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Mechanisms of Tetrazole Formation by Addition of Azide to Nitriles

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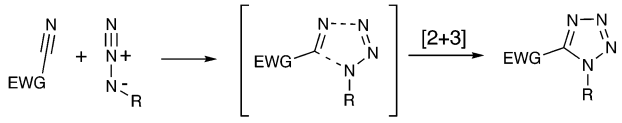
Abstract: It is well-known that azide salts can engage nitriles at elevated temperatures to yield tetrazoles; however, there is continued debate as to the mechanism of the reaction. Density functional theory calculations with the hybrid functional B3LYP have been performed to study different mechanisms of tetrazole formation, including concerted cycloaddition and stepwise addition of neutral or anionic azide species. The calculations presented here suggest a previously unsuspected nitrile activation step en route to an imidoyl azide, which then cyclizes to give the tetrazole. The activation barriers are found to correlate strongly with the electron-withdrawing potential of the substituent on the nitrile.

I. Introduction

Tetrazoles are an increasingly popular functionality[1] with wide-ranging applications. They have found use in pharmaceuticals as lipophilic spacers[2] and carboxylic acid surrogates,[3] in specialty explosives[4] and photography and information recording systems,[5] not to mention as precursors to a variety of nitrogen-containing heterocycles.[6] The most direct method to form tetrazoles is via the formal [2 + 3] cycloaddition of azides and nitriles. However, evidence in the literature indicates that the mechanism of the reaction is different for different azide species.

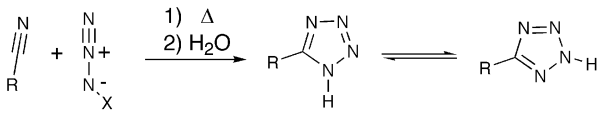
When an organic azide is used as the dipole, only certain highly activated nitriles are competent dipolarophiles.[7] In these cases the reaction is regioselective, and only the 1-alkylated product is observed.[8] It is commonly accepted that in these cases the reaction proceeds via a traditional [2 + 3] mechanism (see Scheme 1).[1,9]

Scheme 1



Of greater interest to us here is the mechanism behind the formally similar addition of azide salts and nitriles to give 1*H*-tetrazoles. It has long been known[10] that simple heating of certain azide salts with a nitrile in solution (typically 100−150 °C) produces the corresponding tetrazole in high yield (see Scheme 2). This variant is much more synthetically useful, as

Scheme 2



R = C, N, S; X = H, HNR_3, M

the scope of nitriles that are competent reactants in this reaction is very broad, in contrast with the case of organic azides. In addition, a wide variety of metal−azide complexes are competent azide donors.[11]

Mechanistically, these cases are considerably more complicated: several possible reaction pathways can be envisioned.

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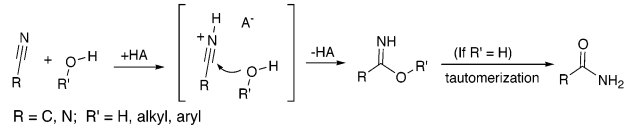
Claims have been made for both an anionic two-step mechanism[12,13] and a concerted [2 + 3] cycloaddition,[14] but the data are not conclusive. Moreover, there is evidence against both of these mechanisms. For example, Koldobskii et al.[14a] showed that while protic ammonium salts of azide are competent azide donors, tetraalkylammonium salts were *not*, refuting the strictly anionic two-step mechanism. Also, while virtually all nitriles are engaged by ammonium azide salts at elevated temperature, organic azides only react with the most activated nitriles.[15] The fact that these azide salts and organic azides are electronically very similar, yet have significantly different reactivities, indicates that different mechanisms are likely in effect.

Other similar reactions involving nucleophilic attack on nitriles are known, including acidic hydrolysis of a nitrile to an amide,[16] and the Pinner synthesis of imidates;[17] relevant mechanistic studies prove illuminating. In these reactions, it has been shown that the rate-limiting step involves the activation of the nitrile by a protic acid to give an activated nitrile (see Scheme 3). Surprisingly, previous mechanistic work on tetrazole

Scheme 3



formation has not paid heed to these parallels. Is it possible that 1*H*-tetrazole formation follows a similar reaction pathway to these reactions, wherein the azide moiety engages the nitrile with the help of this protic nitrile activation step?

