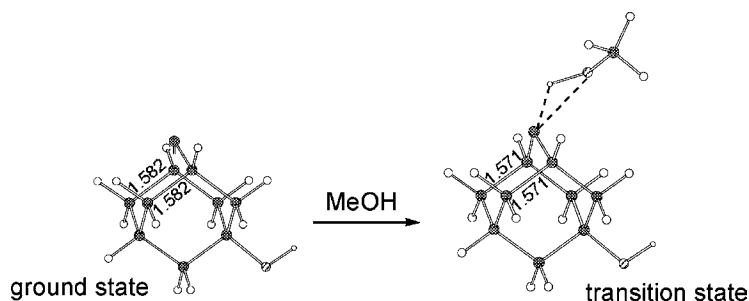# Origin of Facial Diastereoselection. Evidence for Negative Role of Antiperiplanar Hyperconjugation Effects in the Transition State of Carbene Insertion

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ABSTRACT

Quantitative analysis of the transition state (TS) structures of the insertion reactions of 5-X-2-adamantanylidenes (X = H, OH, NH$_2$, SiMe$_3$) into MeOH or cyclohexane revealed that the magnitude of antiperiplanar hyperconjugative stabilization involving the incipient bond effects (the AP effect) decrease at TS, strongly suggesting that the AP effect contributes "net destabilization" of TS (i.e., increase in activation energy), in sharp contrast to the proposals of the Felkin–Anh and the Cieplak models. The equilibrium population between two carbene bridge-flipping *proximal–distal* conformers was found to be the origin of facial diastereoselection of these carbenes.

The origin of facial diastereoselection remains a controversial issue.[1] Most arguments are based on the assumption that the transition state stabilization arising from antiperiplanar hyperconjugation effects involving the incipient bond (the AP effect) should be essential.[2,3] On the basis of Feynman's electrostatic theorem,[2−4] we have recently deduced the following remarkable theoretical findings on the mechanism of the AP effect:[5] (1) such stabilization effects should lead to elongation and reduction in bond population of the vicinal antiperiplanar bond (AP bond) (weakening of the two AP bonds); (2) they should operate against bond formation

process (conversely, they should facilitate bond dissociation process); (3) and accordingly, irrespective of earliness of transition state, they should not be essential to facial diastereoselectivity. These conclusions are entirely inconsistent with the two previous models, which claim such transition state stabilization effects to be the origin of facial diastereoselection.[2,3]

Herein we show the first clear-cut evidence against the conventional models[2,3] and present a theoretical rationale on the nature of facial diastereoselection. The insertion reaction of 5-substituted 2-adamantanylidene[6] was selected as a model for the following reasons: (1) the two AP bonds in the

(1) For recent reviews, see: le Noble, W. J., Gung, B. W., Ed.; Special issue on Diastereoselection; *Chem. Rev.* **1999**, *99*, 1069.
(2) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.
(3) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
(4) Feynman, R. P. *Phys. Rev.* **1939**, *56*, 340.
(5) Tomoda, S. *Chem. Rev.* **1999**, *99*, 1243.

(6) (a) See the preceding paper: Knoll, W.; Bobek, M. M.; Kalchhauser, H.; Rosenberg, M. G.; Brinker, U. H. *Org. Lett.* **2003**, *5*, 2943. (b) Bobek, M. M.; Brinker, U. H. *J. Am. Chem. Soc.* **2000**, *122*, 7430. (c) Knoll, W.; Bobek, M. M.; Giester, G.; Brinker, U. H. *Tetrahedron Lett.* **2001**, *42*, 9161.

conformationally rigid carbon framework are both C−C (C1−C8/C3−C10 for *syn*-attack and C1−C9/C3−C4 for *anti*-attack); (2) the electrically neutral and highly reactive nature of the singlet carbene center (C2) should magnify the AP effect to a significant extent; and (3) elaborate experimental data are available.[6]

