Stereoelectronic Effect of a Vicinal Fluorine Substituent on the Diastereoselectivity of Radical Reactions

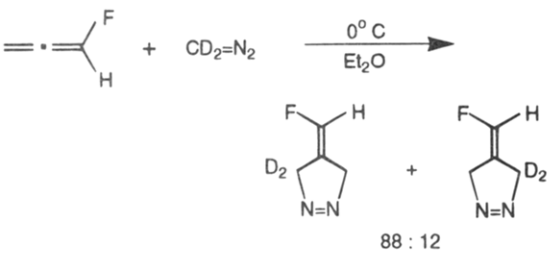
William R. Dolbier, Jr.,* and Michael D. Bartberger

Department of Chemistry, University of Florida, Gainesville, Florida 32611

Received June 16, 1995

The stereoselectivity of free radical reactions is an area of considerable current interest.[1,2] Studies by Giese on five- and six-membered ring radicals as well as on vinylic radical systems have clearly demonstrated the dominance of steric influences of vicinal substituents in determining the facial selectivity in *anti*-selective alkene addition and hydrogen-transfer reactions.[1,3,4]

A single fluorine substituent is virtually unique in that it does not give rise to a steric influence on reaction rates except in the most demanding of transition states. For example, we have demonstrated clearly that the *nonsteric* influences of the vicinal fluorine substituent in fluoroallene (MFA) outweigh any possible steric effect in giving rise to the *syn*-selectivity which is generally observed in cycloadditions to MFA's C_2-C_3 bond.[5]



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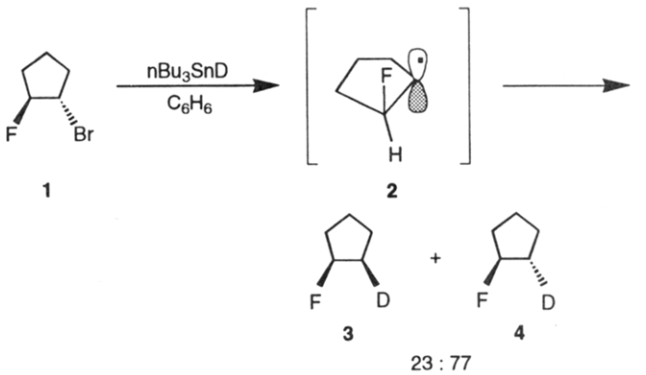
Believing that factors which influence the *p*-diastereoselectivity exhibited by radicals in their various reactions should be closely related to those which determine π-diastereoselectivity in reactions of π-bonds, we have initiated a program to elucidate the influence of vicinal fluorine substituents on the diastereoselectivity of *radical* reactions. In this report we present preliminary results which contrast the *anti*-selectivity exhibited by the β-fluorocyclopentyl radical **2** with the *syn*-selectivity of the β-fluoro-α-styryl radical **6** in their hydrogen-abstraction reactions with *n*-Bu_3SnH.

In probing the behavior of the 2-fluorocyclopentyl radical, *trans*-2-bromofluorocyclopentane, **1**,[6] was treated with *n*-Bu_3SnD in benzene at 50 °C, and the 2-deuteriofluorocyclopentane product mixture was examined by ^{2}H-NMR spectroscopy. The ^{1}H-decoupled spectrum showed two doublets (due to ^{19}F-coupling) at δ 1.93 and 1.73 with $^3J_{DF}$ couplings of 3.7 and 5.5 Hz and with a ratio of 23:77, respectively. The minor doublet at δ 1.93 was demonstrated, by virtue of an independent synthesis,[8,9] to be due to the *cis*-2-deuterio isomer **3**, which derived from deuterium abstraction *syn* to the vicinal fluorine substituent.



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Although the stereoselectivity of *reduction* of other β-substituted cyclopentyl radicals is not known, Giese has found that β-methyl- and β-ethoxy substituents direct attack of acrylonitrile and other alkenes with significant *anti*-selectivity.[1,3] A steric rationale was, of course, preferred to explain these results. Can a steric rationale also be used to explain our 2-fluorocyclopentyl radical results? In view of the MFA results and those of the β-fluoro-α-styryl radical which will follow, this seems unlikely.

The interaction of the fluorine substituent with the radical site in the 2-fluorocyclopentyl radical **2** differs significantly from that in MFA because the C–F bond in **2**, unlike that in MFA, is not eclipsed with the p orbital. Indeed, an optimization of the geometry of **2** (UHF/6-31G*) indicates that its C–F bond is in an almost perfectly staggered position relative to the SOMO orbital and the $H-C_1-C_2$ plane (Figure 1).

A radical system which better emulates the substituent interactions in MFA is the β-fluoro-α-styryl radical **6**, which can be formed by photoinitiated decomposition of

(1) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969–980.

