Quantum Chemical Characterization of Cycloaddition Reactions between the Hydroxyallyl Cation and Dienes of Varying Nucleophilicity[†]

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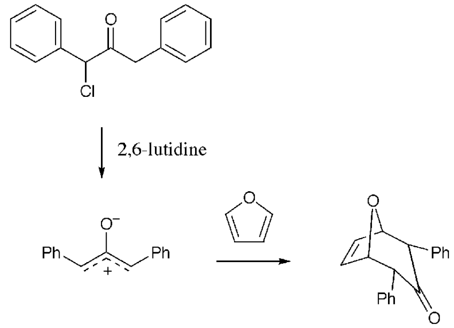
Hydroxyallyl cation prefers to undergo cycloaddition reactions with dienes in a stepwise fashion. Analysis of positive charge distribution in the intermediate formed after initial C−C bond formation provides a simple unifying method for rationalizing changes in reactivity as a function of diene nucleophilicity. Predicted product distributions are consistent with results from experimental studies. Interestingly, for the initial intermediate generated from 1,3-butadiene, [3 + 2] cycloaddition reactions are favored, but closure to form a C−O bond as the second step results in an intermediate that can undergo a low-energy Claisen rearrangement to form a seven-membered-ring product identical to that expected from compact [4 + 3] cycloaddition.

Introduction

Seven-membered carbocycles are found in many classes of natural products and tend to be synthetically more difficult to access than five- and six-membered homologues. The first report of seven-membered-ring construction by a [4 + 3] cycloaddition reaction[1] appeared in 1962, with Fort describing the preparation of an 8-oxabicyclo[3.2.1]oct-6-en-3-one derivative (Scheme 1).[2−4] The key reaction involved the coupling of an α-chlorodibenzyl ketone with furan in the presence of 2,6-lutidine as a base. Mechanistically, α,α′-dehydrohalogenation generates a zwitterionic oxyallyl cation (a valence tautomer of a cyclopropanone) that acts as an electrophile in the cycloaddition. This discovery of the oxyallyl cation's electrophilic reactivity, and subsequent utilization of heterosubstituted allyl cations as three-carbon components in [4 + 3] cycloaddition reactions,[5−17] proved an important innovation in the preparation of seven-membered carbocycles. A recent preparation of the C1−C9 fragment of bryostatin provides a nice example of the utility of this reaction as a tool in the synthesis of complex natural products,[18] and the technology has also been extended to use chiral allyl cations.[19]

Scheme 1



The reactive allyl cation can also undergo [3 + 2] cycloadditions with isolated double bonds to form five-membered-ring carbocycles.[20−24] A related reaction is the cationic variant of the classical [4 + 2] Diels−Alder

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[†] Taken in part from the Ph.D. Thesis of S. E. Barrows, University of Minnesota, Minneapolis, 1997.

(1) Throughout this article, "[*m* + *n*] cycloaddition" will imply construction of a ring of size *m* + *n*—no inference as to the number of p (or s) electrons involved in a possibly pericyclic process is implied.

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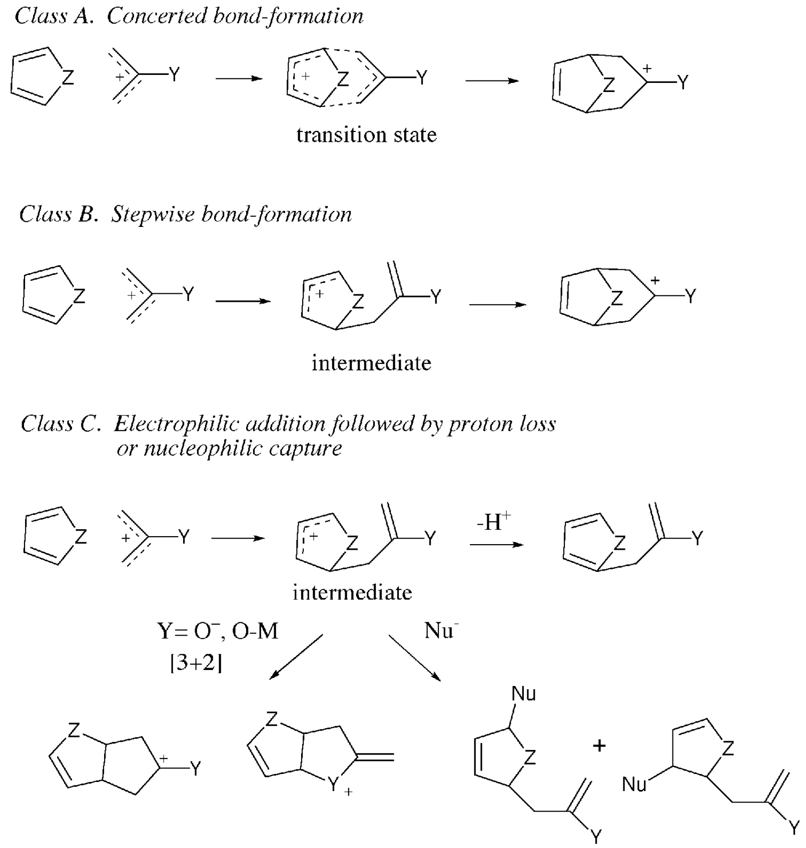

Figure 1. Hoffman's classification of reaction mechanisms for the [4 + 3] or [3 + 2] reactions of allyl cations with dienes.

reaction.[25−30] Such [4 + 2] cycloaddition reactions,[25,30] as well as other ring-forming reactions involving the allyl cation,[31] have been found to proceed in a stepwise fashion. Initial computational studies have suggested that [4 + 3] cycloaddition reactions involving the unsubstituted allyl cation behave similarly.[32] Several reviews of the mechanistic and synthetic aspects of both the [4 + 3] and [3 + 2] cycloaddition reactions involving allyl cations are available.[28,33−37]

Hoffman has proposed a classification scheme and a range of mechanisms for the cycloaddition to explain the results for different substrates (Figure 1).[28] In particular, Hoffman defines class A reactions to follow a concerted mechanism, class B reactions to follow a stepwise mechanism, and class C reactions to involve proton loss or intra- or intermolecular nucleophilic capture of the intermediate formed after an initial C−C bond-forming event (i.e., class B and class C reactions have a common first step but then partition via alternative product-forming pathways). Intramolecular capture can, inter alia, lead to [3 + 2] cycloadducts. The mechanism of any particular [4 + 3] cycloaddition depends on (i) the nucleophilicity of the diene, (ii) the electrophilicity of the allyl cation, (iii) the electronic character of a substituent Y on the allyl cation, and (iv) solvent. When a concerted class A reaction occurs, the allyl cation can interact with the diene in either a so-called "compact" or boatlike transition state or in a so-called "extended" chairlike transition state (Figure 2).[33] The analogous [4 + 2] cycloaddition transition states would be described as "endo" and "exo", respectively.

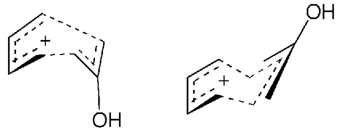

Figure 2. Compact (left) and extended (right) ideal transition state structures for [4 + 3] cycloaddition.