In the present study, we use quantum chemical calculations to probe the energetics of various reaction mechanisms for addition of azides to nitriles. This study will focus on hydrazoic acid as the dipole, and the simplest and most widely used[18] procedure involving amine salts of hydrazoic acid.[13,14,19] The theoretical method employed is the hybrid Hartree−Fock/density functional theory method B3LYP,[20] which has been applied extensively in organic chemistry in recent years.

II. Computational Details

All geometries and energies presented in the present study are computed with the B3LYP[20] density functional theory method as implemented in the Gaussian98 program package.[21] Geometry optimizations were performed with the triple-ζ plus polarization basis set 6-311G(d,p), followed by single-point energy calculation using the larger basis set 6-311+G(2d,2p). Hessians were calculated at the B3LYP/6-311G(d,p) level of theory. Hessians provide a control that the stationary points localized are correct, with no imaginary frequencies for minima and one imaginary frequency for transition states, and also to evaluate the zero-point vibrational effects on energy. Unless otherwise stated, solvation energies were added as single-point calculations by use of the conductorlike solvation model COSMO[22] at the B3LYP/6-311G(d,p) level. In this model, a cavity around the system is surrounded by polarizable dielectric continuum. The dielectric constant was chosen as the standard value for water, $\epsilon = 80$. Some of the experiments were done in DMF, which has a dielectric constant of $\epsilon = 37$. As the solvation energy to a first approximation is proportional to $(1 - {}^3/_2\epsilon)$ for large ϵ,[23] the water and DMF values give almost identical solvation energies. Since we are mainly interested in reaction barriers (reactant − transition state) and relative barriers, the differences are not significant. This is probably best demonstrated by a numerical example. For the [2 + 3] cycloaddition of HN_3 to MeCN, the difference in solvation energy between $\epsilon = 37$ and $\epsilon = 80$ is 0.11 kcal/mol for the reactants and 0.19 kcal/mol for the transition state. The difference for the barrier is hence lower than 0.1 kcal/mol. Also, geometry optimization under solvation gives very small differences compared to optimization in gas phase and then addition of solvation energy as a single-point calculation.

The barriers reported in this paper are calculated relative to free reactants. In gas phase, this will introduce an error of several kilocalories per mole, since the depth of the hydrogen-bonding precursor is completely neglected. However, when solvation is included, the precursor complex has a very similar energy to the free reactants. Tests showed that the differences were on the order of 0.1 kcal/mol.

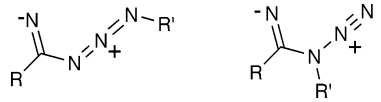
To be able to optimize the transition states, it was found crucial to start the optimization with a Hessian of a somewhat good quality; typically the HF/3-21G level was used.

All the energies presented in the present paper are enthalpies to which solvation energies are added. Zero-point energy (ZPE) effects are included.

III. Results and Discussion

A. Neutral Cycloaddition. When the azide is bound to an organic substrate, it seems clear that the reaction proceeds by a traditional concerted [2 + 3] mechanism (see Scheme 1). It is possible that azide salt species simply play the role of a covalently bound azide, a situation very similar electronically to that of organic azides. These two cases are considered in this section. Our calculations show that intermediates such as those shown in Chart 1 are not stable; thus, as previous studies

Chart 1



have shown, a concerted [2 + 3] cycloaddition is the most likely pathway for the bimolecular addition of nonionic azides to nitriles.

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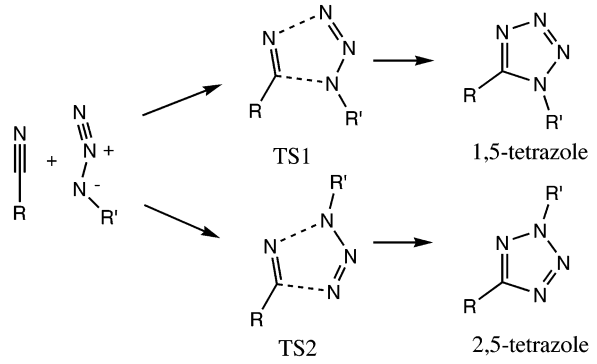
In the context of the concerted cycloaddition, two different isomers of tetrazole, the 1,5- and 2,5-disubstituted, can be formed (see Scheme 4). We have calculated the transition states

Scheme 4



for the cycloaddition of methyl azide (MeN_3) and hydrazoic acid (HN_3) to a number of substituted nitriles, with substituents ranging from electron-donating (methyl) to very electron-withdrawing (fluorine). The barriers and reaction energies are presented in Table 1, and the transition-state and tetrazole

Table 1. Calculated Barriers and Exothermicities[a] for Neutral [2 + 3] Cycloaddition Reaction of RCN with R′N_3

