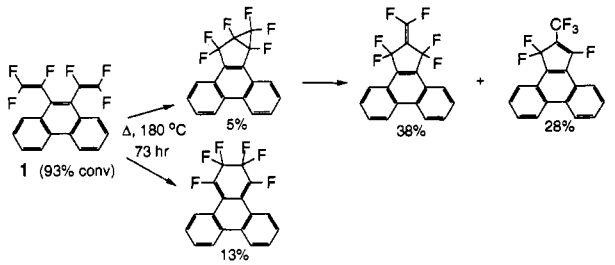
Effect of Terminal Fluorine Substitution on the Cope Rearrangement: Boat versus Chair Transition State. Evidence for a Very Significant Fluorine Steric Effect

William R. Dolbier, Jr.,* and Keith W. Palmer

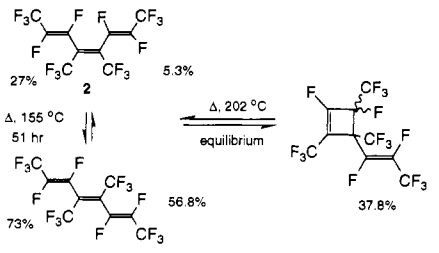
Department of Chemistry
University of Florida
Gainesville, Florida 32611

Received June 1, 1993

In view of the observed remarkable kinetic effects of fluorine substituents on the 4-π-electron, conrotatory, electrocyclic interconversion of cyclobutene and butadiene,[1,2] results which hastened the invention of the concept of "torquoselectivity" [3,4] for such reactions, it seemed appropriate to determine if similar torquoselectivity effects could be observed and quantified for the analogous 6-π-electron, disrotatory conversion of 1,3,5-hexatrienes to 1,3-cyclohexadienes. An early attempt to probe such effects through a thermal study of 9,10-bis(trifluorovinyl)phenanthrene (**1**) gave evidence that such an electrocyclic process was for some reason inhibited in this system to such an extent that the molecule rearranged via a relatively high-energy alternative reaction pathway.[5] Such behavior, of course, precluded a definitive kinetic and stereochemical study of torquoselectivity effects using such systems.

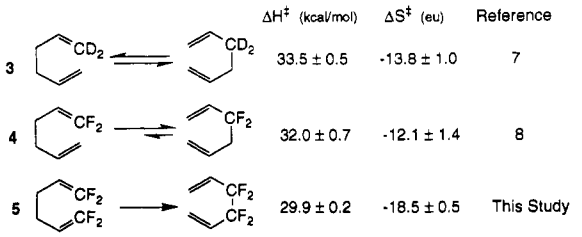


We have since observed a similar inhibition of cyclization of a simple, acyclic, fluorinated 1,3,5-hexatriene system (**2**) which was found to be resistant to 6-π-electron electrocyclic cyclization at temperatures up to 200 °C. (An analogous hydrocarbon system cyclizes readily at 160 °C.[6])



In this report, results are presented which demonstrate that terminal fluorine substitution, although it enhances the thermodynamic driving force for such cyclizations, substantially inhibits the attainment of the reaction's required boatlike transition state through the intervention of a rarely encountered but in this case potent fluorine steric effect.

It is widely recognized that there is a significant thermodynamic driving force for the conversion of an sp^2 CF_2 group to an sp^3 CF_2 group, which generally translates into a kinetic advantage as well. For example, as seen below in the Cope rearrangements of 1,5-hexadienes **3**, **4**, and **5**, geminal fluorine substitution at one or both termini of the diene led to a progressive lowering of enthalpy of activation, consistent with expectations.



Since, in the cases of **4** and **5**, terminal fluorine substitution was not observed to inhibit Cope rearrangements which were capable of proceeding via chair transition states, it seemed probable that the problem with fluorine substitution in the 1,3,5-hexatriene cyclizations derived from their required *boatlike* transition states. Moreover, we felt that this hypothesis could be tested through examination of the effect of terminal fluorine substitution upon the rate of a Cope rearrangement, which is constrained to proceed via a boatlike transition state (**6**) which is similar in nature to that proposed for the 6-π-electron electrocyclic process (**7**).

The bis-methylenecyclopentane system, **8**, which has been utilized effectively by Shea to compare the activation energies of Cope rearrangements which proceed via chair versus boat transition states, is ideal for such a probe.[9] Our task was thus simply to synthesize and rearrange the analogous fluorinated *meso*- and *d,l*-dienes, **9** and **10**. In analogy to the study of Shea, it would be predicted that the *d,l* isomer, **9**, would rearrange unambiguously via a chairlike transition state, while the *meso* isomer, **10**,*must* undergo its Cope rearrangement via a boatlike transition state.

Dienes **9** and **10** were synthesized (in 28% yield, in a 5.4:1 ratio of **9**:**10**) from a mixture of Shea's diketone precursors via a bis-difluoro Wittig reaction,[10] and the kinetic data from their thermolyses are included on the diagram below.

