Transition State of the Silicon-Directed Aldol Reaction: An ab Initio Molecular Orbital Study

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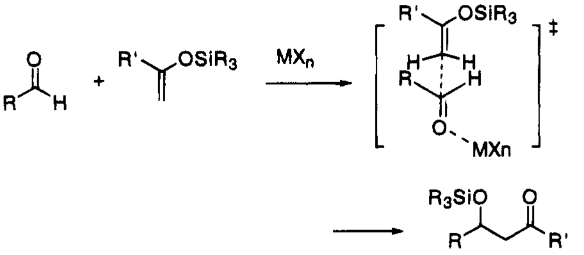
The transition state structure for the silicon-directed aldol reaction between the enol silane **1** and formaldehyde producing 3-(silyloxy)propanal (**2**) is located at the MP2/6-31G* level of theory. A boatlike six-membered ring with a pentavalent trigonal bipyramid silicon species is described. The formaldehyde oxygen occupies the apical position with the Si−O bond length of 2.01 Å. The enol silane oxygen assumes the equatorial orientation with the Si−O bond distance of 1.81 Å. The calculated Si−O bond length is 1.69 Å in the starting enol silane **1** and 1.68 Å in the product **2**. The distance between the bond-forming sp^2 carbons of **1** and formaldehyde is 2.07 Å in the transition state. A secondary kinetic isotope effect of k_H/k_D = 0.80 was calculated, which is in excellent agreement with the experimental value of 0.76.

Introduction

In 1974, Mukaiyama reported a variation from the aldol condensation, in which enol silanes react with aldehydes and ketones under the influence of Lewis-acid catalysts.[1] The Mukaiyama reaction has become extremely popular among synthetic organic chemists primarily because of the diastereoselective nature of the carbon−carbon bond forming process.[2] A few mechanistic studies have been reported recently for the Lewis acid-catalyzed reactions.[3,4] An open transition state is proposed (eq 1),[3] and a Lewis-acidic species has been suggested to serve as the real catalyst.[4]



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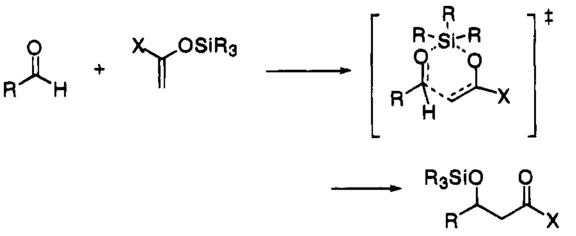

(2)

Recently, a previously-unprecedented silicon-directed aldol condensation has been reported (eq 2, X = NR$_2$).[5a] *O*-Silyl derivatives of amides undergo facile addition to aldehydes without the presence of Lewis acid at or below room temperature. Myers has suggested that a *boatlike transition state* with a pentavalent organosilicon species is preferred in the uncatalyzed addition of *N,O*-ketene silyl acetal to aldehydes.[5b,c] This suggestion was based on studies of enantioselective addition of a prolinol-derived enol silane to aldehydes at ambient temperature without a catalyst. One representative reaction was determined to proceed in second order with activation energy $\Delta H^‡$ = 12.0 ± 0.5 kcal/mol. In an independent study, Denmark has established that the silyl group transfer in the uncatalyzed aldol reaction proceeds through an intramolecular pathway by a double-labeled cross-over experiment.[6] A computational study at the semiempirical level was carried out, which supports a boatlike transition state involving a pentavalent silicon.[6] The two studies have reached the same conclusion with regard to the silicon species. However, the exact nature of the transition state is still unknown. As far as we know, there is no *ab initio* MO study for the silicon-directed aldol reaction.

Our interest in the conformations of chiral alkenes[7] and the origins of diastereofacial selectivity[8] led us to investigate the ground state conformations of enol silane and the transition state of the thermal silicon-directed aldol reaction by the *ab initio* MO methods.[9] It is reported that the transition state structure for the reaction between the prototype of enol silane and formaldehyde is located at the MP2/6-31G* level of theory.[10] The *ab initio* MO study supports the previous conclusions and reveals the nature of the transition state.