	R	R′	TS1	TS2	Δ(TS1 – TS2)	Δ*H* 1,5-tetrazole	Δ*H* 2,5-tetrazole	ΔΔ*H*
1	Me	Me	31.6	37.8	−6.2	−19.4	−19.0	−0.4
2	Ph	Me	32.5	37.8	−5.3	−17.4	−20.4	+3.0
3	tBu	Me	34.8	38.7	−3.9	−14.5	−17.3	+2.7
4	MeS	Me	28.5	33.6	−5.1	−20.4	−20.1	−0.3
5	MeO	Me	25.9	33.9	−8.0	−27.9	−28.3	+0.4
6	CH_2F	Me	27.8	33.5	−5.7	−22.9	−24.7	+1.8
7	CHF_2	Me	23.3	29.7	−6.4	−31.8	−29.0	−2.8
8	CF_3	Me	21.8	27.7	−5.9	−29.3	−31.9	+2.6
9	$MeSO_2$	Me	20.4	26.1	−5.7	−26.4	−29.6	+3.2
10	F	Me	18.1	27.8	−9.7	−35.7	−38.9	+3.2
11	Me	H	35.1	41.7	−6.6	−13.7	−12.5	−1.2
12	$MeSO_2$	H	23.7	29.7	−6.0	−21.1	−24.9	+3.8
13	F	H	21.9	31.9	−10.0	−29.5	−31.9	+2.3

[a] Values are in kilocalories per mole.

geometries for two of these reactions (with methyl and methylsulfonium substituents) are displayed in Figure 1.

Of primary note is that all reactions are strongly exothermic, with the more electronegative substituents on the nitriles yielding greater exothermicities. The actual exothermicities are somewhat overestimated, as entropy effects are not included in the calculations.

Experimentally, the 1-substituted tetrazole is exclusively formed, as mentioned above. This is consistent with calculations which show that TS1, for all substituents, is considerably lower than TS2. The difference ranges from 9.7 kcal/mol for the extremely electron-poor fluoronitrile, to 3.9 kcal/mol for the relatively electron-rich and very bulky *tert*-butyl nitrile. A general trend is that the more activated the nitrile, the larger the difference between TS1 and TS2. Also, the size of the substituents affects the difference, as there is less steric repulsion in TS2 than in TS1.

From Table 1 we can see that the barriers for the [2 + 3] cycloaddition (TS1) are correlated with the electron-withdrawing power of the substituents. Accordingly, the lowest barriers are found for the very electronegative sulfonium and fluorine groups (lines 9 and 10). This effect is also seen in the series where the substituents are -CH_3, -CH_2F, -CHF_2, and -CF_3 (lines 1, 6, 7, and 8): the barriers for the reactions of these with methyl azide are 31.6, 27.8, 23.3, and 21.8 kcal/mol, respectively. A secondary factor is the steric bulk of the substituent. For instance, *tert*-butyl nitrile has a barrier 3.2 kcal/mol higher than that of methylnitrile (34.8 vs 31.6 kcal/mol).

Transition-state geometries change slightly depending on the substituent. The $C_{nitrile}–N_{azide}$ distance of TS1, for example, varies between 1.80 and 1.99 Å, with the electronegative substituents causing shorter distances. The $N_{nitrile}–N_{azide}$ distance varies between 1.96 and 2.40 Å, with the electronegative substituents now causing longer distances. The angles adjust accordingly; the NNN angle of the azide varies between 131° and 139°, while the RCN angle varies between 139° and 147°. Hence, the more electron-withdrawing substituent has the more asymmetric transition state.

It is interesting to note that the energy needed to bend the RCN angle varies considerably with the substituents. For instance, the energy needed to bend the CCN angle in methylnitrile from linear to 140° (the approximate angle at the transition state) is 13.5 kcal/mol, while the energy needed to bend the SCN angle in sulfonylnitrile to the same degree is 6.4 kcal/mol. This explains in part the lower barrier found for the electronegative substituents.

It is also interesting to note that in gas phase, as previous studies have found,[24] the 2,5-tetrazoles are generally slightly more stable than the corresponding 1*H*-isomers. However, the 1,5-isomer has in general a higher dipole moment (6.2 vs 2.6 D for dimethyltetrazole, for example) and hence solvates better, which results in relative stabilities of the 1,5- vs 2,5-isomers very close to one another, in the range of ±3 kcal/mol, depending on the size and electronegativity of the substituents.

