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The Phototransposition in Acetonitrile and the Photoaddition of 2,2,2-Trifluoroethanol to the Six Isomers of Dimethylbenzonitrile

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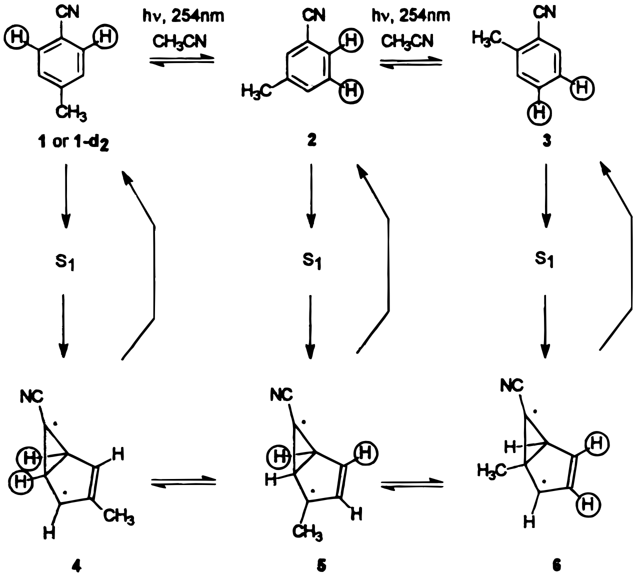
The six dimethylbenzonitriles can be divided into two independent triads in their photochemical reactivity. The first triad is comprised of the 2,3-dimethyl, 3,4-dimethyl, and 2,6-dimethyl isomers (**11-2,3**, **11-3,4**, and **11-2,6**, respectively); the second triad is comprised of the 2,4-dimethyl, 2,5-dimethyl, and 3,5-dimethyl isomers (**11-2,4**, **11-2,5**, and **11-3,5**, respectively). In acetonitrile, phototransposition converts the members of one triad to other members of the same triad, although only **11-3,4** was reactive enough to have significant conversion approaching a steady-state composition. Irradiation in 2,2,2-trifluoroethanol (TFE) resulted in the formation of addition products, 6-cyano-*X*,*Y*-dimethylbicyclo[3.1.0]hex-3-en-2-yl 2,2,2,-trifluoroethyl ethers, but in significant yield only from **11-3,4** of the first triad and **11-2,4** of the second triad. The **11-3,4** isomer gave seven major regio- and stereoisomers; the **11-2,4** isomer gave three different regio- and stereoisomers. These addition products were all explained by formation of bicyclo[3.1.0]hex-3-en-1-yl cations resulting from protonation by TFE at C6 followed by nucleophilic trapping by TFE. From these and previous results on aromatic nitriles, a consistent mechanistic picture is obtained where the critical carbon in determining the products of the phototransposition and photoaddition reactions is the cyano substituted one.

Introduction

Recently, we reported on the photochemical equilibration of *p*-, *m*-, and *o*-methylbenzonitriles, **1**, **2**, and **3**, in acetonitrile[1] and on the photoaddition of 2,2,2-trifluoroethanol (TFE) to the same isomers, as well as to benzonitrile.[2] Irradiation of either the para or meta isomer in acetonitrile led to a steady-state mixture of **1**:**2**:**3** = 7:26:67. This ratio is consistent with the relative reactivity of **1**:**2**:**3** = 32:4:1; i.e., the most reactive isomer (para) ends up as the minor component as expected for a photochemical equilibration. The quantum efficiency for these reaction is low ($\Phi = 0.025$ for para to meta and 0.003 for para to ortho) but the mass balance is good (90% at 50% conversion of the para isomer). Also, both 1,2- and 1,3-transpositions are occurring as primary photochemical events. For instance, the ratio of meta/ortho obtained from the para is 4.2:1 even at conversions under 3% and there is no delay in the formation of the ortho isomer as would be required if it was being formed in a secondary photochemical event from the meta isomer. In contrast to these results for the para and meta isomers, the ortho isomer was very unreactive and a steady-state composition could not be reached. Finally, using the deuterium labeling of **1-d$_2$**, we demonstrated that only the cyano-substituted carbon was undergoing migration for conversion of para to meta and ortho.