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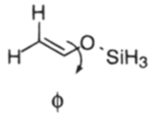
Computational Methods

Ab inito calculations are carried out by the GAUSSIAN 92 program[11] implemented on the Cray Y-MP/8 supercomputer. The conformational search for enol silane **1** and for 3-(silyloxy)propanal (**2**) was carried out by varying the torsional angles, ϕ, and ϕ_1, ϕ_2, and ϕ_3, respectively. Two energy minima were found for **1**, and six were found for **2**. Structural optimizations for **1** and **2** were initially carried out by using the 3-21G* split-valence basis set with polarization function, which was found to give reasonable Si−O bond lengths. Calculations were progressively continued at the 6-31G* and the MP2/6-31G* levels. The calculation for formaldehyde (**3**) was started directly at the 6-31G* level. All parameters, including bond lengths, bond angles, and dihedral angles, were fully optimized for each structure. Harmonic frequencies were calculated for each equilibrium structure at the 6-31G* level. The optimized structures all have positive frequencies, which is an indication of true minima on the 6-31G* potential surface. Transition state (**TS**) geometry optimization was carried out initially starting from the midpoint of the starting materials (**1** and formaldehyde) and the product **2** using the 3-21G* basis set. The transition structure was fully optimized without any constraint and was characterized by vibrational frequency calculations. Only one negative frequency was found. The 3-21G* transition structure was further optimized using the Moller−Plesset electron correlation (MP2/3-21G*) and then the larger basis set 6-31G* and the electron-correlation (MP2/6-31G*) theoretical models. The structures presented in this article including the starting materials (**1**, **3**), the product (**2**), and the transition state (**TS**) are all optimized at the final level of MP2/6-31G* level of theory. Single point calculations were performed for each structure at the MP2/6-31G** level. The zero point energies involving the deuterated species were obtained by using the command “Freq = Readisotopes” in the Gaussian 92 program.



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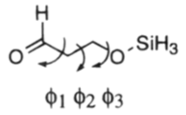

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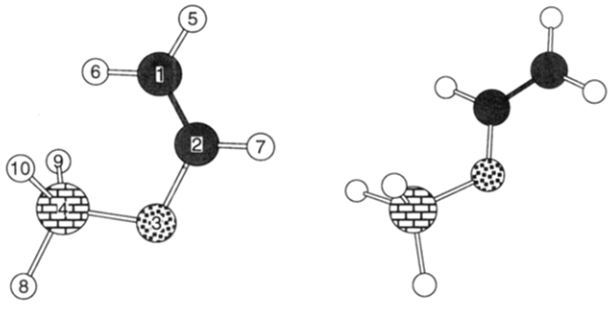
Results and Discussion

A. Structure of the Enol Silane 1. The optimized structures (MP2/6-31G*) of enol silane **1** are presented in Figure 1. The graphics were created using CHEM3D. The relative energies at different levels of theory and the total energy at the MP2/6-31G* level are listed in Table 1. The s-*cis* conformation **1a** is more stable than the s-*trans* isomer **1b**. This is similar to the structures of methyl vinyl ether, which has been studied extensively both experimentally and theoretically.[12] The relative stability of the conformations of methyl vinyl ether has been interpreted in several different models. The latest explanation attributes the difference between the s-*cis* and the s-*trans* forms to intramolecular electrostatic interactions, i.e., the s-*cis* isomer has a smaller dipole moment.[12] The current calculation shows that the s-*cis* isomer **1a** has a dipole moment of 0.72 Debye and the s-*trans* isomer **1b** has a dipole moment of 1.30 Debye. Thus, the same explanation can be applied to the enol silane.



1a **1b**

Figure 1. Optimized structures (MP2/6-31G*) of enol silane **1**.

Table 1. Relative Energies (kcal/mol) and Total Energies (in parenthesis in atomic units) for Enol Silane 1

conformer	STO-3G	3-21G*	6-31G*	MP2/6-31G*	MP2/6-31G**[a]
1a	0.00	0.00	0.000	(−443.511978) 0.00	0.00
1b	1.23	1.32	0.638	(−443.510604) 0.862	0.806

[a] Single point calculations using the MP2/6-31G* structure.

