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Ab Initio Studies of [1,5]-H Shifts: Pentadiene and Beyond

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Ab initio calculations of the [1,5]-H shift in (3*Z*)-penta-1,3-diene and other substituted pentadienes and heteroanalogues using the hybrid density functional Becke3LYP with the 6-31G* basis set are presented. Electron-donating substituents, such as methoxy in (3*Z*)-3-methoxypenta-1,3-diene **1**, or heteroatoms such as a nitrogen atom in (*Z*)-ethylidenevinylamine **2**, (1*Z*)-buta-1,3-dienylamine **3**, (2*Z*)-but-2-enylideneamine **4**, (*Z*)-allylidenemethylamine **5**, and methylene-(*Z*)-propenylamine **6** are introduced. The electron-withdrawing fluoride is substituted for the hydrogen atoms in (3*Z*)-3-fluoropenta-1,3-diene **7**, (3*Z*)-2,4-difluoropenta-1,3-diene **8**, (3*Z*)-1,1′,2,3,4,5,5′-heptafluoropenta-1,3-diene **10**, (1*E*,3*E*)-1,3,5-trifluoropenta-1,3-diene **11**, and (1*Z*,3*E*)-1,3,5-trifluoropenta-1,3-diene **13**. A detailed analysis of the geometries, energies, and electronic characteristics of the sigmatropic transposition compared to those of the unsubstituted case provides insights into substituent effects of this prototype of pericyclic reaction. The inductive and mesomeric effects of heteroatoms or heterosubstituents are of a great importance and in a continuous balance in the energetics of the transformation. Sterics can also play an important role due to the geometrical constraints of the reaction. As a general trend, decreasing the electron density of the π system destabilizes the aromatic transition structure and increases the activation energy, and vice versa.

Introduction

The [1,5]-hydrogen shift reaction of (*Z*)-1,3-pentadiene is one of the classical examples of a pericyclic reaction with a concerted mechanism and an aromatic transition state, as shown by structural, energetic, and magnetic criteria.[1] The energy of concert[2] for this reaction has been estimated to be about 40 kcal/mol. Because of the unequivocally concerted character of the reaction, it has been studied as a model system by a number of ab initio[3−5] and semiempirical methods.[6,7] It has its use in synthesis, in the thermal isomerization of the sesquiterpenes isovelleral and merulidial,[8] in the thermolysis of a morphinan alkaloid from a (*Z*)-stilbene-derived bis(orthoquinone monoketal),[9] or in the rearrangement of α-sulfonyl-*o*-quinodimethanes in vinyl sulfones.[10] It enters in competition with the nitric oxide chelotropic trap 7,7,8,8-tetramethyl-*o*-quinodimethane[11] or with the intramolecular Diels−Alder reaction of 1,3,8-nonatriene.[12] Finally, a few pericyclic reactions are encountered in the biosynthetic pathway; vitamin B12[13−15] and uroporphyrinogen III[16] are two examples.

The transition state structure is more polarizable than the reactant, susceptible to positive point charge or Li^+ complexation leading to an electrostatic acceleration of [1,5]-H shifts as shown by Schleyer et al.[1] The π electron distribution is crucial in the energetics of the transformation. Sterics plays an important role as well due to the geometrical constraints the reactant adopts, as pointed out by Houk et al.[17]

Nevertheless, there are so far few systematic studies of substituent effects in this prototypical pericyclic reaction. The allene effect has been studied theoretically[18] and observed experimentally,[19] and the degenerate rearrangement of bicyclo[3.2.0]hepta-1,3,6-triene has been calculated to be 34 kcal/mol at the CCSD(T)/TZ//BLYP/6-31G* level of theory.[20] The photo-Fries rearrangements of phenyl acetate, believed to involve [1,3] and [1,5] sigmatropic hydrogen shifts, have been studied by laser flash photolysis, and the theoretical consideration was made according to the tunnel effect theory proposed by Formosinho.[21,22] Ab initio and semiempirical calculations of [1,5]-H shifts in pyrroles, furans, and thiophenes have been performed.[16] Pyrroles and phospholes have been investigated in comparison with cyclopentadiene.[23] Pyrazoles (Alphen−Hüttel rearrangements) along with ami-

