Torquoselectivity and Hyperconjugation in the Nazarov Cyclization. The Effects of Inner versus Outer β-Methyl and β-Silyl Groups[1]

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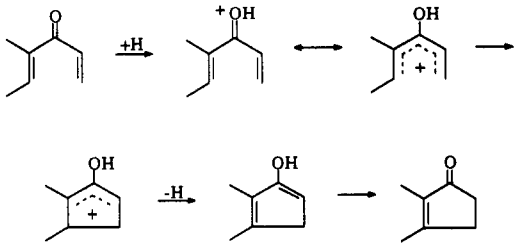
The effect of inner (*Z*) and outer (*E*) β-methyl and β-silyl groups on the conformations and electrocyclization of the protonated 1,4-pentadien-3-one cation was studied using ab initio molecular orbital theory. The energy of activation is significantly lower for electrocyclizations in which the β-silyl groups are inside rather than outside; this is primarily attributed to hyperconjugation in the transition state. However, β-methyl groups at the inner rather than outer position increase the energy of activation due to torquoselectivity. Cyclizations of systems containing a β-silyl substituent are exothermic due to the extra stability from hyperconjugation in the cyclized products while systems containing only a β-methyl substituent are endothermic.

Introduction

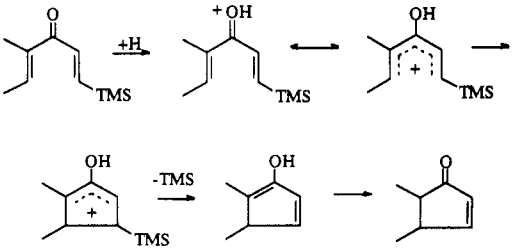
The Nazarov cyclization (Scheme I) has gained prominence as a useful reaction[2] for the construction of unsaturated five-membered rings in tricyclic systems[3] as well as natural products[4] due to the stereoselectivity and controllable regioselectivity of the reaction. The electrocyclization of the divinyl ketone to the cyclopentenone product normally gives the most substituted double bond, i.e. the thermodynamic product. The less-substituted double bond (kinetic) product can be produced regioselectively through the use of silicon substituents β to the carbonyl carbon (Scheme II).[5]

We have previously studied the acid-catalyzed electrocyclization of the parent system, 1,4-pentadien-3-one,[1b] and the effects of outer β-silyl and -methyl groups[1a] on the conformational behavior and the electrocyclization. In this paper we turn our attention to a comparison of the effects of β substituents on the inner (*Z*) versus outer (*E*) positions since the stereochemistry of the β-substituted vinyl moiety is determined during the synthesis of the cyclization substrate. As such, there are two stereochemically distinct conrotatory processes which may result in the same cyclized product as depicted in Scheme III. The *E*-substituent on the vinyl moiety must rotate "outward" while the *Z*-substituent must undergo "inward" rotation during cyclization. It has been shown that electronic effects of the substituent control the preferred mode of rotation and greatly influence the energetics of conrotatory electrocyclizations. Much of this work to date has been limited to the cyclobutene/butadiene cycloreversion, although recently reports on the pentadienyl/cyclopentenyl cation and octatetraene systems have appeared.[6] Unlike recent studies of conrotatory cycloreversions where the focus was on the preferred mode of rotation and hence the resulting stereochemistry of the acyclic product, our study focuses on the stereochemical effect of a substituent on the energetics of the Nazarov cyclization since the stereochemistry of the starting material can be synthetically

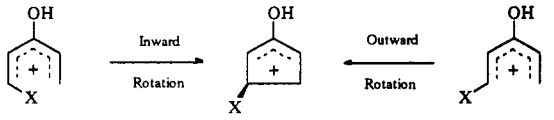
Scheme I



Scheme II



Scheme III



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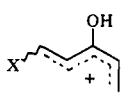
controlled. Calculations on protonated 1-silyl-1(*E*),4-pentadien-3-one, **1**, protonated 1-silyl-1(*Z*),4-pentadien-3-one, **2**, protonated 1-methyl-1(*E*),4-pentadien-3-one, **3**, protonated 1-methyl-1(*Z*),4-pentadien-3-one, **4**, protonated 1-silyl,1-methyl-1(*E*),4-pentadien-3-one, **5**, and protonated 1-silyl,1-methyl-1(*Z*),4-pentadien-3-one, **6**, are reported herein as part of our computational efforts to understand the Nazarov cyclization.

