



Ab initio study of the 1,3-cycloaddition of methyl azide to fluorinated acetonitriles

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Abstract

Transition state structures for polar 1,3-cycloaddition of methyl azide to fluorinated acetonitriles have been optimized by ab initio molecular orbital calculations at the RHF/3-21G basis set level. The activation energies were also evaluated by single-point calculations at the RHF/6-31+G* level on the RHF/3-21G geometries. Additionally, the reactivity was rationalized in terms of the number of fluorine atoms in the molecules and the charge on the nitrile carbon. The regioselectivity is correctly predicted by the activation energy differences, by the HOMO–LUMO interactions, and by the charge interactions.

1. Introduction

It is generally agreed that 1,3-dipolar cycloadditions follow a concerted mechanism [1–3], like Diels–Alder reactions. This is supported by their high regio- and stereoselectivity, among other factors [2]. The 1,3-dipolar cycloaddition reactions have been explained by the HOMO (dipole)–LUMO (dipolarophile) or, for some, by the LUMO (dipole)–HOMO (dipolarophile) interactions. The smaller the energy gap between the controlling orbitals, the faster the reaction. The reaction is controlled by both electron-donating and electron-withdrawing substituents on either component [2]. Regioselectivity of the 1,3-cycloaddition is controlled by the magnitude of the atomic orbital coefficients in the concerted

transition state structure. The atoms in each component with the largest coefficients interact, but this may not be the case for every HOMO and LUMO interaction [3]. For example, in the reaction of phenyl azide with 1-hexene, which is a LUMO (dipole)–HOMO (dipolarophile) interaction, 1-phenyl-5-butyltriazoline is obtained. On the other hand, when the reaction is carried out with methyl acrylate, the 1-phenyl-4-methyltriazoline isomer is obtained. The reaction can be explained as HOMO (dipole)–LUMO (dipolarophile) controlled by the closest HOMO–LUMO interactions [4], although in some reactions electronically preferred orientations may be disfavored by steric effects [3].

Cycloaddition of organic azides with nitriles may lead to 1,5-disubstituted or 2,5-disubstituted tetrazoles. When the nitrile contains electron withdrawing substituents such as perchloro- or perfluoroalkyl groups, the 1,5-disubstituted tetrazoles are readily formed [5]. As a matter of

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fact, this reaction was not successful unless strong electron withdrawing groups were present in the nitrile, and only the 1,5-disubstituted tetrazoles were obtained [6]. In this paper we report the results of semiempirical and ab initio calculations of the addition of methyl azide to fluorinated acetonitriles.

2. Computational methods

The transition states were obtained by the SADDLE search routine with the PM3 [7] method in MOPAC6.0 [8] and refined with NLLSQ. These optimized transition state structures were used as input files for Gaussian 92 [9] 3-21G [10] optimizations at the restricted Hartree–Fock theory level. Single-point energy calculations at the HF/6-31+G* basis set level were performed on the HF/3-21G optimized structures. Although this model

chemistry is known to overestimate the activation energies, the obtained data are useful for comparing the origin and the relative reactivities in a series of similar reactants. Frequency calculations were carried out for the transition states, and these stationary points on the potential energy surface were confirmed to be true transition states by having only one imaginary frequency.

3. Results and discussion

On the basis of accumulated experimental and computational data for cycloaddition reactions, a concerted transition state structure for the addition of organic azide to nitriles was considered [11]. Moreover, our attempts to generate the first transition state in a two step addition by MOPAC was unsuccessful [12]. The transition states obtained by HF/3-21G are divided into two categories. In