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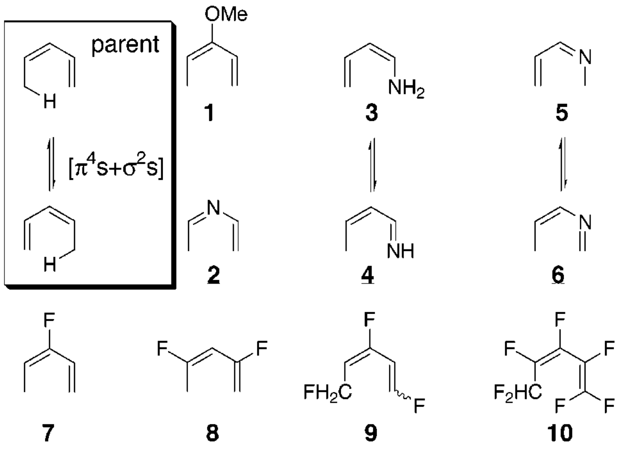

Figure 1. Compounds studied, **1**−**10**, and parent reaction.

noazadiene[24] as well as tetrazole have been studied.[25] All these studies deal with either pure hydrocarbon compounds or fairly complex substitution patterns. Surprisingly, the effect of the electronic structure on the activation energy of this important reaction has to the best of our knowledge not been studied in a detailed manner.

We therefore investigated the [1,5] hydrogen shift of several substituted 1,3-pentadienes as well as heteroanalogues to study the electronic and steric effects on the reaction. After a brief presentation of the B3LYP results for the parent 1,3-pentadiene, we will discuss the compounds **1**−**6** shown in Figure 1 where addition of electron density in the transition structure is available via the free electron pairs of the heteroatoms. We will then discuss the effect of electron-withdrawing fluoride substituents at different positions in compounds **7**−**10**.

Computational Methodology

The majority of the calculations published in the past were performed according to Hartree−Fock theory, which neglects correlation between electrons of opposite spin. Thus, the calculated activation energies for pericyclic reactions are systematically too high and there could be systematic errors in geometries. Furthermore, the comparison between a concerted reaction and a possible stepwise mechanism involving a diradicaloid intermediate is generally not possible, because restricted Hartree−Fock theory (RHF) cannot be used for open-shell species, and the energies of the unrestricted HF (UHF) wave functions of the diradicaloid species are too low compared to RHF calculations on closed-shell species. The inclusion of electron correlation by Møller−Plesset (MPn) perturbation theory or truncated configuration interaction (CI) calculations can address this problem. However, such calculations limit the size of the molecule to be studied practically to about 10 non-hydrogen atoms with current computers.

Recently, density functional theory (DFT) has evolved as a viable alternative approach for molecular structure calculations. As has been pointed out, DFT-based methods include electron correlation explicitly in the exchange-correlation functional at a moderate computational cost.[26] These methods are therefore promising for highly accurate calculations of chemically interesting systems, as shown by a comparison of the results from DFT calculations with the extensive results from Hartree−Fock calculations and other MO-based methods.[17,27,28]

We therefore adopted a computational strategy in which all structures were fully optimized and characterized by harmonic frequency analysis at the B3LYP/6-31G* level of theory to ensure that all species have the correct number of negative eigenvalues. The one negative eigenfrequency of the transition structures was animated using MOLDEN[29] to ensure that the optimized stationary point corresponds to the transition structure of the desired reaction. In cases where the imaginary normal mode in the transition structure was not unambiguous, an intrinsic reaction path calculation (IRC) was performed. All energies reported were corrected for zero-point vibrational energies from B3LYP calculations and are given in kcal/mol relative to the reactant in the given conformation (italic values in brackets in all figures). Partial charges are calculated by the Mulliken method. All calculations were performed using the Gaussian94[30] and Gaussian98[31] series of programs running on IBM SP1/SP2 and SGI Origin2000 at the High Performance Computing Complex at the University of Notre Dame, as well as on the SGI Origin2000 at the National Center for Supercomputer Application (NCSA).

