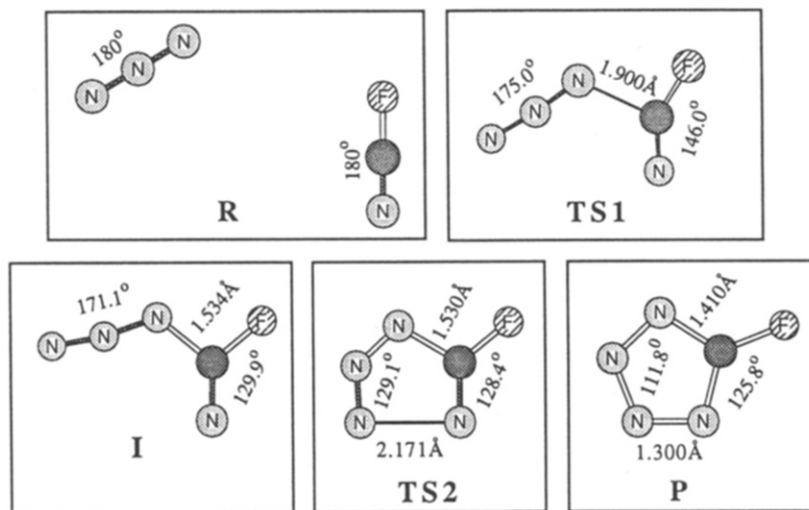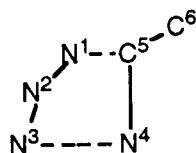

Fig. 5. The AM1 calculated structures in the two-step azide anion addition to fluorocyanide.

Table 1
Geometric parameters of the transition structures

Organic cyanide	$N^4-C^5-C^6$ angle (deg)		Bond length (Å)	
	TS1	TS2	TS1 (N^1-C^5)	TS2 (N^3-N^4)
Acetonitrile	142.8	129.6	1.784	2.175
Propionitrile	142.8	129.3	1.790	2.176
Isobutyronitrile	140.1	127.8	1.821	2.179
Pivalonitrile	140.7	128.4	1.828	2.178

Table 2
Thermodynamic properties of the first and second transition states in the addition of azide anion to alkylcyanides at 403 K obtained by AM1

Organic cyanide	E_{total} (kcal mol^{-1})	ΔH_{total} (kcal mol^{-1})	ΔS_{total} (cal K^{-1} mol^{-1})
Acetonitrile			
R	74.76	8.10	98.58
TS1	101.82	7.14	87.66
I	100.40	7.07	87.66
TS2	139.46	6.21	81.35
P	58.65	5.74	78.61
Propionitrile			
R	72.27	9.73	117.24
TS1	96.00	8.58	97.46
I	94.59	8.40	98.44
TS2	133.55	7.56	90.68
P	52.88	7.09	90.17
Isobutyronitrile			
R	68.27	11.24	126.68
TS1	95.05	9.91	104.69
I	90.65	9.79	103.73
TS2	130.25	9.02	100.71
P	49.10	8.56	101.17
Pivalonitrile			
R	66.81	12.62	131.30
TS1	93.47	11.38	112.35
I	89.036	11.21	110.89
TS2	128.48	10.46	106.47
P	47.39	10.00	103.95

RHF/3-21G. It would be interesting to compare it with the even higher ab initio model chemistries. It is well established that ab initio calculations give more reliable results than semiempirical calculations, but our experience in calculations of polar cycloaddition or elimination reactions shows that AM1 calculations are as good as small-set ab initio calculations if not better.
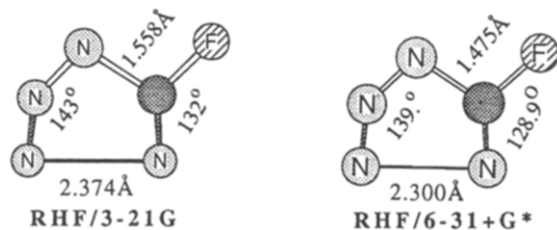
Fig. 6. The structures of the second transition states in the two-step mechanism of azide anion addition to fluorocyanide calculated by GAUSSIAN 92.

3.2. Addition of azide anion to alkylcyanide

In this series we studied the addition of an azide anion to acetonitrile, propionitrile, isobutyronitrile and pivalonitrile. It is well established that unactivated alkyl nitriles essentially will not react with the azide anion [16]. To confirm this, a mixture of acetonitrile and sodium azide was heated for seven days at reflux. Judging from the ^{1}H NMR spectra there was only a small amount of the corresponding tetrazole in the acetonitrile mixture. If ammonium azide was used, only 20% product was observed. This low reactivity of alkylnitriles should be related to the low positive charge on the nitrile carbon and consequently to the high activation energy.