Allyl cations heterosubstituted at the 2-position have been observed to give good yields of cycloadducts with open-chain 1,3-dienes such as 1,3-butadiene, isoprene, and 2,3-dimethyl-1,3-butadiene—Noyori and co-workers have provided most of the data for cycloadditions of 2-oxyallyl cations with acyclic 1,3-dienes, employing diene−iron carbonyl complexes instead of the free diene in order to fix the *s-cis* configuration of the diene and increase its nucleophilicity.[7,22,23,34,38] Shimizu and Tanaka have described the reaction of silyl enol ether **1** with isoprene to yield the often targeted karahanaenone **2** together with regioisomer **3** (Scheme 2).[39] Compound **4**, on the other hand, in the presence of a zinc/copper couple reacts with isoprene to yield not only **2** and **3** but also **5**, suggesting that this reaction either proceeds in a step-

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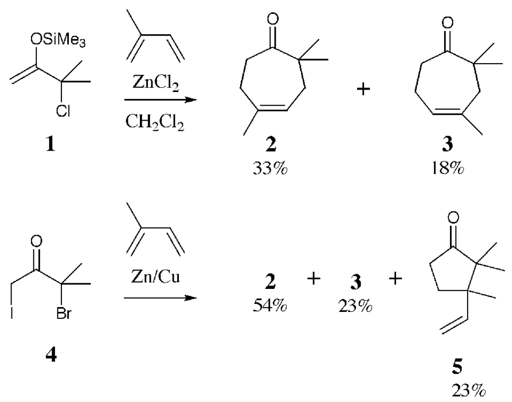
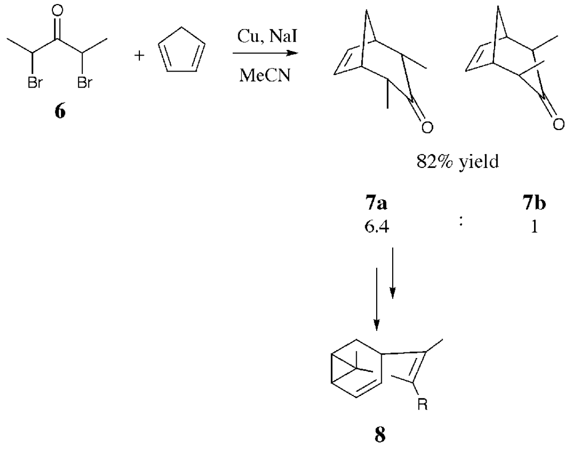
Scheme 2



Scheme 3

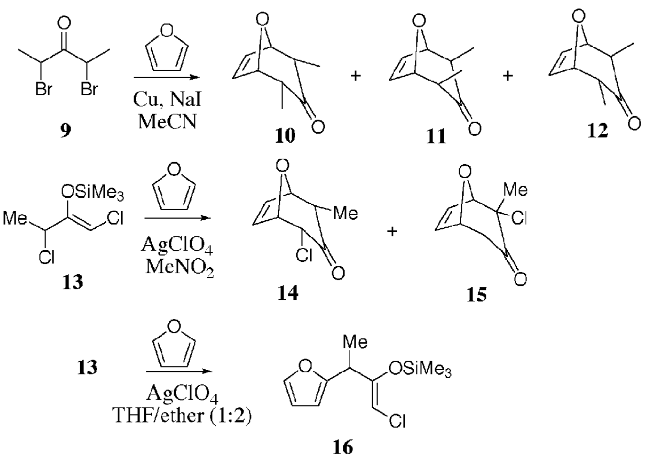


wise fashion or that two mechanisms are operative, one of which is stepwise.[40] The regioselectivity of the latter reaction is highly dependent on solvent; products from class C pathways (including **5**) increase in less polar solvents.[40] The possibility of Lewis acid–Lewis base interactions between the oxyanion and the various metal salts present in the reaction mixture cannot be discounted, and it is likely that this too influences the observed product distributions.

Cyclic 1,3-dienes are generally better substrates for [4 + 3] cycloadditions than their acyclic congeners. For instance, cyclopentadiene reacts with 2-oxyallyl cation generated from **6** to give bicyclo[3.2.1]oct-6-en-3-ones **7a** and **7b** in high yield (Scheme 3).[5,6] The predominant cycloadduct **7a** has served as a precursor to functionalized barbaralanes **8**.[41]

As already noted for the work of Fort,[2-4] the cycloaddition of allyl cations with furans is useful for the preparation of 8-oxabicyclo[3.2.1]oct-6-en-3-ones, which are widely used starting materials for the synthesis of such natural products as analogues of thromboxane A$_2$[42] and B$_2$,[43] C-nucleosides,[44] muscarine analogues,[45] pyrrolizidine alkaloids,[46] and troponoids.[38,47-49] Thus, reaction of **9** with furan provides good yields of **10** and **11** together with trace amounts of **12**, which either derives from a stepwise process or from trace amounts of the syn,anti allyl cation.[38] With increasing electrophilicity of the oxyallyl cation, however, there is considerable loss of stereoselectivity observed for the reaction, suggesting a class B process.[28] This reaction with furans can also be highly sensitive to the solvent. For instance, when silyl enol ether **13** is reacted with furan in nitromethane, the reaction proceeds via an apparently concerted pathway with retention of configuration of the allyl cation and good yields of cycloadducts (Scheme 4).[50] In THF/diethyl ether, on the other hand, a stepwise mechanism is favored and electrophilic substitution dominates to yield product **16**.[50]

Scheme 4



Pyrrole and its *N*-alkyl derivatives can also be used as dienes with less electrophilic oxyallyl cations.[51-53] More electrophilic oxyallyl cations yield exclusively substitution products, i.e., they exhibit class C reactivity. Given the known instability of pyrrole-derived [4 + 3] products in the presence of Lewis acids at elevated temperatures,[35] cycloadducts produced by the class B process under such conditions appear to be in equilibrium with open intermediates that can go on to electrophilic substitution products (Scheme 5).

Finally, when the oxyallyl cation is generated by dehydrohalogenation of an α-halogenated propanone derivative, the resulting intermediate reacts with furans to afford exclusively [4 + 3] cycloadducts by what is presumed to be a class B mechanism (Scheme 6).[54] In this case, it is not clear whether the reacting three-carbon unit is an oxyallyl or a hydroxyallyl cation. The latter species represents the extreme in electrophilicity one might expect for varying atoms coordinating oxygen (e.g.,

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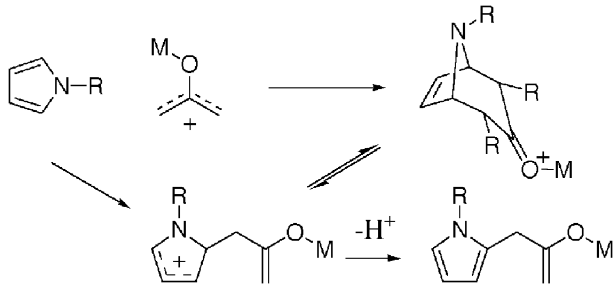
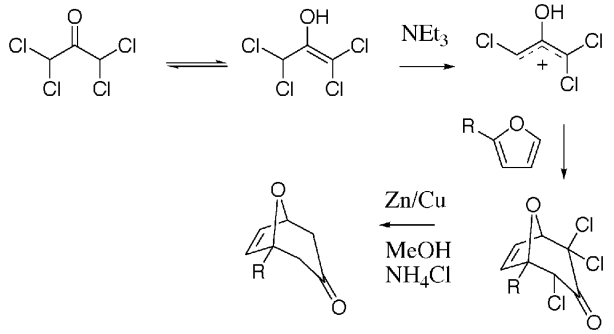
Scheme 5



Scheme 6



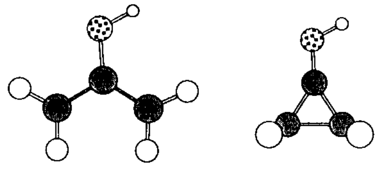
metals, Lewis acids, etc.), while simple oxyallyl, being zwitterionic, represents the other extreme of minimal electrophilicity.