Computational Methods

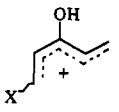
Ab initio calculations were carried out using GAUSSIAN 88 and 90[7] on a Cray Y-MP/864. Structures were completely optimized starting from the previously obtained outer β-substituted geometries[1b]; no symmetry or other constraints were imposed. Restricted Hartree–Fock calculations leading to stationary 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. The 6-31G** basis set includes d-type polarization functions on all non-hydrogen atoms and p-type polarization functions on hydrogens.[10]

Results and Discussion

The β-substituted systems exhibit four stable acyclic conformations. The nomenclature chosen to represent these conformations indicates the orientation of the terminal methylenes to the hydroxyl group. These compounds are derived conceptually from the unprotonated *E*- or *Z*-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).



SA(S)



SA(A)

The relative conformational energies of the acyclic compounds **1**–**6** are given in Table I. At the MP3/6-31G** level the SA(A) conformer is the most stable conformer followed by the SA(S) for the *E*-silyl and -methyl substituted systems **1** and **3**. We attribute this to better orbital overlap for extended conjugation, including the substituents, in the transoid enone-like moiety as compared to the cisoid and the destabilizing steric interactions between the vinyl substituent at C1 and the vinyl hydrogen at C2 in the SA(S) conformation.[1b] Supporting evidence is found in the inner monosubstituted and disubstituted systems **2** and **4**–**6** where the SA(S) conformation is the most stable followed by the SS. There are no destabilizing steric interactions between the substituent and the vinyl hydrogen at C2 in the SA(S) conformation. The SA(S) conformation is planar in all compounds **1**–**6**. The *Z*-substituted and disubstituted SA(A) conformations are destabilized by steric interactions between the *Z*-substituent and the vinyl hydrogen at C4, resulting in deviation from planarity of the dihedral angle of the substituted enone moiety by about 20°. The AA conformations in all systems are high-energy conformations due to the nonplanarity and decreased orbital overlap brought about by steric interactions between the terminal methylene inner hydrogens/substituent.

Table I. Relative Energies of 1–6 in kcal/mol

compound	conformation	RHF/3-21G(*) relative energy	MP3/6-31G**// RHF/3-21G(*) relative energy
1	AA	5.1	1.3
(*E*-silyl	SA(A)	0.0	0.0
Z-hydrogen)	SA(S)	0.4	0.4
	SS	0.6	1.4
2	AA	8.4	2.6
(*Z*-silyl	SA(A)	4.2	1.5
E-hydrogen)	SA(S)	0.0	0.0
	SS	0.3	0.9
3	AA	5.1	1.2
(*E*-methyl	SA(A)	0.1	0.0
Z-hydrogen)	SA(S)	0.0	0.1
	SS	0.0	0.8
4	AA	7.0	2.4
(*Z*-methyl	SA(A)	1.6	0.5
E-hydrogen)	SA(S)	0.2	0.0
	SS	0.0	0.4
5	AA	7.7	3.4
(*E*-silyl	SA(A)	1.9	1.1
Z-methyl)	SA(S)	0.3	0.0
	SS	0.0	0.3
6	AA	9.6	3.2
(*Z*-silyl	SA(A)	5.4	2.0
E-methyl)	SA(S)	0.2	0.0
	SS	0.0	0.4

We also note that monosubstituted conformations with a *Z*-substituent are less stable than the corresponding *E*-substituted conformations. This effect is greater for methyl-substituted than for silyl-substituted systems; the effects are nearly additive in the disubstituted systems (Table II).

