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Geminal bond participation in the uncatalyzed Mukaiyama aldol reaction

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Abstract—We predicted that uncatalyzed Mukaiyama aldol reactions are under the control of the geminal bond participation. At the transition state of the model reaction, addition of $CH_2{=}O$ and $CH_2{=}CH(OSiH_3)$, the interbond energy IBE is negative between the σ-bonding orbital at the *Z*-position of the enolate terminal and $\pi^*_{C=O}$, and positive between that at the *E*-position and $\pi^*_{C=O}$. These results led us to predict that the electron-donating σ-bond at the *Z*-position enhances the reactivity. We calculated the enthalpies of activation of the reactions of a variety of the R-substituted silyl enolates and confirmed the prediction by showing that the reactivity of the *Z*-isomers relative to that of the *E*-isomers increases with the energy of the bonding orbital of the σ bond at the *Z*-position (the axial position at the transition state of the chair form). We demonstrate that the geminal bond participation is general not only to the pericyclic reactions but also to the aldol reaction, which is one of the most fundamental C–C bond forming reactions.

σ-Bonds vicinal to the reaction centers have been proposed so far to participate in the reactions.[1,2] In the Felkin–Anh model,[3] the nucleophile attacks the carbonyl carbon on the opposite side of the most electronegative atom X at the α-position (Fig. 1a). The electrophilic attack is promoted by the electron-donating bond of the α-substituent at the backside (the anomeric effect, Fig. 1b).[4] The substituent effects are based on the interactions with the σ-bond vicinal to the reacting bonds.

We proposed that the σ-bonds geminal to the reaction centers should control the reactivity/selectivity in the pericyclic reactions.[5–10] For example, an electron-donating geminal σ-bond at the *Z*-position of the diene terminal enhances the reactivity in the Diels–Alder reaction.[5]

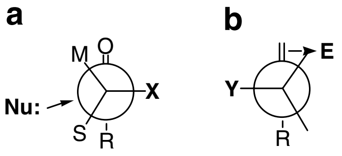

Figure 1. Vicinal bond participations.

The enthalpies of activation of the Cope rearrangements[6] and sigmatropic [1,5]-hydrogen shifts[7] are lowered by electron-donating geminal σ-bond at the *Z*-position. An electron-donating geminal σ-bond was shown to prefer the inward rotation in the ring-opening reactions of cyclobutenes[8] and the cheletropy reactions.[9] An electron-donating σ-bond at the *Z*-position of the enophile olefin terminal enhances reactivity in the Alder ene reactions.[10]

The geminal bond participation is associated to the cyclic orbital interaction or the orbital phase continuity property (Fig. 2). Cyclic orbital interaction is required to meet the orbital phase continuity conditions:[11] (i) electron-donating orbitals are out of phase; (ii) the electron-donating orbital and the electron-accepting orbital are in phase; (iii) electron-accepting orbitals are in phase. When the geminal σ-bonds are donors, both of the σ orbitals combined out of phase cannot be in phase with the vacant orbital a* simultaneously (Fig. 2). For

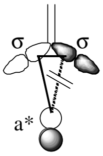

Figure 2. Orbital phase in the geminal bond participation.

Keywords: Geminal bond participation; Mukaiyama aldol reaction; Bond model analysis.

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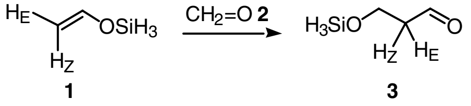


Scheme 1.

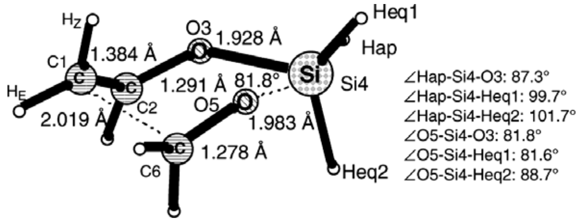


Figure 3. The transition structure (B3LYP/6-31G(d)).