On the basis of these results, we have proposed the mechanism outlined in Scheme 1. The excited singlet state (S_1) of the aromatic nitrile forms a bicyclo[3.1.0]hexenyl biradical by σ bond formation between the two carbons ortho to the nitrile functional group. This increased bond order between the carbons ortho to the nitrile functional group parallels the observation of the enhanced photochemical reactivity of *m*-cyano-substituted aromatic ethers,[3] i.e., the "meta effect".[4] Three of these (**4**, **5**, and **6**) are possible,[5] and one will be formed from

Scheme 1. Mechanism for the Phototransposition of 1−3 in Acetonitrile



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* To whom correspondence should be addressed. Phone: 902-494-3324. Fax: 902-494-1310.

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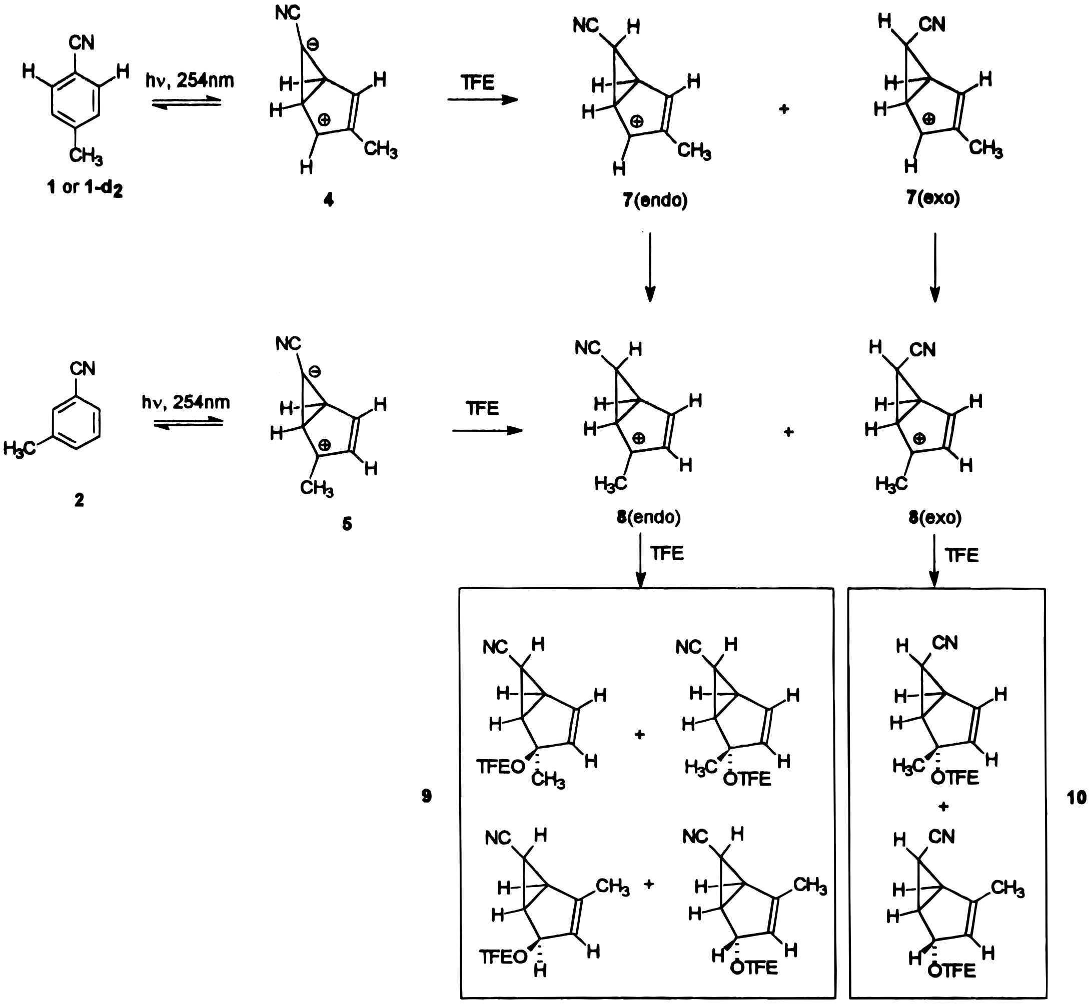
10.1021/jo000701e CCC: $19.00