This article specifically examines the reactivity of the highly electrophilic hydroxyallyl cation as a function of varying diene nucleophilicity. In particular we computationally characterize the cycloaddition reactions of the hydroxyallyl cation with four 1,3-dienes: *s-cis*-1,3-butadiene, cyclopentadiene, furan, and pyrrole. We focus in particular on how the nucleophilicity of the diene affects the relative energies and geometries of various potential transition state structures and intermediates. Consistent with experiment, we find that weakly electrophilic dienophiles do require strongly nucleophilic dienes in order for class A or B reactions to occur, and we find that for the least nucleophilic diene, pyrrole, the class C processes become competitive. Interestingly, we find the production of [4 + 3] cycloadducts by initial [3 + 2] cycloaddition followed by Claisen rearrangement to be a lower energy process than direct [4 + 3] cycloaddition, whether stepwise or concerted, for 1,3-butadiene and cyclopentadiene. We rationalize predicted barrier heights and product distributions based on cationic charge distribution in initially formed intermediates.

Computational Methods

Molecular geometries for all species were optimized at the Hartree–Fock (HF), second-order perturbation (MP2), and density functional (DFT) levels of theory using the 6-31G* basis set.[55–57] The DFT calculations employed a mixture of exact exchange with the gradient-corrected exchange functional of Becke[58] and the gradient-corrected correlation functional of Lee et al.[59] following the adiabatic connection scheme first proposed by Becke[60] and as implemented in Gaussian 94[61] (B3LYP). Local minima and transition state structures were verified by calculations of analytical force constants at the HF level, and at higher levels when warranted by large changes in geometry upon reoptimization. Transition states were further characterized by calculation of intrinsic reaction coordinates[62] (IRC) to identify the minima on either side of the saddle point; such calculations were typically at the HF/3-21G level. The HF frequencies were used to compute zero-point vibrational energies (ZPVE) and 298 K thermal contributions ($H_{298} - H_0$ and S_{298}) for all species. Composite G_{298} is defined to be the sum of the gas-phase electronic energies calculated at the MP2/6-31G* level and thermal free energy contributions from the HF/6-31G* level. In certain instances, coupled cluster calculations including all single and double excitations (CCSD),[63,64] sometimes with a perturbative estimate of the effect of triple excitations (CCSD(T)),[65] were undertaken to clarify issues unresolved at the lower levels of theory.

Table 1. Relative Energies (kcal/mol) of 17 and 18



17 **18**

	17	18[a]
B3LYP/6-31G*	0.0	0.0
MP2/6-31G*	3.3	0.0
CCSD(T)/6-31G*//MP2/6-31G*	0.2	0.0

[a] Absolute energies (E_h): −192.187 91, −191.579 90, −191.631 83.

To account for solvation effects, solvation model 2[66] (SM2) calculations were carried out for the gas-phase MP2 geometries. SM2 is a model for aqueous solvation, and it is chosen not because these reactions are likely to take place in water but because we are interested in the qualitative effects of polar solvation as an extreme alternative to the gas phase, and water represents such an extreme with its dielectric constant of 78.3. Since all of the interesting species are charged, electrostatic solvation effects dominate, and unique first-solvation shell effects that might be expected in water will be small enough in magnitude so as not to cloud interpretation. The SM2 calculations were carried out with AMSOL version 5.2.1.[67] Solution G_{298} is defined to be the sum of composite G_{298} and the SM2 free energies of aqueous solvation.

Results and Discussion

Theoretical Considerations. The results in this article are not at a sufficiently high level of theory to be considered quantitatively reliable. However, they *are* expected to be trustworthy in a qualitative sense. Thus,

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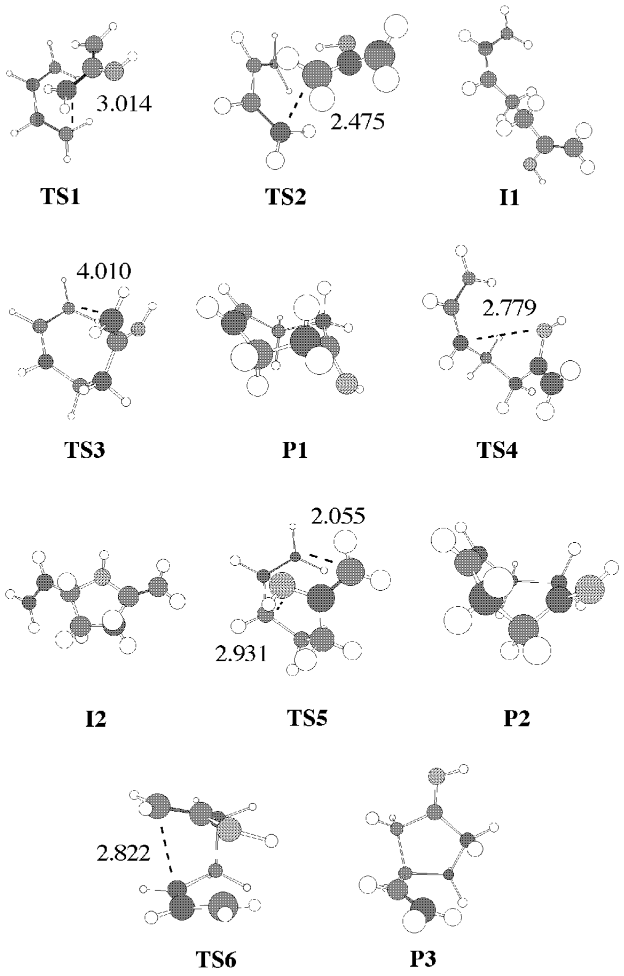

Figure 3. MP2/6-31G* optimized structures of stationary points on the potential energy surface for the reaction of 1,3-butadiene with hydroxyallyl cation; forming and breaking heavy atom bond lengths are shown in angstroms.

while barrier heights may not be particularly accurate, the *relative* barrier heights for competing reaction paths are likely to be much more trustworthy—probably to within 2 or 3 kcal/mol. While HF frequencies are useful for computing thermal contributions to the gas phase free energies, HF relative energies are very poor as judged by comparison to the higher levels. Moreover, HF occasionally predicts stationary points to exist that are no longer stationary at higher levels of theory. As a result we do not discuss the HF results below. While there is more general agreement between the MP2 and the B3LYP results, significant discrepancies arise in several instances, most of which are discussed further below. We consider the MP2 level to be more reliable, given the known tendency of DFT to "over-delocalize" charge[68,69] and spin,[70,71] which can be an issue in some of the systems described below. Single-point calculations at the CCSD or CCSD(T) levels of theory for select instances bear this analysis out, and we therefore largely confine the discussion below to MP2 results.

