Facile Uncatalyzed Mukaiyama Aldol Reactions: An ab Initio Study of the Effects of Substituents

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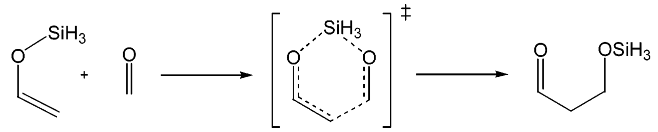


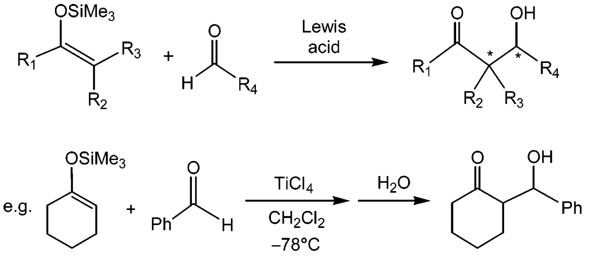
High-level ab initio molecular orbital calculations at the G3(MP2) level of theory were carried out to investigate the effects of substituents on the energetics of the uncatalyzed Mukaiyama aldol reaction between trihydrosilyl enol ether and formaldehyde. The concerted pathway, via a twist-boat six-membered ring transition state, is strongly favored over the stepwise pathway which involves a four-membered ring oxetane intermediate. Six substituents (CH_3, NH_2, OH, F, SH, and CHO) on trihydrosilyl enol ether and eight substituents (CH_3, CF_3, NH_2, F, CHO, $COOCH_3$, $CH{=}CH_2$, and C_6H_5) on formaldehyde were considered. We find that the reaction exothermicity is the main factor that dominates reactivity. The calculated barriers vary considerably from 30 to 131 kJ mol^{-1}. With the exception of halogen substitution, the nucleophilicity of silyl enol ether and the electrophilicity of the aldehyde are important in promoting the reactivity of this class of aldol addition. The roles of frontier molecular orbital interactions and electrostatic interactions are also discussed. In addition, our study has revealed that employing substituents on both reactants can act in a cooperatively manner to reduce the activation barrier further. In particular, we predict that the reactions between NH_2-substituted enol silane and CHO-, $COOCH_3$-, and CF_3-substituted aldehydes have remarkably low barriers (<12 kJ mol^{-1}). Thus, these reactions may proceed readily without a catalyst below room temperature. Several substitutions on the silicon group, namely SiF_3, $SiCl_3$, $SiMe_3$, and silacyclobutyl, were considered. In agreement with experiment, the *O*-(silacyclobutyl) and *O*-(trichlorosilyl) derivatives are found to promote aldol reactivity.

Introduction

The Mukaiyama aldol reaction, a catalyzed aldol reaction between a silyl enol ether and a carbonyl compound, has emerged as an important and versatile synthetic tool in organic and biochemical domains.[1] It provides a synthetic route for β-hydroxylcarbonyl compounds via carbon−carbon bond formation (Scheme 1).

Most Mukaiyama aldol reactions involved the use of Lewis acids to activate the carbonyl compounds. The first reaction was reported by Mukaiyama and co-workers, which utilized titanium tetrachloride ($TiCl_4$) as catalyst.[2]

SCHEME 1



This aldol addition occurred even at −78 °C with high yield (Scheme 1). In recent years, many efficient catalysts have been developed which give high selectivities and good yields.[3] Current research efforts focus mainly on the development of asymmetric Lewis acid/base catalysts to yield an enantioselective product.[4]

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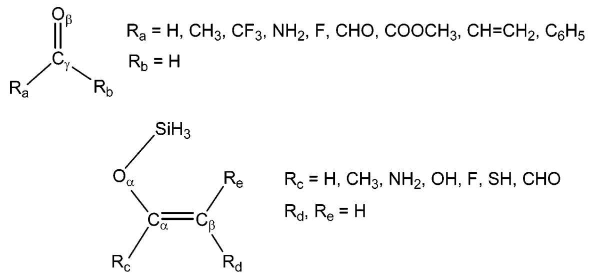
Myers et al.,[5] Denmark et a1.,[6] and Miura et al.[7] have independently shown that the Mukaiyama aldol reactions can proceed without a catalyst by increasing the acidity of silicon on the silyl enol ether. Uncatalyzed reactions under high pressure[8] and in water[9] have also been reported. Both experimental[5b,6a,10] and theoretical[6a,11] investigations have been carried out to elucidate the mechanism of the uncatalyzed silicon-directed aldol reactions. Based on an elegant double-label crossover experiment, Denmark et al. have established convincingly that the uncatalyzed Mukaiyama aldol reactions proceed through a direct intramolecular silicon group transfer.[6a] Gung et al. have reported the transition state for the concerted mechanism of the reaction between enol silane and formaldehyde, which has a boatlike six-membered ring geometry with a pentavalent trigonal bipyramid silicon.[11] From the calculated structural changes, they deduced that the silicon-directed aldol reaction is mainly driven by the nucleophilicity of the enol double bond.