1 : X = H
2 : X = OH
3 : X = SiMe$_3$
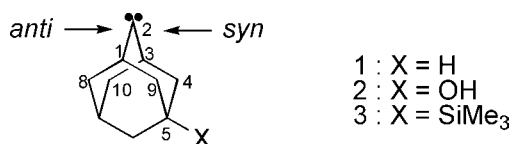
The transition states (TS) for the insertion of 5-X-2-adamantanylidenes (**1**, X = H; **2**, X = OH; **3**, X = SiMe$_3$) into methanol (MeOH) or cyclohexane (C$_6$H$_{12}$) were optimized.[7] IRC analyses of these TS showed that they were indeed desired TS. Each TS showed a single imaginary frequency that corresponded to the stretching vibration localized between the OH bond of MeOH or the equatorial C−H of C$_6$H$_{12}$ and the carbenic center (C2). The TS structures of **2** with MeOH or C$_6$H$_{12}$ are reproduced in Figure 1. Total energy difference (ZPE-corrected) between the *anti*
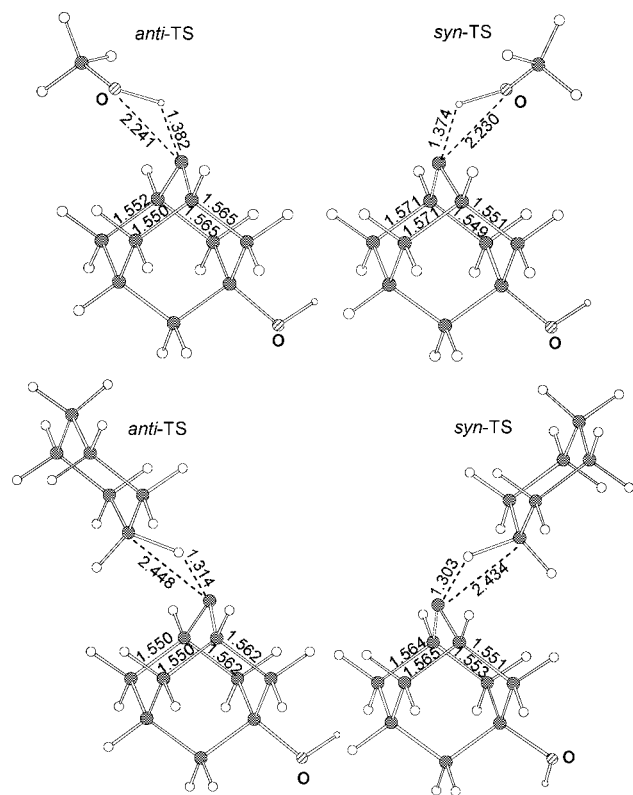

Figure 1. Transition states of the insertion of carbene **2** into MeOH (top) or cyclohexane (bottom) (B3LYP/6-31+G(d,p)). Bond lengths are in Å.

and *syn* transition states (*anti*-TS and *syn*-TS, respectively) for **2** ($\Delta E = E_{anti} - E_{syn}$) was 1.35 (MeOH) and 0.91 (C$_6$H$_{12}$) kcal mol^{-1} in favor of *syn*-TS in fair agreement with

experiment (*syn*:*anti* = 85:15 (MeOH) and 89:11 (C$_6$H$_{12}$)).[6] The corresponding value of ΔE for **3** was −0.23 (MeOH) and −0.37 (C$_6$H$_{12}$) kcal mol^{-1} in favor of *anti*-TS, in decent agreement with experiment (*syn*:*anti* = 31:69 (MeOH); 37:63 (C$_6$H$_{12}$)).[6] The close resemblance in diastereoselection between MeOH and C$_6$H$_{12}$ shows that the reactions may not be affected by polar effects.[6]

The most notable changes in the diastereomeric TS structures compared to the corresponding ground-state carbene (**1**, **2**, or **3**) were the distances of the AP bonds. The magnitudes of the AP effects were evaluated for the TS of **1**, **2**, and **3** as the difference between ground state (GS) and transition state (TS) by two quantities: percent bond elongation of AP bond (%BE)[8] and the difference in NBO bond population (ΔBP)[9] (Table 1).