(2) (a) Bodepudi, V. R.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001–2006. (b) Thoma, G.; Curran, D. P.; Geib, S. V.; Giese, B.; Damm, W.; Wetterich, F. *J. Am. Chem. Soc.* **1993**, *115*, 8585–8591. (c) Porter, N. A.; Rosenstein, I. J.; Breyer, R. A.; Bruhnke, J. D.; Wu, W.-X.; McPhail, A. T. *J. Am. Chem. Soc.* **1992**, *114*, 7664–7676. (d) Curran, D. P.; Sun. S. *Tetrahedron Lett.* **1993**, *34*, 6181–6184. (e) Adcock, W.; Clark, C. I.; Trout, N. A. *Tetrahedron Lett.* **1994**, *35*, 297–300.

(3) (a) Giese, B.; Heuck,K.; Lenhardt, H.; Lüning, U. *Chem. Ber.* **1984**, *117*, 2132–2139. Henning, R.; Urbach, H. *Tetrahedron Lett.* **1983**, *24*, 5343–5346.

(4) (a) Giese, B.; Lachhein, S. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 768–775. (b) Giese, B.; Gonzalez-Gomez, J. A.; Lachhein, S.; Metzger, J. O. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 479–478. (c) Geise, B.; Farshchi, H.; Hartmanns, J.; Metzger, J. O. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 600–601.

(5) (a) Dolbier, W. R., Jr.; Wicks, G. E.; Burkholder, C. R.; Palenik, G. J.; Gawron, M. *J. Am. Chem. Soc.* **1985**, *107*, 7183. (b) Dolbier, W. R., Jr. *Acc. Chem. Res.* **1991**, *24*, 63–68.

(6) Prepared in 78% yield by the reaction of cyclopentene with *N*-bromosuccinimide/Et_3N·3HF in CH_2Cl_2 at 0 °C.[7]

(7) Alvernhe, G.; Laurent, A.; Haufe, G. *Synthesis* **1987**, 562–564.

(8) Minor product *cis*-2-deuteriofluorocyclopentane, **3**, was prepared independently by two methods, proceeding from *trans*-2-deuteriocyclopentanol[10] in each case. In the first instance, the alcohol was treated with (diethylamido)sulfur trifluoride (DAST)[11] in $CFCl_3$ at −78 °C to give a 72% yield of **3**. To insure that an inversion mechanism had indeed been followed, the alcohol was converted to the tosylate (78%), which was subsequently treated with "anhydrous" TBAF[12] in $CHCl_3$ to yield exclusively the same product as from the DAST reaction.

(9) Curiously, the cis $^3J_{DF}$ coupling of **3** was found to be smaller than the trans $^3J_{DF}$ coupling of **4**. Such coupling constants are, however, consistent with fluorocyclopentane existing primarily in an envelope form with fluorine occupying an axial position.[13,14] We have confirmed this by our own *ab initio* calculations (RHF/6-31G*) combined with a fitting of the weighted time average of structures into the Karplus curve for coupling constants.[15]

(10) Streitweiser, A., Jr.; Jogow, R. H.; Fahey, R. C.; Suzuki, S. *J. Am. Chem. Soc.* **1958**, *80*, 2326–2332.

(11) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574–578.

(12) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216–3219.

(13) Ekejiuba, I. O. C.; Hallam, H. E. *Spectrochim. Acta* **1970**, *26A*, 67–75.

(14) Cremer, D.; Binkley, J. S.; Pople, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 6836–6839.

(15) Taken from a table of variation of $^3J_{FH}$ vs dihedral angle in substituted ethanes and adjusted with γ^2H/γ^1H.[16]

(16) Emsley, J. W.; Phillips, L. Wray, V. *Fluorine Coupling Constants*; Pergamon Press: London, 1977; p 109.

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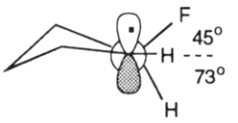

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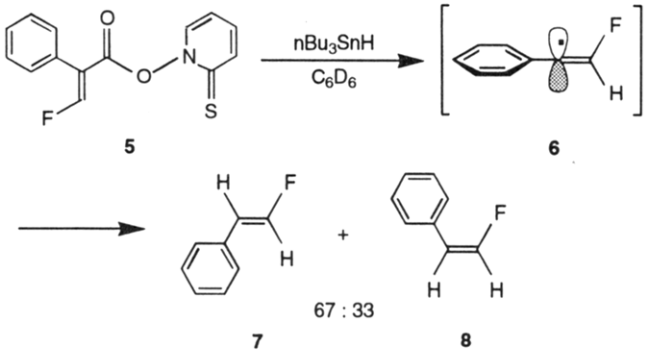
Figure 1.

Barton ester **5**.[17] In this linear, π-radical system,[20] both the C−F and the C−H bonds are fully eclipsed with the



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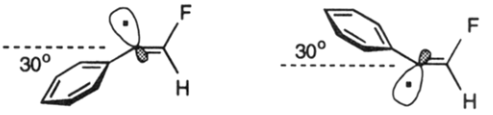
phenyl-delocalized singly-occupied p orbital. Thus one would expect that the relative impact, both steric and electronic, of these two substituents should be maximized in this system. When **6** was generated in the presence of 1.1 equiv of n-Bu_3SnH, reduction products **7** and **8** were formed in a ratio of 67:33.[21] The *syn*-selectivity exhibited by **6** in this process precludes steric effects from having been the decisive factor in determining the stereoselectivity of H-atom transfer to either cyclopentyl radical **2** or α-styryl radical **6**. That being the case, what then is causing their disparate stereoselectivities?