To further shed light on the reactivity of this class of silicon-directed aldol addition reaction, we have carried out a systematic study on several uncatalyzed Mukaiyama reactions using the high-level G3(MP2) theory. Our objectives of this paper are 4-fold. First, we investigated other plausible mechanisms, such as a stepwise pathway, of the uncatalyzed aldol reaction. Second, we examined the effects of substituents in order to understand the governing factors of the reactivity. To this end, we have considered various substituents on trihydrosilyl enol ether ($SiH_3O-CH=CH_2$) and formaldehyde ($CH_2=O$) (Scheme 2). The substituents studied here represent various degrees of electron-withdrawing and -donating properties. Third, we investigated the effect of substitution on the silicon group of enol silane. Previous experimental studies have demonstrated that substituents on silicon have a dramatic effect on the reactivity of aldol reactions.[5-7] Finally, we wish to design appropriate substituents so that the uncatalyzed aldol reaction can occur under mild conditions. Eliminating the need for a catalyst or drastic conditions (e.g., high pressure) is highly beneficial as the catalysts used are generally expensive and difficult to recover after the reaction.

SCHEME 2



R_a = H, CH_3, CF_3, NH_2, F, CHO, $COOCH_3$, $CH=CH_2$, C_6H_5
R_b = H

R_c = H, CH_3, NH_2, OH, F, SH, CHO
R_d, R_e = H

Computational Details

Standard ab initio and density functional calculations were performed using the Gaussian 98 suite of programs.[12] The structures and energies of the reactants (silyl enol ethers and aldehydes), transition states, and products were examined by the G3(MP2) theory.[13] This method was employed as it gives accurate energies while requiring significantly less computational effort compared to the G3 theory.[14] The G3(MP2) theory corresponds effectively to the QCISD(T)/GTMP2Large//MP2-(full)/6-31G* energy. This is achieved through a series of single-point energy calculations at the QCISD(T)/6-31G* and MP2/GTMP2Large levels, together with the additivity approximation at the MP2 level. Zero-point energy (ZPE) correction (HF/6-31G*) together with a higher-level correction (HLC) are also included in the G3(MP2) energies. The nature of the calculated stationary points was verified by frequency calculations. Equilibrium structures are characterized by all real frequencies, while transition states have one and only one imaginary frequency. Atomic charges were obtained using the natural bond orbital (NBO) analysis,[15] based on the MP2(full)/6-31G* wave function. NBO atomic charges of small molecules have recently been demonstrated to agree well with experimental values obtained from X-ray diffraction data.[16] The effect of solvent was studied using Onsager's reaction field model (SCRF).[17] The hybrid density functional B3LYP[18] method in conjunction with the 6-31G* basis set was employed for the solvation calculations as the G3(MP2) method does not allow us to take into consideration solvent effects. A scaling factor of 0.9804[19] was used to correct for the calculated zero-point energies at the B3LYP/6-31G* level.

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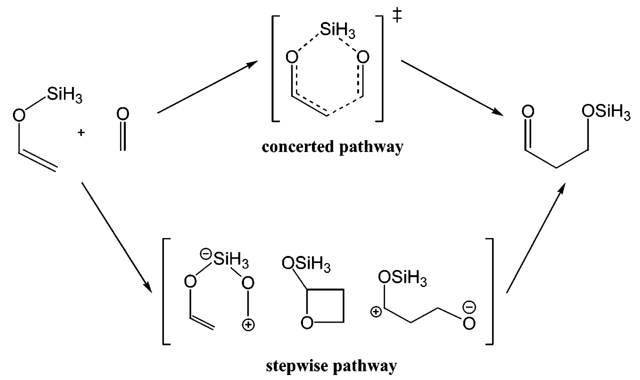
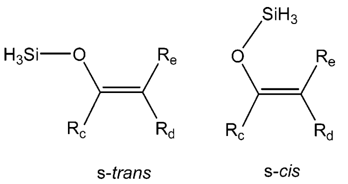
SCHEME 3



Results and Discussion

1. Mechanism of Uncatalyzed Reaction. Let us first examine in detail the mechanism of the uncatalyzed Mukaiyama aldol reaction of the parent system, i.e., between trihydrosilyl enol ether and formaldehyde. The concerted pathway has been examined previously by Gung et al.[11] and Denmark et al.[6a] However, they did not consider the alternate stepwise mechanism. Several reports have suggested that the Mukaiyama aldol reactions proceed via a stepwise mechanism with an open transition state.[20] In particular, [2 + 2]-addition intermediates have been observed for reactions which involved a chiral europium catalyst.[21] Here, we have investigated both concerted and stepwise pathways of the uncatalyzed aldol reaction (Scheme 3).

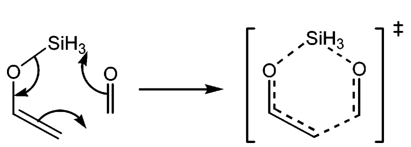
The conformational behaviors of the reactant trihydrosilyl enol ether and the product 3-(silyloxy)propanal have been studied by Gung et al.[11] They showed that the s-cis conformation is the preferred structure based on MP2/6-31G* calculations. Our G3(MP2) calculations confirm that the s-cis form is slightly more stable, by 3.5 kJ mol^{-1}. Both conformers are calculated to have significantly different dipole moments, 0.71 and 1.30 D (MP2(full)/6-31G*), for s-cis and s-trans conformers, respectively. The difference in dipole moment results from the different orientations of the C=C and OSiH$_3$ group dipoles: they are opposed in the s-cis conformer while they are additive in the s-trans form. The calculated rotational barrier between the two conformations is very small, 5.7 kJ mol^{-1}. This result demonstrates that the silyl group has an extremely flexible rotational potential.