Table 1. Antiperiplanar Effects for Insertion Reactions of 2-Adamantanylidenes **1**−**3** to Methanol or Cyclohexane[a]

1, 2, or 3		AP bond length (Å)			bond population (*e*)		
X	TS	GS	TS	%BE[b]	GS	TS	ΔBP[c]
			methanol				
H		1.580	1.571	−0.55	1.924	1.932	+0.008
OH	anti	1.571	1.565	−0.35	1.929	1.934	+0.005
	syn	1.582	1.571	−0.68	1.919	1.930	+0.011
SiMe$_3$	anti	1.587	1.577	−0.59	1.920	1.928	+0.008
	syn	1.576	1.568	−0.49	1.927	1.933	+0.007
			cyclohexane				
H		1.580	1.565	−0.92	1.924	1.944	+0.020
OH	anti	1.571	1.562	−0.55	1.929	1.942	+0.012
	syn	1.581	1.565	−1.06	1.920	1.943	+0.023
SiMe$_3$	anti	1.586	1.568	−1.15	1.919	1.942	+0.023
	syn	1.577	1.562	−0.94	1.924	1.944	+0.020

[a] B3LYP/6-31+G(d,p) except for the TS of **3** with C$_6$H$_{12}$ for which B3LYP/6-31G(d) was used; GS = ground state; TS = transition state; AP bond = antiperiplanar bond; BP = bond population (unit, electron = *e*). Averaged values of two parallel AP bonds are shown. [b] % Bond elongation; see ref 8 for definition. Minus sign indicates shortening of AP bond at TS. [c] Difference in bond population of AP bond between TS and GS (calculated with NBO method).[9] Plus sign indicates an increase of BP in AP bond at TS.

The following notable features are seen: the magnitudes of %BEs and ΔBPs are substantially larger than the usual

(7) All computations were performed on *Gaussian 98* (revision A.7) (Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 1998) at the B3LYP/6-31+G(d,p) level except for the TS of **3** with C$_6$H$_{12}$ (B3LYP/6-31G(d)).
(8) Percent Bond Elongation (%BE) = ($\Delta r/r_{GS}$) × 100, where Δr = the difference in the bond lengths between the vicinal antiperiplanar (AP) bond in transition state (r_{TS}) and the corresponding bond of ground-state carbene (r_{GS}); $\Delta r = r_{TS} - r_{GS}$.
(9) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899. NBO program ver. 4.0 was used throughout this work.

values.[10] Importantly, the former is negative and the latter is positive without exception, suggesting that the AP bonds are shortened along the reaction coordinate, namely, the AP effect is reduced toward TS along the reaction coordinate of carbene capture by MeOH or C_6H_{12}. This evidently implies that the AP effect, which is commonly recognized as an element that stabilizes TS,[1] can decelerate the reaction (increase in activation energy), in sharp contrast to the premise of the historical debate on facial diastereoselection.[1] These observations should provide strong disproof against the current models.[2,3]

Comparison between the data of *syn*- and *anti*-TS of **2** or **3** reveals that AP effects operate against facial diastereoselection: the negative AP effect is more effective in the more selective diastereoselection process irrespective of the nature of the insertion bond involved (OH or CH). For example, the diastereomeric transition states of **2** show larger negative AP effects in *syn*-TS (%BE/ΔBP = −0.68%/+0.011*e* (MeOH); −1.06%/+0.023*e* (C_6H_{12})) than those in *anti*-TS (−0.35%/+0.005*e* (MeOH); −0.55%/+0.012*e*(C_6H_{12})). Exactly the same trend is apparent for TS of **3**: larger negative AP effects in *anti*-TS (−0.59%/+0.008*e* (MeOH); −1.15%/+0.023*e* (C_6H_{12})) than those in *syn*-TS (−0.49% and +0.007*e* (MeOH); −0.94% and +0.020*e* (C_6H_{12})). It is concluded that the more favorable the reaction process is, the weaker is the positive AP effect (the stronger is the negative AP effect), again contrary to the proposal of the two representative models of diastereoselection.[2,3] The results presented here are entirely consistent with our previous theoretical conclusions derived from analogous analyses of $LiAlH_4$ reductions of various ketones such as 2-adamantanones, cyclohexanones, and other cyclic ketones.[10]

