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Origin of facial diastereoselection in 2-adamantyl cations. Theoretical evidence against the Felkin–Anh and the Cieplak models☆,☆☆

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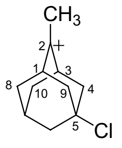
Abstract—Quantitative analysis of the transition state (TS) structures for the reactions between 5-Cl- or 5-SiMe$_3$-2-adamantyl cations and methanol revealed that the magnitude of antiperiplanar hyperconjugative stabilization involving the incipient bond (the AP effect) decrease at TS, strongly suggesting that the AP effect contributes to '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 bridge(C1–C2–C3)-flipping *E–Z* cation conformers was found to be the origin of facial diastereoselection of these carbocations.

The origin of facial diastereoselection in addition reactions to trigonal carbon center has attracted active debate since Cieplak proposed his conceptual model.[1] Most arguments were based on the premise that transition state stabilization arising from the antiperiplanar hyperconjugation effects involving the incipient bond (the AP effect) be essential: Cieplak model emphasized stabilization due to electron flow into the antibonding orbital of the incipient bond from a vicinal antiperiplanar bond, whereas exactly opposite mechanism was assumed by the Felkin–Anh model.[2]

We have recently made qualitative argument on the mechanism of such 'transition state stabilization' effects considering the direction of force vectors acting at each atom in an antiperiplanar hyperconjugation model.[3] Three important conclusions were derived: (1) such stabilization effects should lead to elongation and reduction in bond population of the vicinal antiperiplanar bond (AP bond) (weakening of AP bond), (2) they should operate against bond formation process (conversely, they should facilitate bond dissociation process) and accordingly (3) they should not be essential to facial diastereoselectivity. In complete agreement with these remarkable findings, we have recently reported that the AP effects contribute to 'net destabilization, that is increase in activation energy' in intramolecular carbene insertions of 5-substituted 2-adamantanylidenes.[4]

Herein we report another clear-cut evidence that fortifies the previous conclusions[4] and present theoretical analysis for the origin of facial diastereoselectivity. The model system (2-adamantyl cation) was chosen for the following reasons: (1) the two AP bonds in the conformationally rigid carbon framework are both carbon–carbon bonds (C1–C8/C3–C10 and C1–C9/C3–C4), (2) the highly reactive destabilized nature of the reaction center at C-2 should magnify the AP effect to a significant extent, which should make theoretical analysis easier and more accurate, and (3) elaborate experimental data are available.[5]



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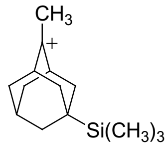

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Keywords: Facial diastereoselectivity; Ab initio molecular calculation; Adamantyl cation; Cieplak model; Felkin–Anh model.

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The transition states (TS) for the nucleophilic attack of methanol (MeOH) at two representative 2-methyl-5-X-2-adamantyl cations (**1**; X = Cl and **2**; X = $SiMe_3$) were calculated at the HF/6-31G(d) level (Fig. 1).[6] Frequency analysis of each TS showed a single imaginary frequency that corresponds to the stretching vibration localized between MeOH oxygen and the reaction center (C-2). Electronic energy difference ($\Delta E = E_{anti} - E_{syn}$; ZPVE-corrected) between the *anti* and *syn* transition states (*anti*-TS and *syn*-TS) for **1** is 0.82 kcal mol^{-1} in favor of *syn*-TS in fair agreement with experiment (*syn*:*anti* = 84:16).[5] The corresponding value of ΔE for **2** is 0.50 kcal mol^{-1} in favor of *anti*-TS in decent agreement with experiment (*syn*:*anti* = 14:86).[5] The incipient bond lengths fall within 1.9 2.1 Å and the approaching angles of MeOH oxygen are 94°–97°. The most notable changes in the TS structures compared to the corresponding ground state cations are the AP bond distances.

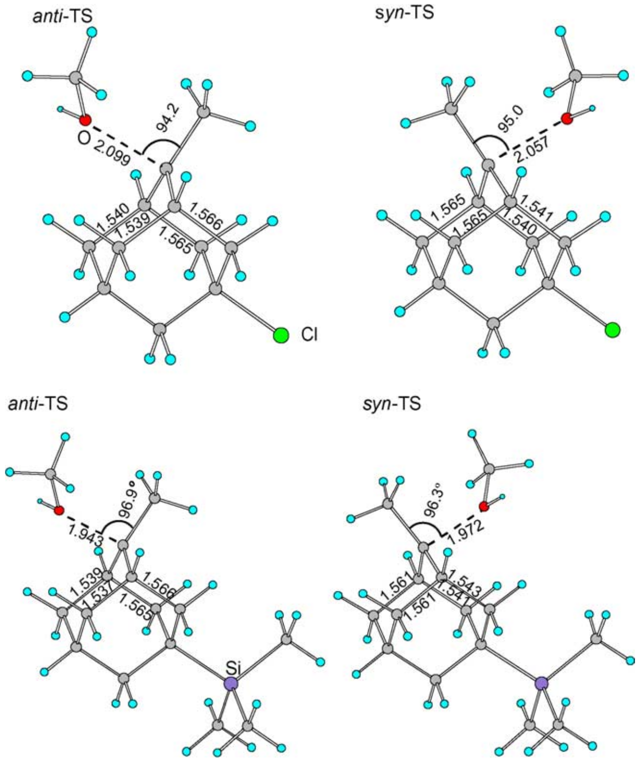


Figure 1. Transition state structures of MeOH addition to **1** (top) and **2** (bottom) (HF/6-31G(d)). Bond lengths are in Å and angles are in degree.