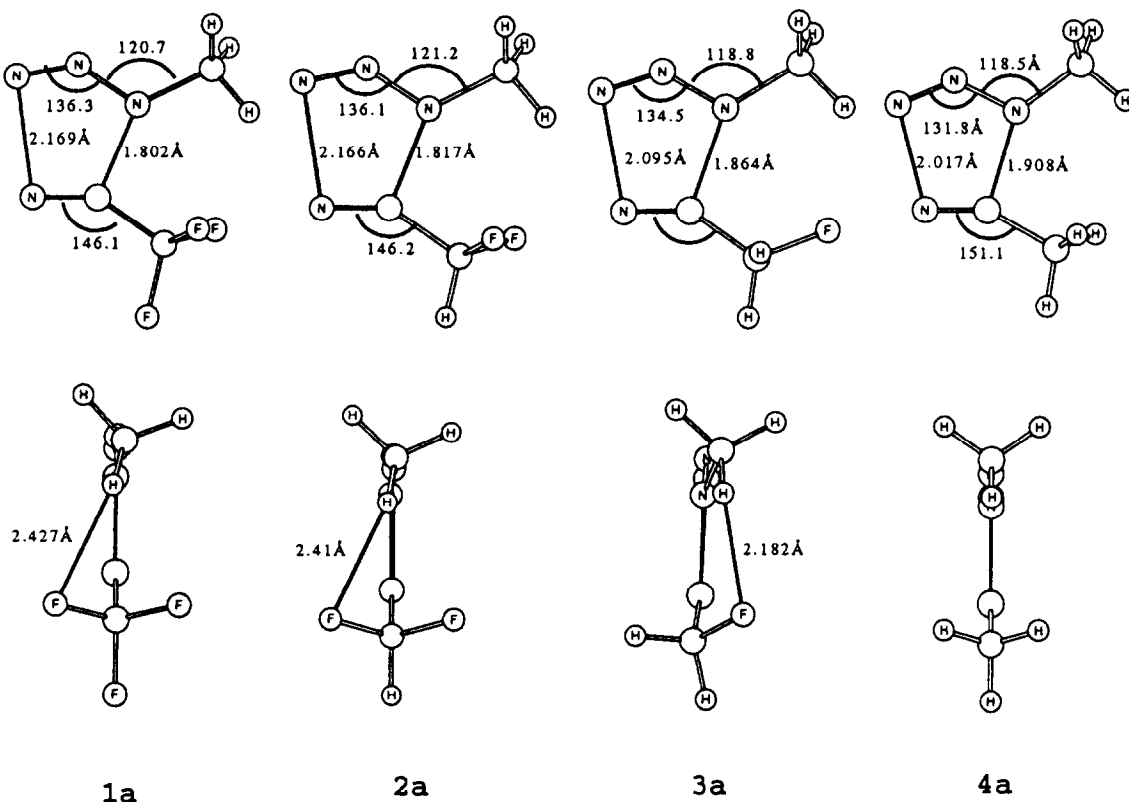


Fig. 1. The transition state structures generated by HF/3-21G that lead to the experimentally obtained products.