Scheme 2. Mechanism for the Photoaddition of TFE to 1 and 2



each of three starting positional isomers (**1**, **2**, and **3**, respectively). Equilibration of these bicyclic intermediates by a 1,4-sigmatropic rearrangement provides a pathway for phototransposition. The intermediates and pathway(s) for these interconversions are probably much more complex than indicated by Scheme 1. For instance, for benzene itself, cyclopentadienyl carbene is known, by calculations, to be similar in stability to the corresponding biradical and is, therefore, probably a species, perhaps an intermediate, on the potential energy surface.[6,7] We are in the process of doing similar calculations for substituted cases. The circled hydrogens in Scheme 1 indicate the results for the deuterium-substituted para isomer, **1-d$_2$**, and the specific positions observed in the products for its phototransposition.

Irradiation of these isomers in TFE supported this mechanism.[2] The products that resulted from irradiation of the para isomer, **1**, could all be rationalized by protonation of the bicyclic biradical/zwitterion **4** at C6 by TFE to give the cations **7**(*endo*) and **7**(*exo*) followed by rapid 1,4-sigmatropic rearrangement to form the more stable cations **8**(*endo*) and **8**(*exo*), Scheme 2.[8] Although there is no way of knowing, we assume that this rearrangement proceeds with inversion of configuration (**7**(*endo*) to **8**(*endo*) and **7**(*exo*) to **8**(*exo*)) at the migrating carbon as predicted by orbital symmetry arguments and as observed and described in detail by Zimmerman and co-workers for similar bicyclic cations.[9] Six regio- and stereoisomers of the addition products **9** and **10** were characterized. For the meta isomer, **2**, the more stable cations **8** are formed directly, not via **7.** Again, the ortho isomer proved to be very unreactive, and no photoaddition products were observed.

Although the deuterium labeling of **1-d$_2$** was essential in formulating the mechanistic proposal in Schemes 1 and 2, labeling is not synthetically very convenient for substrates other than the symmetrical para isomer. We therefore chose to study the dimethylbenzonitriles so that the additional methyl group could be used to track the path of a third carbon atom. There are six of these, **11-2,3**, **11-2,4**, **11-2,5**, **11-2,6**, **11-3,4**, and **11-3,5**, where the numbers indicate the position of methyl substitution. We now report on their phototransposition reactivity in acetonitrile and the photoaddition of TFE.

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(5) Actually, five are possible but four of them comprise two sets of enantiomeric pairs. Therefore, only three are necessary to explain the observed achiral products.

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(8) Again, the intermediates **8** are chiral and will be formed as enantiomeric pairs as will the products.

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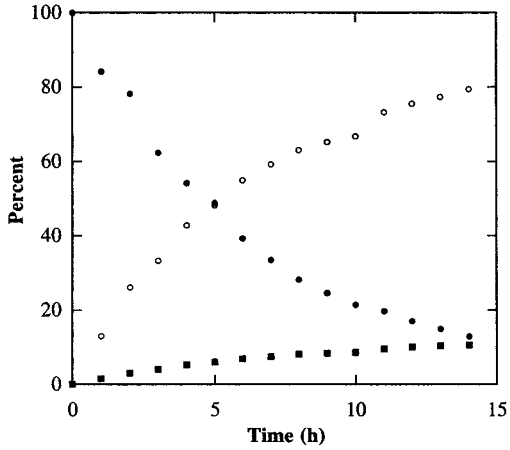
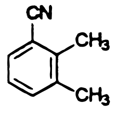
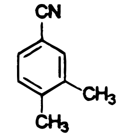
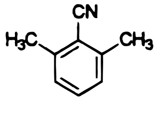
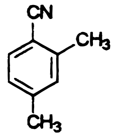


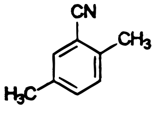
Figure 1. Plot of the phototransposition in acetonitrile for **11-3,4** (●) to **11-2,3** (○) and **11-2,6** (■).