The structural parameters at the MP2/6-31G* level of theory are compiled in Table 1 in the supplementary materials. Previous *ab initio* studies of silyl ethers have concluded that the lone pairs on oxygen may interact with the $\pi^*(SiH_3)$ as a result of delocalization,[13] which is responsible for the relatively low basicity of silyl ethers.[14] The reason for this delocalization is because that the π^*-(SiH_3) is relatively low in energy comparing to the π^*-(CH_3).[13] The current structural data also shows a similar effect as indicated by the longer Si(4)−H(9) and Si(4)−H(10) bonds (1.485 Å vs 1.477 Å for Si−H(8)). The calculated bond angle C−O−Si (for conformer **1a**: 124.6° and for conformer **1b**: 121.8°) is characteristic of silyl ethers, i.e., wider than a C−O−C angle. The syn conformation **1a** has a 0° dihedral angle CCOSi while the anti conformer **1b** has a gauche dihedral angle ($\tau_{CCOSi} = 148.7°$, instead of 180°). This is similar to the structure of methyl vinyl ether, which also has two minima and the less stable form is gauche.[15,16] Avoiding the torsional strain from an eclipsing HCOC has been suggested to favor the gauche arrangement, rather than the anti, by methyl vinyl ether.[16] The same torsional strain should also operate in the anti isomer **1b** preventing a symmetrical anti form ($\tau_{CCOSi} = 180°$).

This unsymmetric arrangement of the silyl group causes distortion in the double bond, as evidenced by the deviations in torsional angles ($\tau_{H(5)-C(1)-C(2)-O(3)} = 177.3°$

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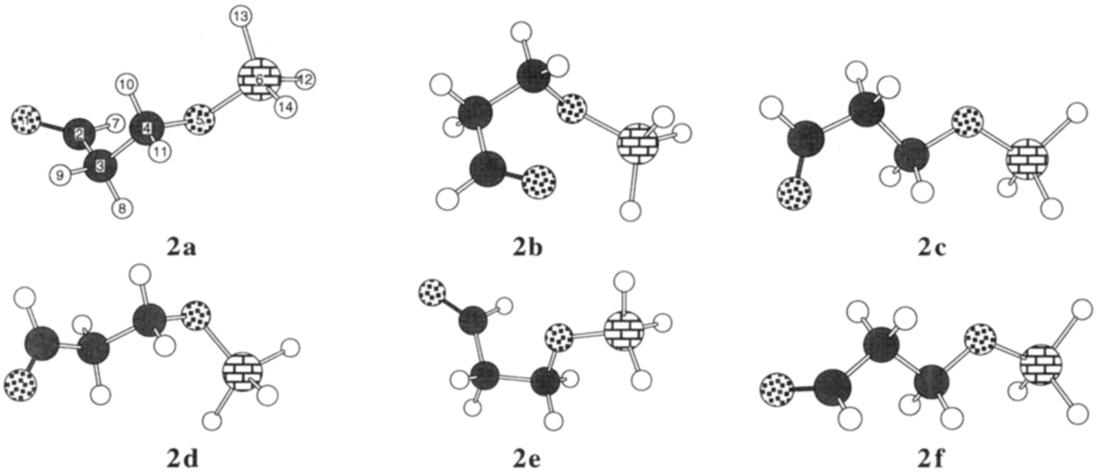


2a **2b** **2c**

2d **2e** **2f**

Figure 2. Optimized structures for the conformers of 3-siloxypropanol (**2**).

Table 2. Relative Energies (kcal/mol) and Total Energies (in atomic units) for the Conformers of 3-Siloxypropanal (2)

conformer	3-21G*	6-31G*	MP2/6-31G*	MP2/6-31G**[a]
2a	3.38	1.13	(−557.729586) 1.87	1.99
2b	0.00	0.21	(−557.732559) 0.00	0.00
2c	2.18	0.00	(−557.731248) 0.82	0.98
2d	5.98	3.09	(−557.726599) 3.74	3.74
2e	4.16	1.26	(−557.729719) 1.78	1.85
2f	5.63	2.40	(−557.727479) 3.19	3.23

[a] Single point calculations using the MP2/6-31G* structures.