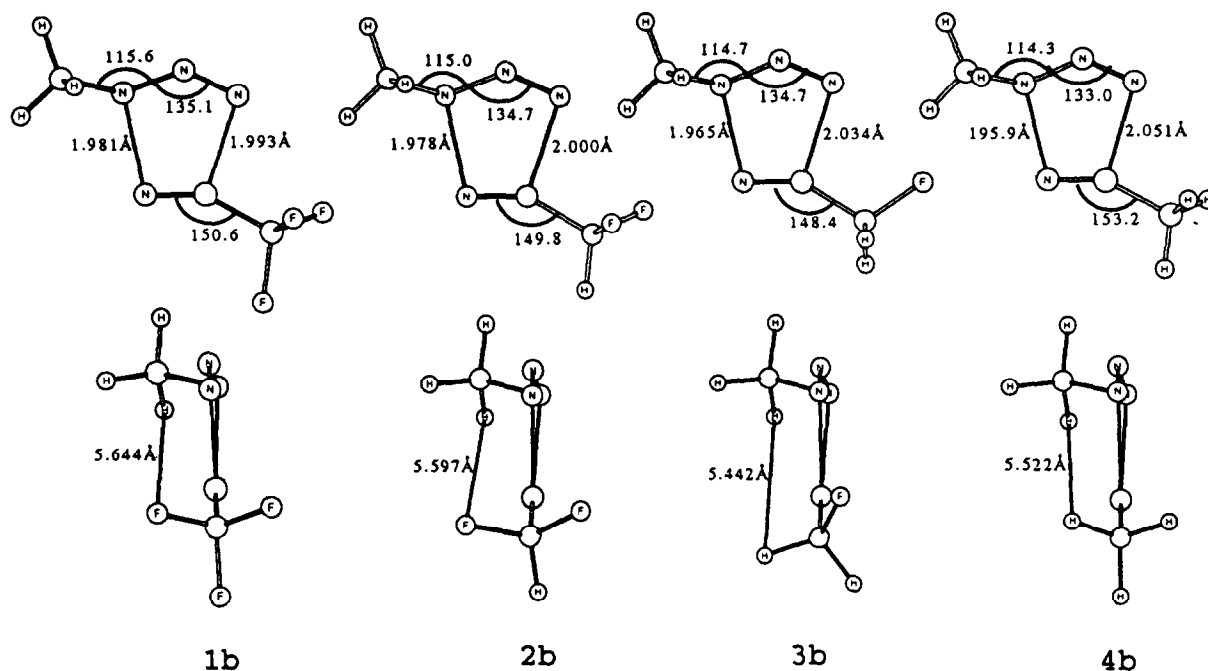


Fig. 2. Transition state structures generated by HF/3-21G level calculations that do not lead to the experimentally obtained products.

the first are the states that generate the experimentally obtained 1,5-disubstituted tetrazoles (Fig. 1) and in the other are those isomers not experimentally obtained but theoretically possible (Fig. 2). The calculated total energies of the fluorinated acetonitriles–methyl azide cycloaddition and the activation energies in relation to the reactants are given in Tables 1 and 2, respectively.

Table 1

Total energies (a.u.) of reactants and transition structures in the 1,3-cycloaddition of fluorinated acetonitriles with methyl azide

Species	HF/3-21G	HF/6-31 + G*//HF/3-21G
CH ₃ N ₃	-201.69003	-202.86980
CF ₃ CN	-426.14555	-428.49030
CHF ₂ CN	-327.81143	-329.62550
CH ₂ FCN	-229.49095	-230.76970
CH ₃ CN	-131.19180	-131.93104
1a	-627.80586	-631.30024
1b	-627.78352	-631.27983
2a	-529.46820	-532.43399
2b	-529.44466	-532.41225
3a	-431.14111	-433.57097
3b	-431.12022	-433.55111
4a	-332.83050	-334.72517
4b	-332.81562	-334.70776

3.1. Energetics of the transition structures

From the experimental data we know that the reactivity of the fluorinated acetonitriles increases with the number of fluorine atoms. Consequently, the calculated activation energy should decrease in the same series. Comparison of the PM3 calculated activation energies for the 1,3-cycloaddition of methyl azide to fluorinated acetonitriles are in the range 38.89–40.42 kcal mol⁻¹. PM3 tends to give the same activation energy for all transition states.

Table 2

Calculated activation energies (kcal mol⁻¹) for the 1,3-cycloaddition of fluorinated acetonitriles with methyl azides

Transition structure	PM3	HF/3-21G	HF/6-31 + G*//HF3-21G
1a	39.58	18.65	37.66
1b	43.69	32.65	50.38
2a	38.94	20.82	38.47
2b	40.63	35.62	52.10
3a	38.89	25.00	43.00
3b	40.83	38.11	55.46
4a	40.42	31.81	47.48
4b	42.36	41.15	58.41

Furthermore, although in all cases the 1,5-disubstituted tetrazole isomer was preferred over that arising from 1,3-disubstitution, the order of reactivity does not follow the experimental observations. According to PM3, the most reactive substituted acetonitrile is CH_2FCN , and accordingly this method cannot be used for evaluation of the reactivity in the studied cycloaddition.