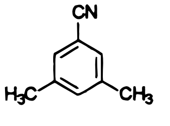

11-2,3


11-3,4


11-2,6


11-2,4


11-2,5

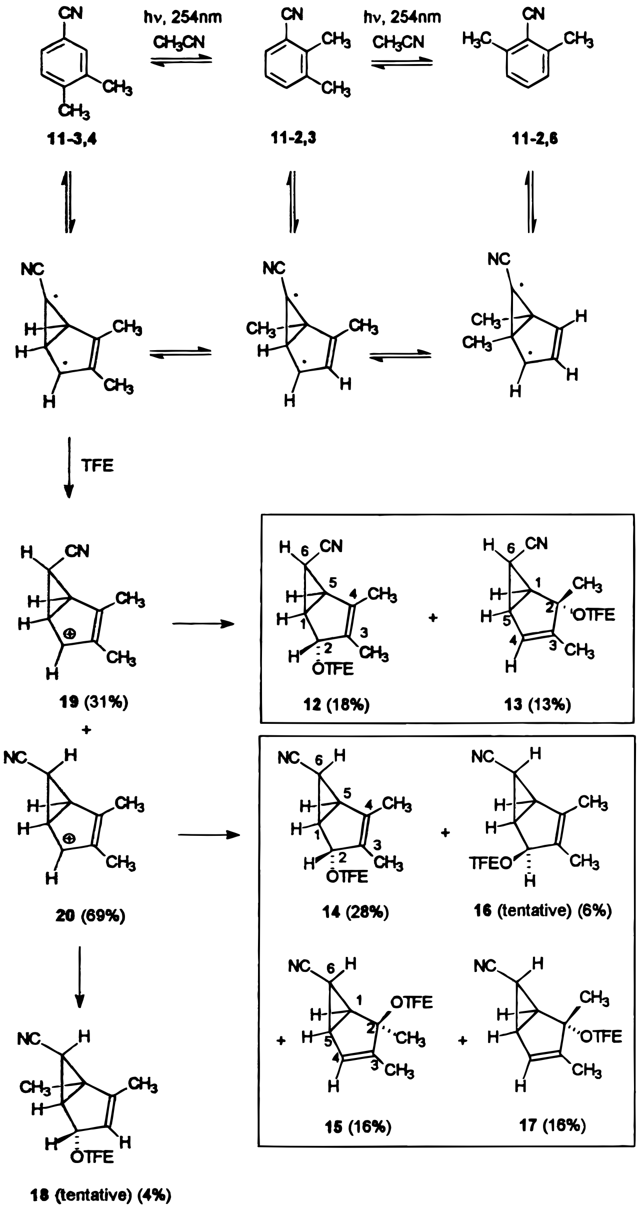

11-3,5

Results and Discussion

All the isomers of **11** were synthesized from the corresponding amine by diazotization followed by reaction with cuprous cyanide.[10] They are all known compounds, and their melting or boiling points and ^1H NMR spectra agreed with literature values (where available). The six could be easily analyzed by GC/FID as baseline resolution was obtained.

Photochemistry of Isomers 11 in Acetonitrile. The dimethylbenzonitrile isomers (50 mg) in acetonitrile (100 mL) were irradiated at 254 nm and 25 °C in a Rayonet reactor with nitrogen purging. The isomer **11-3,4** was by far the most reactive, and a plot for its phototransposition is shown in Figure 1. The mass balance, 99% at 50% conversion, was essentially quantitative. Of the five possible isomers that could be obtained by phototransposition only two are observed, **11-2,3** and **11-2,6**, Scheme 3. Moreover, at very low conversions, the ratio of **11-2,3**:**11-2,6** = 8.8:1 indicated that both products formed in the primary photochemical event. The same observation was made previously in the phototransposition of *p*- and *m*-methylbenzonitrile, **1** and **2**, respectively.[1] These results agree nicely with our previous mechanism, Scheme 1. Excitation to S_1 leads to the bicyclic diradical, Scheme 3 (top), with cyano substitution at C6. Migration of this carbon around the five-membered ring can give three[3] different positional isomers. Therefore, only three of the six isomers of **11** are possible. This observation parallels that observed for the phototransposition of the dimethylpyridines where the six possible isomers are divided into two independent triads.[11] From the plot in Figure 1, **11-3,4**, which has almost disappeared by 14 h, is predicted to be the most reactive of the members of this triad. In agreement with this prediction, photolysis of either of the other two resulted in only very low conversions to other members of the triad: **11-2,3** gave **11-3,4** (2.8%) and **11-2,6** (2.3%) and **11-2,6** gave no observable phototransposition after 14 h. As described above, the same effect was observed for the methylbenzonitriles in that substitution of a methyl group ortho to the cyano group leads to the lowest reactivity. This is perhaps a consequence of steric crowding in the bicyclic intermediates by the methyl group at the bridgehead position. This effect would be maximized for **11-2,6**. Therefore, its