For 3-(silyloxy)propanal, a detailed study by Gung et al. has shown that there are several low-lying conformations.[11] The global energy minimum we located at the G3(MP2) level is similar to that reported by Gung et al. The structures corresponding to the first-formed product and the global energy minimum for the aldol reaction between trihydrosilyl enol ether and formaldehyde are shown in Figure 1. The first-formed reaction product lies 6 kJ mol^{-1} above the global minimum.

The aldol reaction between s-cis trihydrosilyl enol ether and formaldehyde is predicted to be exothermic, by 95 kJ mol^{-1}. In agreement with the results obtained by Gung et al.,[11] a boat-shaped six-membered-ring transition state (**TS$_C$**, Figure 1) is located for the concerted pathway. This concerted transition state involves a simultaneous C−C bond formation and SiH$_3$ shift, which is characterized by a pentacoordinate silicon. At the G3(MP2) level, the calculated activation barrier of 77 kJ mol^{-1} is significantly higher than that reported previously at the MP2/6-31G** level (56 kJ mol^{-1}).[11] For the s-trans conformation of trihydrosilyl enol ether, it is a more exothermic reaction (−104 kJ mol^{-1}) but inhibited by a higher activation barrier of 83 kJ mol^{-1}.

Analysis of the frontier orbitals indicates that there is a favorable in-phase orbital overlap between the HOMO of trihydrosilyl enol ether and the LUMO of formaldehyde (Figure 2). The most favorable overlap occurs when the $O_\alpha C_\beta C_\gamma O_\beta$ atoms are coplanar, where the $C_\beta \cdots C_\gamma$ and $O_\alpha \cdots O_\beta$ interactions are maximized. Indeed, the calculated torsional angle in **TS$_C$** is close to planarity (−3.6°). This readily explains the preference of a twisted boat geometry of the cyclic transition state (Figure 1). The key structural changes on going from the reactants to the transition state **TS$_C$** are as follows: (1) the lengthening of the Si−O$_\alpha$ bond from 1.683 to 1.807 Å, (2) the shortening of the O$_\alpha$−C$_\alpha$ bond from 1.371 to 1.295 Å, (3) the lengthening of the C$_\alpha$−C$_\beta$ bond from 1.337 to 1.378 Å, and (4) the lengthening of the C$_\gamma$−O$_\beta$ bond from 1.220 to 1.279 Å. The $C_\beta \cdots C_\gamma$ and $O_\beta \cdots Si$ forming bonds in the transition state are calculated to be 2.076 and 2.004 Å, respectively. The optimized geometry and the normal mode vibration of the imaginary frequency of **TS$_C$** clearly indicate that the C−C bond formation is well in advance of the formation of the new O−Si bond. In other words, this concerted transition state is best considered as asynchronous. The “concerted” nature of **TS$_C$** is confirmed by intrinsic reaction coordinate (IRC) calculations. The pericyclic reaction described here resembles that of a typical [4 + 2] cycloaddition such as Diels−Alder reaction, of which 6π [4π + 2π] electrons are participated in the cyclic transition state. However, in the silicon-directed aldol reaction, 4π and 2σ electrons [(2π, 2σ] + 2 π] are involved.



This uncatalyzed aldol reaction may proceed via a stepwise mechanism, either through the formation of a zwitterionic type of intermediate or a four-membered-ring intermediate (Scheme 3). Attempts to locate the two

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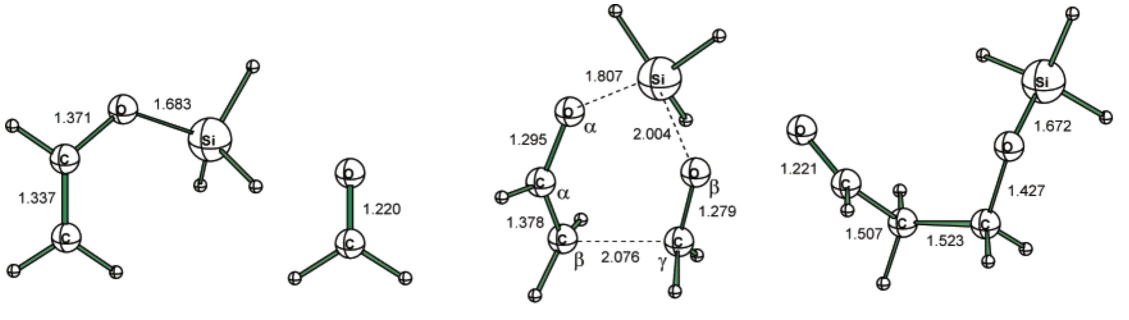
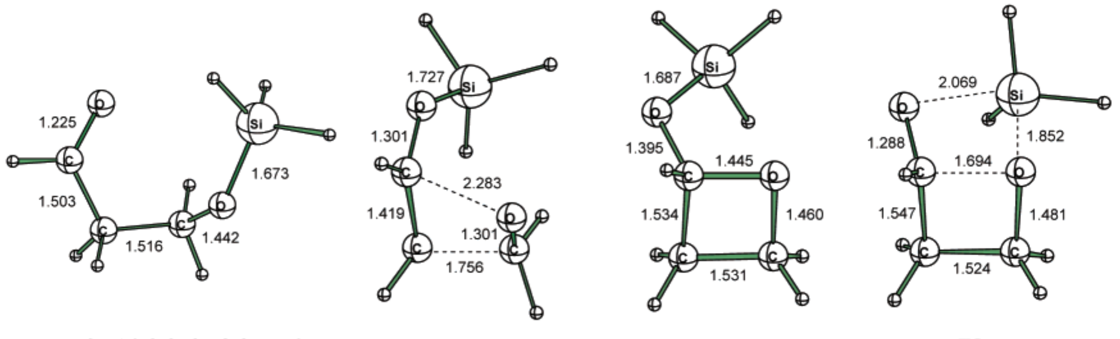