Table 2. Relative Energies (kcal/mol) of Stationary Points for the Reaction of Hydroxyallyl Cation and 1,3-Butadiene

Reactants, initial C−C TS Structures, and Intermediate Common to All Stepwise Pathways				
	reactants	TS1	TS2	I1
B3LYP/6-31G*	79.2	70.3	64.7	31.6
MP2/6-31G*	90.7	79.1	72.3	41.7
composite G_{298}	102.3	69.0	61.3	35.7
solution G_{298}	33.9	66.7	64.7	39.2
Direct [4 + 3] Closure to Chair Cycloadduct				
	TS3	P1		
B3LYP/6-31G*	36.4	−1.6		
MP2/6-31G*	46.2	−2.4		
composite G_{298}	43.9	−1.3		
solution G_{298}	50.9	0.2		
[3 + 2] Cycloaddition/Claisen Rearrangement				
	TS4	I2	TS5	P2[a]
B3LYP/6-31G*	34.3	25.2	31.3	0.0
MP2/6-31G*	41.1	25.5	36.8	0.0
composite G_{298}	36.9	23.6	31.2	0.0
solution G_{298}	43.8	33.1	40.5	0.0
All-Carbon [3 + 2] Cycloaddition				
	TS6	P3		
B3LYP/6-31G*	33.2	5.3		
MP2/6-31G*	38.7	3.9		
composite G_{298}	37.7	2.7		
solution G_{298}	45.7	−0.3		

[a] Absolute energies (E_h): −348.300 56, −347.137 57, −346.807 40, −346.895 37.

A separate issue involves the valence tautomerism of the planar C_s hydroxyallyl cation **17** with protonated cyclopropanone **18**. At the MP2/6-31G* level, **18** is predicted to be somewhat lower in energy, while both species are equal in energy at the B3LYP/6-31G* level (Table 1). Single-point CCSD(T)/6-31G* calculations at the MP2 geometries indicate **17** to be higher in energy by just 0.2 kcal/mol. This equilibrium, including its sensitivity to solvent, has been extensively studied for simple cyclopropanones.[72−82] While the different predictions for this equilibrium from the MP2 and B3LYP levels of theory can lead to substantially different transition state structures for the first C−C bond-forming reaction in stepwise reactions of dienes with the three-carbon cation, the energetic effects of such geometric changes appear to be small (i.e., the potential energy surfaces are quite flat in this region) and this ambiguity is unlikely to materially affect our predictions for reaction selectivity, particularly with respect to later reaction steps. Note that solvation will be expected to strongly favor **18** since it has a more localized charge (the preference is some 11 kcal/mol at the SM2 level). The provides additional

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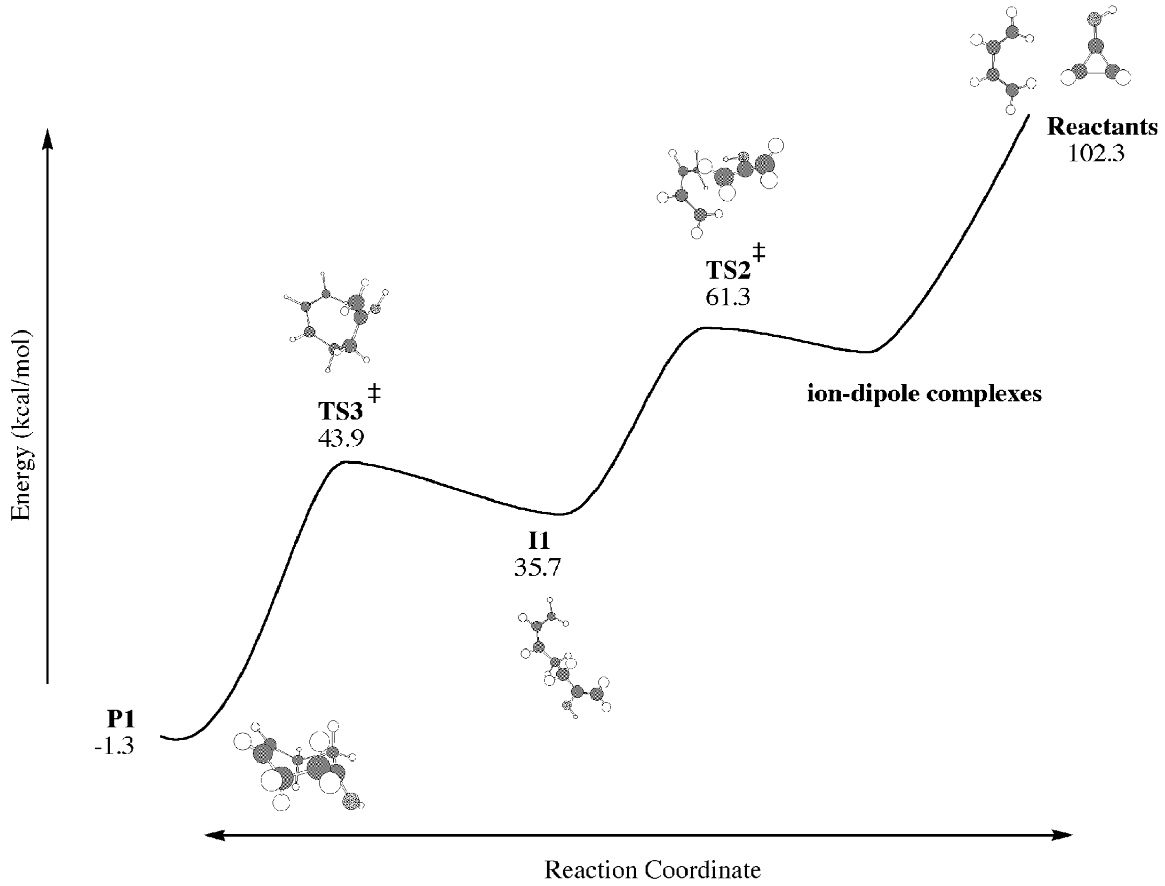

Figure 4. IRC (mass scaled internal coordinates) for stepwise extended [4 + 3] cycloaddition of hydroxyallyl cation with 1,3-butadiene.

motivation for our preference for MP2 structures over B3LYP beyond those described above—they are more likely to resemble the situation in solution.

We now proceed to examine the reaction of **17**/**18** with specific dienes. The discussion proceeds in order of increasing diene nucleophilicity.