Results and Discussion

The Parent Rearrangement. Although the results of B3LYP/6-31G* calculation of [1,5]-H shift in (3*Z*)-penta-1,3-diene have previously been published,[24,32] we would like to briefly address some issues pertinent to this comparative study. The results for the degenerate rearrangement of the unsubstituted system are similar to previous reported calculations using highly correlated methods,[1] as shown in Figure 2.

The transition state, a Hückel ($4n + 2$) π-electron array, has the C_s symmetry and a suprafacial topology predicted by Woodward and Hoffmann.[33] An IRC con-

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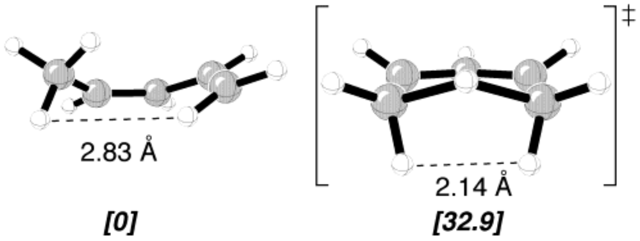

Figure 2. Structure of the parent compound (3*Z*)-penta-1,3-diene (left) and the [1,5]-H shift transition structure (right).

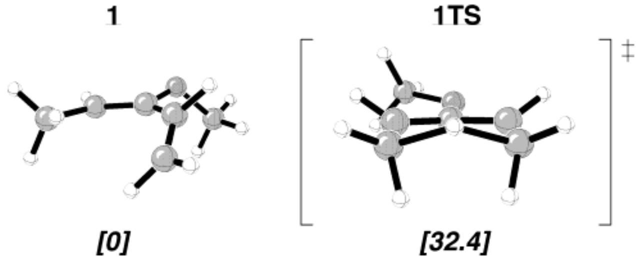

Figure 3. Structure of the compound (3*Z*)-3-methoxypenta-1,3-diene **1** (left) and the [1,5]-H shift transition structure **1TS** (right).

nects this transition state to the local minimum *s-cis* pentadiene. However the global minimum is an *s-trans* conformation and according to the Curtin−Hammett principle the *s-trans* C_s conformation must be taken into account for comparison with experiment, as was pointed out by Carpenter et al. in another density functional analysis of pericyclic reactions.[34]

The activation energy for this transformation is found to be 32.9 kcal/mol from the *cisoid* conformation, but 36.6 kcal/mol from *s-trans* pentadiene, close to the experimental value of 36.3 ± 0.5 kcal/mol obtained using ^{1}H NMR.[35] It is also close to the values of 35.9, 38.2, and 36.2 kcal/mol, obtained at the RMP2/6-31G*, RQCISD-(T)/6-311G**, and RMP4SDTQ/6-311G** levels of theory, respectively.[1] We therefore conclude that the B3LYP method yields satisfactory results for this reaction. For the study of the following analogues, the activation energy will be given relative to the *s-cis* reactant for convenience.