reactants **TS$_C$** **product**



product (global minimum) **TS$_{S1}$** **oxetane intermediate** **TS$_{S2}$**

FIGURE 1. Optimized geometries (MP2(full)/6-31G*) of the equilibrium structures and transition states for the concerted and stepwise pathways of the uncatalyzed aldol reaction between trihydrosilyl enol ether and formaldehyde. Bond lengths are given in Å.

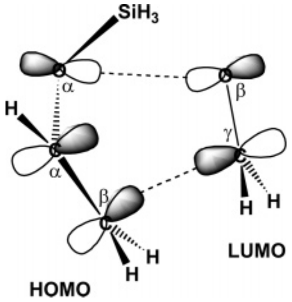


FIGURE 2. Molecular orbital diagram showing the favorable interaction between the HOMO of trihydrosilyl enol ether and the LUMO of formaldehyde.

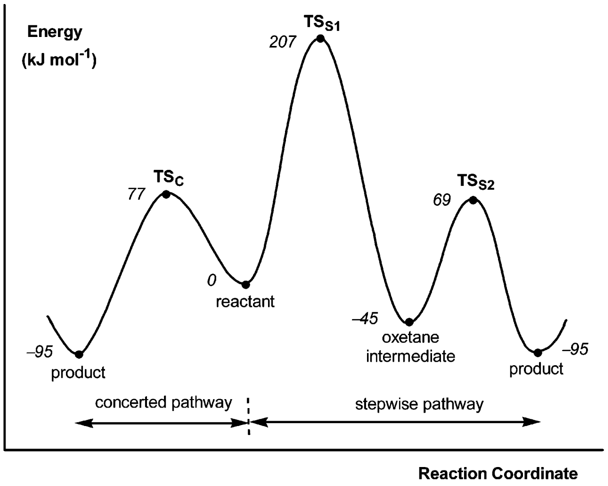


FIGURE 3. Schematic potential energy diagram showing the concerted and stepwise pathways of the uncatalyzed aldol reaction between trihydrosilyl enol ether and formaldehyde. G3(MP2) relative energies are given in kJ mol^{-1}.

plausible zwitterionic intermediates at the MP2/6-31G* level failed. This is perhaps not surprising as these intermediates are highly polar and we do not expect their formation to be favorable in the isolated state. However, these zwitterionic intermediates can be stabilized in the presence of a Lewis acid catalyst.

On the other hand, a stable oxetane intermediate (Figure 1) and its associated transition states were successfully been located. The four-membered ring intermediate is stable with respect to the reactants, by 45 kJ mol^{-1}. The first step of this stepwise process corresponds to a [2 + 2] cycloaddition with a simultaneous C−C and C−O bond formation, via transition state **TS$_{S1}$**. As expected, this symmetry-forbidden process is inhibited by a substantially higher energy barrier of 207 kJ mol^{-1}. The second step of the stepwise pathway involves a simultaneous C−O cleavage and 1,3-SiH$_3$ shift, via transition state **TS$_{S2}$**. This occurs with a relatively lower activation barrier of 114 kJ mol^{-1}. The optimized geometries of the oxetane intermediate and the corresponding transition states (**TS$_{S1}$** and **TS$_{S2}$**) are shown in Figure 1.

The calculated relative energies of both concerted and stepwise pathways are summarized in a schematic energy diagram, as shown in Figure 3. It is obvious that the concerted pathway is strongly preferred for the uncatalyzed Mukaiyama aldol reaction. Hence, our calculations readily confirm the experimental finding that a direct intramolecular silicon group transfer is involved.[6a] For all subsequent substituted Mukaiyama aldol reactions, we will consider only the concerted mechanism.