An attempt to obtain the CTS for the addition of azide to alkylcyanide with AM1 was unsuccessful. In numerous attempts only a structure with two imaginary vibrations was obtained. Again, AM1 prefers the two-step mechanism. The transition

states for the reaction of the azide anion with pivalonitrile are presented in Fig. 7. All TS2 structures for alkylnitriles presented herein are similar to the one in Fig. 5. The structure of the first transition state TS1 is sensitive to the size of the alkyl group. The structural features of the two transition states for different alkyl nitriles are listed in Table 1. This is quite understandable because the nucleophile (azide anion) must approach the carbon atom of the nitrile group. The second bond (N^3–N^4) is relatively far from the alkyl substituent and its influence on the bond distance is negligible. The thermodynamic properties of different structural species calculated with AM1 are presented in Table 2. It is interesting to note that the energy differences between the first transition state and the intermediate are very small, especially in the case of acetonitrile (1.42 kcal). It is also noteworthy that the activation energy of the second transition state is about 39 kcal mol^{-1} in all four cases. The low energy difference between the first transition state and the intermediate suggests that the "real" reaction barrier is the energy difference between the second transition state and the reactants. Anyway these compounds have very high and similar activation energies (Table 2).

The observation that the azide anion addition to the alkylcyanide is a very slow reaction because of the low charge polarization, and in some cases because of the steric hindrance of the alkyl group, encourages us to take a closer look at the concerted

Table 3
Bond distances and angles of the optimized TS1 and TS2 structures for azide anion addition to fluorinated acetonitriles
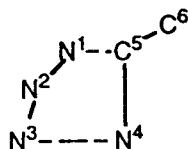
Organic cyanide	N^4–C^5–C^6 angle (deg)		Bond length (Å)	
	TS1	TS2	TS1 (N^1–C^5)	TS2 (N^3–N^4)
Acetonitrile	142.8	129.6	1.784	2.175
Fluoroacetonitrile	144.3	113.2	1.842	2.166
Difluoroacetonitrile	146.5	129.8	1.871	2.159
Trifluoroacetonitrile	149.3	127.7	1.967	2.140

Table 4
Thermodynamic properties of the first and second transition states in the addition of azide anion to fluorinated acetonitriles at 403 K obtained by AM1

Organic cyanide	E_{total} (kcal mol^{-1})	ΔH_{total} (kcal mol^{-1})	ΔS_{total} (cal K^{-1} mol^{-1})
Acetonitrile	74.76	8.10	98.58
R	101.82	7.14	87.66
I	100.40	7.07	87.66
TS2	139.46	6.21	81.35
P	58.65	5.74	78.61
Fluoroacetonitrile			
R	27.29	8.57	106.33
TS1	52.73	7.65	93.57
I	47.24	7.36	90.80
TS2	88.87	6.65	87.13
P	7.86	6.15	84.11
Difluoroacetonitrile			
R	−16.64	9.24	111.02
TS1	−2.30	8.31	98.40
I	−8.27	8.05	96.99
TS2	33.06	7.29	93.52
P	−46.43	6.74	86.90
Trifluoroacetonitrile			
R	−58.91	10.13	23.67
TS1	−56.36	9.04	102.26
I	−69.19	8.77	100.49
TS2	−23.47	7.99	96.00
P	−102.455	7.52	95.58

transition state. The formation of the reaction intermediate is not an extremely favorable reaction. Location of the CTS with AM1 failed for all alkylcyanides. RHF/3-21G was able to locate the synchronous unsymmetrical transition state

(Fig. 8) that has one imaginary vibration and an energy above the one optimized by MOPAC.

