

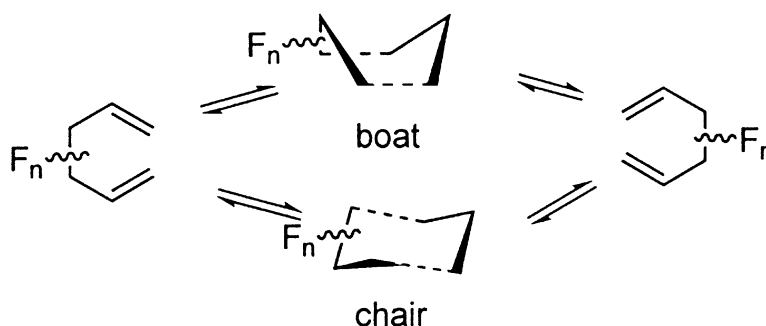
Article

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Dissociative and Associative Mechanisms of Cope Rearrangements of Fluorinated 1,5-Hexadienes and 2,2'-Bis-methylenecyclopentanes

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Abstract: The effects of fluorine substitution on the Cope rearrangements of 1,5-hexadiene and 2,2'-bis-methylenecyclopentane have been examined computationally using (U)B3LYP/6-31+G(d,p) and CASPT2/6-31G(d) methodology. The calculations indicate that fluorine substituents at the hexadiene termini generally stabilize the transition states relative to the ground states of the chair conformations and destabilize pathways that occur via boat conformations, in accord with the experimental observations of Dolbier. With *meso*-2,2'-bis(difluoromethylene)cyclopentane, this destabilization is sufficient to favor a relatively dissociative concerted transition state resembling weakly interacting allyl radicals over a normal aromatic concerted boat transition state. This preference is due partly to an increase in the activation enthalpy for the concerted rearrangement coupled with the more favorable entropy for dissociation. In octafluoro- and decafluoro-hexadienes, the situation is reversed, and reaction through a cyclohexane-1,4-diyl is favored. Even in the octafluoro system with no radical stabilizing substituents at C(2) and C(5), the preference of fluorine for sp^3 centers causes reaction via the cyclohexane-1,4-diyl. In establishing methodology for this study, the conformations of 1,2-difluoroethane and 1,1,2,2-tetrafluoroethane were also examined thoroughly by the B3LYP method using three basis sets.

Introduction

Fluorine substitution significantly influences the rates of many pericyclic reactions. A careful examination of these effects in the case of the 4π electron, conrotatory electrocyclic reaction of cyclobutene¹ inspired studies that led to the concept of torquoselectivity.² In the case of the 6π electron system, 9,10-bis(trifluorovinyl)phenanthrene, fluorine substitution inhibits the rate of electrocyclic ring closure to such an extent that this product (13% yield) is a relatively minor component relative to isomeric materials resulting from an alternate normally high-energy pathway (Figure 1).³ Similarly, electrocyclic closure of perfluoro-3,4-dimethyl-1,5-hexadiene did not occur at temperatures up to 200 °C,⁴ while the analogous hydrocarbon system cyclizes at 160 °C.⁵

Fluorine substitution also influences the energetics of 3,3-sigmatropic shifts such as the Cope rearrangement.⁶ This

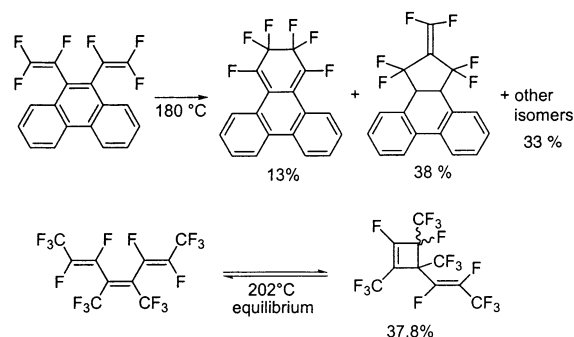


Figure 1. Fluorine effects in electrocyclic ring openings.

rearrangement has attracted considerable experimental and theoretical attention because subtle variations of the reaction free-energy surface can lead to major changes in structures associated with the high-energy transition states.^{7,8} The parent hydrocarbon is known to react in a concerted manner through a delocalized, aromatic transition structure with a chair con-

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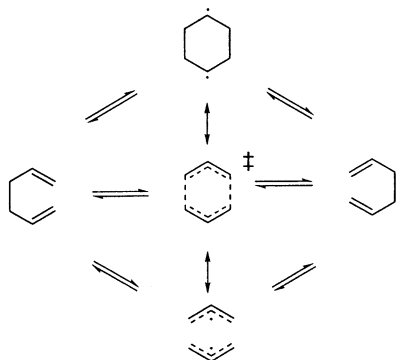


Figure 2. Canonical mechanistic descriptions of the Cope rearrangement.

formation with an activation enthalpy (ΔH^\ddagger) of 33.5 ± 0.5 kcal/mol (Figure 2).⁹ An alternate two-step process through a 1,4-cyclohexadienyl intermediate, long thought to be close energetically, actually occurs only in cases with strong radical stabilizing substituents at C(2) and C(5) such as 2,5-diphenyl-1,5-hexadiene.¹⁰ For this diphenyl derivative, the diradical pathway was calculated using density functional theory (DFT) at the (U)B3LYP/6-31G(d) level to be 0.3 kcal/mol below the transition structure for the concerted pathway. A commonly considered third reaction pathway, dissociation into a pair of resonance stabilized allyl radicals followed by reclosure, is typically not competitive. For the prototypical case of 1,5-hexadiene, experimental work sets the enthalpy change for this dissociation at 61.4 kcal/mol, well above the observed enthalpy of activation of 27.9 kcal/mol for the Cope reaction for the deuterium labeled derivative.¹¹ Recent elegant work by Doering, Klärner, and co-workers provides an interesting case for a dissociation process in the reaction of 1,3,4,6-tetraphenyl-1,5-hexadiene stereoisomers.¹² Aside from a positive entropy of reaction, and stereochemistry requiring a nonpericyclic process, evidence for the competing formation of diphenylallyl radicals was obtained.¹²

Geminal fluorine substitution at one (2) or both (3) termini of 1,5-hexadiene (Figure 3) lowers the activation enthalpy for the Cope process by 1.5 and 3.6 kcal/mol, respectively, and renders the reaction exothermic.¹³ In contrast to this activating effect of limited fluorine substitution, perfluoro-1,5-hexadiene derivatives appear to “Cope” only reluctantly, with other avenues of thermal rearrangement proceeding more rapidly (Figure 4).¹⁴ Heating perfluorobicyclo[2.2.0]hexane (4) to 250 °C allows it to equilibrate with perfluoro-1,5-hexadiene, while further heating to 300 °C results in irreversible conversion to the perfluorobicyclo[3.1.0]cyclohexane. These results implicate a 1,4-cyclohex-

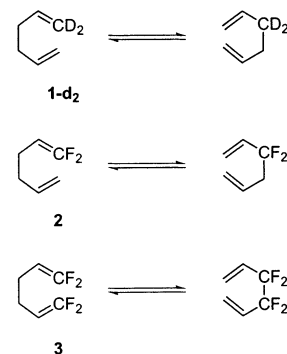


Figure 3. Fluorine derivatives of 1,5-hexadiene.