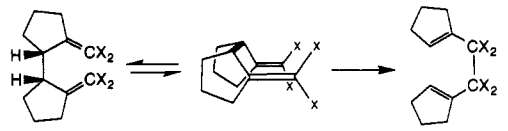
As one can see, **9**, which has no structural constraints which preclude a chairlike transition state, undergoes its Cope rearrangement with significant enhancement of rate relative to its hydrocarbon counterpart, a result consistent with expectation based upon the increased exothermicity of the reaction. In contrast, **10** is strongly inhibited in undergoing its Cope rearrangement, exhibiting activation parameters much more consistent with a dissociative transition state than a pericyclic one. (Note

(1) Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Heinze, P. L.; Bailey, A. R.; Shaw, G. S.; Hansen, S. W. *J. Am. Chem. Soc.* **1987**, *109*, 219.
(2) Dolbier, W. R., Jr.; Gray, T. A.; Celewicz, L.; Koroniak, H. *J. Am. Chem. Soc.* **1990**, *112*, 363.
(3) Houk, K. N. In *Strain and Its Implications in Organic Chemistry, Organic Stress and Reactivity*; NATO ASI Series, Series C 273: Kluwer Academic: Dordrecht, The Netherlands, 1988, p 25.
(4) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099.
(5) Dolbier, W. R., Jr.; Palmer, K.; Koroniak, H.; Zhang, H. Q.; Goedken, V. *J. Am. Chem. Soc.* **1991**, *113*, 1059.
(6) Marvell, E. N.; Caple, G.; Schatz, B.; Pippin, W. *Tetrahedron* **1973**, *29*, 3781.
(7) Doering, W. v. E.; Toscano, V. G.; Beasley, G. H. *Tetrahedron* **1971**, *27*, 5299.
(8) Dolbier, W. R., Jr.; Alty, A. C.; Phanstiel, O., IV. *J. Am. Chem. Soc.* **1987**, *109*, 3046.
(9) Shea, K. J.; Phillips, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 3156.
(10) Naae, D. G.; Burton, D. J. *Synth.Commun.* **1973**, *3*, 197.

0002-7863/93/1515-9349$04.00/0

9 (X = F) X = H, $\Delta H^{\ddagger}$ = 28.0 ± 1.1 kcal/mol
$\Delta S^{\ddagger}$ = -11.3 ± 2.6 eu

X = F, $\Delta H^{\ddagger}$ = 22.4 ± 0.2 kcal/mol
$\Delta S^{\ddagger}$ = -17.5 ± 0.4 eu



10 (X = F) X = H, $\Delta H^{\ddagger}$ = 41.6 ± 0.5 kcal/mol
$\Delta S^{\ddagger}$ = -0.7 ± 1.0 eu

X = F, $\Delta H^{\ddagger}$ = 49.5 ± 1.0 kcal/mol
$\Delta S^{\ddagger}$ = 8.1 ± 1.7 eu

the virtually unheard of significant *positive* $\Delta S^{\ddagger}$ which is observed for the reaction.) Also, the observed $\Delta H^{\ddagger}$ for rearrangement of **10** is but 4.6 kcal/mol below that which would be expected for a mechanism involving dissociation to two allyl radicals. This is a Cope rearrangement which does not want to be pericyclic!

The contrasting behaviors of **9** and **10** provide convincing evidence that the observed inhibition of the Cope rearrangement of **10**, as well as the earlier observed inhibitions of the 6-π-electron electrocyclic cyclizations of **1** and **2**, is due to *steric repulsions* of the *cis*-fluorine substituents at the C_1 and C_6 positions.[11]

Lack of steric impact is perhaps the most significant and widely recognized characteristic of fluorine as a substituent, and along with its often dramatic electronic effects on reactivity, this property constitutes a main driving force for the currently wide-spread interest in the incorporation of fluorine into pharmaceutical and agricultural chemicals. Indeed, it is justifiably understood that fluorine steric effects intervene only in the *most* demanding of transition states. Consistent with this point of view, our results appear to derive from the unusually stringent steric demands which are inherent to the boatlike transition states for the rearrangements of **1**, **2**, and **10**, and they constitute a particularly dramatic example of a sterically-derived, inhibitory kinetic effect resulting from fluorine substitution.

Thus, with steric effects appearing to play a dominant role in 6-π-electron electrocyclic processes with even the smallest of substituents, it will be difficult to design a system which will allow one to dissect out the effects due to torquoselectivity. Indeed, even deuterium substitution at the cis positions of 1,3,5-hexatriene gives rise to a secondary isotope effect which can be most easily be rationalized as a sterically-derived kinetic isotope effect.[12]

Acknowledgment. Support of this research in part by the National Science Foundation and by the Division of Sponsored Research of the University of Florida is gratefully acknowledged.

Supplementary Material Available: Complete experimental details (23 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS. Ordering information is given on any current masthead page.

(11) Although modeling indicates that overlap of the van der Waals radii of the *cis*-fluorines occurs, there will also, no doubt, be an *electrostatic* component to the inhibition of the boatlike transition state of **10**, the relative importance of which is yet unknown. Also, although it may be reasonable to assume that the observed effects derive largely from interactions of the *cis*-fluorine substituents, additional experiments on *singly*-substituted substrates will be required to demonstrate this fact unambiguously.

(12) Baldwin, J. E.; Reddy, V. P.; Hess, B. A., Jr.; Schaad, L. J. *J. Am. Chem. Soc.* **1988**, *110*,8554.