As noted previously,[5,10] these observations suggest that the AP effect may be regarded as a mere internal energy relaxation process that is not directly related to the facial difference in the magnitude of reaction driving force. We propose that facial diastereoselection in the 2-adamantanylidene system most probably may arise from the difference in equilibrium concentration of two bridge-flipping conformers (i.e., the *proximal*- and the *distal*-carbenes) rather than rate constant alone. Total energies of 5-substituted(X) 2-adamantanylidenes (X = H, OH, $SiMe_3$, NH_2) were calculated at the B3LYP/6-31+G(d,p) level.[7] As depicted in Figure 2, excellent linear correlation ($r^2 = 0.99$) was

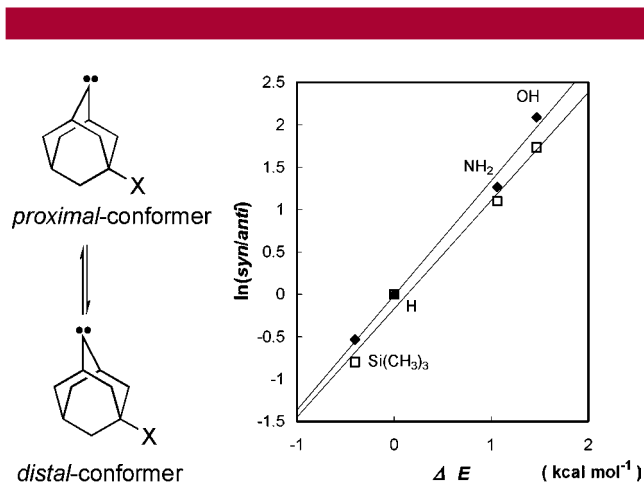**Figure 2.** Correlation between the energy difference between *proximal*- and *distal*-5-substituted 2-adamantanylidenes ($\Delta E = E_{pro} - E_{dis}$)[7] and observed stereoselectivity ($\ln(syn/anti)$) with MeOH (open square) or C_6H_{12} (filled square).[6]

obtained between relative energies of the bridge-flipping conformers ($\Delta E = E_{pro} - E_{dis}$)[7] and observed diastereoselectivities ($\ln(syn/anti)$)[6] for both insertion reactions. The results most probably indicate that one *proximal−distal* conformer should exclusively give rise to single stereoisomer that is different from the one produced by the other *proximal−distal* conformer.[11]

In conclusion, it is demonstrated that antiperiplanar effect should not be the origin of diastereoselection in insertion reactions of 2-adamantanylidenes. Our previous reports[10] suggest that this can be generalized to common facial selection processes. The equilibrium between two bridge-flipping conformers may be a major factor of diastereoselection of these carbenes.

Supporting Information Available: Three-dimensional coordinates of all ground-state structures and transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Tomoda, S.; Senju, T. *Tetrahedron* **1999**, *55*, 5303. (b) Tomoda, S.; Senju, T. *Chem. Commun.* **1998**, 423. (c) Tomoda, S.; Senju, T. *Tetrahedron* **1999**, *55*, 3871. (d) Tomoda, S.; Kaneno, D.; Senju, T. *Heterocycles* **2000**, *50*, 1435. (e) Tomoda, S.; Zhang, J.; Kaneno, D.; Segi, M.; Zhou, A. *Tetrahedron Lett.* **2000**, *41*, 4597. (f) Butkus, E.; Stoncius, A.; Mallinauskiene, J.; Tomoda, S.; Kaneno, D. *Can. J. Chem.* **2001**, *79*, 1598.

(11) Supporting evidence for this has been obtained by EFOE (exterior frontier orbital extension) analysis.[5] It is shown that steric as well as electronic effects are important. Full details will be reported in due course.