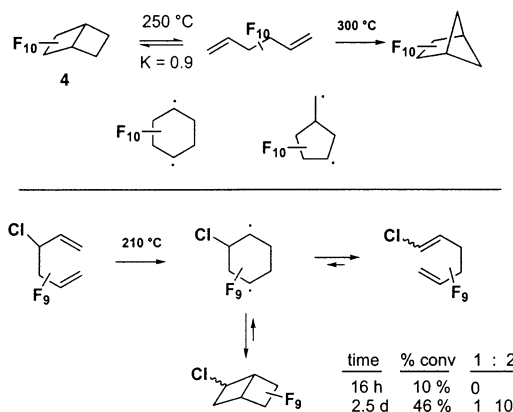


Figure 4. Thermal reactions of perfluorohexadiene.

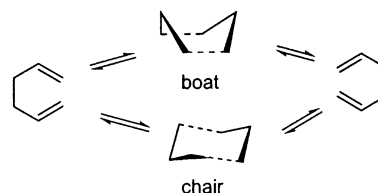


Figure 5. Chair and boat conformations of transition structures of the concerted Cope rearrangement.

anediyl intermediate. The C(3) monochloro derivative of perfluorohexadiene rearranges to the bicyclo[2.2.0]hexane isomer at 210 °C, with the “Cope” product appearing as a minor process after long reaction times (Figure 4). The reverse reaction from 3-chloroperfluoro-1,5-hexadiene at higher temperature produced only the bicyclo[2.2.0]hexane isomer. Here too a 1,4-diyl is the likely intermediate common to both the Cope process and the formation of the bicyclic isomer. However, the experiments do not distinguish a completely radical pathway from one in which the diyl always forms the bicyclic isomer, and the Cope process is accounted for by an energetically close concerted pathway.

A second level of mechanistic complexity arises with recognition that the concerted Cope process could occur through more than one transition structure conformation (Figure 5).¹⁵ Whereas the chair conformation is strongly preferred (estimated

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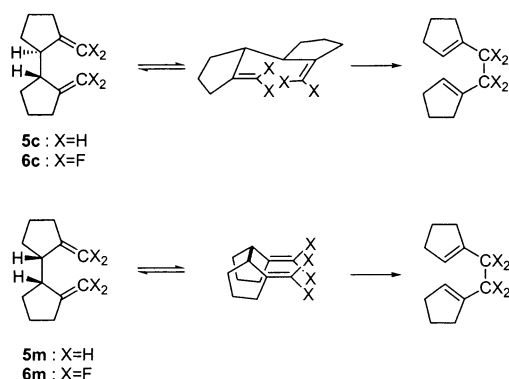


Figure 6. Cope rearrangement of 2,2'-bis-methylenecyclopentane.

$\Delta\Delta H^\ddagger \approx 11.2$ kcal/mol for 1,5-hexadiene^{15c}), reaction via either the chair or the boat can be coerced using the two diastereomers of 2,2'-bis-methylenecyclopentane, **5**. In this cleverly designed system of Shea and Phillips, the concerted Cope reaction of the chiral diastereomer, **5c**, can only proceed by way of a chair conformation, while the *meso* compound, **5m**, must pass through a boat transition-state conformation (Figure 6).¹⁶ The enthalpy of activation for the reaction of **5c** through the chair conformation is 13.8 kcal/mol more favorable than the reaction of **5m** by way of a boat conformation.

Dolbier and co-workers exploited the specificity of this bis-cyclopentyl system to test their prediction that fluorine substitution at the alkene termini would affect very differently the energetics of the chair and boat reaction pathways, further favoring the chair conformation while slowing rearrangement via the boat conformation.^{13b} This was verified using fluorine derivatives **6c** and **6m**. Fluorine substitution in **6c** led to a 5.6 kcal/mol *decrease* in activation enthalpy, consistent with the influence of fluorine in **2** and **3**. All of these are expected to react by way of a concerted process through a chair transition structure, and the preference of F for sp^3 centers is reflected in the lowered activation barriers.

The effect of fluorine substitution in **6m** was also as predicted, *increasing* the activation enthalpy by 7.9 kcal/mol relative to the analogous hydrocarbon, **5m**. Here F–F repulsion must override the sp^3 preference. Equally dramatic were the unanticipated effects on the activation entropy in these reactions. Stereotypical Cope rearrangements have large negative entropies of activation (–10 to –18 eu), consistent with well-ordered, cyclic transition structures.^{7a} For the chiral isomer reacting through a chair transition structure, the effect of fluorine substitution was to render ΔS^\ddagger more negative by 6.2 eu (–11.3 eu for **5c** and –17.5 eu for **6c**). However, fluorine substitution in the *meso* isomer led to an *increase* in ΔS^\ddagger by 9.4 eu (–0.7 eu for **5m** and +8.7 eu for **6m**). Dolbier attributed this result to steric repulsions between eclipsed fluorines at the C(1) and C(6) positions, while at the same time recognizing that fluorine is widely known to have little steric impact in most reactions. In light of the very significant influence of fluorine in **6m**, he concluded that, “This is a Cope rearrangement which does not want to be pericyclic!”

In this work, density functional theory is used to better understand the origin of both the accelerating and the inhibiting effects of fluorine substitution on the Cope process in **2**, **3**, **4**,

5, **6**, and 1,1,3,3,4,4,6,6-octafluoro-1,5-hexadiene (**7**). In choosing the methodology appropriate for these goals, we were cognizant of two particular challenges which come together in these systems. The first is the ever present challenge of modeling realistically the delicate potential energy hypersurface of the Cope rearrangement. We are guided by previous work in which we and others have demonstrated that density functional theory using the hybrid functional Becke3LYP¹⁷ (B3LYP) reproduces experimental activation parameters and transition-state geometries for pericyclic reactions, and particularly the Cope reaction, remarkably well.¹⁸ This is particularly true when one can reasonably expect that the electronic state can be represented well by a single electron configuration with added correlation corrections. For the exploration of pathways involving regions of the hypersurface corresponding to singlet diradical intermediates, UB3LYP has proven to be an effective method, and we employ it here. Whether or not there are more effective functionals for handling singlet diradical systems remains an active area of investigation.¹⁹ However, there is theoretical support for the use of this functional for the description of singlet diradicals.²⁰ On the other hand, a fully balanced treatment of dissociation, association, and concerted pathways requires a balanced treatment of dynamical and nondynamical correlation, as provided by CASPT2 calculations²¹ or by the recent MR-CISD and MR-AQCC calculations with large basis sets that establish the geometry of the parent to Cope transition state to have partial single bond lengths of 1.90 Å in the chair and 2.19 Å in the boat,²² both about 0.1 Å shorter than that found here using B3LYP.

Fluorine substitution itself provides the second challenge. This substituent has at least three influences on reactivity that are relevant to this study and which must be handled well by the calculation. First, substitution of fluorine at sp^3 centers is known to be thermodynamically preferable to substitution at sp^2 centers. This strongly affects the enthalpy of the Cope process in hexadienes with fluorine substitution at carbons 1, 3, 4, or 6, because these positions involve a change in carbon hybridization from sp^2 to sp^3 or vice versa.^{23a} Fluorine substitution also stabilizes adjacent carbon radicals, as would be found in the pathway involving dissociation of hexadiene into allyl radicals and in the mechanism involving closure to a cyclohexane-1,4-diyl species.^{23b} The final impact of fluorine relevant to this study is the “gauche effect”, the unusual enthalpic preference for the gauche over anti conformation in structures as simple as 1,2-difluoroethane.^{23c} This last influence is particularly important as the putative transition structures and intermediates to be

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compared in this study have a mix of gauche, anti, and eclipsed fluorine substituents along one or both partially formed C–C bonds. Handling these interactions well is important in predicting the proper relative energetics of different reaction pathways. However, even establishing the magnitude of the gauche conformation energy preference in 1,2-difluoroethane has proven a challenge to both experimental and computational methods.