B. Anionic Cycloaddition. In reactions where NaN_3 is added to nitrile in nonprotic organic solvents, such as dimethylformamide (DMF) or glyme,[12,25] it has been found that yields are generally lower, and higher reaction temperatures are required. In these cases, there are two possible mechanisms, assuming the cation does not play a role, either a direct [2 + 3] cycloaddition or a two-step sequence wherein the azide first nucleophilically attacks the nitrile, followed by ring closure. In this section the barriers for the cycloaddition of the azide anion to nitriles have been calculated, with the same set of nitriles as in the previous section. The results are listed in Table 2, and

Table 2. Calculated Barriers and Exothermicities[a] for Anionic [2 + 3] Cycloaddition Reaction of RCN with N_3^-

	R	barrier	tetrazole
1	Me	33.8	−14.8
2	Ph	32.4	−16.5
3	tBu	37.2	−11.3
4	MeS	26.5	−17.1
5	MeO	22.3	−24.2
6	CH_2F	24.6	−23.6
7	CHF_2	18.9	−29.5
8	CF_3	12.8	−34.0
9	$MeSO_2$	10.7	−31.2
10	F	5.3	−39.5

[a] Values are in kilocalories per mole.

two typical transition-state geometries are given in Figure 2.[26]

As in the case of the neutral [2 + 3] cycloaddition, the barrier for anionic [2 + 3] cycloaddition decreases with increasing electron-withdrawing potential of the substituent on the nitrile.