TABLE 1. Calculated G3(MP2)[a] Barriers and Enthalpies (kJ mol^{-1})[b]

R_a	R_b	R_c	R_d	R_e	barrier	enthalpy
H	H	H	H	H	76.6	−94.9
CH_3	H	H	H	H	82.9	−77.3
CH_3	CH_3	H	H	H	92.8	−66.1
CF_3	H	H	H	H	54.9	−117.2
NH_2	H	H	H	H	131.4	−11.9
F	H	H	H	H	103.2	−54.5
CHO	H	H	H	H	63.8	−100.3
$COOCH_3$	H	H	H	H	60.9	−108.5
$CH{=}CH_2$	H	H	H	H	85.9	−69.9
C_6H_5	H	H	H	H	78.1	−73.9
H	H	CH_3	H	H	63.7	−102.8
H	H	NH_2	H	H	30.1	−162.0
H	H	OH	H	H	37.8	−161.1
H	H	F	H	H	54.3	−154.4
H	H	SH	H	H	50.5	−132.9
H	H	CHO	H	H	79.0	−89.5
H	H	H	NH_2	H	70.2	−99.3
H	H	H	H	NH_2	82.4	−103.5
CHO	H	NH_2	H	H	11.6	−165.8

[a] G3(MP2) E_0 values; the G3(MP2) energies of the reactants, transition states, and products are given in Tables S1 and S2 (Supporting Information). [b] Unless otherwise noted, the s-cis conformation of trihydrosilyl enol ether and the first-formed product were employed in all energy calculations.

2. Effects of Substituents. To provide further insights into the governing factors of the reactivity of the silicon-directed aldol reactions, we have examined the effects of several prototypical substituents on both silyl enol ether and aldehyde (Scheme 2). The calculated barrier heights and reaction enthalpies are summarized in Table 1, and the structural parameters of the equilibrium structures and transition states are presented in Tables S5 and S6 (Supporting Information), respectively.

2.1. Transition States. The transition structures obtained for the various substituted aldol reactions are similar to those calculated for the parent system. They exhibit the simultaneous C−C bond formation and SiH_3 shift. The key structural parameters are summarized in Table S6 (Supporting Information). In all cases, the geometry shows lengthening of the $C_\alpha-C_\beta$, $Si-O_\alpha$, and $C_\gamma-O_\beta$ bonds and a shortening of the $O_\alpha-C_\alpha$ bond. Interestingly, the bond distances of the $C_\beta\cdots C_\gamma$ and $O_\beta\cdots Si$ forming bonds have a rather wide range, 1.881−2.242 Å and 1.847−2.267 Å, respectively. These transition states also exhibit asynchronicity similar to that of the parent system (**TS$_C$**). There are strong correlations between the barrier height and the $C_\beta\cdots C_\gamma$ and $O_\beta\cdots Si$ forming bond distances. Excluding the R_a = F case, the correlation coefficients are 0.87 and 0.80 for $C_\beta\cdots C_\gamma$ and $O_\beta\cdots Si$ bond distances, respectively. These correlations are not unexpected as reaction enthalpy is a key governing factor of the reactivity. The unexpectedly short $C_\beta\cdots C_\gamma$ bond length for the exceptional halogen case (R_a = F) can be explained in terms of the charge distribution in the transition structure (see section 2.5).

2.2. Exothermicities. As evident in Table 1, all the substituted aldol reactions are predicted to be exothermic. However, the exothermicity depends strongly on the nature of the substituent, ranging from 12 to 162 kJ mol^{-1}. A strong correlation is found to exist between the calculated barrier and enthalpy ($R^2 = 0.97$, Figure 4). In particular, an excellent correlation is calculated for the substituted aldehydes reacting with trihydrosilyl enol ether ($R^2 = 0.99$). These high correlation values indicate that the exothermicity has a substantial influence on the reactivity of these systems.

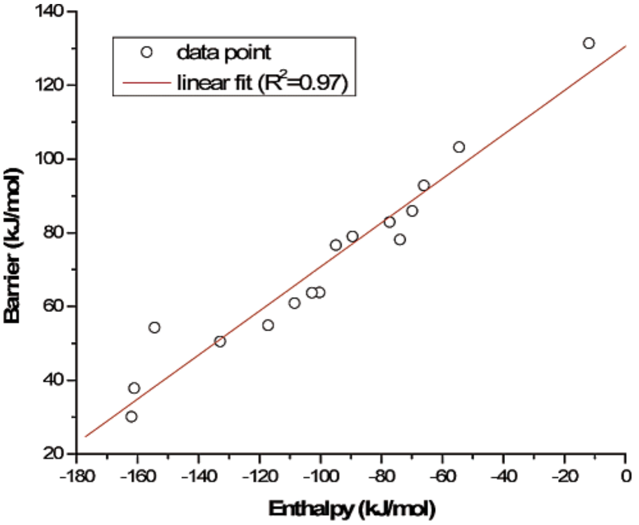


FIGURE 4. Plot of barrier height against reaction enthalpy.

2.3. Barriers. Let us first consider the effects of substituents on formaldehyde. As evident in Table 1, introduction of an electron-donating substituent (CH_3 or NH_2) on formaldehyde increases the energy barrier, while substituting of an electron-withdrawing group (CF_3, CHO, or $COOCH_3$) reduces the energy barrier. The effect of dimethyl substitution, comparing to the monomethyl substitution, indicates that ketone is less reactive than aldehyde. This result is consistent with experimental observation. Unexpectedly, the fluoro substituent, being electron-withdrawing in nature, increases the activation energy of the reaction. Among the reactions of various aldehydes with trihydrosilyl enol ether, CF_3 substitution leads to the lowest activation barrier of 55 kJ mol^{-1}. In general, a vinyl group ($CH{=}CH_2$) is used to model the effect of phenyl substitution. A slightly higher barrier (by 10 kJ mol^{-1}) is predicted for a vinyl substitution. On the other hand, a direct calculation of phenyl substitution shows little effect (Table 1). Thus, caution is required to interpret the results using a simple model. Here, we conclude that π-electron-donating substituents on aldehyde have minor energetic consequence on the aldol reaction.