Experimental investigations of 1,2-difluoroethane have relied on electron diffraction,²⁴ microwave,²³ fluorine and proton NMR,²⁶ and high-resolution Raman and far IR²⁷ analyses to determine the geometric features and the relative energy of both conformers. These data have been summarized and discussed elsewhere.^{23c,28} While estimates of the gas-phase energy difference vary from 0.6 to 2.0 kcal/mol, recent results from high-resolution NMR, Raman, and IR studies seem to be in reasonable agreement with the value converged on by high level ab initio molecular orbital calculations, about 0.8 kcal/mol.^{26b,27c,28,29} The many calculations on this system have demonstrated that to reproduce this value requires both post-Hartree–Fock corrections for electron correlation and large basis sets which include added polarization and diffuse functions.

Muir and Baker provided a systematic study of several fluoroethanes using DFT methods to calculate structures, potential energy surfaces, and vibrational frequencies for comparison to experimental data and to the results of other theoretical methods.³⁰ They concluded that the hybrid B3LYP functional was the best of the functionals examined and also that it provided results which compared very favorably to those of the MP2 method. When comparing 6-31G(d) to a triple- ζ double-polarization basis set, they concluded that, as with ab initio methods, the larger basis set was beneficial in the application of DFT methods to fluorinated systems. (The gauche–anti energy gap was calculated to be 0.5 kcal/mol using the 6-31G(d) basis set and 1.0 kcal/mol using the TZ2P basis set relying on single-point energy calculations with ZPE corrections based on the HF wave function.)

In light of the basis set dependence in the above results, we decided to examine more carefully the effectiveness of the B3LYP functional in handling fluorine substituents as a function of three basis sets potentially useful in this study, 6-31G(d), 6-311G(d,p), and 6-31+G(d,p). We report the results of that exploration below along with our work on the Cope reaction of the polyfluorinated hexadiene systems.

Computational Methods

All DFT calculations were carried out using methods and basis sets (6-31G(d), 6-311G(d,p), and 6-31+G(d,p)) implemented in the Gaussian

Table 1. Energy^a and Geometric Data for the Conformers of 1,2-Difluoroethane (B3LYP)

| | 6-31G(d) | 6-311G(d,p) | 6-31+G(d,p) |
|--------------------------------|----------|-------------|-------------|
| anti conformer | 0.00 | 0.00 | 0.00 |
| anti \rightarrow gauche TS | 2.03 | 1.65 | 1.21 |
| gauche conformer | −0.50 | −0.58 | −0.83 |
| gauche \rightarrow gauche TS | 6.37 | 6.78 | 6.66 |
| gauche dipole (D) | 2.45 | 2.69 | 3.01 |
| gauche F–C–C–F tor. (deg) | 69.9 | 71.7 | 72.5 |

^a Energies given in kcal/mol.

suite of programs (G98.A7 and G98.A9).³¹ The reactants, chair and boat transition structures, radical intermediates, and products were fully optimized using the (U)B3LYP functional. Normal-mode analysis was used to establish all stationary points, to distinguish ground and transition structures, to provide zero-point energy (ZPE) corrections (based on a frequency scaling of 0.9804³²), and to calculate enthalpies and entropies of formation (calculated at 298.15 K unless otherwise noted). The focus of discussion will be the results from the density functional calculations. However, selected structures were subjected to single-point calculations using a 6-electron/6-orbital CASSCF/6-31G-(d) wave function with second-order Moller–Plesset (MP2) corrections to handle dynamic correlation as implemented through the CASPT2 method in the MOLCAS program (V5).³³

Results and Discussion

1,2-Difluoroethane and 1,1,2,2-Tetrafluoroethane Conformations. To assess the effectiveness of three different basis sets in handling fluorine substituents, the B3LYP functional was used to calculate all conformational stationary points for two compounds, 1,2-difluoroethane and 1,1,2,2-tetrafluoroethane, for which experimental data and other theoretical studies are available for comparison. In contrast to previous theoretical work using this functional,³⁰ these results are based on the full optimization and frequency calculation within the given basis set. The relative energies are reported in Table 1. Key structural information using the 6-31+G(d,p) basis set is provided in Figure 7.

The gauche–anti energy difference is most relevant to the structural situation present in the chair transition structures and in several reactants and products. The larger 6-31+G(d,p) basis set is most effective at predicting this energy difference, giving a value of 0.83 kcal/mol. The need for added polarization and diffuse functions to handle the electrostatics of the fluorine substitution is consistent with the results of ab initio work.^{27b,28,29} The inclusion of ZPE and thermal corrections is important to correctly predicting the energy gap, as relying only on single-

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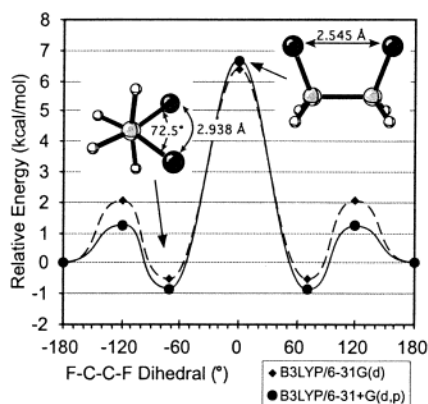


Figure 7. Conformational energetics of 1,2-difluoroethane as calculated with B3LYP.

point electronic energies predicts a smaller energy gap by 0.15–0.20 kcal/mol for all basis sets. The torsional angle and dipole moment are included for comparison to experimental values of 71° and 2.76 D, respectively.

A model compound even more analogous to our structural situation would be 1,1,2-tetrafluoroethane. All experimental studies show the conformer with anti C–H bonds to be lowest in energy. Three studies relying on IR, Raman, and electron diffraction data found the gauche–anti energy difference to be between 1.16 and 1.18 kcal/mol.³⁴ One NMR study estimates this gap at 2.4 kcal/mol.³⁵ A recent ab initio study places this energy difference at 1.65 kcal/mol (MP2/6-31G(d,p)),³⁶ in good agreement with a previous calculation (1.73 kcal/mol at the MP4/6-311G(d,p)//HF/6-31G(d) level).³⁷ Our results (Table 2) place this energy gap at 1.62 kcal/mol using the 6-31+G(d,p) basis set. Geometric data at the B3LYP/6-31+G(d,p) level are provided in Figure 8.

While the theoretical work is internally consistent, if the experimental value of ~1.17 kcal/mol from three studies were correct for the conformational enthalpy difference, then even at this level the calculations could be underestimating the enthalpic preference for the gauche over anti conformation of vicinyl C–F bonds. This could result from a slight error in calculating the interaction energy of anti or gauche C–F bonds. However, the F–C–C–F dihedrals in the “gauche” structure (50.0° and 68.7°) are significantly reduced from that found in the less crowded 1,2-difluoroethane (72.5°). Any overestimate of the destabilizing interactions between C–F bonds would also creep in as destabilization of the gauche conformation relative to the anti conformation.

Calculating correctly the energetics of *eclipsed* C–F bonds impinges directly on our ability to compute the energetics of the boat transition structures for the rearrangements of **3**, **4**, **6**, and **7** (discussed later), in which fluorine substituents are eclipsed along one or both partially formed C–C bonds. A comparison of calculated and experimental barriers to rotation from one gauche conformation to another through the fully eclipsed conformation provides a test of DFT methods for the

Table 2. Energy^a Data for the Conformers of 1,1,2,2-Tetrafluoroethane (B3LYP)

| | 6-31G(d) | 6-311G(d,p) | 6-31+G(d,p) |
|--------------------|----------|-------------|-------------|
| gauche conformer | 1.67 | 1.89 | 1.62 |
| anti conformer | 0.00 | 0.00 | 0.00 |
| anti → gauche TS | 2.92 | 2.75 | 2.69 |
| gauche → gauche TS | 5.70 | 6.00 | 6.12 |

^a Energies given in kcal/mol.