The activation energies calculated from HF/3-21G generated transition state structures follow the experimentally observed trend. According to both HF/3-21G and HF/6-31+G**/HF3-21G the most reactive nitrile is trifluoroacetonitrile and the least reactive is acetonitrile. Although the activation energies for the compounds studied are not available, the activation energy for the addition of *n*-pentyl azide to trichloroacetonitrile is 21 kcal mol⁻¹. We can estimate that the activation energy between trifluoroacetonitrile and methyl azide should be < 21 kcal mol⁻¹. Indeed, that result was obtained by HF/3-21G, whereas the result from HF/6-31+G**/HF3-21G tends to be above the expected values (Table 2). This is not unexpected, as correlation energy is not accounted for at the Hartree–Fock level of theory. The biggest difference in activation energy is between difluoro- and monofluoroacetonitrile (4.18 and 4.53 kcal mol⁻¹).

3.2. Regioselectivity

An important outcome of the computational

study of cycloaddition reactions is the accurate prediction of regioselectivity. The regioselectivity of the reaction can be predicted by various qualitative methods. In the present case the formation of the 1,5-disubstituted tetrazoles can be explained in at least three terms: the difference in the energy of activation, the symmetry of the frontier orbitals, and the polar interactions between atoms that will make bonds.

The PM3 frontier molecular orbitals of trifluoroacetonitrile and methyl azide are presented schematically in Chart 1. According to PM3 calculations in terms of frontier molecular orbitals, the polar 1,3-cycloaddition of methyl azide to trifluoroacetonitrile is controlled by the HOMO of the azide and the LUMO of the nitrile [$\Delta E_{(\text{LUMO})\text{CF}_3\text{CN}} - \Delta E_{(\text{HOMO})\text{CH}_3\text{N}_3} = 9.68\text{eV}$, and $\Delta E_{(\text{LUMO})\text{CH}_3\text{N}_3} - \Delta E_{(\text{HOMO})\text{CF}_3\text{CN}} = 14.44\text{eV}$]. Chart 1 shows that in the case of CF_3CN the LUMO coefficients at nitrogen make this orbital a more likely target than the one at carbon, and in the case of CH_3N_3 the closer distribution can be explained by the similar nature of the atoms in positions 1 and 3. According to the frontier orbital theory [13], the regioselectivity is controlled by the magnitude of the atomic orbital coefficients — the atoms with the largest coefficients interact (Chart 1, case A) — and this interaction leads to the 1,5-disubstituted tetrazole.

The regioselectivity can also be explained on the basis of the charge interactions. Certainly the principal interactions are not solely charge interactions and so we cannot say that the reaction is

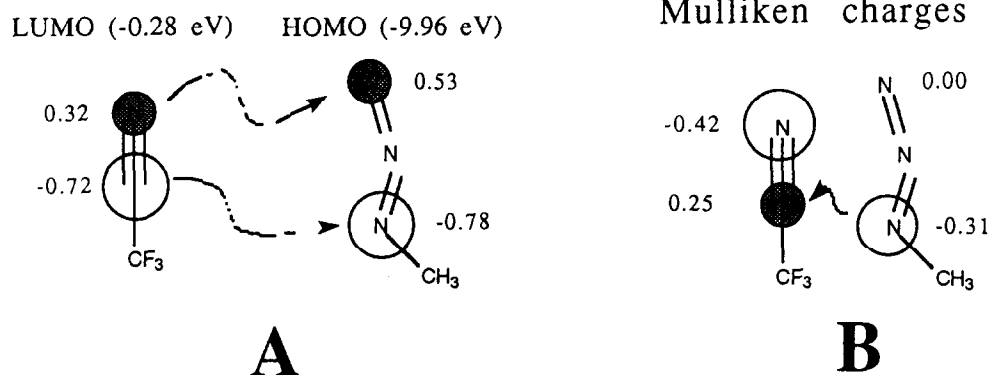


Chart 1. (A) PM3 atomic orbital coefficients for LUMO–HOMO and (B) HF/3-21G calculated Mulliken charges for CF_3CN and CH_3N_3 .

charge controlled, but the formation of the correct isomer can be predicted by Mulliken charge interactions that are present in the reactants (Chart 1, case B), which decrease in the transition state and in the product.