It seems quite possible that even the 1,3-dipolar addition reaction of the azide anion to unreactive alkylcyanide has two steps.
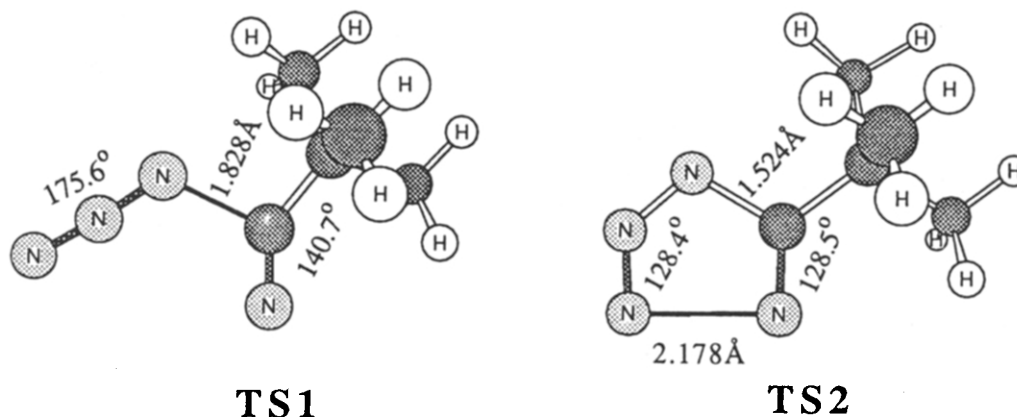

TS1   **TS2**

Fig. 7. Two transition states of the addition of the azide anion to pivalonitrile calculated by AM1.
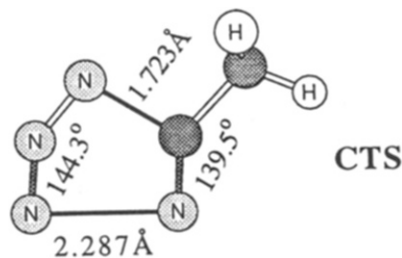
Fig. 8. The concerted transition state structure calculated by the RHF/3-21G theoretical model.

### 3.3. Addition of azide anion to fluorinated acetonitrile

As mentioned above, unactivated alkylcyanides are very poor starting materials for the preparation of tetrazoles. Their reactivity can be improved by using aluminum azide instead of sodium azide [17]. The fluorinated alkylcyanides react fairly well with sodium azide. For example, at atmospheric pressure and room temperature, trifluoroacetonitrile in acetonitrile as solvent reacts exothermally with sodium azide to give sodium 5-trifluoromethyl-tetrazole [18]. The reaction is so rapid that the rate of the reaction was controlled by the rate trifluoroacetonitrile was introduced into the mixture of acetonitrile and sodium azide. The mechanism of the reaction that was proposed by the author includes attack of the azide ion on the carbon of the nitrile group followed by ring closure to give the salt of tetrazole [18].

The reaction mechanism was studied both with AM1 and RHF/3-21G. Again the AM1 method prefers the two-step mechanism outlined in Fig. 2. The structural properties of TS1 and TS2 of the addition are presented in Table 3. The bond-making distances in the series studied strongly depend on the charge distribution in the starting nitriles. In TS1 it increases, making better charge separation, and in TS2 it decreases because the negative charge on the former nitrile nitrogen is more delocalized on increasing the number of fluorine atoms. The N^1-C^5 distance and $N^4-C^5-C^6$ angle are in perfect inverse correlation (Table 3). The thermodynamic properties of the addition to fluorinated acetonitriles is presented in Table 4. The second activation energy actually increases with the number of fluorine atoms in acetonitrile (for CH_3CN, 39.06 kcal mol^{-1}; CH_2FCN, 41.63 kcal mol^{-1}; CHF_2CN, 41.33 kcal mol^{-1}; CF_3CN, 45.72 kcal mol^{-1}). Following strictly the law of the rate determining step of the reaction, acetonitrile should have the highest reactivity in this series. However, acetonitrile serves as a solvent for the azide addition reaction to tri-fluoroacetonitrile [18]. Again only the energy difference between the second transition state (TS2) and reactants (R) [19] makes sense. The activation energies calculated in this way are in good correlation with the experimental observations, and trifluoroacetonitrile is selected as the most reactive nitrile studied (the activation energies are for CH_3CN, 64.70 kcal mol^{-1}; CH_2FCN, 61.58 kcal mol^{-1}; CHF_2CN, 49.70 kcal mol^{-1}; CF_3CN, 35.44 kcal mol^{-1}).