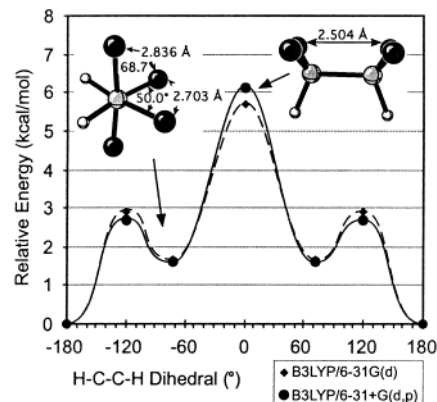


Figure 8. Conformational energetics of 1,1,2,2-tetrafluoroethane as calculated with B3LYP.

evaluation of eclipsed C–F bonds. Experimental values for this barrier to rotation in 1,2-difluoroethane have been assessed by electron diffraction²⁴ (4.52 kcal/mol), by microwave analysis²⁵ (6.3 kcal/mol), and most recently by IR and Raman spectroscopy (5.72).^{27c} The significant variation in the experimental values gives pause when using them as a benchmark for theoretical work. However, it is notable that all of these are lower than the consensus of 7–8 kcal/mol based on ab initio calculations using MP2–MP4 methods with large basis sets. The data in Table 1 set the gauche-to-gauche energy barrier at 7.49 kcal/mol at the B3LYP/6-31+G(d,p) level (6.66 + 0.83 kcal/mol). Unfortunately, no comparable experimental data for conformational barriers in 1,1,2,2-tetrafluoroethane are available. On the basis of the results above, we have chosen to use the 6-31+G(d,p) basis set for calculations discussed in this paper.

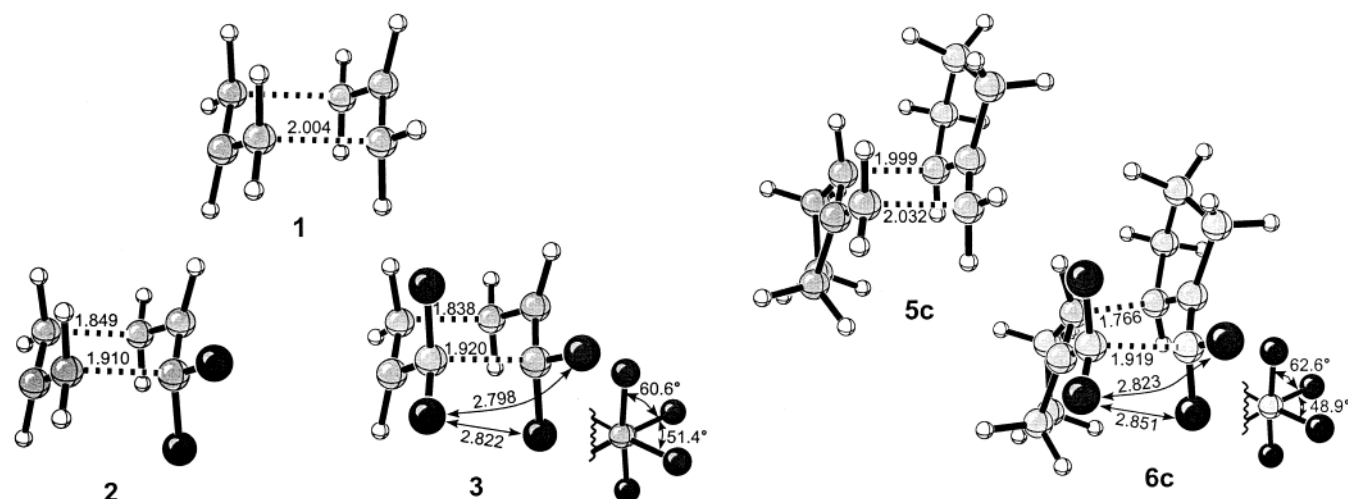
Concerted Cope Rearrangement Pathways: Chair Transition Structures of Hexadiene, Bis-methylenecyclopentane, and Fluorinated Analogues. The B3LYP/6-31+G(d,p) calculated activation enthalpies and entropies for the rearrangements of **1**, **2**, **3**, **5**, and **6** by way of both chair and boat transition structures are reported along with experimental values in Table 3. While discussion will focus on the energetic and geometric predictions of the larger basis set, the results from the 6-31G(d) basis set are very similar. For the chair conformations, the computed enthalpies of activation are remarkably close to the experimental values where they exist for comparison. For the parent hydrocarbon **1**, the experimental and theoretical values agree within 0.5 kcal/mol (the estimated experimental error); the largest discrepancy between calculated and experimental results is 2.2 kcal/mol, and this case has an unusually large negative entropy of activation. Experimentally, the addition of the two fluorines at C(1) in **2** lowers the activation enthalpy by 1.5 kcal/mol, while calculations slightly overestimate this reduction at 2.8 kcal/mol. This stabilization of the transition structure results from the conversion of the site of fluorine substitution from an sp² to sp³ carbon during the reaction. This

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Table 3. Energy^a Data for the Chair and Boat Transition Structures, Dissociation to Two Allyl Radicals, and the Cope Product ((U)B3LYP/6-31+G(d,p))

| compd. | experimental | | | | chair TS | | boat TS | | dissociation | | |
|-----------|---------------------|---------------------|-------------------------|--------------------------|---------------------|---------------------|---------------------|---------------------|----------------------------|--------------------------|-------------------------|
| | ΔH^\ddagger | ΔS^\ddagger | ΔH_{rxn} | ΔH_{diss} | ΔH^\ddagger | ΔS^\ddagger | ΔH^\ddagger | ΔS^\ddagger | ΔH_{diss}^b | ΔS_{diss} | ΔH_{rxn} |
| 1 | 33.5 ± 0.5 | -13.8 ± 1.0 | 0 | 61.4 ± 1.8 | 34.0 | -8.1 | 41.2 | -6.1 | 49.3 | 40.8 | 0.0 |
| 2 | 32.0 ± 0.7 | -12.1 ± 1.4 | -5.1 ± 0.2 | | 31.2 | -10.8 | 40.6 | -8.0 | 50.0 | 41.1 | -7.1 |
| 3 | 29.9 ± 0.2 | -18.5 ± 0.5 | | | 32.1 | -14.0 | 43.9 | -8.8 | 50.6 | 43.1 | -7.2 |
| 5c | 28.0 ± 1.1 | -11.3 ± 2.6 | | | 27.0 | -5.6 | | | 38.3 | 47.4 | -9.2 |
| 6c | 22.4 ± 0.2 | -17.5 ± 0.4 | | | 24.2 | -8.5 | | | 40.9 | 52.6 | -17.8 |
| 5m | 41.6 ± 0.5 | -0.7 ± 1.0 | | | | | 35.3 | -4.3 | 38.6 | 45.5 | -8.9 |
| 6m | 49.5 ± 1.0 | 8.1 ± 1.7 | | | | | 39.8 | -3.6 | 41.7 | 50.9 | -17.0 |

^a Energies given in kcal/mol relative to starting material; entropies in eu (cal/deg mol). ^b See the Dissociative Pathway section for a discussion of these values, especially the underestimation of the dissociation energies by these calculations.