Table 3. Comparison of Structural Parameters (MP2/6-31G*) for the Silicon-Directed Aldol Reaction (the numbering system is set for convenience in comparison of the starting materials, TS, and the product, not according to conventional rules)

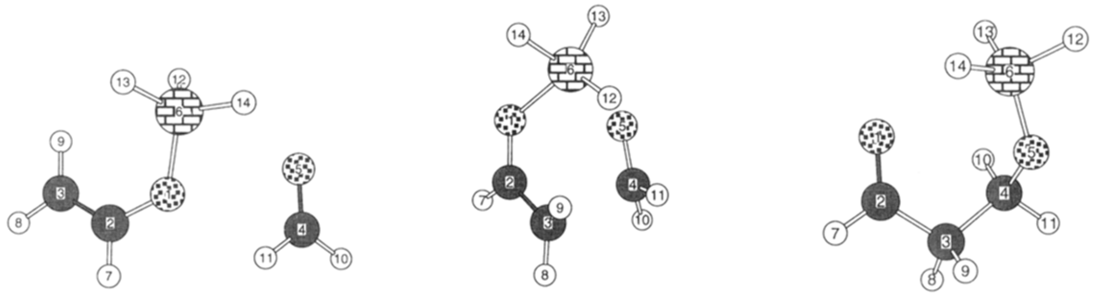
	starting material		transition state	product
	1a	$CH_2{=}O$		**2b**
	Bond Length, Å			
C(2)−C(3)	1.338		1.380	1.505
C(2)−O(1)	1.372		1.296	1.226
O(1)−Si(6)	1.685		1.812	3.095
O(5)−C(4)		1.221	1.281	1.424
C(4)−H		1.104	1.097	1.097
C(4)−H		1.104	1.094	1.095
O(5)−Si(6)			2.010	1.675
C(3)−C(4)			2.071	1.518
	Bond Angle, deg			
H(7)−C(2)−O(1)	110.8		114.5	120.0
H(7)−C(2)−C(3)	122.1		121.6	116.0
O(1)−C(2)−C(3)	127.1		123.1	123.8
C(2)−O(1)−Si(6)	124.6		128.5	18.6
C(2)−C(3)−H(8)	119.0		118.2	107.9
C(2)−C(3)−H(9)	123.7		118.2	108.9
H(8)−C(3)−H(9)	117.4		116.2	106.3
H(10)−C(4)−O(5)		122.1	119.4	111.3
H(10)−C(4)−H(11)		115.8	115.2	108.0
O(5)−C(4)−H(11)		122.1	117.5	107.5
O(1)−Si(6)−O(5)			76.3	31.6
O(1)−Si(6)−H(12)	111.1		117.9	5.8
O(1)−Si(6)−H(13)	111.1		118.0	73.9
O(1)−Si(6)−H(14)	104.8		90.0	85.7
O(5)−Si(6)−H(12)			86.9	106.0
O(5)−Si(6)−H(13)			83.9	110.3
O(5)−Si(6)−H(14)			166.2	112.7
H(12)−Si(6)−H(13)	108.8		118.9	109.4
H(12)−Si(6)−H(14)	110.5		101.1	107.8
H(13)−Si(6)−H(14)	110.5		101.6	110.3
	Torsional Angle, deg			
H(7)−C(2)−O(1)−Si(6)	180.0		−152.9	−68.0
C(3)−C(2)−O(1)−Si(6)	−0.0		16.8	29.2
H(7)−C(2)−C(3)−H(8)	−0.0		−10.3	60.0
H(7)−C(2)−C(3)−H(9)	180.0		−159.1	−54.9
O(1)−C(2)−C(3)−H(8)	180.0		−179.5	−118.9
O(1)−C(2)−C(3)−H(9)	−0.0		31.9	126.2
C(2)−O(1)−Si(6)−H(12)	−60.6		−27.9	−67.8
C(2)−O(1)−Si(6)−H(13)	60.6		126.3	131.4
C(2)−O(1)−Si(6)−H(14)	−180.0		−130.5	−110.0

and $\tau_{H(6)-C(1)-C(2)-O(3)} = -2.0°$). The slight pyramidalization at the sp^2 carbons might be accountable for the reactivity of the enol silanes. The anti conformation could be the only stable form if the substituents on silicon are bulky alkyl groups, such as the cases in synthetic preparations.[1−6]