Electron-Donating Substituents. We studied the methoxy analogue **1**, which allows participation of the free electron pairs on the oxygen by resonance, thus increasing the electron density in the diene system without breaking the degeneracy of the transformation. However, the effect on the activation energy with a lowering of 0.5 kcal/mol is small, as shown in Figure 3. This indicates that the substituent effects in the reactant and the transition structure are comparable. On the one hand, a closer analysis of the transition structure reveals that the mesomeric effect is very small. The C3−O bond character in the reactant is 85% single bond on the basis of bond length (1.39 Å, when a C−O is 1.42 Å and C═O is 1.22 Å),[36] with only a bond shortening of 0.02 Å in the transition structure. Even though a conjugated aromatic methoxy group gives $\sigma_{\text{para}} = -0.27$ in structure−reactivity relationships, here the inductive effect of the oxygen atom predominates and withdraws electron density from the aromatic transition structure, destabilizing it. On the other hand, analysis of the electron distribution shows that the participation of the lone pair of electrons in an n−π repulsion is stronger in the reactant than in the transition structure, thus destabilizing the reactant relative to the transition structure. Therefore, the two effects cancel, and the reaction is not effectively accelerated by a methoxy substituent.

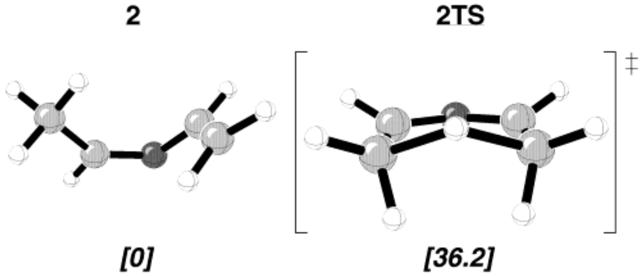

Figure 4. Structure of the compound (*Z*)-ethylidenevinylamine **2** (left) and the [1,5]-H shift transition structure **2TS** (right).

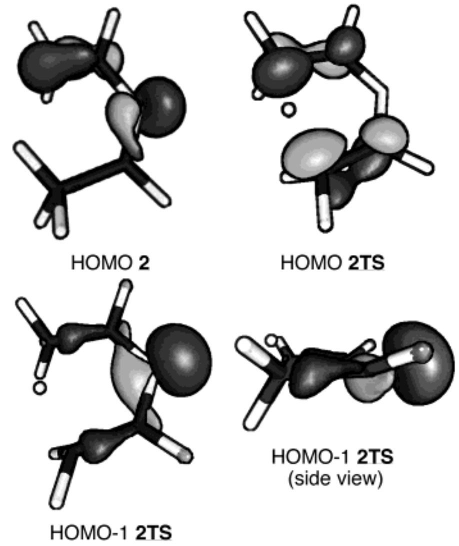

Figure 5. HOMO of **2**, HOMO and (HOMO-1) of the [1,5]-H shift transition structure **2TS**.

A series of nitrogen analogues have been studied to clarify the ability of the lone pair to participate in the π electron system and its effect on the transformation. Our results for the symmetric azapentadiene **2** are summarized in Figure 4. The degeneracy is kept, and the activation energy is found to be 36.2 kcal/mol, an increase of 3.3 kcal/mol as compared to that of the parent reaction.

This increase in the activation energy can be rationalized by an analysis of the molecular orbitals of the reactants and transition structures, giving a measure of the interaction between the lone pairs and the π system via geometrical and energetic criteria. The HOMO of the reactant, shown on the left in Figure 5, gives only a weak n−π repulsion because of the dihedral angle π−C−N−n = 88°. This was calculated given the fact that the imine hydrogen is aligned with the lone pair and the π system is perpendicular to the vinyl plane; the dihedral angle C2−N3−C4−H is equal to 178°. However, the HOMO of

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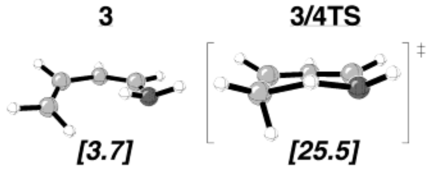

Figure 6. Structures of the compounds (1*Z*)-buta-1,3-dienylamine **3** (left), (2*Z*)-but-2-enylideneamine **4** (right), and the [1,5]-H shift transition structure **3/4TS** (middle).