**Figure 9.** Calculated chair transition structures for the Cope rearrangements of **1**, **2**, **3**, **5c**, and **6c** (B3LYP/6-31+G(d,p)).

preference is reflected more strongly in ΔH_{rxn} , which is experimentally determined to be -5.1 kcal/mol. Calculation at this level sets the reaction enthalpy at -7.1 kcal/mol, consistent with the slight overestimation of the transition-state stability.

Adding a second pair of fluorines at C(6) to generate **3** experimentally lowers the energy barrier by another 2.1 kcal/mol. While the effect is additive in the experimental results, calculation predicts that the second pair of fluorines slightly increases (0.9 kcal/mol) the reaction barrier, leaving it just 1.8 kcal/mol below that calculated for the hydrocarbon. Calculation also predicts a nonadditive effect on the reaction enthalpy for **3**, with the calculated value (-7.2 kcal/mol) just 0.1 kcal/mol more exothermic than that calculated for the difluoro system **2**. There is no experimental value for comparison, but this small net effect is likely the result of destabilization in the product, 3,3,4,4-tetrafluoro-1,5-hexadiene, due to two anti and two gauche fluorine interactions in the energetically favored C_i symmetric conformer. The rise in ΔH^\ddagger with no change in ΔH_{rxn} from the addition of the second pair of fluorines suggests a small but selective destabilization of the transition structure due to fluorine-fluorine interactions.

The chair transition structure for the Shea hydrocarbon **5c** is also well calculated at this level of theory, with the computed enthalpy relative to the reactant (27.0 kcal/mol) just 1.0 kcal/mol less than the experimental value. The Dolbier tetrafluoro derivative **6c** is again handled well, with computations capturing correctly the stabilizing effect of the fluorine substitution. However, as with tetrafluorohexadiene **3**, the computations underestimate slightly the magnitude of that stabilization, with

the computed transition-state enthalpy 1.8 kcal above the experimental value. While no experimental value is available for the enthalpy of reaction for either **5c** or **6c**, the computed values are -9.2 and -17.8 kcal/mol, respectively. Exothermicity attributable to the conversion of four fluorine-bearing carbons from sp^2 to sp^3 is about 8.6 kcal/mol, very similar to that found for hexadiene **3** (7.2 kcal/mol).

Calculated entropies of activation (Table 3) for the chair transition structures in systems **1**, **2**, **3**, **5c**, and **6c** are not as negative as the experimental values. This is primarily due to an incomplete assessment of entropy in the ground-state structure, due to inadequate treatment of hindered internal rotations as harmonic oscillators and effectively considering only a single conformation in the ground state.³⁸ However, this systematic error in the absolute values does not obscure the trends as a function of the degree of substitution, which clearly reflect the geometric variations in the cyclic transition structures (Figure 9). The presence of two fluorines at C(1) results in a tightening of the transition structure. Both the forming and the breaking bonds are shorter than those in hydrocarbon **1**. Adding fluorine to an sp^2 center in a typical ground-state structure shortens neighboring σ bonds as the orbitals involved in those bonds take on more s character. In the transition structure, the

(38) (a) Ayala, P. Y.; Schlegel, H. B. *J. Chem. Phys.* **1998**, *108*, 2314–2325. To more properly estimate the activation entropies would require a much more complete exploration of the conformational space for both ground and transition structures in these relatively large molecules. In addition, the free-energy maximum may be substantially displaced from the enthalpic maximum: Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 4293–4294. (b) Houk, K. N.; Rondan, N. G.; Mareda, J. *Tetrahedron* **1985**, *41*, 1555–1563.

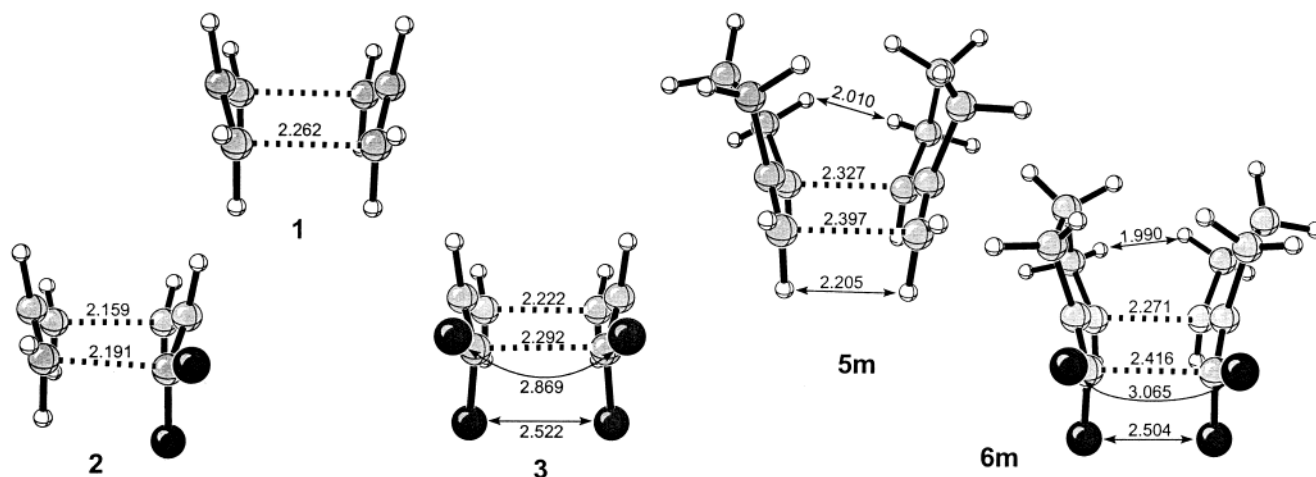


Figure 10. Calculated boat transition structures for the Cope rearrangements of **1**, **2**, **3**, **5m**, and **6m** (B3LYP/6-31+G(d,p)).

effect is more dramatic, as the shortening of the partial bond in the transition structure increases sp^3 character at the reacting carbon center. Interestingly, adding a second pair of fluorines at C(6) results in less structural change. The breaking bond is shortened, consistent with a further tightening of the earlier transition structure; however, the forming bond between the two carbons bearing the fluorine substituents actually lengthens by 0.01 Å. The calculated entropy of activation becomes a bit more negative as is consistent with the overall tightening of the transition state. The distances between the staggered fluorine atoms (2.798 and 2.822 Å) in the chair transition structure of **3** are actually shorter than the fluorine–fluorine distance in gauche 1,2-difluoroethane (2.938 Å) and very similar to those found in 1,1,2,2-tetrafluoroethane (2.703 and 2.836 Å) calculated at the same level of theory. This close fluorine proximity is due to the more planar geometry at the reacting carbon centers offsetting the relatively long partial C–C bond. The same close fluorine–fluorine proximity is found in the chair transition structure for tetrafluoro-bis-methylenecyclopentane derivative **6c**.

In trying to understand the small, but seemingly systematic, failure of calculation to capture the full stabilizing effect of fluorine in the chair transition structures for tetrafluoro derivatives **3** and **6c**, we note that the torsional angles between vicinyl fluorine substituents are significantly less than those found in gauche 1,2-difluoroethane. In **3**, for example, they are 51.4° and 60.6° versus 72.5° in gauche 1,2-difluoroethane. Compressing the angle in 1,2-difluoroethane to the same values increases the energy by 0.4 and 1.3 kcal/mol at the B3LYP/6-31+G(d,p) level of calculation. If the theoretical methods are overemphasizing the repulsive interaction between eclipsed fluorines, as might be indicated in the 1,2-difluoroethane calculations, this could account for the small added destabilization of the tetrafluoro transition structures.