Hydroxyallyl Cation + *s-cis*-1,3-Butadiene. Figure 3 illustrates 11 critical stationary points found on the potential energy surface for the reaction of these two species. Relative energies are provided in Table 2. In the gas phase, the separated reactants are at very high energy and there are a number of ion−dipole complexes lower in energy than the reactants that precede initial C−C bond-forming transition state (TS) structures and that we have not characterized in any detail (as expected, solvation effects reduce the energy of the reactants to be well below bond-forming TS structures). A careful search for TS structures involving C−C bond formation reveals two unique geometries. The first, **TS1**, corresponds to a highly asynchronous concerted [4 + 3] process to create extended product **P1**. The second, **TS2**, is about 7 kcal/mol lower in energy and corresponds to a single C−C bond formation that leads to a (floppy) intermediate **I1**. Polar solvation reduces the bias toward **TS2** to only 2 kcal/mol, but the stepwise process remains favored over the concerted cycloaddition. Further reaction of **I1** can proceed along three separate pathways: C−C closure to form **P1** (Figure 4), C−O bond formation in a [3 + 2] sense to form protonated 3*H*-dihydrofuran intermediate **I2** (Figure 5), and C−C bond formation in a [3 + 2] sense to form protonated 3-vinylcyclopentanone product **P3** (Figure 6). Relative to **I1**, the gas phase free energies of activation for these processes are 8.2, 1.2, and 2.0 kcal/mol, respectively; in polar solution these are predicted to be 11.7, 4.6, and 6.5 kcal/mol, respectively.

Reaction to produce **P3** is sufficiently exothermic to be irreversible, and this product represents a class C trap for reactants. Intermediate **I2**, on the other hand, is an allyl vinyl ether and can undergo Claisen rearrangement to produce (apparent) compact [4 + 3] cycloadduct with an activation free energy of about 7.5 kcal/mol in either the gas phase or polar solution (Figure 6).

The salient aspects of this complex potential energy surface are that (i) both concerted and stepwise pathways leading to extended [4 + 3] cycloadduct are found, with the stepwise process being lower in energy; (ii) the lowest energy pathway generating a seven-membered-ring product involves dipolar [3 + 2] cycloaddition followed by Claisen rearrangement; (iii) [3 + 2] cycloaddition in an all-carbon sense is energetically competitive with the [3 + 2]/Claisen process; and (iv) polar solvation has a noticeable impact on barrier heights but has relatively little effect on the predicted selectivities for reaction of **I1**.

The preference for [3 + 2] processes over direct [4 + 3] closure derives from the nature of the intermediate allyl cation **I1**. Substitution at one end stabilizes positive charge at that position, and the enol functionality preferentially reacts at that position, whether at the C or O atom of the enol. In the latter case, subsequent Claisen rearrangement is driven by favorable thermochemistry. Such an effect of substitution on the regiochemistry of ring closure is consistent with similar directing effects observed by Gassman and Gorman in

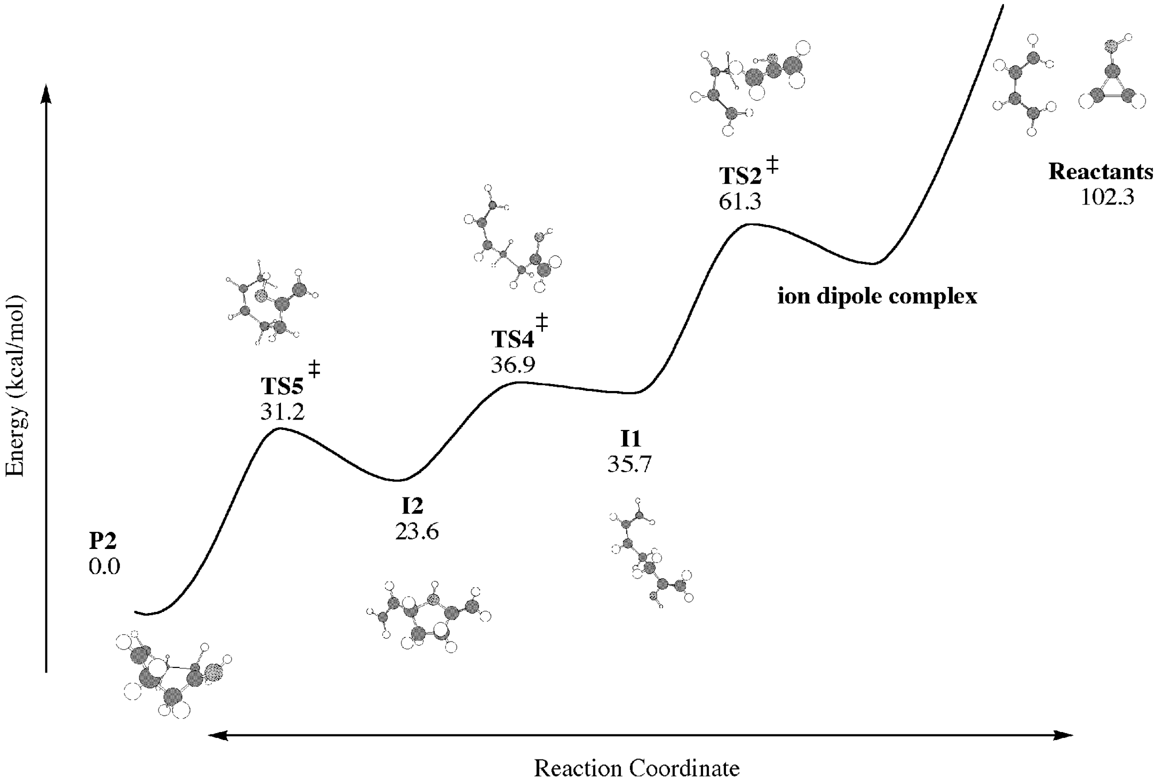

Figure 5. IRC (mass scaled internal coordinates) for stepwise enol [3 + 2] cycloaddition of hydroxyallyl cation with 1,3-butadiene and subsequent Claisen rearrangement.