Scheme 3. Mechanism for the Phototransposition of 11-3,4, 11-2,3, and 11-2,6 in Acetonitrile and the Photoaddition of TFE to 11−34



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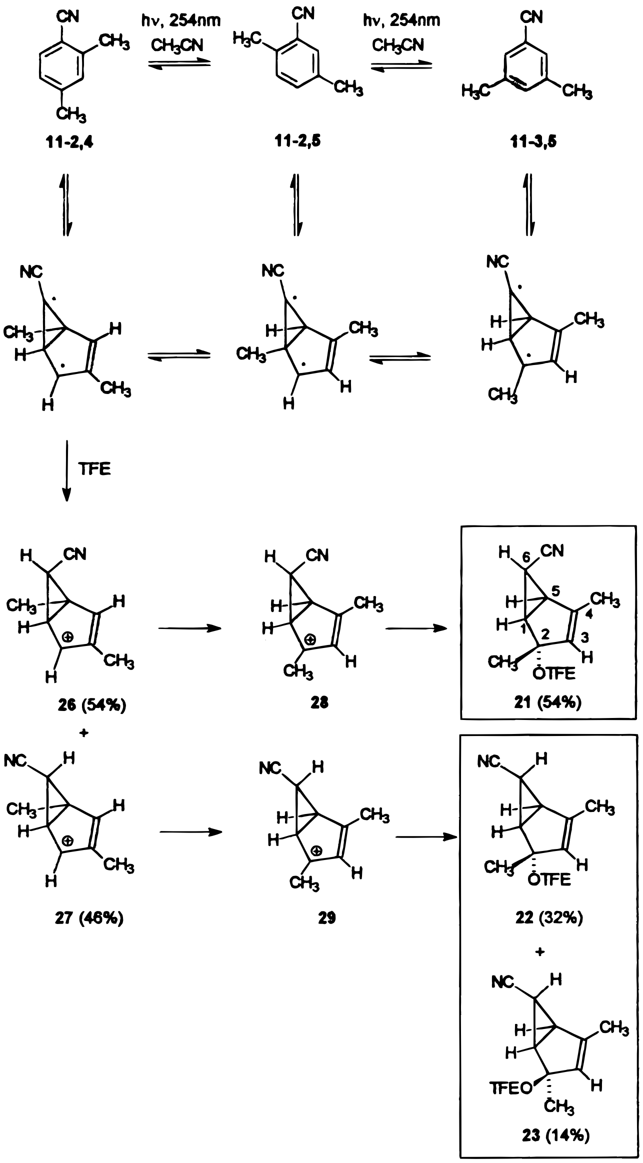
Scheme 4. Mechanism for the Phototransposition of 11-2,4, 11-2,5, and 11-3,5 in Acetonitrile and the Photoaddition of TFE to 11-24



excited state must decay by other pathways (fluorescence, internal conversion, etc.) rather than by meta bonding.

As with the dimethylpyridines,[8] an examination of the structures of the six isomers, **11**, in the context of the pathway in Scheme 3, reveals that they should be divided into two triads, the first group as outlined in Scheme 3 and the second group comprised of **11-2,4**, **11-2,5**, and **11-3,5**, Scheme 4. This turned out to be true, although **11-2,4** and **11-2,5**, both *o*-methyl-substituted, again proved to be very unreactive. However, even after 14 h of irradiation, no mixing with the first triad was observed: **11-2,4** gave only **11-2,5** (1.3%) and **11-3,5** (2.8%); **11-2,5** gave only **11-3,5**; and **11-3,5** gave **11-2,5** (1.2%) and **11-2,4** (2.7%).