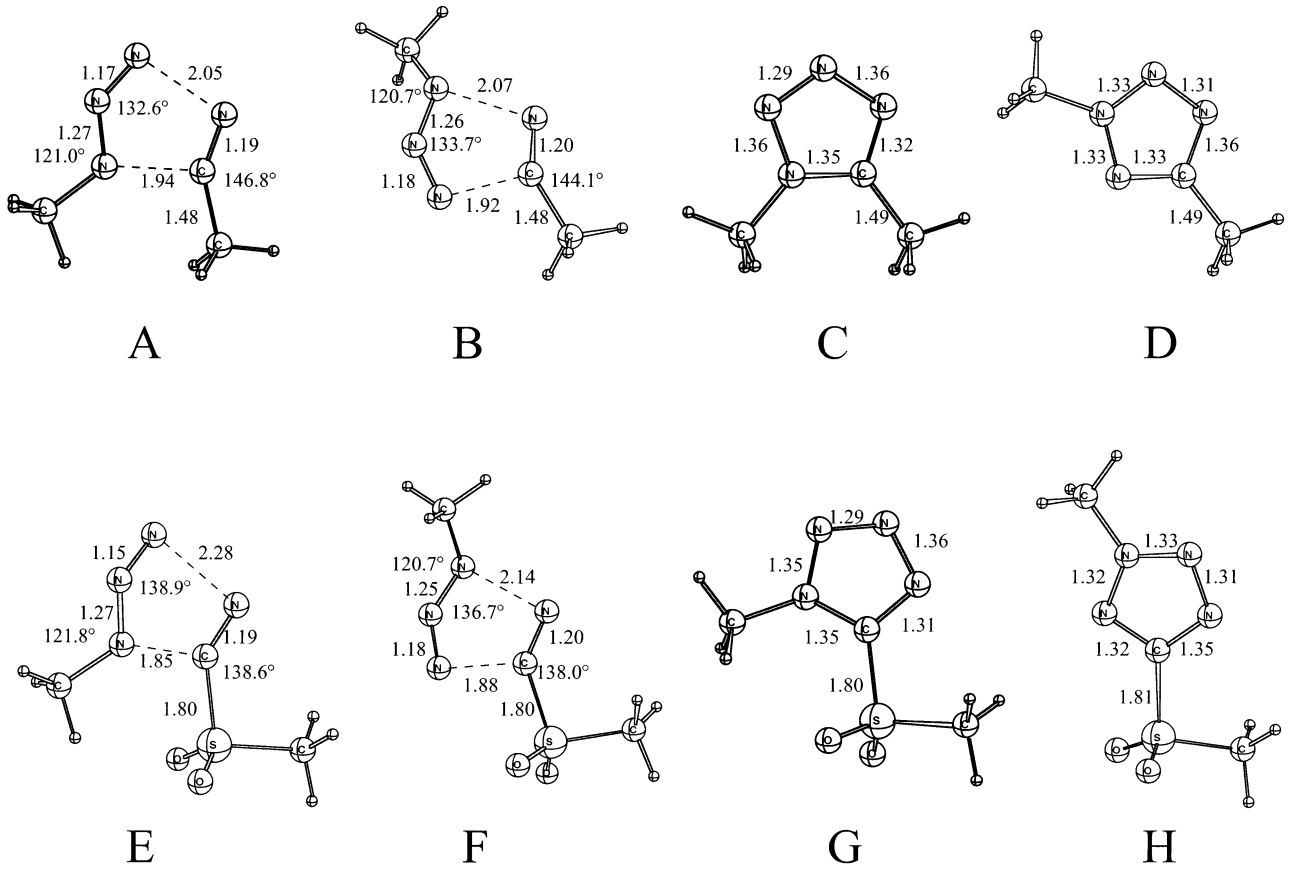


Figure 1. Optimized structures of transition states 1 (A, E) and 2 (B, F) and corresponding tetrazole products (C, D, G, H) formed from cycloaddition of methyl azide and acetonitrile (Table 1, line 1; structures A−D) or methyl azide and sulfoniumnitrile (Table 1, line 9; structures E−H). Bond lengths are given in angströms.

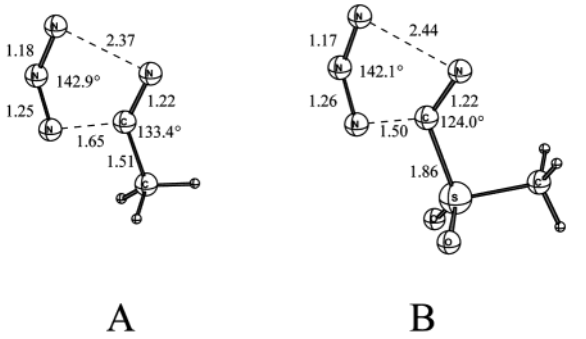


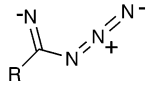
Figure 2. Optimized transition-state structures for addition of N_3^- to methylnitrile (A) and methane sulfonylnitrile (B).

However, in this case, the slope of the change in barrier versus electronic character is greater (see Figure 6). For example, the barriers for the anionic reaction with the relatively electron-rich acetonitrile and *tert*-butylnitrile (Table 2, lines 1 and 3) are slightly more than 2 kcal/mol higher than for the concerted neutral reaction. The relatively electroneutral benzonitrile (Table 2, line 2) has an almost identical barrier, and the electron-poor methylcyanate (MeOCN) and extremely electron-poor methanesulfonyl cyanide (Table 2, lines 5 and 9) have barriers which are 3.6 and 9.7 kcal/mol lower, respectively, than the comparable concerted neutral reaction.

The geometry of the transition state of anionic reaction is more asymmetric than for the neutral reaction; the $C_{nitrile}-N_{azide}$ distance is significantly shorter than the $N_{nitrile}-N_{azide}$ distance. The difference grows with the electron-withdrawing potential of the substituent. For acetonitrile, for example, the N−C distance is 1.65 Å and the N−N distance is 2.37 Å, while for sulfonyl cyanides the same distances are 1.50 and 2.44 Å, respectively.

For very strong electron-withdrawing groups, like F^- or RSO_2^-, an intermediate such as that found in Chart 2 could be

Chart 2



found. However, it is weakly bound, as seen for instance from the rather long N−C bond length (1.57 Å for FCN and 1.49 Å for CH_3SO_2CN). The intermediate is at about the same energy as the free reactants, with a very small barrier for its formation (transition state could not be optimized, but linear transit calculations gave an estimate of the barrier to be less than 4 kcal/mol). Despite the existence of this intermediate for the strongly activated nitriles, the transition state for the ring closing turns out to be identical to the concerted [2 + 3] transition state, indicating that the two pathways are essentially the same.

C. Proton Involvement. As mentioned in the Introduction, Koldobskii et al.[14a] showed that only ammonium salts of azide

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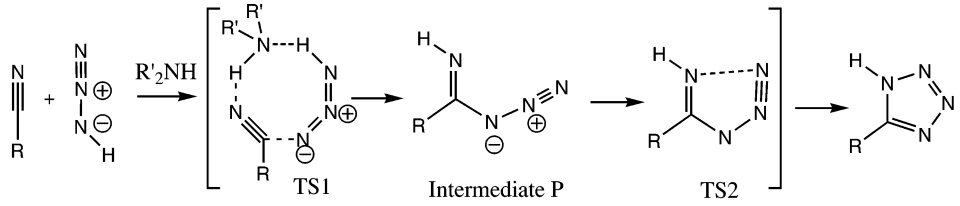
(26) A word of caution regarding the solvation energy of N_3^- is in place here. Negatively charged molecules of this small size tend usually to be undersolvated with the methods used here. This would mean that the barriers calculated here are somewhat underestimated. However, since the error is constant, this should not affect relative barriers.

