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Theoretical Studies of the Nazarov Cyclization. 2. The Effect of β Silyl and β Methyl Groups

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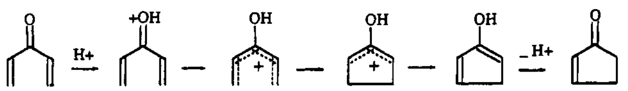
Ab initio molecular orbital calculations have been carried out at the RHF/3-21G(*) level on the protonated form of 1,4-pentadien-3-one bearing a methyl, silyl (SiH_3), or no (i.e., H) substituent at the β position. Electron correlation was accounted for by MP3/6-31G** single-point calculations. Substituent effects on the rate of reaction are steric and inductive, while the trends observed for heats of cyclization are attributed primarily to hyperconjugation, in agreement with earlier work by Jorgensen on the effects of these substituents on carbenium ions. Cyclization of the unsubstituted (-2.4 kcal/mol) and β-SiH_3-substituted (-5.9 kcal/mol) compounds are exothermic, while the β-CH_3-substituted cyclization is endothermic by 4.5 kcal/mol. The transition states for the electrocyclization reactions are all reactant-like and relatively invariant as a function of β substituent; the newly forming C-C bond length varies from 2.09 Å with no substituent to 2.07 Å for β-SiH_3 to 2.05 Å for β-CH_3. The activation energies are 20.4, 21.7, and 21.9 kcal/mol, respectively.

Introduction

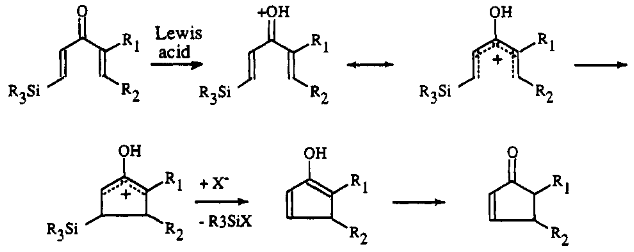
The Nazarov cyclization[1] has gained prominence as a synthetically useful reaction for the construction of cyclopentenone rings (Scheme I). In its original form, the reaction of a 1- or 2-substituted divinyl ketone gives the thermodynamically favored double-bond regioisomer, i.e., the more highly substituted cyclopentenone. In a dramatic example of the silicon β effect, addition of a silyl group β to the carbonyl carbon provides the less substituted double-bond regioisomer (Scheme II).[2] A modification of this reaction leading to linearly fused tricyclic compounds has recently been shown to exhibit complete stereoelectronic control of torquoselectivity.[3,4]

The regiodirecting effect of the silicon substituent (β effect) is manifest upon Lewis acid promoted C-Si bond cleavage after the electrocyclization step. However, the electrocyclization is the rate-limiting step in the reaction, and silicon substituents have been noted to cause a decrease in the rate of reaction.[5] We have previously[6] studied the cyclization of the parent system 1 and now turn our attention to studying the effects and origin of the effects (e.g., steric versus electronic) of substituents located on a terminal vinyl carbon β to the hydroxyl-bearing carbon on the rate and selectivity of cyclization. SiH_3 was chosen as a computationally feasible model of silyl substituents in order to evaluate the silicon α and β effects on the cation, while CH_3 was chosen as a prototypical inductively donating alkyl group. Calculations on protonated 1-silyl-1(*E*),4-pentadien-3-one, (2) and protonated 1-methyl-1(*E*),4-pentadien-3-one (3) and comparison of these systems to 1 are reported herein as part of our computational efforts to understand the Nazarov cyclization.