According to Gandolfi,[23] the cause of the observed *syn*-selectivity of MFA in its cycloadditions has to do with how the stabilizing vicinal interactions of the eclipsed fluoro- and hydrogen-substituents accommodate the bending of the allene which takes place as one approaches the respective *syn* and *anti* transition states. When similar calculations (UHF/AM1) were applied to the β-fluoro-α-styryl radical system **6**, we found that, as in the case of MFA, the process of *syn*-pyramidalization (**9**) (a bending of 30°) was easier than the process of *anti*-pyramidalization (**10**) by about 1 kcal/mol. This difference can be attributed to the apparent fact that the C−F bond tolerates *syn*-pyramidalization better than does the C−H bond,[23] since it was found that the change in energy upon *syn*-pyramidalization of **6** was lower than that of an equal degree of pyramidalization of its pure hydrocarbon analog, the α-styryl radical, again by ca. 1 kcal/mol.



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Since cyclopentyl radical **2** does not have any β-bonds eclipsed with the SOMO orbital, such interactions as described for **6** should have considerably less importance in the case of **2**. Consistent with our approach to the analysis of **6**, we examined the energetic impact of *syn* versus *anti*-pyramidalization of radical **2**. Such calculations (UHF/6-31G*)[24] indicated that a 15° bending toward the *anti* transition state was favored by ca. 0.8 kcal/mol over an equal degree of bending toward the *syn* transition state. From an examination of the optimized pyramidalized radical structures, which are meant to emulate the competing *syn* and *anti* transition states, we believe that torsional strain differences are the likely source of the observed disparity in the energy required to effect *anti*- versus *syn*-pyramidalization.

Although one can not yet be certain as to the exact combination of factors which cause the 2-fluorocyclopentyl radical's observed *anti*-selectivity, what is clear is that steric effects are *not* involved. It is also clear that systems which are rigid and have their β-vicinal C−X and/or C−H bonds coplanar with the reactive AO or MO are uniquely influenced by the β-substituent, and that any deviation from such coplanarity leads to a completely different mode of substituent interaction. Moreover, our results indicate that, in interpreting results on the stereochemical directing influence of other β-substituents, particularly nonalkyl substituents, one should be cognizant that factors other than steric may play a significant role.

Acknowledgment. Support of this research in part by the National Science Foundation and by Academic Computing and Network Services at Florida State University are acknowledged with thanks.

JO9510907

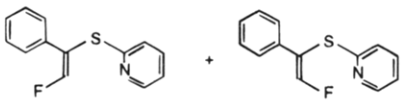
(17) Barton ester **5** was synthesized in the usual manner[18] from its carboxylic acid precursor, which was prepared by a procedure similar to that of McDonald et al.[19] The carboxylic acid was fully characterized, including CH analysis, while **6**, prepared almost quantitatively *in situ* because of its great thermal and photochemical lability, was characterized spectroscopically (^{19}F, δ −105.0, C_6D_6)

(18) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901−3924.

(19) McDonald, I. A.; Lacoste, J. M.; Bay, P.; Palfreyman, M. G.; Zreika, M. *J. Med. Chem.* **1985**, *28*, 186−193.

(20) EPR studies indicate that the α-styryl radical is linear: Bennett, J. E.; Howard, J. A. *Chem. Phys. Lett.* **1971**, *9*, 460−462; and our own UHF/AM1 calculations confirm that placing a β-fluoro substituent on the α-styryl radical does not cause it to deviate from this linear structure.

(21) Products **7** and **8** were formed (by irradiation of **5** with a 150 W white flood lamp) in 30% yield (δ −130.3, $^3J_{HF}$ = 19.3 Hz , and δ −122.8, $^3J_{HF}$ = 45.0 Hz, respectively, in the ^{19}F NMR, and compared to those of an independent synthesis[22]), along with 24% yield of a mixture of the (*E*)- and (*Z*)-2-pyridyl sulfides **11**,



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(at δ −102.2 and −108.0) in a ratio of 58:42 (relative stereochemistry yet unknown). Both sets of products were demonstrated to be formed under kinetic control, with the ratio of products remaining unchanged during the course of the reaction.

(22) Cox, D.; Gurusamy, N.; Burton, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 2811−2812.

(23) Rastelli, A.; Bagatti, M.; Gandolfi, R. *J. Am. Chem. Soc.* **1995**, *117*, 4965−4975; we thank Professor Gandolfi for sharing his results with us prior to publication.

(24) The UHF/6-31G* optimization of the 2-fluorocyclopentyl radical at various degrees of pyramidalization was performed by locking the angles of the three substituents bound to the α-carbon with respect to a point in space above and colinear with the radical p orbital and allowing all other geometric parameters to be optimized.