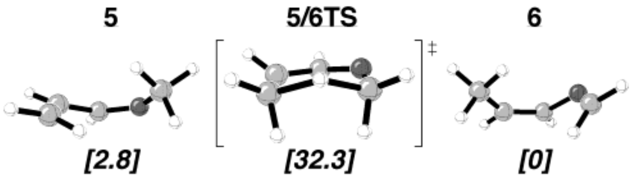

Figure 7. Structures of the compounds (*Z*)-allylidenemethylamine **5** (left), methylene-(*Z*)-propenylamine **6** (right), and the [1,5]-H shift transition structure **5/6TS** (middle). The values in parentheses are the Mulliken charges.

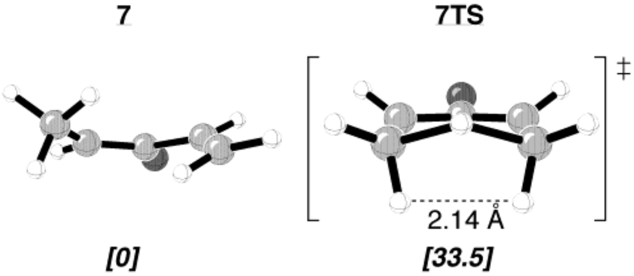

Figure 8. Structure of the compound (3*Z*)-3-fluoropenta-1,3-diene **7** (left) and the [1,5]-H shift transition structure **7TS** (right).

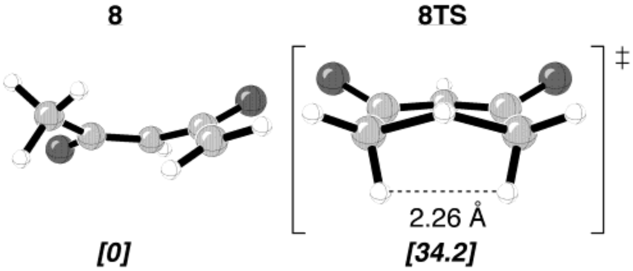

Figure 9. Structure of the compound (3*Z*)-2,4-difluoropenta-1,3-diene **8** (left) and the [1,5]-H shift transition structure **8TS** (right).

the transition structure shows no involvement of the nitrogen lone pair. It is constituted of two π systems with a node plane going through N3 and perpendicular to the plane of the π system. This situation is similar to that of the unsubstituted pentadiene. The lone pair of the nitrogen constitutes the HOMO-1 with a very small energy difference of only 0.012 eV or 0.3 kcal/mol relative to the HOMO. From a side view, shown on the bottom right in Figure 5, the lone pair is aligned with the C2−H bond. The angle of the lone pair with the plane of the transition structure is about 30° (H−C2−C4−C5 = 151°) with a perpendicular π system. The overlap between the filled orbitals HOMO and HOMO-1 is nonzero, thus leading to a destabilization in the transition structure, nonexistent in the reactant, hence the increase in the activation energy.

Substituting a nitrogen atom for one of the other carbons in the chain leads to the four analogues **3**−**6**. **3** can be transformed to **4**, and **5** can react to **6** via the [1,5] hydrogen shift. The reaction of **3** is exothermic by 3.7 kcal/mol. The activation energy is calculated to be 21.8 kcal/mol (see Figure 6). The reaction energy can be rationalized by considering the bond dissociation energies (BDE) from the literature. The π bond of C=N is stronger than the π bond of C=C by 10.2 kcal/mol.[37,38] The BDE of a vinylic C−H bond is 85 kcal/mol,[39] whereas the BDE of a vinylic N−H bond is 92 kcal/mol,[38] thus a difference of 7 kcal/mol in favor of the N−H bond. The BDE analysis gives a shift of the equilibrium by 3.2 kcal/mol. Although not all the relevant bonds have been considered in this BDE analysis, the approximated value is in good agreement with the calculated one. The activation energy is lowered by a significant amount due to the involvement of the lone pair of the nitrogen atom in the aromatic π system of the transition structure, as shown by a MO analysis similar to that for **2**, whereas a repulsive n−π interaction prevails in the reactants. This repulsive interaction is smaller in **4**, revealing the origin for the energetics of the transformation and supporting the above BDE analysis.