Concerted Boat Transition Structures. Concerted rearrangement via a boat conformation is calculated to be of significantly higher energy for all systems (Table 3). For the parent system, the calculated activation enthalpy is placed at 41.2 kcal/mol, 7.2 kcal/mol higher than that for the chair pathway. Studies by Goldstein and Benzon place this enthalpy difference at 11.2 kcal/mol.^{15c} The reason for this underestimate in the activation enthalpy by RB3LYP methods is not entirely clear. The higher experimental values may reflect a looser

transition structure with a more positive (favorable) entropy than that produced by calculation of the transition structure, based on the electronic energy saddle point.

Addition of the two fluorines in hexadiene **2** lowers the enthalpy of activation for the boat pathway by 0.6 kcal/mol at the B3LYP/6-31+G(d,p) level, and the transition-state structure (Figure 10) shows a shortening of the breaking and forming C–C bonds as was evident in the analogous chair transition structures. However, addition of a second pair of fluorines in **3** significantly destabilizes (+3.3 kcal/mol) the boat conformation, with the enthalpy barrier now 2.7 kcal/mol higher than that calculated for the hydrocarbon. The geometric changes induced by this second pair of fluorines are more pronounced in the boat transition structure than the chair; both the breaking and the forming bonds lengthen, clearly reflecting repulsion between the two pairs of eclipsed vicinal fluorines. The pseudoaxial fluorines are only 2.522 Å apart, a distance which is even shorter than that found between eclipsed fluorines in syn 1,2-difluoroethane (2.545 Å). The predicted entropies of activation for these boat transition structures are all slightly more positive than those for the corresponding chair pathways, in agreement with looser transition structures in which breaking/forming bond distances are longer by 0.2–0.3 Å. This result provides clear support for the prediction of Dolbier that fluorine–fluorine interactions across the reacting bonds would be significantly destabilizing to the boat transition structures.

The *meso*-1,2-bis-methylenecyclopentane system (**5m**) provides a rare experimental opportunity for one to determine directly the reaction parameters for a Cope process proceeding by way of a boat transition structure. The experimental work of Shea and co-workers places this transition structure 41.6 kcal/mol above the ground state and, therefore, 13.6 kcal/mol higher than for the reaction of **5c** through the chair transition structure. The boat transition structure calculated for the concerted reaction of **5m** at the B3LYP/6-31+G(d,p) level is 35.3 kcal/mol above the ground state, 6.3 kcal/mol lower than the experimental enthalpy of activation. In this putative transition structure (Figure 10), steric repulsion between the cyclopentyl rings lengthens the breaking and forming bonds by 0.07–0.14 Å relative to the boat transition state for 1,5-hexadiene. This loosening of the structure is captured in the more positive entropy of activation (−4.3 eu) relative to that calculated for the chair transition structure (−5.6 eu). However, this small difference

of +1.3 eu does not mirror well the much larger difference observed experimentally (+10.6 eu) between the chair and boat activation entropies for **5c** and **5m**. This deviation makes clear that **5m** rearranges by a pathway which is significantly different from that involving the transition structure calculated by the restricted DFT calculation.

The situation with the *meso*-tetrafluoro derivative **6m** is similar but more dramatic. The experimental enthalpy of activation for the boat pathway, 49.5 kcal/mol, is 27.1 kcal/mol higher than that for the analogous chair pathway of **6c**, reflecting the strong disfavoring of the boat transition structure. Calculation at the B3LYP/6-31+G(d,p) level provides a transition structure for the hypothetical concerted pathway which is quite high energy ($\Delta H^\ddagger = 39.7$ kcal/mol), but which is 9.7 kcal/mol lower than the experimental value. In this transition structure, the pseudoaxial fluorine–fluorine distance is only 2.504 Å, and this along with the proximity of the cyclopentyl rings prevents significant tightening along the partial bonds. The breaking bond shortens by 0.06 Å, and the forming bond lengthens by 0.02 Å relative to hydrocarbon **5m**. Not surprisingly, the calculated ΔS^\ddagger of –3.6 eu for this concerted pathway is 4.9 eu more positive than that calculated for the chair pathway. However, this calculated difference of 4.9 eu dramatically underestimates the experimentally observed 25.6 eu difference in ΔS^\ddagger values for the boat (+8.1 eu) and chair pathways (–17.5) for **6m** and **6c**, respectively. Clearly, the restricted DFT method provides transition structures for a concerted process which are not adequate representations of the rearrangement of either **5m** or **6m**.

Concerted Pathway with Dissociative Character. The positive entropy of activation determined experimentally for the tetrafluoro *meso* compound **6m** suggests that the transition state involves a greater degree of dissociation than is predicted by B3LYP. With hydrocarbon **5m**, the experimental data are also consistent with a looser transition state than that predicted computationally. The dissociations of **5m** and **6m** were calculated at the UB3LYP/6-31+G(d,p) level (Table 3). The calculated enthalpies of dissociation (ΔH_{diss}) are 41.7 kcal/mol for tetrafluoro derivative **6m** and 38.6 kcal/mol for hydrocarbon **5m**. These values are certainly too low. The calculated enthalpy change for the dissociation of 1,5-hexadiene to two allyl radicals is 49.3 kcal/mol, a value which is 12.1 kcal/mol lower than the current experimental value (61.4 ± 1.8 kcal/mol).¹¹ A correction of this magnitude applied to the calculated ΔH_{diss} for **6m** and **5m** leads to a prediction that $\Delta H_{\text{diss}}'$ would be 53.8 kcal/mol for **6m** and 50.7 kcal/mol for **5m**. (We will use a prime symbol to label energy values with this correction.) These estimated enthalpies of dissociation are higher than the experimental enthalpies of activation for the same process (49.5 kcal/mol for **6m** and 41.6 kcal/mol for **5m**). While B3LYP underestimates the dissociation energies substantially, CASPT2 methods have been found to give dissociation energies much closer to experimental values.²¹ This method has not been applied here, because the size of these compounds would make the computations very difficult to accomplish. We have, however, explored how the large entropy increase that occurs for dissociation might alter the position of the transition states for the rearrangements of **5m** and **6m**.

The calculation of allyl fragments at the UB3LYP/6-31+G(d,p) level provides an estimate of the entropy of dissociation

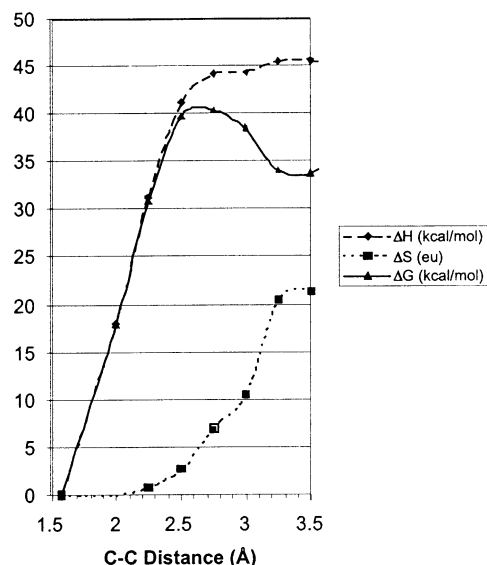


Figure 11. Energetics of dissociation for tetrafluoro-bis-methylenecyclopentane **6m** ((U)B3LYP/6-31G(d)).

to be 46 and 51 eu at 298 K for **5m** and **6m**, respectively. A constrained optimization for the singlet diradical of **5m** was carried out at the UB3LYP/6-31G(d) level; the bond connecting the two methylenecyclopentane fragments was stretched in 0.25 Å increments from the equilibrium bond length to 3.50 Å, in a boatlike geometry similar to that shown in Figure 10. A frequency calculation at each point was used to assess the enthalpy and entropy change as a function of the bond distance. This allowed an approximate evaluation of the free-energy changes along this enthalpic coordinate. These data are plotted in Figure 11 for system **6m** calculated at the reaction temperature, 557 K.