B. Structure of 3-(Silyloxy)propanal (2). The optimized structures (MP2/6-31G*) of 3-(silyloxy)propanal (**2**) are depicted in Figure 2. The relative energies at different levels of theory and the total energies at the MP2/6-31G* level are listed in Table 2. The structural parameters at the MP2/6-31G* level of theory are listed in Table 2 of the supplementary materials. The most stable conformer **2b** has a cyclic structure, where the silicon atom is 3.1 Å from the carbonyl oxygen atom. This clearly shows an attractive electrostatic interaction between the silicon and the carbonyl oxygen. On the other hand, the energy difference between **2b** and the straight chain conformer **2c** is relatively small (0.81 kcal/mol at the MP2/6-31G* level). Silanes are not known as Lewis acids, and no stable complex of silane and aldehyde could be detected.[5] Although the current result shows that the association of the silicon and the carbonyl oxygen is preferred, entropic contribution could render an intermolecular complexation less favorable. However, this small attractive interaction might be responsible for the preassociation of the two reactants required in the mechanism suggested for the uncatalyzed silicon-directed aldol condensation.[5b,c]

C. Structure of the Transition State. The optimized transition state structure (MP2/6-31G*) is shown in Figure 3 along with the relevant starting materials and product. Table 3 contains the structural parameters for the transition state and for the related starting material and product for comparison purpose.

The calculated transition state structure is best described as a boatlike, six-membered ring with a pentavalent trigonal bipyramid silicon atom. The aldehyde oxygen (O5) and one of the hydrogen atoms on the silicon occupy the apical positions. The bond angle $\angle_{O5SiH14}$ is 166°. The enol oxygen (O1) and the other two hydrogen atoms assume the equatorial orientation. The bond angles between the equatorial enol oxygen and the two



1 **3** **TS** **2b**

Figure 3. Optimized transition state structure for the silicon-directed aldol reaction between enol silane **1** and formaldehyde (**3**) (the numbering system is set for convenience in comparison of the starting materials, **TS**, and the product, not according to conventional rules).

Table 4. Total Energies (in atomic units) for the Starting Materials (1a, 3), the Product (2b), and the Transition State (TS), and the Calculated Activation Energy ($\Delta E^{\ddagger}$), the Heat of the Reaction ($\Delta H_{\text{reaction}}$), and the Secondary Kinetic Isotope Effect (k_H/k_D)

species	6-31G*	MP2/3-21G*	MP2/6-31G*	MP2/6-31G**[a]
1a	−443.005034	−441.114408	−443.511978	−443.5602470
formaldehyde (**3**)	−113.863608	−113.439860	−114.167747	−114.1834809
TS	−556.823017	−554.536434	−557.657672	−557.7225852
2b	−556.917912	−554.604237	−557.732559	−557.7966462
$\Delta E^{\ddagger}$ (kcal/mol)[b]	28.6	11.2	13.8	13.3
$\Delta H_{\text{reaction}}$ (kcal/mol)[c]	−30.9	−31.4	−33.2	−33.2
k_H/k_D[d]			0.80	

[a] Single point calculations using the MP2/6-31G* structure. [b] $\Delta E^{\ddagger} = E_{\text{total}}$ (**TS**) − E_{total} (**1a**) − E_{total} (CH_2O) without correction for zero point energy differences. [c] $\Delta H_{\text{reaction}} = E_{\text{total}}$ (**2b**) − E_{total} (CH_2O) without correction for zero point energy differences. [d] Calculated secondary kinetic isotope effect using eq 3 and zero point energies obtained through Gaussian 92.

equatorial hydrogen atoms are 117.9° and 118°, respectively. On the other hand, the bond angles between the apical aldehyde oxygen (O5) and the two equatorial hydrogen atoms are 87.9° and 83.9°, respectively. The forming O5−Si bond is 2.07 Å, and the breaking O1−Si bond is 1.81 Å. The formaldehyde C=O bond length has stretched from 1.22 to 1.28 Å. The C(4)−H bond of the formaldehyde has shortened from 1.104 to 1.097 Å. Although this appears to be a very small change, the C(4)−H distance of the transition state is identical to that in the product, i.e., the change in C(4)−H distance has completed in the transition state. The bond angles $\angle_{\text{OCH}}$ of the formaldehyde have changed from 122.1° to 119.4° and 117.5°, respectively, indicating changing hybridization of the C(4) carbon from sp^2 to sp^3.