The reaction of **5** to form **6** is exothermic by 2.8 kcal/mol, and the activation energy is calculated to be 29.5 kcal/mol (see Figure 7). Although the types of bond broken and created are the same, the relative strength of these bonds needs to be considered. A C−H bond is stronger when adjacent to an sp^2 hybridized carbon atom than when adjacent to an sp^2 hybridized nitrogen atom, because the more electronegative atom destabilizes the C−H$^{\delta+}$. This is supported by the gas-phase thermochemistry data[40] of the protonation of the CH$_2$=CHCH$_2$ anion ($\Delta H^\circ_{\rm rxn} = 391 \pm 2$ kcal/mol)[41] and of the CH$_2$=NCH$_2$ anion ($\Delta H^\circ_{\rm rxn} = 385 \pm 5$ kcal/mol)[42] which gives a difference of 6 kcal/mol, close to the 2.8 kcal/mol calculated, given the additional conjugation. Furthermore, a methylene vinyl imine is more stable than a methyl imine. This is supported by an orbital analysis. A stabilizing interaction via the low-lying excited state is achieved between the lone pair of the nitrogen located in the HOMO and the C=C π* located in the LUMO of **6** (the HOMO−LUMO gap has an energy of 4.6 kcal/mol). This stabilization is more important than that in **5**, where the same gap exists but a longer range of interaction lowers its contribution. Finally, it is counterbalanced by an n−π repulsive interaction in the HOMO of **6**.

With an augmentation of the electron density due to the nitrogen atom participation, the effect observed for the [1,5]-H shift in analogues **1** and **3**−**6** is a decrease in the activation energy.

Electron-Withdrawing Substituents. The effect of electron-withdrawing substituents on the reaction was

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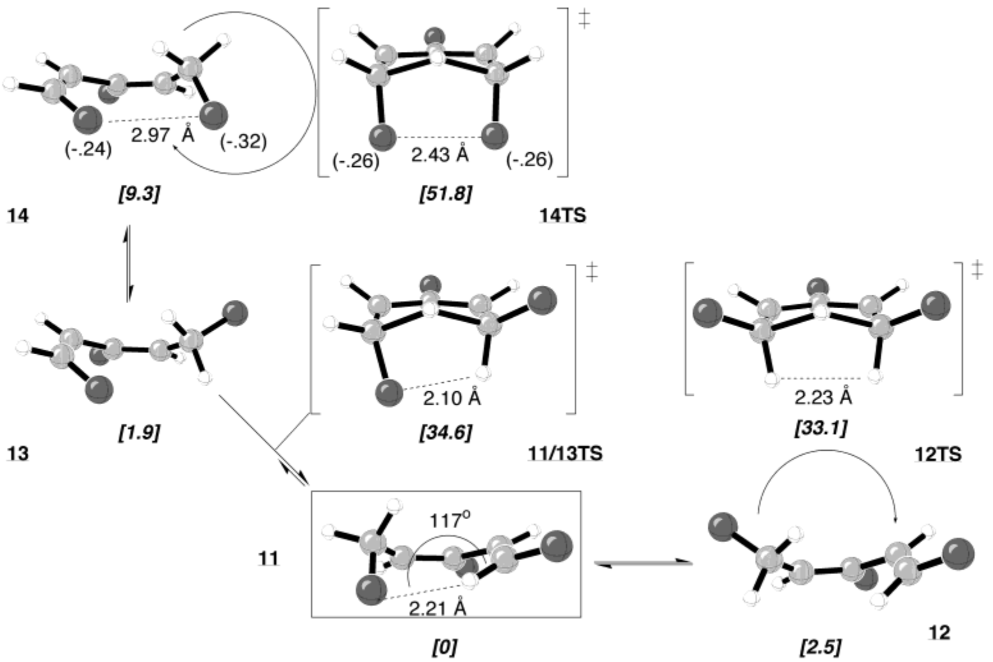