Scheme I



Scheme II



Computational Methods

The ab initio calculations were carried out using GAUSSIAN 86 on various VAX computers and GAUSSIAN 88 on the Ohio Supercomputer Center Cray Y-MP/864.[7] Structures were completely optimized starting from the previously obtained geometries[6] of the protonated ketone 1; no symmetry or other constraints were imposed. Restricted Hartree-Fock calculations leading to stationary points on the potential surface were calculated using the 3-21G(*) split valence basis set, which includes d-type polarization functions on silicon, and were confirmed by frequency calculations.[8] Third-order Moeller-Plesset electron correlation corrections[9] were calculated as MP3/6-31G**//RHF/3-21G(*) single points using the default frozen core option.[10] The 6-31G** basis set includes d-type polarization functions on all non-hydrogen atoms and p-type polarization functions on hydrogens.[11]

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Table I. Relative Energies of Protonated Ketone 1

	RHF/3-21TG*	MP3/6-31G**// RHF/3-21G*
1SS	0.35	1.14
1SA	0.00	0.00
1AA	4.71	0.91
1TS	30.67	20.36
1CP	5.59	-2.39

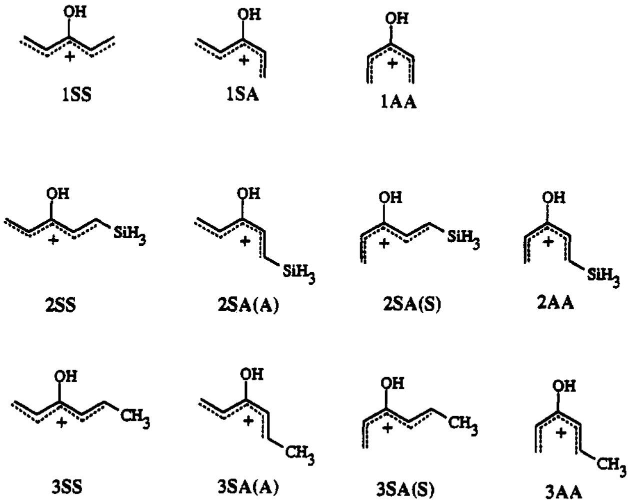
Table II. Relative Energies of β Silyl Protonated Ketone 2

	RHF/3-21G*	MP3/6-31G**// RHF/3-21G*
2SS	0.55	1.36
2SA(A)	0.00	0.00
2SA(S)	0.36	0.38
2AA	5.09	1.26
2TS	32.42	21.72
2CP	4.15	-5.90

Table III. Relative Energies of β Methyl Protonated Ketone 3

	RHF/3-21G*	MP3/6-31G**// RHF/3-21G*
3SS	0.002	0.82
3SA(A)	0.09	0.00
3SA(S)	0.00	0.13
3AA	5.15	1.17
3TS	32.47	21.92
3CP	11.68	4.46

Chart I



Molecular orbital plots were produced using Jorgenson's PSI 88 program running on a DECstation 3100.[12]

Results and Discussion

The protonated ketone 1 exhibits three stable conformations. The geometries at the RHF/3-21G(*) level of theory do not differ significantly from those previously calculated using the 6-31G* basis set, nor do the relative single-point energies calculated at the MP3/6-31G** level differ significantly as a function of basis set used for optimization.[6] However, the number of basis functions involved and the expense of the calculations on systems with a β substituent precluded use of the larger basis set for optimization; therefore, we will limit our discussion to the RHF/3-21G(*) geometries and MP3/6-31G**//RHF/3-21G(*) single-point energies. These data are summarized in Table I for the syn, syn (SS), syn, anti (SA), and anti, anti (AA) conformers of 1 as well as for the transition structure, **1TS**, and cyclized system, **1CP**. At the MP3/6-31G**//RHF/3-21G(*) level, the energy of activation for the cyclization step is 20.4 kcal/mol; the cyclization process is exothermic by 2.4 kcal/mol.