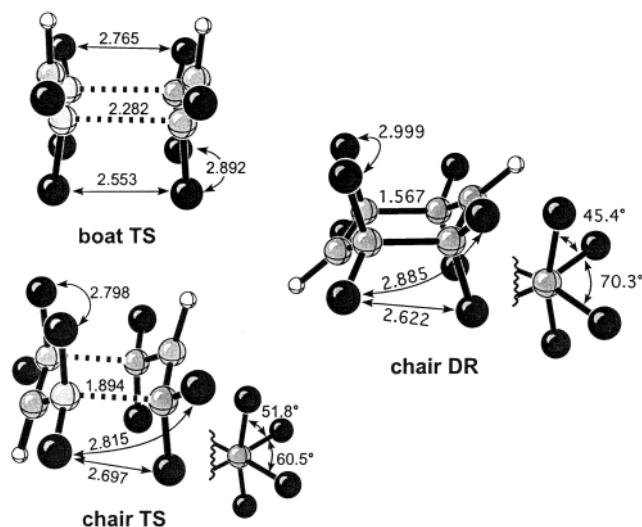
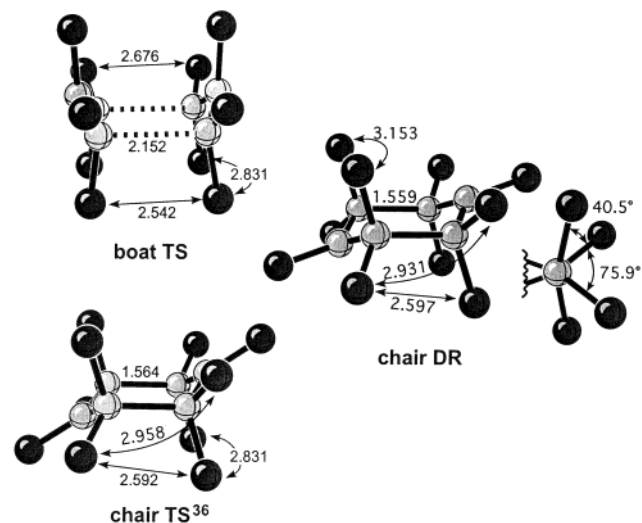
The free-energy maximum was located at a C–C bond breaking distance of about 2.75 Å. The calculated ΔH at this approximate variational transition structure for **6m** is 1.7 kcal/mol lower than the calculated dissociation enthalpy. Subtracting this value from our earlier estimate of $\Delta H_{\text{diss}}'$ gives us an estimated $\Delta H^{\ddagger} = 52.1$ kcal/mol for the variational transition state on the dissociation pathway, which is not too far from with the experimental value of 49.5 kcal/mol. The transition structure bond length of 2.75 Å represents an estimate of the true transition-state bond length. The calculated ΔS^\ddagger at a bond length of 2.75 Å (+6.8 eu) is low as compared to the experimental value of +8.7 eu for **6m**, suggesting the actual transition state is even looser than that obtained from this estimate. This relatively dissociative path still occurs at a distance (~2.8 Å) where some interaction between the termini of the two allyls occurs, worth about 4 kcal/mol relative to the fully dissociated species. It is interesting to note the less positive entropy (+2 eu) of activation in the 1,3,4,6-tetraphenyl-1,5-hexadiene rearrangement that involves a nonpericyclic process likely through a radical pair.¹²

Associative Pathways via Cyclohexane-1,4-diyls for Perfluorohexadiene and Octafluorohexadiene. We have also explored the reaction hypersurface of perfluoro-1,5-hexadiene (**4**) because experimental evidence from the thermolysis of it and a monochloro derivative suggests an associative mechanism on the opposite end of the mechanistic spectrum from the dissociative pathway just discussed (see Figure 4). To separate

Table 4. Energy^a Data for the Reaction of Perfluoro- and 1,1,3,3,4,4,6,6-Octafluoro-1,5-hexadiene (**4** and **7**, Respectively) ((U)B3LYP/6-31+G(d,p))

| cmpd. | | chair TS | boat TS | chair diradical | D2 diradical | TS to chair dirad. |
|----------|---------------------|----------|---------|-----------------|--------------|--------------------|
| 4 | ΔH^\ddagger | 39.2 | 51.6 | 23.8 | 23.9 | 37.2 |
| | ΔS^\ddagger | -9.4 | -8.7 | -9.8 | -9.1 | -11.7 |
| 7 | ΔH^\ddagger | 44.7 | 58.0 | 35.8 | 36.5 | 42.8 |
| | ΔS^\ddagger | -12.0 | -7.8 | -10.4 | -11.2 | -13.0 |

^a Energies given in kcal/mol relative to starting material; entropies in cal/deg mol.

**Figure 12.** Calculated transition structures and diradical intermediates for the rearrangement of **7** ((U)B3LYP/6-31+G(d,p)).**Figure 13.** Calculated transition structures and diradical intermediates for the rearrangement of **4** ((U)B3LYP/6-31+G(d,p)).

the effects of fluorine substitution at carbons 2 and 5 from those of substitution at the reacting carbons 1, 3, 4, and 6, calculations were also performed on the rearrangement of 1,1,3,3,4,4,6,6-octafluoro-1,5-hexadiene (**7**). Reaction parameters calculated at the (U)B3LYP/6-31+G(d,p) level for putative transition structures and reaction intermediates for the rearrangement of **7** and **4** are reported in Table 4, and the associated geometric data are presented in Figures 12 and 13.

Adding fluorine substituents to carbons C(3) and C(4) changes completely the behavior of the system. The activation enthalpy

of the concerted chair transition structure for octafluorohexadiene **7** is calculated to be higher than ΔH^\ddagger for 1,5-hexadiene by 5.7 kcal/mol. The rate accelerating effect of fluorine substitution at C(1) and C(6), as evident in **2** and **3**, is present but now overwhelmed by the inhibitory influence of fluorine substitution at C(3) and C(4), carbons which are changing from sp^3 to sp^2 hybridization in the transition state. The structural response is a further tightening of the calculated transition structure with a breaking/forming bond distance of 1.894 Å. The concerted boat transition structure is characterized by four pairs of eclipsed C–F bonds, and the close proximity of the eclipsed fluorines (2.553 Å for the pseudoaxial F) prevents collapse of the transition structure to a more diyl-like structure which would have greater sp^3 character at the reacting carbon centers. This results in long breaking/forming bonds (2.282 Å) and very high enthalpies of activation (16.8 kcal/mol higher than the boat transition structure for the parent hydrocarbon).

To investigate a possible stepwise mechanism, two cyclohexane-1,4-diyl diradical intermediates and a transition structure leading to the lower energy one were located on the reaction enthalpy surface. A C_{2h} chair diradical intermediate is calculated to be 8.9 kcal/mol below the concerted chair transition state, and the transition structure leading to this diradical is 1.9 kcal/mol lower than the concerted pathway. This places the diyl in a deep potential well of 7.0 kcal/mol.