Table 1. IBE values (a.u.) at the transition state (RHF/6-31G(d)//B3LYP/6-31G(d))

Bond interaction	IBE/a.u.
$\pi_{C1–C2}–\pi^*_{C6–O5}$	−2.500
$\pi_{C6–O5}–\pi^*_{C1–C2}$	0.008
$n_O–\sigma^*_{Si4–H/O}$	−0.697
$\sigma_{C1–H_Z}–\pi^*_{C6–O5}$	−0.039
$\sigma_{C1–H_E}–\pi^*_{C6–O5}$	0.048
$\pi_{C6–O5}–\sigma^*_{C1–H_Z}$	0.003
$\pi_{C6–O5}–\sigma^*_{C1–H_E}$	−0.043

example, at the transition state in the Diels–Alder reaction, the interaction of the LUMO (a^*) of the dienophile is bonding with the σ-bonding orbital at the *Z*-position of the diene and antibonding with that of the σ-bonding orbital at the *E*-position.[5]

Here, we expand the scope of the applicability of the geminal bond participation beyond the pericyclic reactions. Now we predict the reactivity of the unanalyzed Mukaiyama aldol reaction.[12,13] As a model we chose the addition of silyl enolate **1** to formaldehyde **2** (Scheme 1).

The uncatalyzed Mukaiyama reaction proceeds via the six-membered ring transition state.[12] The transition state of the model reaction,[14] addition of vinyloxysilane **1** to formaldehyde **2** (Fig. 3),[13] was subjected to the bond model analysis.[15] We used the interbond energy IBE to evaluate the interactions between the bond orbitals.[16]

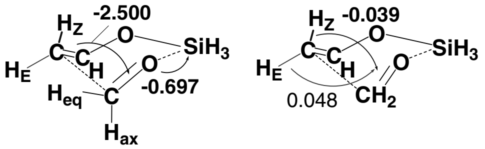
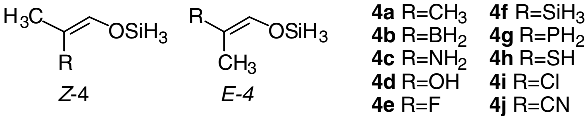


Figure 4. IBE values (a.u.) at the transition state.



Scheme 2.

In the aldol reaction, the enolate is a donor and the carbonyl group is an acceptor. In fact, the bond model analysis showed that the interactions between $\pi_{C1–C2}$ and $\pi^*_{C6–O5}$ (IBE = −2.500 a.u.) and between n_{O5} and $\sigma^*_{Si4–H/O}$ (IBE = − 0.697 a.u.) are the most important in stabilizing the transition state (Table 1). The interaction of $\pi_{C6–O5}$ with $\pi^*_{C1–C2}$ is weak (0.008 a.u.). The IBE value is negative (−0.039 a.u.) between the geminal σ-bonding orbital at the *Z*-position and $\pi^*_{C=O}$ and positive (0.048 a.u.) between that at the *E*-position and $\pi^*_{C=O}$ (Fig. 4). The geminal bond participation makes a significant difference (0.087 a.u.) through the $\sigma_{CH} \rightarrow \pi^*_{C=O}$ interaction. The IBE difference is smaller (0.046 a.u.) between the interactions of $\pi_{C=O}$ with the geminal σ^*_{CH} orbitals at the *Z*- and *E*-positions (see Table 1).

An electron-donating σ-bond at the *Z*-position of the reacting C1 atom in the enolate is predicted to enhance the reactivity. To test our prediction, we calculated the

Table 2. The difference in the enthalpies of activation (kcal mol^{-1}) in the uncatalyzed Mukaiyama aldol reactions between the *E*- and *Z*-substituted enolates

Substrate	$\Delta H^{\ddagger}_Z$[a]	$\Delta H^{\ddagger}_E$[b]	$\Delta H^{\ddagger}_Z - \Delta H^{\ddagger}_E = \Delta\Delta H^{\ddagger}$	r_{CC}[d]	
				Z	*E*
4a (R=CH_3)	18.0(22.5)	—	0.0	2.012	
4b (R=BH_2)	21.1(24.8)	23.4(27.1)	−2.3(−2.4)	2.349	2.415
4c (R=NH_2)	[9.2(13.2)]	[9.9(14.3)]	[c]	—	—
4d (R=OH)	[14.5(19.6)]	[16.6(20.8)]	[c]	—	—
4e (R=F)	22.0(25.1)	17.3(22.0)	4.7(3.1)	2.042	2.010
4f (R=SiH_3)	19.8(23.9)	21.5(25.8)	−1.7(−1.9)	2.004	2.043
4g (R=PH_2)	19.7(24.2)	21.3(25.9)	−1.6(−1.7)	2.060	2.038
4h (R=SH)	18.9(22.9)	19.8(24.1)	−0.8(−1.2)	2.367	2.072
4i (R=Cl)	21.6(25.5)	18.7(23.1)	2.9(2.4)	2.220	2.027
4j (R=CN)	23.5(26.9)	22.1(26.0)	1.0(0.9)	2.407	2.352

B3LYP/6-31G(d) and B3LYP/6-311++G(3df,2p)//B3LYP/6-31G(d), ZPE corrected.