The relative energies of the conformers, transition states, and cyclized products of 2 and 3 are given in Tables II and III. These compounds are derived conceptually from the unprotonated trans-substituted olefins and as such present the possibility of two syn, anti conformations. We refer to the conformer with the silyl or methyl substituent on the vinyl moiety syn to the oxygen as SA(S) and the conformer with the substituent on the vinyl moiety anti to the oxygen as SA(A). The relative order of stability of the conformers of 2 at the MP3/6-31G** level is SA(A) > SA(S) > AA > SS, the same as for the unsubstituted protonated ketone 1 (Chart I). The SA(A) conformer is more stable than the SA(S) conformer by 0.38 kcal/mol, possibly due to better orbital overlap for extended conjugation in the protonated trans enone-like moiety as compared to cis.[13] Destabilizing steric interactions between the SiH_3 group and the vinyl hydrogen at C2 should also disfavor the SA(S) conformation.[13] Indeed, the angle formed by carbons 1–3 is compressed by 3.4° and the Si–C1–C2 angle is 0.5° larger in SA(S) relative to SA(A). In 3, the SA(A) conformer is again more stable than SA(S) but by only 0.13 kcal/mol. Examination of the optimized geometries shows steric effects and angle compression very similar to that described for 2. The difference in relative energies of SA(A) and SA(S) for 2 and 3 is therefore probably electronic (vide supra).

The activation energy for cyclization of the silicon-substituted system 2 (Table II) is calculated to be 1.4 kcal/mol higher than in the unsubstituted system 1. Denmark has observed that the rate of the silicon-directed Nazarov cyclization is typically slower than the rate for the corresponding unsubstituted compound and has suggested that the rate depression may be due to steric and/or electronic effects.[5] Alkyl groups are also known to retard the reaction rate.[14] From the data in Table III for the methyl-substituted system 3 it is apparent that the energy of activation is 0.2 kcal/mol higher than for the cyclization of 2 and 1.6 kcal/mol higher than for the unsubstituted system 1.

Figure 1 shows the charge at each position in compounds 1–3 for three stationary points (AA, TS, CP) along the reaction coordinate. These values are taken from the MP3/6-31G**//RHF/3-21G(*) Mulliken population analyses and are the sum of each heavy atom and all its attached hydrogens. In all three systems, the charge at the terminal vinyl carbons and the hydroxy-bearing carbon becomes less positive while the carbons β to the hydroxyl groups become more positive as the electrocyclization proceeds. Denmark has previously proposed that during the Nazarov cyclization positive charge is transferred from the starred positions of the pentadienyl cation-like starting material to the starred positions of the allyl cation-like cyclized product (Figure 2). Note also that the charge at each of the three nonterminal carbons of the pentadienyl

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(12) We thank Professor Jorgenson and Daniel Severence for a copy of this program.

(13) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14 and references cited therein. Variations in the hydroxyl group's rotomeric state have been examined and discounted as the cause of the relative order of stability of the conformers.

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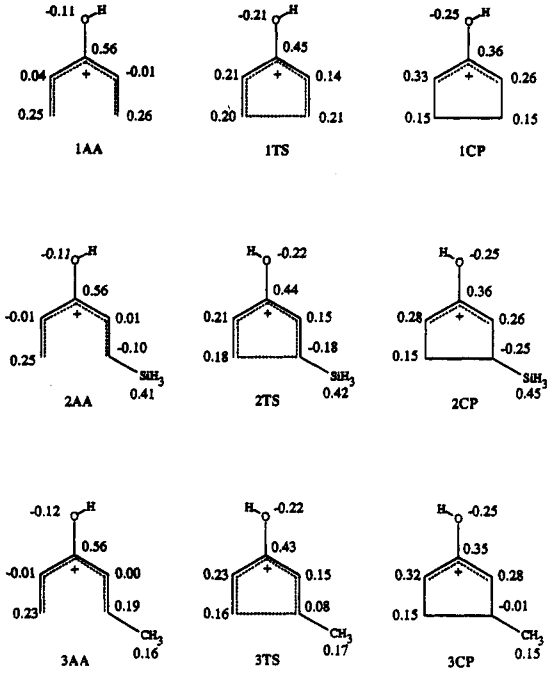

Figure 1. Charge at each position (hydrogens summed into heavy atoms) from Mulliken population analysis.

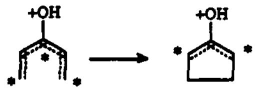

Figure 2. Transfer of positive charge during cyclization.