Table 5
Bond distances and angles of the optimized TS1 and TS2 structures for azide anion addition to benzonitriles
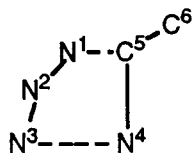
Organic cyanide	$N^4-C^5-C^6$ angle (deg)		Bond length (Å)	
	TS1	TS2	TS1 (N^1-C^5)	TS2 (N^3-N^4)
p-Nitrobenzonitrile	144.8	128.4	1.886	2.157
p-Cyanobenzonitrile	144.1	127.9	1.878	2.163
Benzonitrile	142.9	128.3	1.857	2.171
p-Methylbenzonitrile	143.3	128.5	1.851	2.170
p-Methoxybenzonitrile	143.2	128.8	1.853	2.168

Table 6
Thermodynamic properties of the first and second transition states in the addition of azide anion to para-substituted benzonitriles at 403 K obtained by AM1

Nitrile	E_{total} (kcal mol^{-1})	ΔH_{total} (kcal mol^{-1})	ΔS_{total} (cal K^{-1} mol^{-1})
p-Nitrobenzonitrile			
R	118.48	14.00	142.46
TS1	131.28	13.01	127.10
I	125.25	12.70	123.77
TS2	165.64	11.98	118.88
P	80.93	11.46	114.52
TS2-R	47.16	−2.20	−23.58
p-Cyanobenzonitrile			
R	143.74	13.02	130.76
TS1	162.76	12.19	120.67
I	157.85	11.90	117.25
TS2	197.570	11.15	112.35
P	113.32	10.64	109.54
TS2-R	53.83	−1.87	−18.41
Benzonitrile			
R	116.29	11.59	126.51
TS1	136.13	10.57	111.52
I	132.17	10.28	107.34
TS2	171.42	9.53	101.82
P	87.70	9.02	99.50
TS2-R	55.13	−2.06	−24.67
p-Methylbenzonitrile			
R	109.23	13.40	139.09
TS1	128.86	12.39	123.19
I	124.49	12.08	119.13
TS2	164.58	11.36	114.28
P	81.02	10.86	112.48
TS2-R	55.35	−2.04	−24.81
p-Methoxybenzonitrile			
R	109.22	13.40	139.09
TS1	128.86	12.39	123.18
I	124.49	12.08	119.13
TS2	164.58	11.36	114.28
P	81.02	10.86	112.48
TS2-R	55.36	−2.04	−24.81

The RHF/3-21G theoretical model fails again to determine the TS1 and even the AM1 optimized structure was rejected. The search for the concerted transition state with AM1 led to structures with two imaginary vibrations. The AM1 structures were used as input for the RHF/3-21G transition state optimization and the structures obtained are presented in Fig. 9. They all had only one imaginary vibration. All structures have very unsymmetrical formation of the two bonds. First the C—N bond forms and after that the N—N bond. Although ab initio calculations do not support the two-step mechanism, the transition state is very polarized. It is debatable whether in the transition state with trifluoroacetonitrile, the C—N bond is fully or partially developed (the bond distance is 1.623 Å vs. 1.50 Å in the tetrazolium anion) and actually very close to the one predicted by AM1 for TS2 (the C—N distance is 1.50 Å).
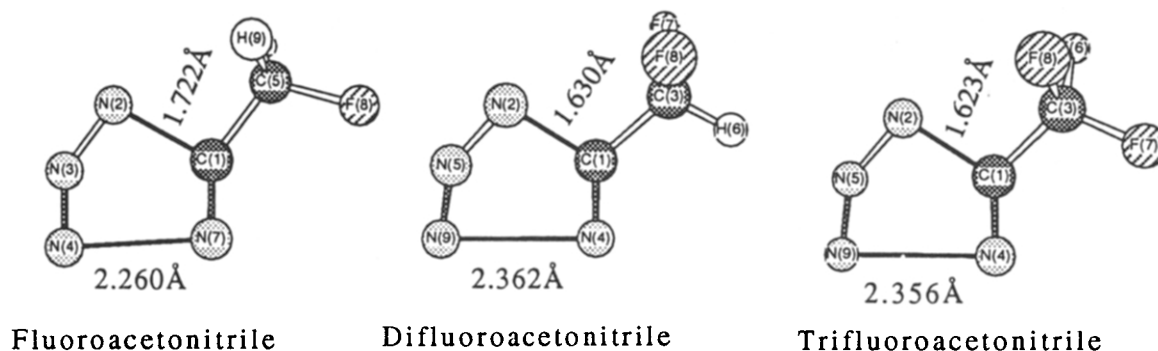
Fig. 9. RHF/3-21G transition state structures with fluorinated acetonitriles.

3.4. Addition of azide anion to substituted benzonitriles

It has been discovered that electrophilic substituents in the para position of the nitrile group facilitate 1,3-dipolar azide ion addition in benzonitriles. The yield of the reaction is much higher in the case of 4-nitrobenzonitriles than 4-methoxybenzonitrile [16]. Consequently, the substituents are very important not only for the rate of the reaction but for the yield which also seems to be affected.