Photochemistry of the Isomers 11 in TFE. On the basis of the results for the photochemistry in acetonitrile, we first examined **11-3,4** in TFE with the idea that it would be the most reactive. This proved to be true. Irradiation of 200 mg in 100 mL of TFE for 96 h[12] gave 40% conversion to nine 6-cyano-*X*,*Y*-dimethylbicyclo[3.1.0]hex-3-en-2-ol TFE addition products ($M^{\cdot}$ = 231, GC/MS), Scheme 3. On the basis of reacted starting material, the total yield was approximately 80%, and seven of the products accounted for 98% of this material. The yields given in Scheme 3 are normalized to 100%. The phototransposition reaction did not occur under these conditions. Moreover, the other two isomers of this triad gave no appreciable yield of these products after a similar time of irradiation. The ^{1}H NMR of the crude reaction mixture from photolysis of **11-3,4**, Figure S1 (Supporting Information), showed the beginning of the appearance of broad featureless bands from δ 3.5−4.6 and 0.8−2.8 (oligomers?) that always accompany these bicyclic TFE adducts. However, the characteristic signals for the low field hydrogens, H2, H3, and H4, and the high field one, H6, for these isomers are apparent (Figure S1, insets, Supporting Information). These NMR samples of the photoaddition products in $CDCl_3$ were not stable even at −4 °C and deteriorated over a few days along with the growth of the broad bands. Consequently, the TFE addition products could not be characterized rigorously.

Flash chromatography on silica gel easily separated the seven products into low yields of two distinct groups, **12** and **13**, with the cyano group endo at C6 and **14**, **15**, **16**, **17**, and **18** with the cyano group exo at C6. The same exo/endo silica gel separation distinction was observed previously for the TFE addition products from the methylbenzonitriles, **1** and **2**.[2] Separation of the groups into individual compounds was not achieved even with rotating disk chromatography. However, fractions of differing composition could be obtained. Fortunately, the diagnostic hydrogens on C2, C3, C4, and C6 are well separated so that a combination of GC and ^{1}H NMR integration along with chemical shift and coupling analysis (COSY) allowed assignment of structures with considerable confidence, even in mixtures. First, when both C3 and C4 are hydrogen substituted, these alkene hydrogens appear as a characteristic doublet of doublets; no signals of this type are observed in any of these addition compounds. Second, H2, H3 and H4 each have characteristic chemical shift ranges of δ 4.5−5.2, 5.2−5.8, and 5.8−6.3, respectively.[2] Third, H6 appears as a triplet because of coupling to two hydrogens at H1 and H5, the magnitude of the coupling constant determining endo ($J \sim 3$ Hz) or exo ($J \sim 7$ Hz) stereochemistry. Assigned signals and spectra are given in the Supporting Information, and only those features necessary for proof of structure will be discussed here.

For **12** and **13**, the exo stereochemistry for H6 was easily assigned on the basis of appearance of a doublet of doublets with coupling constants ranging from 7 to 8 Hz as expected for cis couplings[2] in these cyclopropane derivatives, Figure S2 (Supporting Information). For **12**, the left side of this pattern is visible, the right side hidden by a methyl signal; for **13**, the opposite occurs. The regiochemistry of the TFE substitution was determined by the contrast in chemical shift between H2 (δ 4.39) in **12** (oxygen substituted sp^{3} C2) and H4 (δ 5.91) in **13** (alkene sp^{2} C4). The stereochemistry of H2 as endo in **12** results from the appearance of H2 as a broad singlet indicating small coupling to H1.[2] The stereochemistry of the methyl group as endo in **13** is less certain but was based on the similarity in chemical shift (δ 1.58) with

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[12] By this time, the irradiated solution had turned a deep yellow color and conversion to the photoproducts had essentially stopped.

that observed for a similar stereochemistry (δ 1.66) for the addition products to **1** and **2**.[2]