A reverse pattern is observed for the substituent effects (at R_c) on trihydrosilyl enol ether. Electron-donating substituents (CH_3, NH_2, OH, and SH) decrease the energy barrier, while an electron-withdrawing substituent (CHO) increases the energy barrier. Again, the exceptional behavior of fluorine substitution is noted. This electron-withdrawing substituent decreases the activation energy of the aldol reaction. Among the various substituents considered, amino (NH_2) substitution has the lowest energy barrier of 30 kJ mol^{-1}. It is important to note that substitution at C_α on the trihydrosilyl enol ether has a more pronounced effect on the energy barrier than substitution at C_β (i.e., R_d or R_e), as evidenced in the NH_2 substitution at various positions (see Table 1). Experimentally, silyl enol ethers of ester, thioester, and amide (i.e., R_c = OR, SR, and NR_2, where R = alkyl

TABLE 2. Calculated NBO Atomic Charges of the Transition States[a]

R_a	R_b	R_c	R_d	R_e	C_γ	O_β	Si	O_α	C_α	C_β	CT[b]
H	H	H	H	H	0.08	−0.70	1.26	−0.71	0.29	−0.61	0.23
CH_3	H	H	H	H	0.27	−0.72	1.26	−0.70	0.30	−0.61	0.24
CH_3	CH_3	H	H	H	0.48	−0.74	1.26	−0.71	0.30	−0.60	0.24
CF_3	H	H	H	H	0.15	−0.67	1.25	−0.71	0.30	−0.61	0.31
NH_2	H	H	H	H	0.40	−0.81	1.26	−0.65	0.34	−0.65	0.28
F	H	H	H	H	0.62	−0.75	1.25	−0.70	0.35	−0.63	0.35
CHO	H	H	H	H	0.15	−0.70	1.25	−0.69	0.29	−0.59	0.32
$COOCH_3$	H	H	H	H	0.16	−0.68	1.25	−0.69	0.30	−0.59	0.31
$CH{=}CH_2$	H	H	H	H	0.23	−0.73	1.26	−0.68	0.30	−0.60	0.27
C_6H_5	H	H	H	H	0.25	−0.73	1.26	−0.69	0.30	−0.60	0.28
H	H	CH_3	H	H	0.09	−0.69	1.26	−0.74	0.48	−0.59	0.22
H	H	NH_2	H	H	0.13	−0.66	1.27	−0.81	0.61	−0.67	0.18
H	H	OH	H	H	0.13	−0.66	1.27	−0.81	0.74	−0.66	0.17
H	H	F	H	H	0.11	−0.67	1.26	−0.75	0.85	−0.68	0.17
H	H	SH	H	H	0.11	−0.67	1.26	−0.76	0.27	−0.61	0.18
H	H	CHO	H	H	0.07	−0.70	1.25	−0.69	0.34	−0.56	0.23
H	H	H	NH_2	H	0.07	−0.69	1.25	−0.72	0.29	−0.19	0.24
H	H	H	H	NH_2	0.03	−0.77	1.24	−0.73	0.26	−0.11	0.31
CHO	H	NH_2	H	H	0.20	−0.64	1.27	−0.80	0.61	−0.65	0.26

[a] Based on MP2(full)/6-31G* wave function. [b] Charge transfer (CT) from the enol silane moiety to the aldehyde unit in the transition state.

group) were commonly employed for the silicon-directed aldol addition.[5,6] Since OR, SR, and NR_2 are better electron-donating groups than OH, SH, and NH_2, respectively, these substituents are expected to have a strong influence on the aldol reactivity. In particular, Myers et al. have shown that *O*-silyl enol derivatives of amides can undergo facile uncatalyzed aldol addition.[5] It is important to note that the hydroxyl- and amino-substituted silyl enolates may react as an enol and enamine, respectively. A detailed study of the reaction pathways of these competitive reactions is beyond the scope of the present paper.

2.4. Frontier Orbital Interactions. Our finding on the importance of the nucleophilicity of enol is consistent with the experimental result of Rathore et al.[22] They showed that silyl enol ethers are excellent electron donors as these compounds react readily with quinones to form electron donor−acceptor complexes. Hence, the frontier molecular orbital (FMO) interactions of the reactants are expected to play a significant role in the understanding of the energetics of these reactions. In all cases, the energy difference between the HOMO of silyl enol ether and the LUMO of aldehyde (ΔE_{SA}) is smaller than the energy difference between the HOMO of aldehyde and the LUMO of silyl enol ether (ΔE_{AS}) (Table S4 in the Supporting Information). We have examined the correlation between ΔE_{SA} and the calculated barrier. Correlation values (R^2) of 0.82 and 0.85 are obtained for the substituted aldehydes and substituted enol silane series, respectively. These results support in general the idea that enol silane serves as a nucleophile while aldehyde acts as an electrophile to some extents. However, a smaller barrier is not always associated with a smaller ΔE_{AS} value, as expected from the FMO theory. This is reflected in the substituted aldehyde series. Hence, we may conclude that the frontier molecular orbital interaction may not be the main factor in governing the reactivity, and there is/are additional factor(s) that may influence the energetics of the reaction. We have shown, for instance, that the reaction enthalpy is one of such important factors.