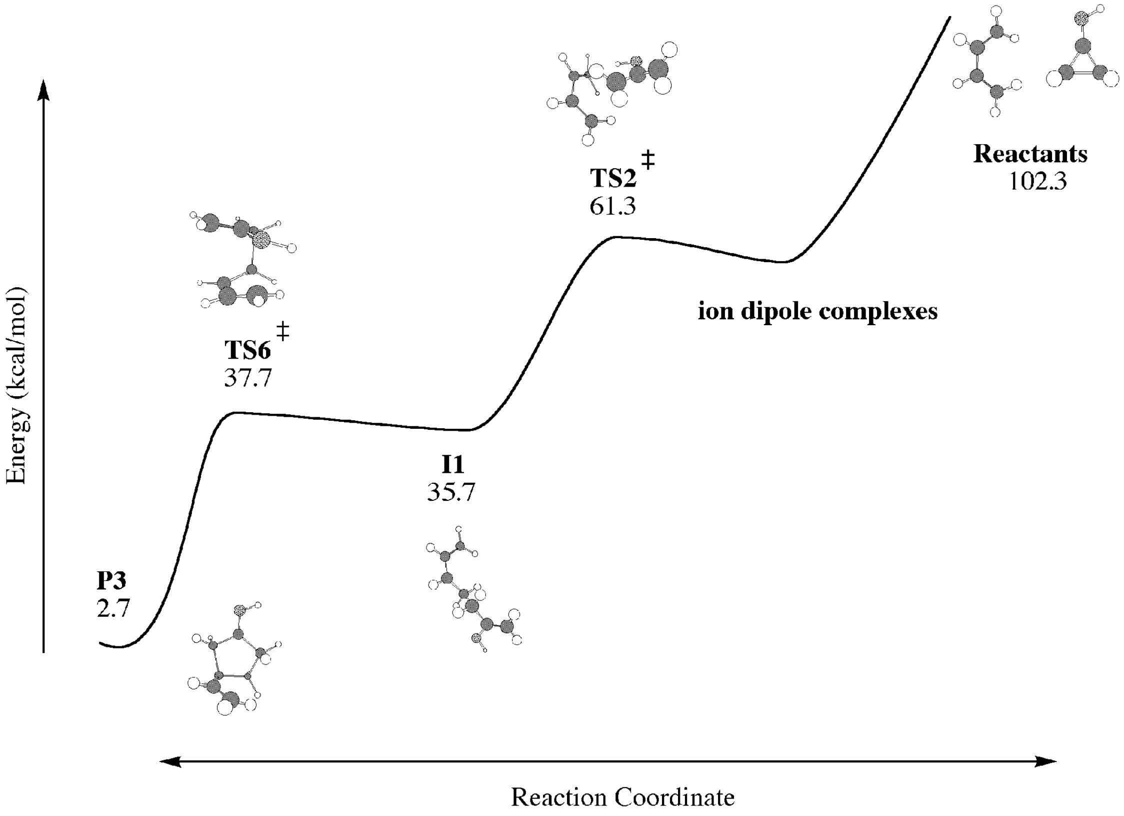

Figure 6. IRC (mass scaled internal coordinates) for stepwise allyl [3 + 2] cycloaddition of hydroxyallyl cation with 1,3-butadiene.

intramolecular ionic Diels–Alder reactions.[29] The weak preference for C–O closure over C–C is consistent with the observation of the all-carbon [3 + 2] product in reactions of zinc oxyallyl cation and isoprene (Scheme 2).

Hydroxyallyl Cation + 1,3-Cyclopentadiene. With this more nucleophilic diene, we find all [4 + 3] and [3 + 2] cycloaddition reactions to be completely stepwise. Extensive searching of the potential energy surface failed

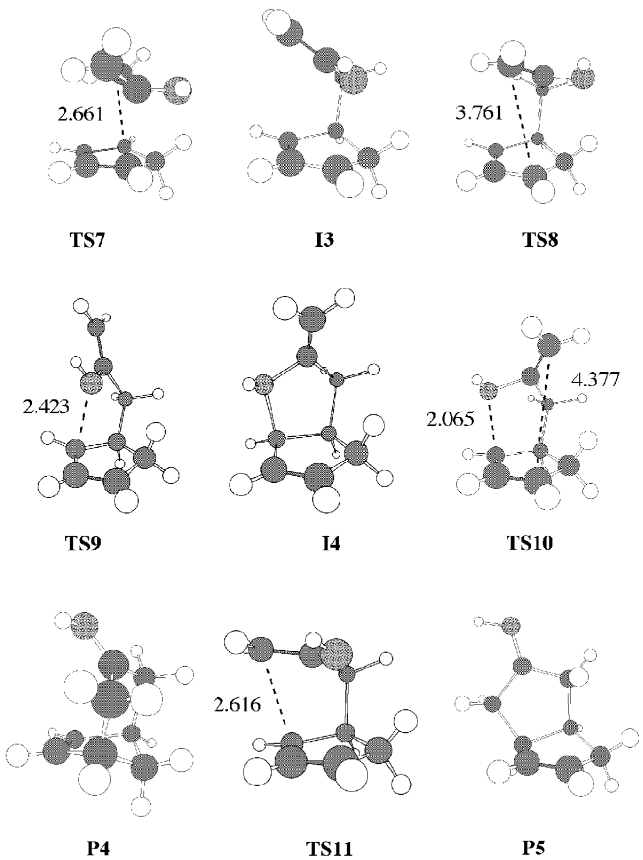

Figure 7. MP2/6-31G* optimized structures of stationary points on the potential energy surface for the reaction of cyclopentadiene with hydroxyallyl cation; forming and breaking heavy atom bond lengths are shown in angstroms.

Table 3. Relative Energies (kcal/mol) of Stationary Points for the Reaction of Hydroxyallyl Cation and Cyclopentadiene

Reactants, Initial C−C TS Structure, and Intermediate Common to All Pathways				
	reactants	TS7	I3	
B3LYP/6-31G*	71.5	61.7	16.4	
MP2/6-31G*	83.5	69.9	24.9	
composite G_{298}	65.2	61.1	21.7	
Direct [4 + 3] Closure in Extended Sense				
	TS8	P4[a]		
B3LYP/6-31G*	18.1	0.0		
MP2/6-31G*	28.0	0.0		
composite G_{298}	27.6	0.0		
[3 + 2] Cycloaddition/Claisen Rearrangement				
	TS9	I4	TS10	P4
B3LYP/6-31G*	17.4	12.9	13.5	0.0
MP2/6-31G*	26.7	20.6	23.1	0.0
composite G_{298}	24.2	20.1	22.9	0.0
All-Carbon [3 + 2] Cycloaddition				
	TS11	P5		
B3LYP/6-31G*	17.4	−1.6		
MP2/6-31G*	25.9	1.0		
composite G_{298}	25.0	0.9		

[a] Absolute energies (E_h): −386.403 02, −385.138 28, −384.792 46.

Table 4. Relative Energies (kcal/mol) of Stationary Points for the Reaction of Hydroxyallyl Cation and Furan

Reactants, Initial C−C TS Structure, and Intermediate Common to All Pathways				
	reactants	TS12		
B3LYP/6-31G*	54.6	45.7	1.6	
MP2/6-31G*	62.5	50.1	5.5	
composite G_{298}	44.1	41.5	2.5	
Direct [4 + 3] Closure in Extended Sense				
	TS13	P6[a]		
B3LYP/6-31G*	7.0	0.0		
MP2/6-31G*	12.5	0.0		
composite G_{298}	11.3	0.0		
Direct [4 + 3] Closure in Compact Sense				
	TS14	I6	TS15	P6
B3LYP/6-31G*	3.1	−1.0	4.6	0.0
MP2/6-31G*	8.6	4.2	5.4	0.0
composite G_{298}	6.1	1.0	4.4	0.0
All-Carbon [3 + 2] Cycloaddition				
	TS16	P7		
B3LYP/6-31G*	11.5	−1.0		
MP2/6-31G*	17.5	0.7		
composite G_{298}	15.5	−0.8		

[a] Absolute energies (E_h) −422.295 53, −420.989 88, −420.857 61.

to yield any concerted transition state structures. Other aspects of this reaction are for the most part similar to the above-discussed 1,3-butadiene case. In this case, nine key stationary points (Figure 7) define the potential energy surface, and their relative energies are provided in Table 3. Like the stepwise reactions for the previous case, an initial transition state structure for C−C bond formation, **TS7**, and a resulting intermediate allyl cation, **I3**, are common to all reaction paths. Additionally, [3 + 2] cycloaddition through **TS9** followed by Claisen rearrangement of **I4** through **TS10** remains the preferred pathway at our best composite level of theory and the reaction coordinate for this lowest energy pathway leading to a seven-membered-ring product (**P4**) is shown in Figure 8. The all-carbon [3 + 2] cycloaddition through **TS11** to produce **P5** has a barrier 0.8 kcal/mol higher in energy. Finally, transition state structure **TS8** leads directly to [4 + 3] cycloadduct with an activation free energy 3.4 kcal/mol above that for reaction through **TS9**. The resulting extended protonated chair cycloheptenone is not stationary and spontaneously converts to **P4**.