Figure 10. Structures of (1*E*,3*E*)-1,3,5-trifluoropenta-1,3-diene **11** (center bottom) and (1*Z*,3*E*)-1,3,5-trifluoropenta-1,3-diene **13** (lower left), together with their different conformations **12** (lower right) and **14** (top left), respectively. Also shown are the [1,5]-H shift transition structures **11/13TS** (center), **12TS** (top right), and **14TS** (center top). The values in parentheses are the Mulliken charges.

studied for the analogues **7**−**10**, shown in Figure 1. Here, only degenerate hydrogen shifts were studied by introducing one, two, three, and five electronegative fluoride substituents.

Substituting one fluoride for a hydrogen in the C3 position of **7** results in a calculated activation energy of 33.5 kcal/mol, an increase of 0.6 kcal/mol as compared to that of the parent system (Figure 8). Substituting two fluorides for hydrogens in the C2 and C4 positions gives an activation energy of 34.2 kcal/mol, an increase of 1.3 kcal/mol (**8** in Figure 9). The effect of withdrawing electron density from the π system is, as expected, an increase in the activation energy by destabilization of the aromatic transition structure. The electronic effect of the fluorides is additive. The geometrical characteristics are essentially the same, with a small relaxation of the structure in the transition structure due to less electron density. The distance between the hydrogen atoms in the axial position, *trans* to the migrating hydrogen, increases slightly from 2.14 Å in the unsubstituted pentadiene to 2.17 and 2.26 Å in **7** and **8**, respectively.

The case of trisubstituted analogue **9** is more complex because of the stereochemistry of the terminal double bond (*E* in **11** and *Z* in **13**) and the different rotamers the CH_2F moiety can adopt, creating more than one starting point for a hydrogen migration. The lowest energy structure is the *cisoid* conformation, **11**, which contains an interesting feature: the partial charge distribution of the carbon−fluoride bond has a favorable Coulombic interaction with the positively polarized hydrogen of the terminal double bond. Although the geometrical characteristics shown in Figure 10 would fulfill the requirements for a hydrogen bond, care must be taken in such an assumption. Surveys of known crystal structures of organofluorines suggest that close hydrogen-bonded contacts involving fluorine are quite rare.[43,44] Cases of C−F groups as weak hydrogen bond acceptors[45,46] and aromatic C−Hs as weak hydrogen bond donors[47] have been reported. However, a thymine isoster, 2,4-difluorotoluene, does not undergo hydrogen bonding. A proton NMR titration of 9-ethyladenine in chloroform with 1-cyclohexyluracil and 2,4-difluorotoluene did not show a binding curve for the fluorinated nucleotide, whereas it is inserted DNA replication.[48] Ab initio calculations and force field modeling in DNA showed only an interaction similar to a van der Waals contact.[49] This lead to a controversy about the reason behind the Watson−Crick pairing and the mechanism of replication.[50−52] In light of these findings, the nature of the interaction in **11** is not clear.

11 can adopt another conformation, **12**, which lacks this feature and lies 2.5 kcal/mol higher in energy than **11**, thus providing an estimate of the strength of the Coulombic interaction. It is smaller than a strong formate−formate hydrogen bond in the gas phase, calculated to be 5.4 kcal/mol at the B3LYP/6-31++G** level of theory,[53] and comparable but bigger to calculations of the interaction of a fluorine atom bound to a vinyl sp^2 hybridized carbon atom with water (1.5 kcal/mol).[43] **12** undergoes a [1,5]-H shift with a calculated activation energy of 30.7 kcal/mol. The *E* isomer **11** can also undergo a [1,5]-H shift, leading to the *Z* isomer **13** which lacks the stabilizing interaction described previously and thus