2.5. Charge Distributions. An NBO analysis was carried out for all the transition states. The atomic charges of the key six atoms in the transition state are given in Table 2. First, we note that strong charges are predicted for most of these atoms. For the $C_\beta \cdots C_\gamma$ and $Si \cdots O_\beta$ forming bonds, the charges of the two bonding atoms are of different sign. Thus, electrostatic attraction may contribute significantly in stabilizing the transition state. The fluoro-substituted aldehyde ($R_a = F$) represents the extreme case, where both carbon atoms bear large charges, +0.62 and −0.63 for C_γ and C_β, respectively. As a consequence, it has a rather short $C_\beta \cdots C_\gamma$ bond distance (1.881 Å) in the transition state (Table S6, Supporting Information). The charges on Si, O_α, and O_β are found to be relatively uniform throughout both substituted enol and aldehyde series (Table 2). The extent of charge transfer from the enol silane moiety to the aldehyde moiety in the transition state is significant in all cases (Table 2), range from 0.17 (R_c = OH) to 0.35 (R_a = F). These data reinforce the importance of the nucleophilicity of enol and the electrophilicity of aldehyde in influencing the reactivity of this class of aldol additions. On going from the reactant (Table S7, Supporting Information) to the transition state, there is a significant increase in the electron populations of both C_γ and O_β in the aldehyde subunit. However, the corresponding decrease of electron population of the enol silane moiety comes mainly from C_α and O_α. Unexpectedly, the electron population of C_β increases.

3. Cooperative Substituent Effects. From the above discussion, it is apparent that the formyl-substituted aldehyde and the amino-substituted silyl enol ether ($R_c = NH_2$) are among the better candidates for facile uncatalyzed Mukaiyama aldol reaction. So, it is intriguing to ask whether there is a cooperative influence between substituents on both reactants. Indeed, the activation energy for the reaction with R_a = CHO and $R_c = NH_2$ is predicted to be just 12 kJ mol^{-1} (Table 1). The combined substituent effect results in a substantial reduction of the activation barrier, by 65 kJ mol^{-1}

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(22) Rathore, R.; Kochi, J. K. *Tetrahedron Lett.* **1994**, *35*, 8577.

compared to the parent system. Interestingly, the magnitude of reduction is greater than the expected value of 58 kJ mol^{-1}, estimated from the sum of the individual substituent effects. With such a small barrier of 12 kJ mol^{-1}, we expect this aldol reaction to proceed readily at room temperature and possibly at temperatures well below 0 °C.

Besides the above combination of substituents, we predict also that the reaction between $COOCH_3$- or CF_3-substituted formaldehyde with NH_2-substituted ($R_c = NH_2$) silyl enol ether to occur readily. The activation energies of these two reactions are likely to be lower than 12 kJ mol^{-1}, as both substituted aldehydes have a lower activation barrier than the CHO-substituted formaldehyde in the reaction with silyl enol ether (Table 1). In summary, our calculations show that substitutions on both reactants may lead to a cooperative influence on the energy barrier. With the right combination of substituents, it is possible for uncatalyzed Mukaiyama reaction to take place readily under mild experimental conditions.

4. Effect of Substitution on the Silicon Group. It is important to note that most Mukaiyama aldol reactions are carried out using trimethylsilyl enol ether ($(CH_3)_3SiO{-}CH{=}CH_2$) derivatives instead of trihydrosilyl enol ether ($SiH_3O{-}CH{=}CH_2$) derivatives examined here. Trihydrosilyl enol ether was chosen in this study as the system is smaller and the computational effort required is less demanding. To compare the effect of $Si(CH_3)_3$ with the simple SiH_3 model, we have computed also the activation and reaction energies between trimethylsilyl enol ether and formaldehyde at the G3(MP2) level. The calculated barrier (97 kJ mol^{-1}) is 20 kJ mol^{-1} higher and the reaction enthalpy is 3 kJ mol^{-1} more exothermic than the corresponding trihydrosilyl system. The lower barrier of SiH_3 is consistent with the experimental observation that the O-$Si(CH_3)_3$ system is less reactive than O-$Si(CH_3)_2H$ derivative.[7] Thus, this information should be taken into consideration when interpreting the values reported herein for the trihydrosilyl enol ether system.

Previous experimental studies have shown that the rate of uncatalyzed aldol reaction is highly dependent on the spectator substituent of silicon. For instance, Denmark et al.[6a] and Myers et al.[5] have demonstrated dramatic accelerations of aldol reactions using *O*-(silacyclobutyl) ketene acetals. To explore further the role of silicon group, we have examined here the aldol reaction of *O*-(silacyclobutyl) ketene acetal with formaldehyde. Compare to the corresponding *O*-(trimethylsilyl) derivative, the calculated reaction enthalpy (−96 kJ mol^{-1}) is similar but it has a significantly smaller energy barrier of 65 kJ mol^{-1}, by 32 kJ mol^{-1}. Thus, our result supports the experimental findings that incorporation of the silicon atom within a four-membered ring is more efficient than the “normal” trimethylsilyl derivative in promoting aldol reactions.