The energies of activation and heats of cyclization are shown in Table III for the cyclization of the substituted systems in all the possible stereochemical permutations, cf. Scheme IV. The systems with the highest energy of activation were found to be those with the methyl group inside, **5** and **4**. Following these are the outer monosubstituted systems, **3** and **1**, with similar energies of activation. All four of these systems show larger activation energies than unsubstituted protonated 1,4-pentadienone, while **6** and **2**, with inner silyl groups, exhibit smaller activation energies.

It is not surprising that the systems bearing inner methyl groups have larger energies of activation than those with

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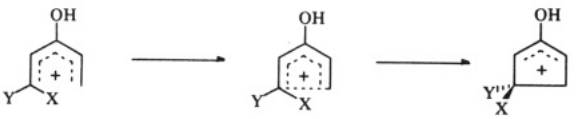
Table II. Relative Energies in kcal/mol of Inner versus Outer Substituted Systems with Identical Functional Groups

	RHF/3-21G(*)		MP3/6-31G**//RHF/3-21G(*)	
	E-silyl *Z*-hydrogen	*Z*-silyl *E*-hydrogen	*E*-silyl *Z*-hydrogen	*Z*-silyl *E*-hydrogen
AA	0.0	4.1	0.0	3.7
SA(A)	0.0	5.0	0.0	3.9
SA(S)	0.0	0.5	0.0	2.0
SS	0.0	0.6	0.0	1.9
	E-methyl *Z*-hydrogen	*Z*-methyl *E*-hydrogen	*E*-methyl *Z*-hydrogen	*Z*-methyl *E*-hydrogen
AA	0.0	5.9	0.0	5.4
SA(A)	0.0	5.5	0.0	4.7
SA(S)	0.0	4.3	0.0	4.1
SS	0.0	4.1	0.0	3.7
	E-silyl *Z*-methyl	*Z*-silyl *E*-methyl	*E*-silyl *Z*-methyl	*Z*-silyl *E*-methyl
AA	1.7	0.0	1.6	0.0
SA(A)	0.0	0.0	0.5	0.0
SA(S)	3.7	0.0	1.4	0.0
SS	3.5	0.0	1.4	0.0

Table III. Energies in kcal/mol. Substituent Positions Refer to Scheme IV

	E_{act}		E_{cyc}	
substituent	RHF/ 3-21G(*)	MP3/6-31G**// RHF/3-21G(*)	RHF/ 3-21G(*)	MP3/6-31G**// RHF/3-21G(*)
X = H, Y = H[a]	30.7	20.4	5.6	−2.4
1, X = H, Y = SiH_3	32.4	21.7	4.2	−5.9
2, X = SiH_3, Y = H	28.5	16.9	3.3	−8.3
3, X = H, Y = Me	32.5	21.9	11.7	4.5
4, X = Me, Y = H	34.4	23.9	7.5	0.3
5, X = Me, Y = SiH_3	35.9	25.7	5.1	−4.3
6, X = SiH_3, Y = Me	29.5	17.6	8.6	−2.9

Scheme IV



outer groups. Based on Houk's discussion of torquoselectivity in the pentadienyl cation cyclization, a high-lying donor orbital (π_{CH_3}) of the methyl group may interact with the $\sigma_{C_1C_5}$ orbital (i.e. the forming C–C bond), causing a destabilizing four-electron interaction.[11] However, both the mono- and disubstituted systems bearing a silyl group seemingly contradict the torquoselectivity rule and prefer the inward position over the outward. This preference is readily explained by hyperconjugation. We have shown[1] that the transition structure involving an outer silyl group exhibits no hyperconjugation since the C–Si σ bond is nearly orthogonal to the cation π system; i.e. the β-silicon effect is conformation dependent.[12] We now show that systems bearing an inner silyl group exhibit transition structures where the C–Si σ bond is nearly parallel to the cation π system, thereby stabilizing the transition structure and lowering the energy of activation through hyperconjugation (Figure 1).