[a] $\Delta H^{\ddagger}_Z = \Delta H^{\ddagger}$ ($R_Z = R$; $R_E = CH_3$).

[b] $\Delta H^{\ddagger}_E = \Delta H^{\ddagger}$ ($R_Z = CH_3$; $R_E = R$).

[c] See Ref. 18.

[d] The incipient C1–C6 bond length at the transition state.

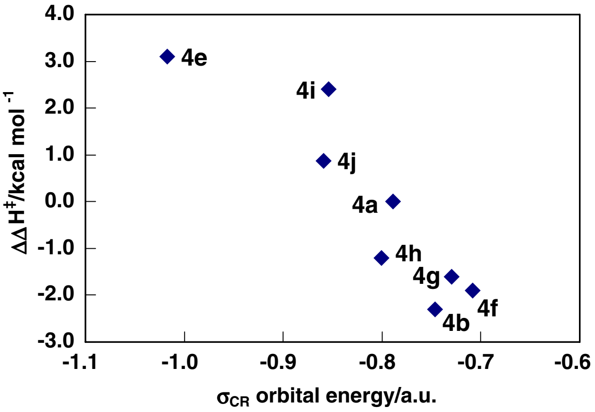


Figure 5. The dependence of the difference $\Delta\Delta H^\ddagger$ in the reactivities between the *E*- and *Z*-enolates on the σ_{CR} energy (B3LYP/6-311++G(3df,2p)//B3LYP/6-31G(d), ZPE corrected).

transition states of the reactions of the R-substituted silyl enolates **4a**–**j** with one substituent fixed to a methyl group to reduce unwanted steric bias (Scheme 2).

The differences in the reactivity or the difference in the enthalpy of activation of *E*/*Z*-isomers ($\Delta\Delta H^\ddagger = \Delta H^\ddagger_Z - \Delta H^\ddagger_E$) are shown in Table 2 and are compared with the σ_{CR} orbital energies (Fig. 5). The difference in reactivity is in a good correlation with the σ_{CR} orbital energy.[17] This result confirmed the prediction that the electron-donating geminal σ-bond at the *Z*-position in the enolate should promote the uncatalyzed Mukaiyama aldol reactions. Furthermore, the incipient C1–C6 bonds (Fig. 3) at the transition states are shorter for the more electron-donating geminal σ-bond at the *Z*-position, as are expected from the geminal bond participation except **4g** and **4h**, for which the carbonyl carbon shifts toward the vinyl α-carbon (C2 in Fig. 3) at the transition states due to the lone pair on the phosphorus or sulfur of the substituents.

In conclusion, the geminal bond participation controls the reactivity in the uncatalyzed Mukaiyama aldol reaction as well as the pericyclic reactions. The reactivity is enhanced by the electron-donating geminal σ-bond at the *Z*-positions in the enolates.