Scheme 5



that contain a proton are competent dipoles; tetrabutylammonium azide does not work.[5] What then is the role of the proton? Could it play the same role as it does in acid-catalyzed hydrolysis of nitriles or in the Pinner synthesis, namely, activation of the nitrile?

On the basis of the calculations, we propose that when a proton is available, the tetrazole reaction proceeds via intermediate P as in Scheme 5 (optimized geometries of the intermediate are shown in Figure 3A,C), instead of a direct [2 + 3] dipolar

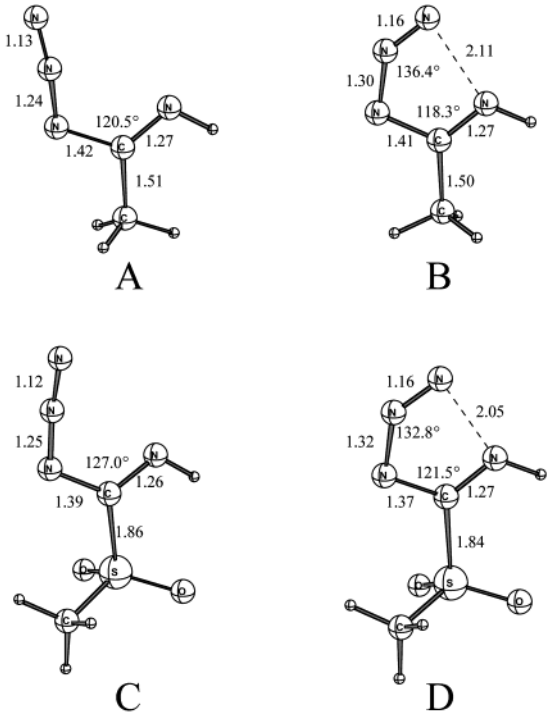


Figure 3. Optimized structures of intermediate P and the ring-closing transition states for methylnitrile (A, B) and methane sulfonylnitrile (C, D).

Table 3. Calculated Energy[a] of Intermediate P Relative to HN_3 + RCN, and the Barrier for Ring Closing from There to Form the Tetrazole

				barrier for formation of intermediate P		
	R	intermediate P	ring closing barrier	direct TS	NH_4^+ TS	water TS
1	Me	+3.3	+15.3	+31.0	+20.8	+26.8
2	MeS	−1.6	+15.9	+29.2	+15.5	+24.8
3	MeO	−12.0	+19.4	+29.1	+12.6	+24.1
4	$MeSO_2$	−11.4	+17.8	+30.1	+5.3	+23.4

[a] Values are in kilocalories per mole. Also included are the three models used to calculate the barrier for the formation of the intermediate, as discussed in the text.

cycloaddition. This intermediate is quite stable; for R = Me it is 3.3 kcal/mol less stable than the free reactants, HN_3 and MeCN. As seen in Table 3, the stability of the intermediate increases with the electron-withdrawing potential of the substituent on the nitrile. For $MeSO_2CN$, for instance, the intermediate has as much as 11.4 kcal/mol lower energy than the free reactants.

From intermediate P, the barrier to close the ring and form 1-tetrazole is very feasible, ca. 15−19 kcal/mol (via TS2) with respect to intermediate P depending on the nature of the substituent (see Table 3). Hence, once the intermediate is created, the tetrazole can readily be formed.

How Then Is Intermediate P Formed? The transition states have been calculated for three scenarios for the creation of intermediate P. The first possibility considered is a direct concerted attack of HN_3 on the nitrile in which the proton is transferred to the nitrile nitrogen and at the same time the N−C bond is formed (typical six-membered ring transition-state structures are shown in Figure 4). This reaction, which assumes