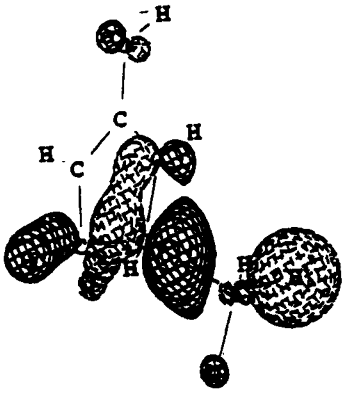

Figure 3. Hyperconjugation in the SHOMO of **2CP**.

system, i.e., those carbons that become the allyl-like system in the cyclized product, is invariant (with one exception, *vide infra*) as a function of substituent on the terminal vinyl carbon, indicating the lack of long-range substituent effects.

Alkyl groups are known to stabilize α alkyl and α vinyl cations as a result of C–H hyperconjugation and a general charge dispersal due to polarization. β stabilization is modest and due primarily to C–C hyperconjugation. Therefore, when R is a methyl group stabilization of the starting material would act in concert with any steric effect to further increase the activation energy and decrease the heat of cyclization. Indeed, the MP3/6-31G**//RHF/3-21G(*) heat of cyclization is endothermic by 4.5 kcal/mol (Table III). The case for silicon is more complex. Theoretical studies have concluded that the alkyl group is only 1–3 kcal/mol more stabilizing for α silyl and α alkyl vinyl cations in the gas phase than is the silyl group.[11,15] Solvolysis studies have shown that for the vinyl cation an α trimethylsilyl group is stabilizing relative to a hydrogen but destabilizing relative to a *tert*-butyl group.[16] Stabilization of a vinyl cation β to the silicon group is significantly larger and due primarily to Si–C hyperconjugation with minor contributions from inductive and polarization effects. The β effect is therefore conformationally dependent.[11] The calculated energy of activation for the cyclization of **2**, 21.7 kcal/mol, is intermediate to that for the unsubstituted **1**, 20.4 kcal/mol, and the methyl-substituted **3**, 21.9 kcal/mol, as might be expected if the transition state is reactant-like, i.e., has either significant α-cation character, considerable double-bond character at carbons 1 and 2, or both. This latter factor would geometrically preclude Si–C hyperconjugation and the resulting significant stabilization of the transition state.

In the cyclized products **1CP** and **3CP** the positions α to the hydroxyl-bearing carbon do not have equal charges, while in the silyl system **2CP** the charges at these positions are essentially identical (Figure 1). Note that the charge on these positions is unequal in **2AA** and the transition state **2TS**. It is only in the cyclized product that the charge on these β positions becomes equal, and it is only in the cyclized product that the β effect is manifest. The Si–C1–C2–C3 dihedral angle is essentially 180° in the SA(S), SA(A), SS, and AA conformations of **2** and only 154.1° in the transition state **2TS**. The Si–C1 bond is therefore almost perpendicular to the π orbital of the delocalized cation and unable to exhibit hyperconjugation. In **2CP** the Si–C1–C2–C3 angle is 107.4° and Si–C p-π overlap is significant. Examination of the molecular orbitals at the calculated stationary points for **2** on the potential energy hypersurface for cyclization reveals that only in the second highest molecular orbital (SHOMO) of the cyclized product is there any hyperconjugation, i.e., interaction between the p-π orbital of the cation and the Si–C antibonding orbital (Figure 3).[17] This provides an explanation for the more exothermic heat of cyclization of this system. The lack of stabilization in the transition state, coupled with the steric and electronic effects discussed previously, further explains the activation energy for cyclization of the silyl-substituted system relative to the unsubstituted and methyl substituted systems.

The transition structures for the cyclization of **1**–**3** are very similar geometrically. Newman projections (Figure 4) show that both the methyl and silyl substituents occupy pseudoequatorial positions. The newly forming bond between C1 and C5 measures 2.09 Å in **1** and 2.07 Å in **2**. This shorter distance and the larger ΔE_{act} are indicative of a slightly later transition state. However, the terminal methylene-bearing the silyl group has rotated less, with respect to the adjacent methine hydrogen, or is less pyramidal than the corresponding methylene in **1**. The transition structure for the methyl-substituted system **3** is the most product-like of the three systems, based on ΔE_{act}, a forming C1–C5 bond length of 2.05 Å, and the largest rotation/pyrmidalization of the terminal methylene (Table IV).