The energies of activation, while synthetically important, may be somewhat misleading since they are calculated as the difference in energy between the transition structure and the most stable acyclic conformation. It therefore follows that the activation energy is partially dependent on the relative stability of the *E* and *Z* acyclic conformations as well as the relative stability of the inner and outer transition structures. Direct comparison of the transition state energies is shown in Table IV. The outer methyl-substituted transition structure is preferred by 6.1 kcal/mol over the inner transition structure. This preference is much smaller than seen by Houk[6] for the 1-aminopentadienyl cation cyclization; in that case the outer amino group is preferred by 14.7 kcal/mol, probably due to the greater π electron-donating ability of the amino group. The inner silyl-substituted transition structure is

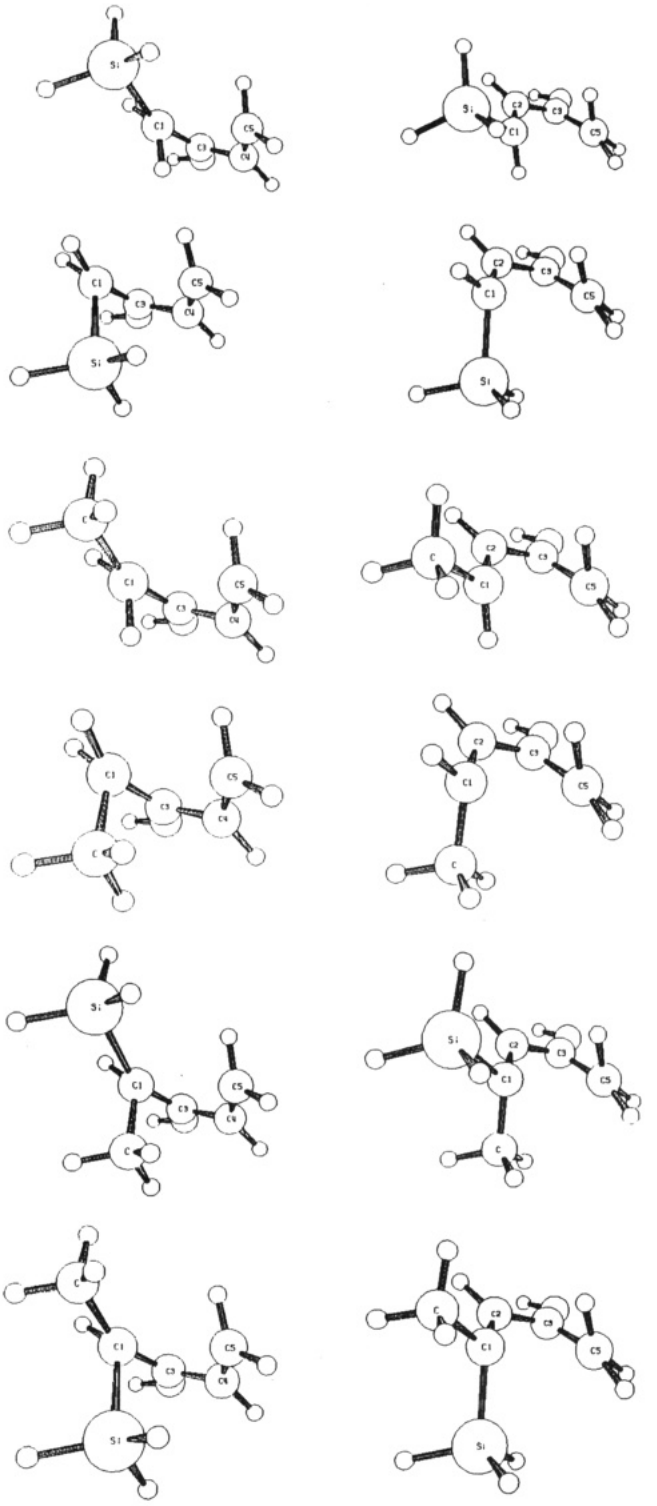
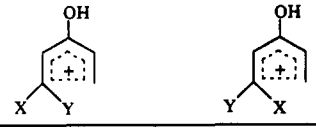


Figure 1. Perspective plots of the transition structures for **1**–**6**. Left: Newman projection along the C_1–C_2 bond. Right: Newman projection along the C_5–C_4 bond.