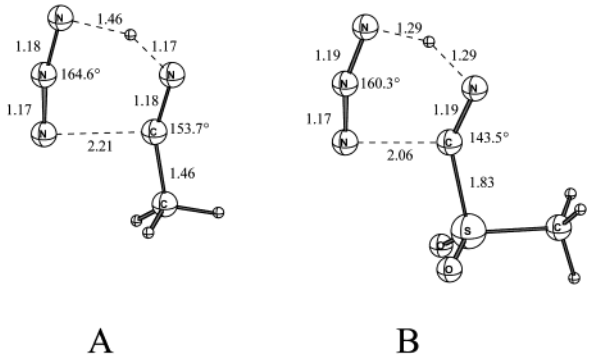


Figure 4. Optimized transition-state structures for the direct concerted attack of HN_3 on the methylnitrile (A) and methane sulfonylnitrile (B), to form intermediate P via a transition state with a six-membered ring.

that the azide is protonated, has a barrier of around 30 kcal/mol, with small variations depending on the nature of the substituent (see Table 3). This is a relatively high activation barrier, which can compete with the neutral and anionic concerted [2 + 3] cycloaddition only for highly inactive nitriles.

Considered second is the mechanism where the proton comes from NH_4^+. This reaction was modeled in two different ways, which, interestingly, gave very similar transition states and almost identical barriers. The first model starts from the neutral species HN_3 and RCN, and ammonia (NH_3) mediates the proton transfer from the azide to the nitrile, with the concomitant formation of the N−C bond. The optimized transition-state structure for R = Me is given in Figure 5A. The second model assumes a deprotonated azide ion (N_3^-) and protonated ammonium species (NH_4^+). Here the geometry optimization had to be performed under the solvation to circumvent the large charge separation that in the gas phase causes the moiety to collapse into neutral molecules. The optimized transition-state structure is given in Figure 5B.

The barriers for these two models are almost identical. For instance, for R = Me the neutral model yields a barrier of 20.8

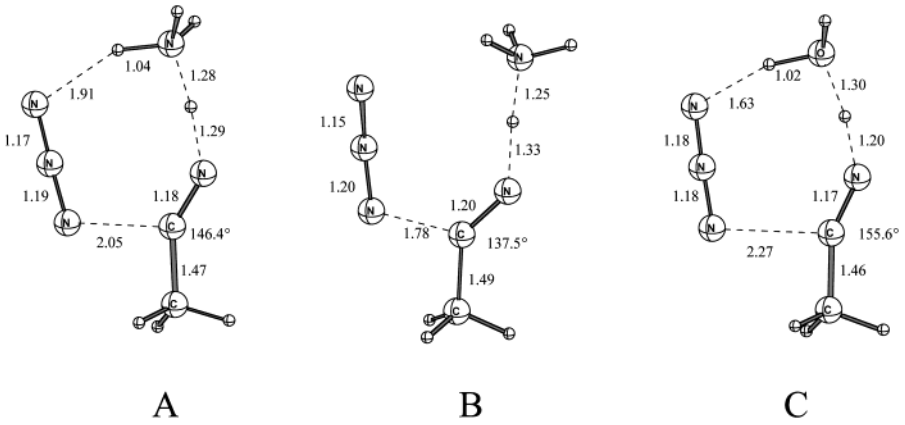


Figure 5. Optimized transition-state structures for the formation of intermediate P according to different models: a neutral model starting from HN_3, NH_3, and MeCN (A); an ionic model starting from N_3^-, NH_4^+, and MeCN, geometry-optimized in solvent (B); and a neutral model starting from HN_3, H_2O, and MeCN (C).

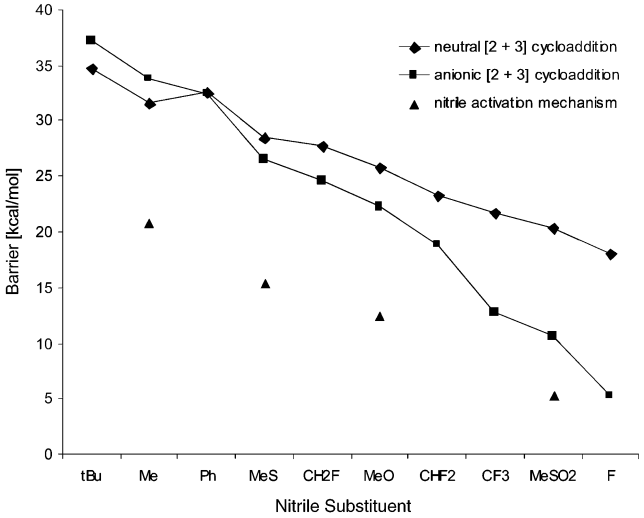


Figure 6. Summary of reaction barriers calculated in the present study. Note that triangles show the barrier only for formation of intermediate P and not for the subsequent ring closing, which has a barrier of ca. 15−19 kcal/mol depending on substituent group (see text and Table 3 for details).