For the isomers **14**−**17**, the endo stereochemistry for H6 was assigned by the appearance of a doublet of doublets or a pseudo triplet with a much smaller coupling constant ranging from 2.6 to 3.7 Hz indicative of a trans coupling[2] in the cyclopropane ring, Figure S3 (Supporting Information). For the minor component **16**, the coupling to H6 could not be observed because H6 is hidden (COSY) by a broad signal for a methyl group; its stereochemistry at C6 is assigned only on the basis of it being a member of this chromatographic group and is therefore only tentative. The regio- and stereochemistry of **14** and **16** was obtained from H2, a broad singlet (δ 4.36) in **14** and a doublet (δ 4.76, J = 5.3 Hz) in **16**. Finally, the regiochemistry of **15** and **17** was assigned by the chemical shift of H4 (δ 5.52 and 5.88) and the stereochemistry at C2 was assigned as *exo*-methyl for **15** (H6 at δ 1.36) and *endo*-methyl for **17** (H6 at δ 0.94) by analogy with the addition products of TFE to **1** and **2**.[2] This assignment is not critical because **15** and **17** are formed in equal amounts.

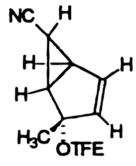
As can be seen from Scheme 3, as compared with Scheme 2, these products can again be explained by protonation of the biradical/zwitterion at C6 to give the allylic cations, **19** (resulting from exo protonation, 31%) and **20** (endo protonation, 69%). Trapping of **19** at either end of the allylic cation by exo attack of TFE gives **12** and **13**. The other minor products which were not identified could possibly be the endo TFE adducts. Trapping of **20** by TFE gives all four of the possible regio- and stereoisomers with almost equal attack at the hydrogen and carbon substituted end of the allylic cation (34% to 32%) but with exo attack of TFE (44% to 22%) preferred, presumably for steric reasons.

The fifth member of this chromagraphic group was formed in only 4% yield and is tentatively assigned as **18** mainly on the basis of the appearance of two low-field, broad singlets for H2 (δ 4.43) and H4 (δ 5.42), Figure S3 (Supporting Information) which are weakly coupled to each other.

The isomers of the second triad, **11-2,4**, **11-2,5**, and **11-3,5**, were very unreactive in TFE. For instance, after 60 h of irradiation, **11-2,4** was converted to approximately 2% (GC/FID) of three addition products ($M^{\cdot +} = 231$, GC/MS), **21**, **22**, and **23**, in a ratio of 4:2.4:1. An important observation is that these three products, on the basis of GC retention times, are different from those obtained from the first triad. Again, these compounds were not separated and also deteriorate with time; only NMR spectra (^{1}H normal, Figure S4 (Supporting Information) and COSY) of the crude mixture were used to assign structures after silica gel chromatography to remove the starting material. Although obtained in very low yield, this mixture was easier to analyze because it only contained three major components. Therefore, assignments are made with considerable confidence.

As observed previously, for gross structure determination, the most diagnostic hydrogens are on C2, C3 and C4. Each of the photoadducts gave only one signal in this downfield region, a broad singlet at δ 5.21 (**21**), 4.96 (**22**), and 5.06 (**23**), characteristic of H3 with methyl groups at C2 and C4.

The methyl groups at C4 were all doublets ($J \sim 1.5$ Hz) coupled to H3 (COSY); the methyl groups at C2 were all sharp singlets (assigned by integration). The major product, **21**, had the cyano group endo at C6 on the basis of the appearance of H6 as a "triplet" (J = 7.4 Hz) indicating cis coupling to the two cyclopropyl hydrogens, H1 and H5. The stereochemistry at C2 in **21** is uncertain but is likely to be as shown because exo attack of TFE should be preferred for steric reasons. The other two products, **22** and **23**, have the cyano group exo on the basis of the appearance of H6 again as a doublet of doublets (J = 2.8, 3.7 Hz) for **22** or as a "triplet" (J = 3.3 Hz) for **23**, characteristic of the trans coupling to H1 and H5 (only the right-hand side of this "triplet" is visible for H6 in **23**, the line on the left is hidden under the signal from a methyl group). The stereochemistry at C2 is more certain for these compounds because of the excellent agreement in chemical shift between H6 at δ 1.00 (**22**) and 1.52 (**23**) with the monomethyl derivatives, **24** (H6 at δ 0.99) and **25** (H6 at δ 1.48).