(11) Kallel, E. A.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 6006.
(12) This has also been shown for the 3-silapropyl cation. See: Wierschke, S. G.; Chandrasekhar, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496.

Table IV. Energies in kcal/mol. Substituent Positions as Indicated



substituent	RHF/ 3-21G(*)	MP3/6-31G**// RHF/3-21G(*)	RHF/ 3-21G(*)	MP3/6-31G**// RHF/3-21G(*)
X = H, Y = H[a]	0.0	0.0	0.0	0.0
X = SiH_3, Y = H	3.1	2.5	0.0	0.0
X = Me, Y = H	0.0	0.0	6.1	6.1
X = SiH_3, Y = Me	9.9	9.5	0.0	0.0

preferred by 3.1 kcal/mol over the outer at the RHF/3-21G(*) level, a value which is in accord with the 5.6 kcal/mol preference for the inner, strong π electron-accepting boryl group in the 1-borylpentadienyl cation cyclization transition structure.[6] The similarity between the silyl group and the electron-accepting BH_2 is not due to back bonding; participation of d-orbitals on silicon has been ruled out since RHF/3-21G calculations on the silyl-containing systems result in the same ordering by relative energy of the transition structures as do the RHF/3-21G(*) calculations.[13] Therefore, hyperconjugation can be the only explanation for the inward rotational preference of the silyl group.

The heats of cyclization reported in Table III are calculated as the energy difference between the cyclized product and the most stable acyclic conformation. Therefore, the relative exothermicity between corresponding *E*- and *Z*-substituted systems depends solely on the relative stability of the *E* and *Z* acyclic conformations. The silyl-substituted systems exhibit a more exothermic heat of cyclization than the methyl-substituted systems due to the previously reported hyperconjugation in the cyclized product.

We were previously able to correlate the length of the forming C_1–C_5 bond in the transition structures with the energy of activation. The C_1–C_5 distances in **4** and **5**, which contain an inner methyl group, are shorter than in **2** and **6**, which contain an inner silyl group, but are longer than in **1** and **3**, the monosubstituted outer silyl and methyl systems. It is not the case, however, that the activation energies for **4** and **5** lie between the inner silyl systems **2** and **6** and the outer substituted systems **1** and **3** (Table V).

Table V. Transition Structure C_1–C_5 Distances and Activation Energies

compound	C1–C5[a]	ΔE_{act}[b]
1	2.070	21.7
2	2.186	16.9
3	2.046	21.9
4	2.116	23.9
5	2.110	25.7
6	2.143	17.6

[a] Distances in angstroms. [b] MP3/6-31G**//RHF/3-21G(*) energies in kcal/mol.

The implications of this work for synthesis involving the Nazarov cyclization are significant. In particular, the large difference in the activation energy when the silicon is inside as opposed to outside suggests that this reaction could be carried out at even lower temperatures and therefore with a higher level of regioselectivity. Recognition that the outside silyl group corresponds to the *E*- and the inside silyl group to the *Z*-vinyl silane in the starting material leads to the conclusion that stereocontrolled *Z*-olefin synthesis directly enhances reactivity and regioselectivity in the electrocyclization.

Acknowledgment. We thank the Ohio Supercomputer Center for a grant of computer time.

Supplementary Material Available: Gaussian archive files, tables of bond lengths and angles for the four conformations and transition structures of **1**–**6** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) Smith, D. A.; Ulmer, C. W., II, unpublished results.