In this case we again considered the two different mechanisms outlined in Fig. 2. Again the structure obtained by AM1 for the concerted mechanism has two imaginary vibrations, and energy approximately $10 \, kcal \, mol^{-1}$ higher than for TS2. AM1 does accept the two-step mechanism with an energy profile similar to the one presented in Fig. 3. The structural properties of TS1 and TS2 of the addition of azide ion to 4-substituted benzonitriles calculated by AM1 are presented in Table 5. The interatomic distances are fairly similar for different substrates. This is because the carbon center, where the nucleophilic addition occurs, is relatively remote from the aromatic substituent, and the steric effect is negligible. Only the electronic effects of the substituents can stabilize or destabilize the transition state. Although there is a consistent change in the N^1-C^5 distance in TS1 of the azide addition to derivatives of benzonitrile related to their reactivity, this effect is not profound (the maximal difference is 0.033 Å). The activation energies are much more reliable parameters for determination of the reactivity of the system. The thermodynamic properties of the addition of azide ion to substituted benzonitriles are presented in Table 6. It is interesting to follow the change of the activation energies for different benzonitriles. The plot of the activation energy of the benzonitriles versus the σ_{para} values [20] is presented in Fig. 10. The graph shows that the activation energy of benzonitriles with electron-donating groups is almost constant until a very strong electron-withdrawing group is introduced when the activation energy decreases substantially. This is related to the amount of charge located on the nitrile carbon. On the basis of this graph one can predict two different mechanisms for the 1,3-polar cycloaddition: a two-step mechanism (p-nitrobenzonitrile), and a concerted mechanism. Benzonitrile, and benzonitriles with electron-donating
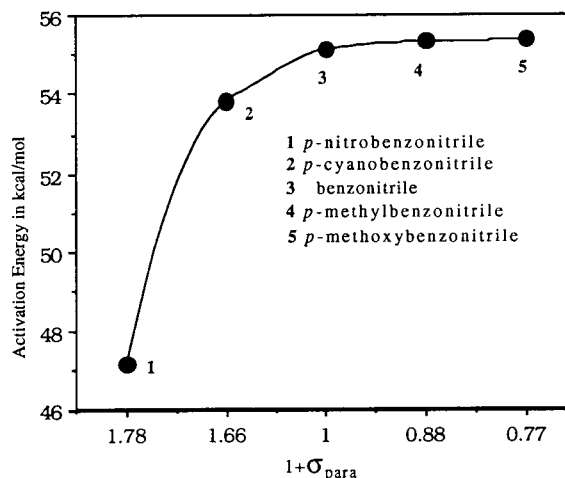

Fig. 10. Plot of the activation energy for the addition of azide ion to the substituted benzonitriles versus σ_{para}.
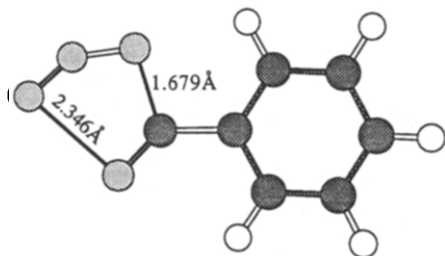
Fig. 11. Concerted transition state for the 1,3-polar cyclo-addition of azide ion to benzonitrile.

groups, according to AM1 calculations, do have almost the same activation energies. In the case of benzonitrile, an AM1 saddle-point search for the concerted transition state was performed. As in all previous cases we were not able to locate the transition state with only one imaginary vibration (the structure has $12.5 \, \text{kcal} \, \text{mol}^{-1}$ higher energy than TS2). The same search was performed with RHF/3-21G. The transition state obtained has concerted nature but is highly unsymmetrical (Fig. 11). As one would expect, it seems that the C–N bond formation occurs earlier than the N–N bond formation of the tetrazole ring.

4. Conclusion

AM1 strongly supports a two-step mechanism for the 1,3-polar addition of the azide ion to organic nitriles. Although RHF/3-21G comes up with a concerted transition state, it is very unsymmetrical and prefers an earlier formation of the C–N bond over the N–N bond in the tetrazole ring closure. It was shown that electronegative substituents bound to the nitrile group decrease the activation energy of the reaction by facilitating the nucleophilic attack of the azide ion and stabilizing the polar transition states. The general mechanism for the reaction elucidated with these two methods is a nucleophilic attack of the azide ion on the carbon of the nitrile group, followed by ring closure of the imino azide to form the tetrazole ring.

Acknowledgments

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