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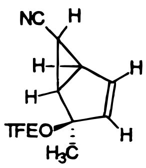

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The mechanism for both phototransposition in acetonitrile and photoaddition of TFE for the second triad are given in Scheme 4 for **11-2,4**. Once again, excitation to S_1 leads to the biradical/zwitterion, which allows phototransposition to **11-2,5** and **11-3,5** but not to members of the other triad, Scheme 3. Protonation of this intermediate by TFE gives the two cations **26** (by exo protonation) and **27** (by endo protonation). As has been observed previously for analogous cases,[2,13,14] these cations undergo rapid sigmatropic rearrangement to their more stable isomers, **28** and **29**, which are methyl substituted at both ends of the allylic cation. The symmetry of **28** and **29** reduces the number of possible products by a factor of 2 so that, after nucleophilic trapping by TFE, only three major ones are observed as compared to six in the previous triad.

Conclusion. On the basis of our previous results for the monomethylbenzonitriles, we had concluded that the cyano-substituted carbon was the critical one for phototransposition in acetonitrile. This argument was made mainly on the basis of the results for the selectively deuterated isomer, **1-d$_2$**, Scheme 1. The results reported here for the dimethylbenzonitriles, chosen so as to identify three carbons for each isomer, provide additional confirmation of this idea. As observed, if the cyano substituted carbon is the one that migrates during phototransposition, then the six isomers are divided into two independent triads. The results for the photoaddition of TFE also support this conclusion because a different set of products is observed for a member of each triad. Moreover, in all cases examined for nitrile substituted benzenes, the bicyclo[3.1.0]hex-2-en-1-yl products result from protonation by TFE at the cyano substituted carbon which becomes C6. Because both endo and exo protonation at C6 is observed, these products are not derived from substituted benzvalene intermediates, which give predominantly endo protonation.[15] The cation formed is trapped (from **11-3,4**, the member of one triad), or undergoes 1,4-sigmatropic rearrangement with retention of configuration to the more stable allylic form that is methyl substituted at both ends (from **11-2,3**, the member of the other triad). We are in the process of doing MO calculations on benzonitrile (and other substituted cases) to understand why the geometry change that occurs in the excited singlet state of aromatic nitriles is so selective for meta bonding between the two carbons adjacent to the nitrile functional group.

Experimental Section

The dimethylbenzonitriles, **11**, were synthesized from the corresponding amines (Aldrich) by diazotization followed by reaction with cuprous cyanide according to a standard procedure.[7] All gave satisfactory ^{1}H NMR spectra and melting points or boiling points in agreement with literature values: **11-2,3** (bp 100 °C at 5 mm),[16] **11-2,4** (bp 220−222 °C),[17] **11-2,5** (bp 218−220 °C),[14] **11-2,6** (mp 87−88 °C),[14] **11-3,4** (mp 64−66 °C),[13] **11-3,5** (40−41 °C).[18]

The photolyses were performed as described previously[1,2] and monitored by GC/FID. For the TFE reactions, the solvent was removed by rotary evaporation and the material chromatographed on silica gel using ethyl acetate/hexane as eluent. The TFE addition products all had essentially the same mass spectrum: (GC/MS) *m*/*z* 231 (27, M), 216 (45), 148 (15), 132 (70), 130 (27), 120 (17), 117 (18), 116 (45), 105 (41), 104 (28), 103 (27), 93 (44), 92 (21), 91 (87), 90 (16), 89 (30), 80 (20), 79 (42), 78 (29), 77 (100), 65 (37), 64 (15), 63 (21), 53 (31), 52 (21), 51 (43). The TFE addition products could not be characterized rigorously because they are unstable and decompose over several days even as NMR samples in $CDCl_3$ stored at − 4 °C. ^{1}H NMR spectra (Figures S1, S2, S3, and S4) and assigned chemical shifts for compounds **12**−**18** and **21**−**23** are reported in the Supporting Information.

Acknowledgment. We thank NSERC of Canada for financial support and Sepracor Canada, Windsor, Nova Scotia, for donation of chemicals. N.H. also thanks NSERC of Canada for an undergraduate student research award.

Supporting Information Available: ^{1}H NMR spectral data for compounds **12**−**18** and **21**−**23** along with selected spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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