Denmark et al. have also employed *O*-(trichlorosilyl) ketene acetal successfully to improve the reaction rates of aldol reactions.[23] Our calculation on the O-$SiCl_3$ system predicts a lower energy barrier of 65 kJ mol^{-1}, 32 kJ mol^{-1} less than the corresponding O-$SiMe_3$ analogue. Again, theory convincingly confirms the importance of using an appropriate silicon group to promote the reactivity of aldol reaction.

TABLE 3. Calculated[a] Barriers and Enthalpies (kJ mol^{-1}) for the Aldol Reactions of Various R*O*-CH=CH$_2$ Derivatives with CH$_2$=O

O-R	barrier	enthalpy
O-SiH_3	76.6 (63.9)	−94.9 (−96.8)
O-$Si(CH_3)_3$	96.8	−98.5
O-SiF_3	46.9	−103.8
O-$SiCl_3$	64.9	−105.9
O-silacyclobutyl	65.4	−96.0
O-GeH_3	(49.2)	(−95.7)

[a] G3(MP2) values, with the B3LYP/6-31G* results in parentheses.

From above calculations, it appears that electronegative substituent on the silicon has a favorable effect on the reactivity. To confirm our speculation, we investigated the aldol reaction involving an *O*-(trifluorosilyl) derivative. Indeed, this reaction has the smallest activation barrier (47 kJ mol^{-1}) among all the silicon groups considered here. Based on DFT calculations, we also predict that a germanium group is more effective than a silicon group in promoting aldol reaction. At the B3LYP/6-31G* level, the O-GeH_3 derivative (i.e., $GeH_3O{-}CH{=}CH_2$) has a smaller activation barrier than trihydrosilyl enol ether, by 15 kJ mol^{-1} (Table S3, Supporting Information). The calculated barriers and enthalpies for the aldol reactions of various R*O*-CH=CH$_2$ derivatives with formaldehyde are summarized in Table 3.

5. Effect of Solvent. The Mukaiyama aldol reactions are commonly carried out in a solvent (e.g., CH_2Cl_2; with dielectric constant ($\epsilon = 8.93$)). Experimentally, it has been reported that the reaction proceeds favorably in solvents that are poor σ-donors, such as CH_2Cl_2, hexane, benzene, and CH_3CN. No reaction occurs when tetrahydrofuran, diethyl ether, or *N*,*N*-dimethylformamide is used.[2,10,24] The computed gas-phase and solution-phase (based on SCRF theory)[17] barriers and enthalpies of the various substituents obtained at the B3LYP/6-31G* level are tabulated in Table S3 (Supporting Information). For the parent reaction, there is a small decrease in the activation energy from 64 kJ mol^{-1} ($\epsilon = 1$) to 60 kJ mol^{-1} ($\epsilon = 9$, represents nonpolar solvent) and to 60 kJ mol^{-1} ($\epsilon = 40$, represents aprotic solvent). Small changes of reaction barriers upon solvation are calculated for other substituted systems (Table S3, Supporting Information). These results suggest that the influence of solvent on the reactivity of the uncatalyzed aldol reactions is likely to be small.

Conclusion

The uncatalyzed Mukaiyama aldol reaction between trihydrosilyl enol ether and formaldehyde is confirmed to proceed via a concerted mechanism. An alternate stepwise pathway via the formation of a four-membered ring oxetane intermediate is calculated to be significantly higher in energy. In general, the aldol reaction is found to be more favorable with electron-donating substituents

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(23) (a) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233. (b) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K. T. *J. Am. Chem. Soc.* **1996**, *118*, 7404.

(24) Munoz-Muniz, O.; Quintanar-Audelo, M.; Juaristi, E. *J. Org. Chem.* **2003**, *68*, 1622.

on trihydrosilyl enol ether (at R_c) and electron-withdrawing substituents on formaldehyde. The notable exception is the fluoro substituent. The study of the effects of substituents on silyl enol ether and aldehyde reveals the following factors in influencing the reactivity of the silicon-directed aldol reactions: (1) exothermicity, (2) nucleophilicity of enol silane, (3) electrophilicity of aldehyde, (4) frontier molecular orbital interactions, and (5) electrostatic interactions. Substitution on both reactants is found to have a cooperative influence on the activation barrier. We predict that the reactions between NH_2-substituted ($R_c = NH_2$) trihydrosilyl enol ether and CHO-, $COOCH_3$-, and CF_3-substituted aldehydes will proceed readily without a catalyst at temperature below 0 °C. In accord with experimental findings, the *O*-(silacyclobutyl) and *O*-(trichlorosilyl) derivatives increase the reactivity of aldol reaction. In addition, we predict that *O*-SiF_3 and *O*-GeH_3 are potential silyl group replacement for facile aldol reactions. Hence, this study demonstrates clearly that the reactivity of the silicon-directed aldol reaction can be increased considerably by introducing appropriate substituents on the reactants.

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Supporting Information Available: Tables S1 and S2, G3(MP2) total energies; Table S3, B3LYP/6-31G* barriers and enthalpies; Table S4, calculated HOMO and LUMO energies; Tables S5 and S6, structural parameters of the reactants and transition states, respectively; Table S7, NBO atomic charges of the reactants; Table S8, Cartesian coordinates and absolute energies of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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