All three transition structures are also very similar electronically. Except for C1, the carbon bearing the

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(17) There is no SHOMO-π (or any other molecular orbital with π) mixing found in any of the conformations of either **1** or **3**.

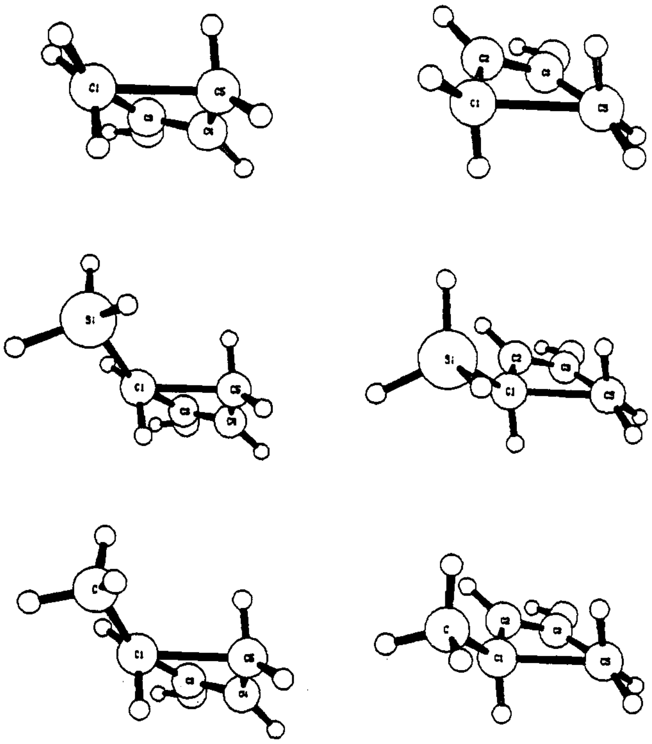

Figure 4. Newman projections of **1TS** (top), **2TS** (middle), and **3TS** (bottom) viewed along the C1–C2 (left) and C5–C4 (right) bonds.

substituent, the absolute charges are virtually identical (cf. Figure 1). Examination of the two highest occupied and the two lowest unoccupied molecular orbitals showed only minor differences. The length of the forming C1–C5 bond and the rotation of the terminal methylene groups differ only slightly.

Denmark has discussed the effects of cation-stabilizing substituents on the rate of electrocyclization in terms of the ground-state cation structures shown in Figure 2. His experimental work suggests the knowledge of the reactant or product-like nature of the transition state is unnecessary because of the complementarity of charge distribution in the limiting cations. Our results parallel the experimental observations made by Denmark of β substituent effects on cyclization rates. We have shown that the differences in rate of reaction and heat of cyclization are readily explained on the basis of stereoelectronic effects and that these effects differ significantly between stationary points. The calculated transition states strongly resemble the reactants; therefore, the β silyl effect does not contradict the expected stabilization by it of the product cation.

Table IV. Selected Transition Structure and Cyclized Product Geometric Parameters

structure	C1–C5[a]	C1–C2[a]	C3–O[a]	C1–R[a]	R–C1–C2–C3[b]
1TS	2.087	1.400	1.331		
1CP	1.548	1.491	1.349		
2TS	2.070	1.411	1.335	1.924	154.1
2CP	1.557	1.453	1.352	1.966	107.4
3TS	2.046	1.416	1.335	1.508	152.0
3CP	1.551	1.493	1.351	1.555	119.3

[a] Distances in angstroms. [b] Angles in degrees.

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Supplementary Material Available: Gaussian archive information from the single-point calculations for all stationary points of compounds **1**–**3** (6 pages). Ordering information is given on any current masthead page.