That the cyclohexane-1,4-diyl would prefer a chair conformation could not be taken as given. Hrovat and Borden have shown that, for the parent hydrocarbon, a C_{2h} symmetric chair diradical is not a stationary point on the potential energy hypersurface at the CASPT2/6-31G(d)//CASSCF/6-31G(d) level.^{39a} At this level of theory, the most stable conformation of cyclohexane-1,4-diyl is a D_2 symmetric “twist-boat”, and this intermediate resides in a shallow well with barriers of just 1.4 and 2.2 kcal/mol for its transformation to bicyclo[2.2.0]hexane and 1,5-hexadiene, respectively. This computational result agrees very well with the experimental work of Goldstein and Benzon for the thermolysis of deuterium labeled bicyclo[2.2.0]hexane.^{38b} For the octafluoro-1,5-hexadiene system **7**, the D_2 symmetric cyclohexane-1,4-diyl was also located as a stationary point. However, in this case, it is found to be 0.7 kcal/mol higher than the chair conformation of the diyl at the UB3LYP/6-31+G(d,p) level.

Stationary points on the reaction surface calculated for the concerted and diradical rearrangement of perfluorohexadiene (**4**) have features quite similar to those found for octafluoro derivative **7**. The stepwise pathway through a chair diradical is again favored over the concerted pathway (by 2.0 kcal/mol), and the D_2 symmetric diyl is just 0.1 kcal/mol higher than the chair diradical.³⁸ The perfluoro system differs from the octafluoro system due to the added radical stabilization at C(2) and C(5). The 1,4-diyl is now in a very deep potential well, 15.4 kcal/mol below the concerted pathway. Interestingly, the perfluoro C_{2h} 1,4-diyl adopts a distinctly flatter chair than that found in the octafluoro system (Figures 12 and 13), even though this change exacerbates the vicinyl fluorine–fluorine repulsions by reducing some F–C–C–F dihedrals to just 40.5°. The compensating factor may be a movement of the radical centers

(39) (a) Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **2001**, *123*, 4069–4072. (b) Goldstein, M. J.; Benzon, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 5119–5121.

away from the fluorine nonbonding electron pairs. Carbons C(2) and C(5) are slightly pyramidalized as is typical of fluorine substituted carbon radicals.

The computational results reported here are completely consistent with the experimental work of Jing and Lemal, which suggests that the thermal rearrangement of perfluoro-1,5-hexadiene **4** preferentially produces a 1,4-cyclohexane-1,4-diyl intermediate, which then partitions between the more favorable process of closure to perfluorobicyclo[2.2.0]hexane (see Figure 9) and a slower “Cope” process. This partitioning of a 1,4-diyl between the two processes is very similar to the result found by Goldstein and Benzoin for the thermolysis of deuterium labeled bicyclo[2.2.0]hexane.^{39b,41} Our result does not entirely preclude the Cope process of perfluoro-1,5-hexadiene going by way of a concerted process, although the strong implication is that it occurs as a two-step process through a cyclohexane-1,4-diyl.

The interesting prediction of this work is that octafluoro-hexadiene **7** also preferentially reacts by a diradical pathway. The strong preference of fluorine to be at sp^3 hybridized carbons drives ring closure to the 1,4-diyl despite a lack of radical stabilization at C(2) and C(5). The same phenomenon effectively destabilizes the transition structure for the concerted process in which carbons 1, 3, 4, and 6 all have significant sp^2 character.

The ability of the B3LYP functional, and DFT methods in general, to reasonably assess the relative energetics of closed shell and singlet diradical species remains an area of concern and active research. In that light, we sought to verify the relative stabilities of key intermediates using completely different theoretical methods very well disposed to the calculation of open shell species. Single-point energy calculations at the 6 electron/6 orbital CASPT2/6-31G(d) level were performed on the B3LYP/6-31G(d) geometries for all stationary points in the rearrangement of the most interesting case, octafluoro derivative **7**. These results are presented in Table 5 along with those of (U)B3LYP/6-31G(d) calculations for comparison. The relative ordering of all intermediates and transition structures remains as calculated by (U)B3LYP. The most significant difference at the CASPT2 level is that the diradical path is of somewhat lower energy and as a consequence more strongly favored over the concerted,

Table 5. Enthalpy of Activation^a Data for the Reaction of 1,1,3,3,4,4,6,6-Octafluoro-1,5-hexadiene (**7**) ((U)B3LYP/6-31G(d) and CASPT2/6-31G(d)//B3LYP/6-31G(d))

| method | chair TS | boat TS | chair diradical | D2 diradical | TS to chair dirad. |
|---------------------|----------|---------|-----------------|--------------|--------------------|
| B3LYP | 43.2 | 56.2 | 37.2 | 38.7 | 42.2 |
| CASPT2 ^b | 43.0 | 60.8 | 31.1 | 34.2 | 36.7 |

^a Energies given in kcal/mol relative to starting material. ^b CASPT2 data are single points with geometries, ZPE, and thermal corrections from B3LYP/6-31G(d) calculations.

one-step process. This provides further corroboration of the DFT methodology and supports our assertion above that both **7** and **4** react through cyclohexane-1,4-diyl intermediates which partition between the Cope process and closure to a bicyclo[2.2.0]-hexane.

Conclusions

The effects of fluorine substitution on the Cope rearrangement depend on the position and degree of substitution. With modest levels of fluorination, such as those found in the di- and tetrafluoro derivatives **2** and **3**, the substituents serve to stabilize and favor the concerted chair transition state. However, in at least two situations, fluorination can alter the pathway toward an associative two-step process involving a singlet cyclohexanediyl diradical intermediate or, alternatively, to a loose transition state resembling two allyl radicals. In the case of *meso*-tetrafluoro-bis-methylenecyclopentane, both the experimental results and the calculations reported here make clear that a pathway tipped toward dissociative character is preferred. However, with the perfluoro and octafluoro derivatives of 1,5-hexadiene, the penchant of the fluorines attached to the reacting centers for sp^3 hybridization is sufficient to also force reaction through a diradical pathway, now involving ring closure to a 1,4-cyclohexanediyl intermediate. Notably, this pathway becomes the favored route even without any radical stabilizing substituents at C(2) and C(5). Like phenyl substituents,^{10,12} fluorine substitution is able to direct the Cope rearrangement in the direction of all three canonical mechanistic possibilities shown in Figure 2, with a 1.2 Å variation in the length of the partial single bonds formed and broken on the reaction pathway: the concerted aromatic (1.9 Å), the bis-allyl dissociative (2.8 Å), or the associative cyclohexane-1,4-diyl pathways (1.6 Å).

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(40) A C_{2h} chair transition state for the rearrangement of perfluoro-1,5-hexadiene can be found with the 6-31G(d) basis set. This very tight transition structure has a breaking/forming bond distance of 1.741 Å. However, with the larger 6-31+G(d,p) basis set, this C_{2h} transition structure collapses to a “diyl” structure with reacting bond distances of just 1.564 Å, even with a RB3LYP calculation. This stationary point is actually a very shallow minimum on the enthalpy surface (the lowest frequency is 26.8 cm^{-1}). The changing character of this stationary point was the most significant difference in structure as a function of the basis set.

(41) This hydrocarbon opens to a 1,4-diyl species which partitions between reclosure to the bicyclic system and opening to a 1,5-hexadiene; reclosure to bicyclo[2.2.0]hexane is slightly favored over opening to 1,5-hexadiene ($\Delta\Delta H^\ddagger$ by 1.6 kcal/mol from the diradical).