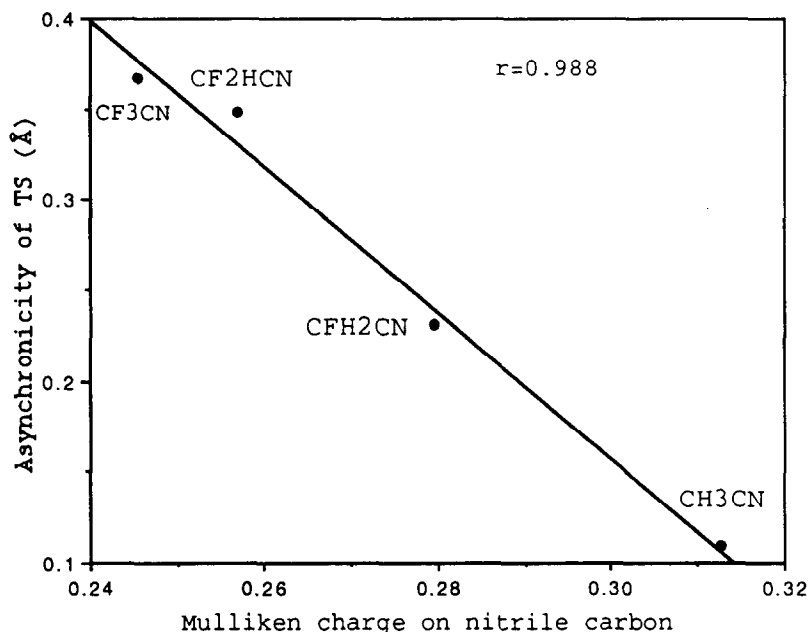
The most reliable predictions of the regioselectivity can be made on the basis of differences in the activation energies for the two isomers. The activation energies in all cases studied here, both by semiempirical and by ab initio methods, predict the correct isomer (Table 2).

3.3. Asymmetry and geometry of the transition structures

The degree of asynchronicity in formation of the two new bonds of polar cycloaddition reactions has been debated for some time [1]. It is generally accepted that the parent reaction of azides with alkenes is synchronous but, by various interactions, asymmetric substituents force the transition state structure to be asynchronous and force the five atoms in the transition state out of the plane. Also, in our case, two different bonds (CC and CN) are being formed and some degree of

asynchronicity is inherently expected. In our case the HF/3-21G optimized transition structures for the polar 1,3-cycloaddition of methyl azide to fluorinated acetonitriles show that these reactions are asynchronous. The lengths of the two forming bonds for structure **1a** (Fig. 1) are 2.169 Å and 1.802 Å ($\Delta r = 0.367$ Å) and it is the most asynchronous transition structure studied here. The influence on the asynchronicity of the number of fluorine atoms on the acetonitrile is demonstrated on Graph 1.

From the transition structures presented in Fig. 1 it can be seen that considerable interactions between the fluorine atoms and hydrogen exist. The interatomic distance is relatively short (≈ 2.4 Å) for transition structures **1a** and **2a**, but it is considerably shorter in transition structure **3a** (2.182 Å). In all structures in Fig. 1 the heavy atoms are almost in one plane, whereas in the case of **3a** the methyl and the fluoromethyl groups are pushed away with a tendency to increase the electrostatic interactions between the hydrogen and the fluorine atoms. These interactions in the transition structures that would lead to the formation of the experimentally unfavorable



Graph 1. Correlation of the asynchronicity of the concerted transition structures with the Mulliken charges on the nitrile carbon of fluorinated acetonitriles.

2,5-disubstituted tetrazoles are not present. The closest fluorine–hydrogen distance is $> 5 \text{ \AA}$. It is interesting to note that, although two groups (methyl and trifluoromethyl) are far apart, they are not in the plane of the new ring being formed. That can, by itself, be viewed as a support of the very strong electrostatic interactions between the substituents.

4. Conclusion

The transition structures generated by ab initio HF/3-21G level calculations are concerted but asynchronous. The degree of synchronicity depends on the polarity of the reactants in the cycloaddition. Increasing the number of fluorine atoms in acetonitrile lowers the activation energy and increases the asynchronicity of the transition state structure. The PM3 semiempirical method seems to be unable to predict the correct reactivity in the fluorinated acetonitriles but predicts the correct isomer. Ab initio energies have been shown to correlate well with experimental knowledge of these reactions.