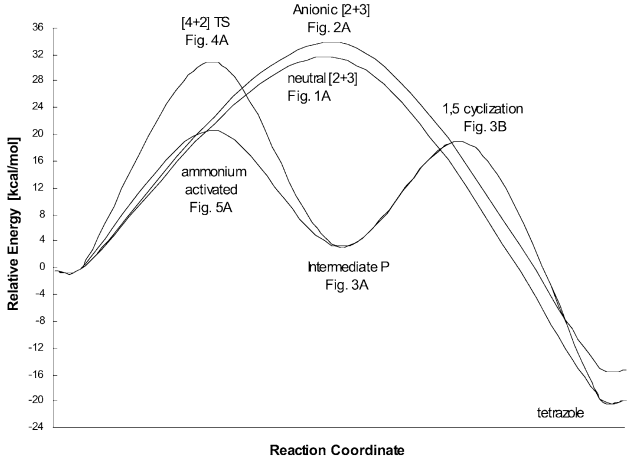


Figure 7. Calculated potential energy surfaces for the various mechanisms considered for the formation of tetrazole from azide and acetonitrile.

kcal/mol, while the ionic model gives a barrier of 21.3 kcal/mol, i.e., a difference of only 0.5 kcal/mol. This barrier is considerably lower than all mechanisms previously considered in this paper. Compare these numbers with those for attack of hydrazoic acid through a six-membered transition state (31.0 kcal/mol), the neutral [2 + 3] cycloaddition of HN_3 to CH_3CN (35.1 kcal/mol), and the anionic [2 + 3] cycloaddition of N_3^- to CH_3CN (33.8 kcal/mol). The same conclusion applies to all other substitution patterns studied (see Table 3). When the nitrile is attached to a methoxy group (methyl cyanate), the ammonium-mediated reaction has a barrier (12.6 kcal/mol) significantly lower than that in the attack of HN_3 through the six-membered transition state (29.1 kcal/mol) or the [2 + 3] cycloaddition of HN_3 (25.9 kcal/mol) or the anionic [2 + 3] cycloaddition of N_3^- (22.3 kcal/mol). Within a few kilocalories per mole, the various mechanisms have the same entropy. Interestingly, as Table 3 indicates, for strongly electronegative substituents, the ring-closing step, which has a barrier of 16−19 kcal/mol, might become the rate-limiting step. However, the entropy effect for the creation of intermediate P should raise the barrier of that compared to the ring-closing step (estimated at ca. 5−7 kcal/mol).

Last, we have investigated whether a water molecule can facilitate the reaction in the same way as ammonia (transition-state structure shown in Figure 5C). As seen from Table 3, although the water molecule reduces the barrier compared to the direct attack, it is still significantly higher than the ammonia-mediated reaction. Furthermore, the barrier shows a very modest decrease with the electronegativity of the substituent. While the barrier difference between R = Me and R = $MeSO_2$ is only 3.4 kcal/mol in the water-catalyzed reaction, it is as large as 15.5 kcal/mol in the ammonium-catalyzed reaction.

To summarize this section, in situations where a proton is readily available, a stepwise reaction through intermediate P is more favorable than [2 + 3] cycloaddition reactions, either neutral or anionic. This mechanism is similar to the known mechanisms of acid-catalyzed nitrile hydrolysis and the Pinner synthesis, with the difference being that the nucleophile is an azide. The key to this mechanism's low-energy TS is that the nitrile is activated by a proton. Experimentally, this is provided by ammonium salt, but of course other proton sources could play the same role.

IV. Conclusions

In the present study we have examined the energetics of different mechanisms for formation of tetrazole from azide and nitriles. This has been done by means of the B3LYP density functional theory method. The barriers for the different mech-

anisms are summarized in Figures 6 and 7. The main result of the calculations is that when a proton is available, the reaction proceeds via the protonated intermediate P, as shown in Scheme 5. The transition state leading to the formation of intermediate P involves the activation of the nitrile by a proton, facilitating the attack of the azide on the carbon of the nitrile. From intermediate P, simple 1,5-cyclization occurs to give the 1*H*-tetrazole. This mechanism is consistent with available experimental results and with similar known mechanisms for related reactions involving nucleophilic attack on nitriles.

Addition reactions such as the ones studied in the present paper usually exhibit large entropic effects. These were not reported in the tables primarily because we are interested in trends and relative effects, and accurate determination of entropies of bimolecular reactions in solution involves a number of subtle issues.[27]

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