The total and relative energies of the starting materials (enol silane **1a** and formaldehyde (**3**)), the transition state, and the product (3-(silyloxy)propanal (**3b**)) are compiled in Table 4. There is no experimental data on the prototype cf the silicon-directed aldol reaction. However, Myers et al. have reported a kinetic study on the uncatalyzed addition of *N*,*O*-ketene silyl acetal to benzaldehyde. It is of interest to compare the calculated structures to the experimental results. We are fully aware that the structures of the enol silanes and the aldehydes in Myers's experiment are different from the prototype of substrates used in the current calculations. Therefore, the surprising agreement between the experimental ($\Delta H^{\ddagger} = 12.0$ kcal/mol) and the calculated activation energy ($\Delta E^{\ddagger} = 11.2$ kcal/mol at the MP2/3-21G* level and 13.8 kcal/mol at the MP2/6-31G* level, Table 4) is probably fortuitous. However, the calculated pentavalent silicon species can be reasonably assumed to be the common intermediate. This is supported by a comparison of the calculated and the observed secondary kinetic isotope effect. An inverse secondary isotope effect ($k_H/k_D = 0.76$) was observed in Myers's experiment, which normally is an indication of the hybridization change from sp^2 to sp^3.[17] The calculated value was obtained by replacing one of the hydrogen atoms of the formaldehyde with a deuterium and calculating the vibrational frequencies for both the starting materials and the transition state. Equation 3[18] was employed to obtain a secondary kinetic isotope effect of $k_H/k_D = 0.80$, which is in excellent agreement with the experimental observation.

$$k_H/k_D = \exp\left[\frac{-1}{T}(0.1865)(\nu_{\ddagger H} - \nu_{rH})\right] \qquad (3)$$

Myers has suggested a late-transition state based on the inverse secondary isotope effect. This prediction is confirmed by our calculated C(4)−H distances in the transition state. However, despite the identical bond distances (C(4)−H) in the transition state and in the product, the other part of the transition state structure indicates an uneven progress in bond-breaking and in bond-forming.

In addition to the clearly unsymmetric O(5)−Si−O(1) bonding (2.07 Å vs 1.81 Å), the bond distance of C(2)−C(3) (C=C in the enol silane) and C(4)−O(5) (C=O in formaldehyde) still remains quite short in the transition state. While these parameters appear to indicate an early transition state, the forming C−C bond distance is similar to those new bond lengths in the transition structures of other reactions that involve the union of two sp^2 centers to form two new sp^3 centers.[19-21] Overall,

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the new C−C bond forming is well in progress while the new O−Si bond forming is lagging behind. This indicates that the silicon-directed aldol reaction is mainly driven by the nucleophilicity of the enol double bond, rather than by the silicon-activating of the aldehyde carbonyl group. This conclusion is supported by the fact that the Mukaiyama reaction is greatly accelerated by added Lewis acid and can be activated by various bases, and the silyl group is transferred intermolecularly in these base-catalyzed reactions.[6] The 2.07 Å C(3)−C(4) bond distance in the transition state also suggests that the rate-determining step is the C−C bond formation, a conclusion reached by Myers based on the kinetic study.

Conclusion

According to *ab initio* calculations at the MP2/6-31G* level, the uncatalyzed silicon-directed aldol condensation occurs through a cyclic transition state, which can be best described as a boatlike six-membered ring with a pentavalent trigonal bipyramid silicon species. The union of the two sp^2 carbons between the enol silane and formaldehyde occurs substantially in the transition state. The breaking and forming of the Si−O bond proceed unevenly. The driving force of the silicon-directed aldol reaction is the nucleophilicity of the enol double bond, rather than the activation of the carbonyl group by the silane.

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