While not presented in detail, for the sake of brevity, polar solvation leaves the relative energies of the [3 + 2] transition states **TS9** and **TS11** unchanged; however, the difference in energy between **TS8** and **TS9** is reduced to 1.3 kcal/mol.

The much smaller preference for [3 + 2] processes over [4 + 3] in this system compared to 1,3-butadiene derives from the nature of the allyl cation **I3**, which is singly substituted at either end. Thus, there is no particular localization of positive charge at either terminus of the allyl cation, and no particular preference for trapping at either end. Nevertheless, all-carbon [3 + 2] products are predicted to be formed competitively with [4 + 3] products for this case.

The increased stability of the disubstituted allyl cation is further indicated by the much smaller energy difference between **I3** and **I4** compared to **I1** and **I2** (the relative stabilities of the protonated 3*H*-dihydrofurans are assumed to be equivalent, implying **I3** to be more stable than **I1**). Indeed, at the MP2 level, **I4** is only very weakly bound, with a C−O bond distance of 1.624 Å. At the B3LYP level, this bond distance increases to 2.472 Å! This appears, however, to be an artifact of DFT preferring structures having more delocalized charge, as noted above. Single-point calculations at the more complete CCSD/6-31G* level predict the MP2 geometry to be lower in energy by 2.0 kcal/mol.

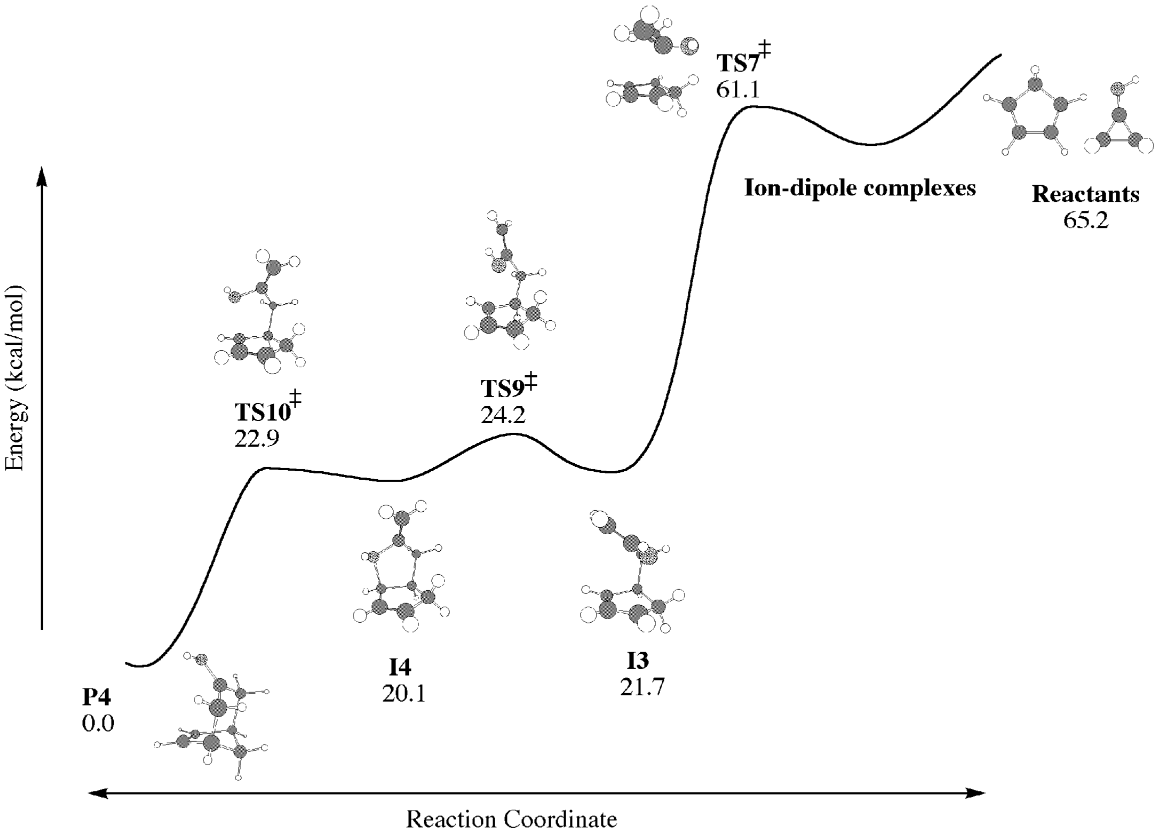

Figure 8. IRC (mass scaled internal coordinates) for stepwise enol [3 + 2] cycloaddition of hydroxyallyl cation with cyclopentadiene and subsequent Claisen rearrangement.

Table 5. Relative Energies (kcal/mol) of Stationary Points for the Reaction of Hydroxyallyl Cation and Pyrrole

	Reactants, Initial C−C TS Structure, and Stable Intermediates			
	reactants	TS17	I7[a]	I8
B3LYP/6-31G*	65.6	51.6	0.0	1.0
MP2/6-31G*	70.9	52.0	0.0	1.6
composite G_{298}	55.1	41.9	0.0	1.3
	All-Carbon [3 + 2] Cycloaddition			
	TS18	P8		
B3LYP/6-31G*	20.5	10.5		
MP2/6-31G*	23.1	6.7		
composite G_{298}	23.2	9.2		

[a] Absolute energies (E_h): −402.458 40, −401.173 75, −400.859 34.

Hydroxyallyl Cation + Furan. Replacement of the methylene group in cyclopentadiene with an oxygen atom induces substantial changes in the various pathways for the reaction of the cyclic diene with **17**/**18**. The nine key stationary points characterizing the relevant potential energy surface are illustrated in Figure 9, and their relative energies are provided in Table 4. All paths continue to be stepwise and to originate from an initial C−C bond formation through a common TS structure, **TS12**, and intermediate, **I5**.

Oxyallyl cation **I5**, however, is very stable, since it has substantial oxonium ion character. As a result, positive charge now concentrates at the oxygen-substituted terminus of the allyl cation, and ring closure to the alternate position in a [3 + 2] sense either fails to occur (oxygen closure) or requires a substantially larger activation free energy than is true for the nonheterosubstituted diene cases (carbon closure). Thus, **TS14** and **I6** do not correspond to a formal [3 + 2] cycloaddition but more closely resemble a simple bond rotation to prepare for compact [4 + 3] closure in a stepwise fashion.