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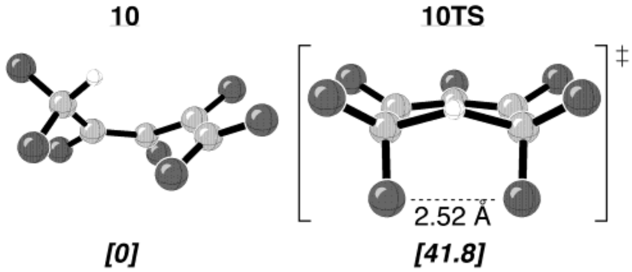

Figure 11. Structure of the compound (3*Z*)-1,1′,2,3,4,5,5′-heptafluoropenta-1,3-diene **10** (left) and the [1,5]-H shift transition structure **10TS** (right).

is endothermic by 1.9 kcal/mol. The activation energy necessary for this transformation is calculated to be 34.6 kcal/mol.

Compound **13** can also adopt another conformation, **14**, which is 9.3 kcal/mol higher in energy than **11** because of an additional repulsive dipole interaction between two fluoride substituents at C1 and C5, which have partial charges of −0.24 and −0.32, respectively. **14** can again undergo a [1,5]-H shift with an activation energy of 42.5 kcal/mol. The trend of activation energies, **14** > **13** and **11** > **12**, is rationalized by the steric (and electrostatic in the case of **14**) interactions going from two fluorides to one hydrogen and one fluoride and finally two hydrogens (where the H−H distance is close to the unsubstituted pentadiene). The distance between the two fluorides in **14TS** is found two be smaller than the sum of the two van der Waals radii, explaining the high activation energy.

The heptasubsituted pentadiene **10** shown in Figure 11 has a very high calculated activation energy of 41.8 kcal/mol. This is not in accordance with the additive effect obtained previously which would predict an activation energy of ca. 37.1 kcal/mol for a compound substituted with seven fluorides. Rather, this is due to the steric interaction of the axial atoms discussed above. The van der Waals radius of fluoride is 0.15 Å larger than the hydrogen's. The distance between the axial fluorides is 2.54 Å, 0.30 Å more than that of the unsubstituted pentadiene. The steric repulsion of these fluorides is the cause of the destabilization of the transition structure. There will also be a steric interaction from the four sets of eclipsed C−F bonds in the transition structure.

With a decrease of the electron density due to the −I effect of the fluoride substituents, the effect observed for the [1,5]-H shift in analogues **7**, **8**, and **10** is an increase in the activation energy, with additional steric and Coulombic interactions in the cases of **10** and **11**−**14**.

Summary and Conclusions

Substituents or heteroatoms in (*Z*)-penta-1,3-diene have a substantial effect on the pericyclic [1,5]-H shift. As a general trend, electron-donating substituents increase the π electron density of the aromatic transition structure and stabilize it, decreasing the activation energy, whereas electron-withdrawing substituents have the inverse effect. However, when the electron-donating and -withdrawing properties of a given substituent are considered, both inductive and mesomeric effects need to be taken into account, as shown in the case of (3*Z*)-3-methoxypenta-1,3-diene **1** or (*Z*)-ethylidenevinylamine **2**.

When substitution breaks the degeneracy of the transformation, the calculated reaction energies can be explained by considering the bond dissociation energies and stability of the species involved. Finally, fluorides have significant steric and electrostatic interactions, leading ultimately to a complex hypersurface in the case of (1*E*,3*E*)-1,3,5-trifluoropenta-1,3-diene **11** and (1*Z*,3*E*)-1,3,5-trifluoropenta-1,3-diene **13**.

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Supporting Information Available: Cartesian coordinates, total energies, imaginary frequencies, and zero-point energies for all structures discussed are available in ASCII format. This material is available free of charge via the Internet at http://pubs.acs.org.

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