Acknowledgments

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References and notes

1. Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2A, pp 125–155; Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 1–110; Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 111–212; Eliel, E. L. In *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994; pp 835–990.
2. Kirby, A. J., Ed.Stereoelectronic Effect; Oxford University Press: Oxford, UK, 1996.
3. Anh, T. D.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61–70.
4. Deslongchamps, P. *Stereoelectronic Effects in Organic Synthesis*; Pergamon Press: Oxfird, UK, 1983.
5. Inagaki, S.; Ikeda, H. *J. Org. Chem.* **1999**, *63*, 7820–7822.
6. Ikeda, H.; Naruse, Y.; Inagaki, S. *Chem. Lett.* **1999**, 364–365.
7. Ikeda, H.; Ushioda, N.; Inagaki, S. *Chem. Lett.* **2001**, 166–167.
8. (a) Ikeda, H.; Kato, T.; Inagaki, S. *Chem. Lett.* **2001**, 270–271; (b) Yasui, M.; Naruse, Y.; Inagaki, S. *J. Org. Chem.* **2004**, *69*, 7246–7249; For an alternative theory see: (c) Krimse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989–7991; (d) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099–2111; (e) Lee, P. S.; Zhang, X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 5072–5079; For some recent interesting observations, see: (f) Murakami, M.; Miyamoto, Y.; Ito, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 189–190; (g) Murakami, M.; Miyamoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6441–6442; (h) Murakami, M.; Hasegawa, M.; Igawa, H. *J. Org. Chem.* **2004**, *69*, 587–590; (i) Murakami, M.; Usui, I.; Hasegawa, M.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 1366–1367; (j) Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840–6841; (k) Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. *J. Org. Chem.* **2004**, *69*, 3912–3916; (l) Mori, S.; Shindo, M. *Org. Lett.* **2004**, *6*, 3945–3948; (m) Shindo, M.; Yoshikawa, T.; Itou, Y.; Mori, S.; Shishido, K. *Chem. Eur. J.* **2006**, *12*, 524–536; For review see: (n) Murakami, M.; Miyamoto, Y.; Ito, Y. *Yuki Gosei Kagaku Kyokaishi* **2002**, *60*, 1049–1054; (o) Murakami, M.; Miyamoto, Y.; Hasegawa, M.; Usui, I.; Matsuda, T. *Pure Appl. Chem.* **2006**, *78*, 415–423.
9. Naruse, Y.; Hayashi, Y.; Inagaki, S. *Tetrahedron Lett.* **2003**, *44*, 8509–8512.
10. Naruse, Y.; Suzuki, T.; Inagaki, S. *Tetrahedron Lett.* **2005**, *46*, 6937–6940.
11. (a) Fukui, K.; Inagaki, S. *J. Am. Chem. Soc.* **1975**, *97*, 4445–4452; (b) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4693–4701; For recent applications, see: (c) Ma, J.; Inagaki, S. *J. Phys. Chem.* **2000**, *104*, 8989–8994; (d) Ma, J.; Ikeda, H.; Inagaki, S. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 273–278; (e) Ma, J.; Inagaki, S. *J. Am. Chem. Soc.* **2001**, *123*, 1193–1198; (f) Ma, J.; Ding, Y.; Hattori, K.; Inagaki, S. *J. Org. Chem.* **2004**, *69*, 4245–4255.
12. For Mukaiyama aldol reaction see: Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011–1014; Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.
13. Ishikawa, S.; Watanabe, M. *Proc. Sc. Sci. Tokai Univ.* **1999**, *34*, 81–87; Wong, C. T.; Wong, M. W. *J. Org. Chem.* **2005**, *70*, 124–131.
14. GAUSSIAN98 Revision A.7 Gaussian, Pittsburgh, PA, 1998.
15. For the bond model analysis, see Ref. 7 (a) Iwase, K.; Inagaki, S. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2781–2789; (b) Inagaki, S.; Yamamoto, T.; Ohashi, S. *Chem. Lett.* **1997**, 977–978; See also: Refs. 5, 6, 8a,b, 9, and 10; for another method of the bond model analysis, see: (c) Ikeda, H.; Inagaki, S. *J. Phys. Chem. A* **2001**, *47*, 10711–10718.
16. IBE is derived as follows:

$$\mathrm{IBE}_{ij} = P_{ij}(H_{ij} + F_{ij})$$

where P_{ij}, H_{ij}, and F_{ij} are the elements of the density, Fock, and core Hamiltonian matrices of the bond orbitals, respectively. See Ref. 15b. For some recent works, see also: (a) Naruse, Y.; Inagaki, S.; Kano, N.; Nakagawa, N.; Kawashima, T. *Tetrahedron Lett.* **2002**, *43*, 5759–5762; (b) Otani, Y.; Nagae, O.; Naruse, Y.; Inagaki, S.; Ohno, M.; Yamagichi, K.; Yamamoto, G.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2003**, *125*, 15191–15199; Naruse, Y.; Takeuchi, K.; Nohara, T.; Inagaki, S. *Tetrahedron* **2006**, *62*, 4491–4497.

17. The σ_{CR} energies were calculated by the bond model analysis. See Refs. 8b and 11f.
18. Enolates **4c** ($R=NH_2$) and **4d** ($R=OH$) react as an enamine and an enol at the C2 position, respectively.