Compact closure takes place with a rate-limiting step 5.2 kcal/mol lower in energy than alternative extended closure, consistent with an experimentally observed preference for compact cycloaddition of furan with iron and zinc oxyallyl cations.[28] This preference derives in part from improved electrostatic interactions between the allyl cation and the enol oxygen atom in the compact TS structure and in part from the greater stability of the chair form of the six-membered ring in bicyclic product **P6** (the boat conformer proves not to be stationary).

Returning to [3 + 2] closure in the all-carbon sense, the relatively higher barrier for this process in the furan case is consistent with failure to observe such products experimentally. It does appear, however, that under conditions of thermodynamic control one might expect to see conversion of [4 + 3] products to fused [3.3.0] bicycles, since the protonated ketones are predicted to be more stable for the latter than the former.

Hydroxyallyl Cation + Pyrrole. The final potential energy surface examined here considers [4 + 3] and [3 + 2] cycloaddition reactions between the hydroxyallyl cation and pyrrole. We note that experimentally cycloadducts are formed only between pyrrole and less electrophilic allyl cations.[51−53] With *more* electrophilic allyl cations, only substitution products deriving from class C pathways are obtained. Figure 10 illustrates five key stationary points on this potential energy surface, and the relative energies for these structures are listed in Table 5.

At the MP2 and B3LYP levels of theory, this reaction fails to proceed to form [4 + 3] cycloadducts after initial

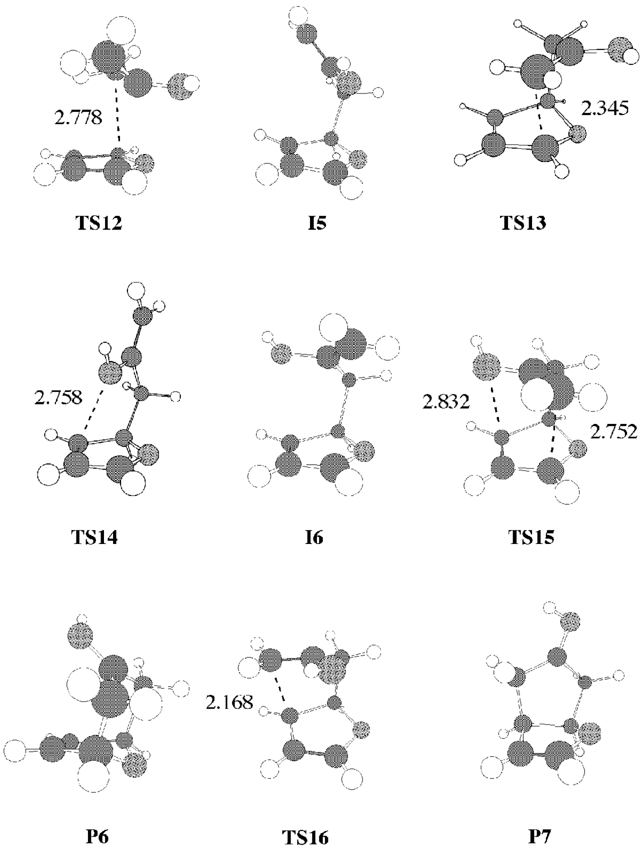

Figure 9. MP2/6-31G* optimized structures of stationary points on the potential energy surface for the reaction of furan with hydroxyallyl cation; forming and breaking heavy atom bond lengths are shown in angstroms.

C−C bond formation through **TS17** to form intermediate **I7**. This can be attributed to the high stability of the 1-azabutadienyl cation present in **I7**; [4 + 3] closure leads to considerably less stable protonated ketones that are not stationary. Closure in a [3 + 2] sense to form protonated 3*H*-dihydrofuran is similarly unfavorable; an intermediate **I8**, which is a conformational isomer of **I7**, was located, but is not prone to closure. An all-carbon [3 + 2] cycloaddition reaction transition state structure, **TS18**, was located, as was fused bicyclic product **P8**. However, the product of this cycloaddition reaction is 9.2 kcal/mol higher in energy than **I7**, suggesting that its formation is unlikely. Thus, consistent with experiment, theory predicts that only class C products arising from electrophilic substitution should result from the reaction of highly electrophilic allyl cations with pyrrole.

Conclusions

The highly electrophilic hydroxyallyl cation prefers to react with dienes in a stepwise fashion to generate various [4 + 3] and [3 + 2] cycloadducts. The relative barrier heights associated with distinct ring closure steps are controlled by the distribution of positive charge in the substituted allyl cation resulting from initial C−C bond formation. For the initial intermediate generated from 1,3-butadiene, [3 + 2] cycloaddition reactions are favored, but such closure to form a C−O bond as the second step results in an intermediate that can itself undergo a low energy Claisen rearrangement, which forms a seven-membered-ring product identical to that expected from compact [4 + 3] cycloaddition. Cyclopentadiene as a substrate diminishes this preference: [3 + 2] barriers are similar to [4 + 3] barriers in this system.

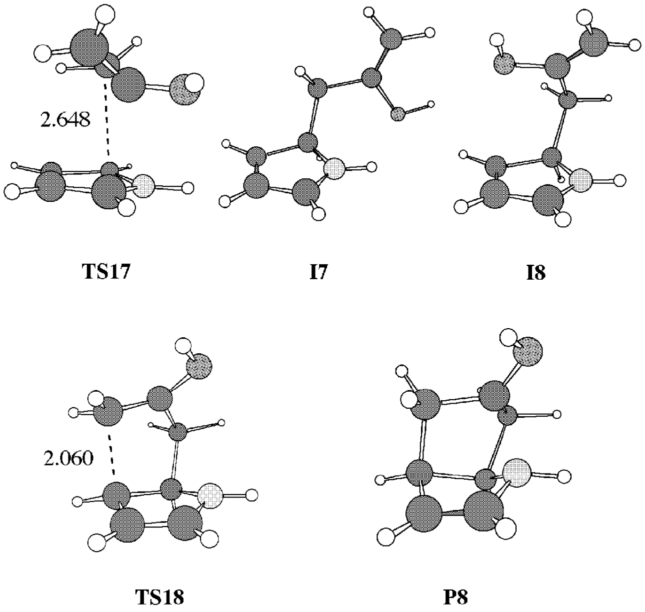

Figure 10. MP2/6-31G* optimized structures of stationary points on the potential energy surface for the reaction of pyrrole with hydroxyallyl cation; forming and breaking heavy atom bond lengths are shown in angstroms.

The intermediate cation generated from furan as a reaction substrate has substantial oxonium ion character and localizes charge so as to favor direct [4 + 3] bond closure. Finally, the 1-azabutadienyl cation created after initial C−C bond formation in the reaction of hydroxyallyl cation with pyrrole is so stable that *no* bond closure steps are energetically favorable, and theory predicts that this reaction should generate only electrophilic substitution products.

These predicted product distributions are consistent with results obtained from many different experimental studies. Analysis of charge distribution in the first intermediate required for stepwise cycloadditions thus provides a simple unifying method for rationalizing changes in reactivity as a function of diene nucleophilicity. Future work will focus on the effects of varying the electrophilicity of the allyl cation in reactions with 1,3-butadiene.

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