References

- [1] R. Huisgen, *J. Org. Chem.*, 41 (1976) 403.
- [2] See, for example, R. Huisgen, in A. Padwa (Ed.), *1,3-Dipolar Cycloaddition Chemistry*, Wiley, 1984, Vol. 1, p. 1; R.J. Huisgen and R. Weinberger, *Tetrahedron Lett.*, 26 (1985) 5119; K.N. Houk, R.A. Firestone, L.L. Munchausen, P.H. Mueller, B.H. Arison and L.A. Garcia, *J. Am. Chem. Soc.*, 107 (1985) 7227; J.J.W. McDouall, M.A. Robb, U. Niazi, F. Bernardi and H.B. Schlegel, *J. Am. Chem. Soc.*, 109 (1987) 4642; H. Quast, D. Regnat, E.-M. Peters, K. Peters and H.G. von Schnering, *Angew. Chem. Int. Ed. Engl.*, 29 (1990) 695; R. Sustmann, W. Sicking and H.J. Quast, *Comput. Chem.*, 13 (1992) 314.
- [3] See, for example, K.N. Houk, J. Sims, R.E. Duke, R.W. Strozier and J.K. George, *J. Am. Chem. Soc.*, 95 (1973) 7287; K.N. Houk, J. Sims, C.R. Watts and L.J. Laskus, *J. Am. Chem. Soc.*, 95 (1973) 7301.
- [4] R. Huisgen, G. Szeimies and L. Mobius, *Chem. Ber.*, 99 (1966) 475; P. Scheiner, *Tetrahedron*, 24 (1968) 349.
- [5] A.A. Mel'nikov, M.M. Sokolova, M.A. Pervozvanskaya and V.V. Mel'nikov, *Zh. Org. Khim.*, 15 (1979) 1861.
- [6] W.R. Carpenter, *J. Org. Chem.*, 27 (1962) 2085.
- [7] For PM3 parametrization of MNDO see J.J.P. Stewart, *J. Comput. Chem.*, 10 (1989) 109; J.J.P. Stewart, *J. Comput. Chem.*, 10 (1989) 221.
- [8] J.J.P. Stewart, MOPAC, QCPE No. 455, 1983.
- [9] GAUSSIAN 92, Revision C, M.J. Frisch, G.W. Trucks, M. Head-Gordon, P.M.W. Gill, M.W. Wong, J.B. Foresman, B.G. Johnson, H.B. Schlegel, M.A. Robb, E.S. Replogle, R. Gomperts, J.L. Andres, K. Raghavachari, J.S. Binkley, C. Gonzalez, R.L. Martin, D.J. Fox, D.J. Defrees, J. Baker, J.J.P. Stewart and J.A. Pople, Gaussian, Inc., Pittsburgh, PA, 1992.
- [10] 3-21G: J.S. Binkley and J.A. Pople, *J. Am. Chem. Soc.*, 102 (1980) 939; 6-31G*: P.C. Hariharan and J.A. Pople, *Theor. Chim. Acta*, 20 (1973) 213.
- [11] Hetero cycloaddition reactions that do not involve anions or cations are predicted to take place through concerted transition structures in a similar way to the all-carbon version; see W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, New York, 1990. Ab initio calculations of hetero Diels–Alder reactions agree with a concerted, slightly asynchronous, transition structure.
- [12] There are two possible first transition states for the formation of 1,5-disubstituted tetrazoles because of the charge distribution in the starting materials. The formation of the C–N bond is more probable than that of the N–N bond. We were unsuccessful in determining the transition state by the available MOPAC optimizers (NLLSQ, SIGMA, TS).
- [13] For the application of molecular orbital theory in organic reactions see Y. Jean, F. Volatron and J. Burdett, *An Introduction to Molecular Orbitals*, Oxford University Press, New York, 1993.