The magnitude of the AP effect was evaluated by two quantities; percent bond elongation of the antiperiplanar bond (%BE)[7] and the difference in bond population (ΔBP) calculated with natural bond orbital (NBO) analysis (Table 1).[8] These quantities were obtained as the difference between ground state (GS) and transition state (TS). The data of the unsubstituted cation (X = H) are also included for comparison. Two features are noteworthy.

First, the magnitudes of %BEs and ΔBPs are substantially larger than the usual values.[9] Importantly the former is negative and the latter is positive without exception, clearly suggesting that the AP bonds are shortened along the reaction coordinate no matter whether the AP bond exists *anti* or *syn* with respect to the substituent at C-5. The four diastereomeric transition states of **1** and **2** show large negative values of %BE (0.19–1.57%; AP bond shortening) and positive values of BP (+0.006∼+0.034 e (electron); increase in bond population in AP bonds) relative to the corresponding ground state cations, the structures of which were optimized at the same level (HF/6-31G(d)). These data strongly suggest that the AP effect is reduced along the reaction coordinate of cation capture by MeOH toward TS. This implies that the AP effect, which is generally regarded as an important element that stabilize TS (a factor that 'reduces' activation energy),[1,2] can 'decelerate' the reaction. Namely, the AP effect may contribute to an 'increase' in activation energy, in sharp contrast to the premise of the historical debate on facial diastereoselection. These observations may provide strong disproof against the current conceptual models of diastereoselection which propose that the AP effects in TS should be the origin of π-facial diastereoselection.[1,2,10]

Secondly, comparison of a pair of the data shown in Table 1 between the *syn*- and *anti*-TS of **1** or **2** reveals that the AP effects operate against facial diastereoselection. Namely, the negative AP effect is more effective in the more selective diastereoselection process. For example, the diastereomeric transition states of **1** show larger negative AP effect in the *syn*-TS (0.82% and

Table 1. Antiperiplanar effects of MeOH addition to **1** and **2**[a]

Cations		AP bond length (Å)			Bond population (e)		
X	TS	GS	TS	%BE[b]	GS	TS	ΔBP[c]
H	—	1.577	1.564	−0.84	1.920	1.940	+0.021
Cl	*anti*	1.568	1.566	−0.19	1.928	1.934	+0.006
	syn	1.578	1.565	−0.82	1.918	1.938	+0.020
$SiMe_3$	*anti*	1.590	1.566	−1.57	1.908	1.942	+0.034
	syn	1.570	1.561	−0.55	1.927	1.942	+0.015

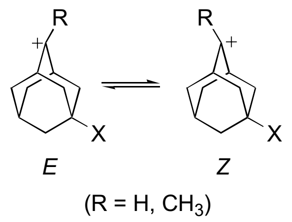
[a] HF/6-31G(d); GS = ground state; TS = transition state; AP bond = antiperiplanar bond; BP = bond population (unit; electron = e). Averaged values of two parallel AP bonds are shown.

[b] % Bond elongation; see Ref. 7 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).[8] Plus sign indicates an increase of BP in AP bond at TS.

+0.020 e) than that in *anti*-TS (0.19% and +0.006 e). Exactly the same trend is apparent for TS of **2**: larger negative AP effect in *anti*-TS (1.57% and +0.034 e) than that in *syn*-TS (0.55% and +0.015 e). 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.[1,2] The results are entirely consistent with our previous conclusions derived from analogous analyses of $LiAlH_4$ reductions of various ketones such as adamantan-2-one, cyclohexanones, and other cyclic ketones.[9] As noted previously,[3] these observations suggest that the AP effects 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. They facilitate (accelerate) bond dissociation processes, such as solvolysis reactions, but they decelerate bond formation processes.

Our interest is to find the origin of diastereoselection of these cations. Hyperconjugation models and electrostatic model have been proposed to explain the stereoselection of 2-adamantyl cations.[5] Recently, Speranza and co-workers reported elegant kinetic analysis of gas phase addition of MeOH to 2-methyl-5-X-2-adamantyl cations (X = F or $SiMe_3$).[11] They showed that activation barriers for the *anti*-addition process are uniformly lower than those of the *syn*-attack and suggested activation entropy effect as an important factor of diastereoselection.



These discussions are based on the facial difference in rate constants (activation energy). They all show correct facet of the truth contained in one molecule of the cation. We propose that the origin of facial diastereoselection in the 2-adamantyl cation system may most probably arise from the equilibrium concentration of two bridge(C1–C2–C3)-flipping conformers (i.e., *E*-and *Z*-cations; as shown above)[12] rather than rate constant alone. Accordingly, the equilibrium constants for a variety of 2-adamantyl cations with a substituent at C5 were calculated at the HF/6-31G(d) level. As depicted in Figure 2, excellent linear correlation ($r^2 = 0.97$) was obtained between the relative energies of the two conformers (ΔE) and the observed diastereoselectivities ($\ln(syn/anti)$) (R = H).[5] The results most probably indicate that one *E–Z* conformer should give a single stereoisomer that is different from the one produced from the other *E–Z* conformer.

In conclusion, it is demonstrated that antiperiplanar effect should not be the origin of diastereoselection in nucleophilic addition to 2-adamantyl cations. Our previous reports[9] suggest that this can be generalized to common facial selection processes. The equilibrium between the two bridge-flipping *E–Z* conformers may be a major factor of diastereoselection of these carbocations.

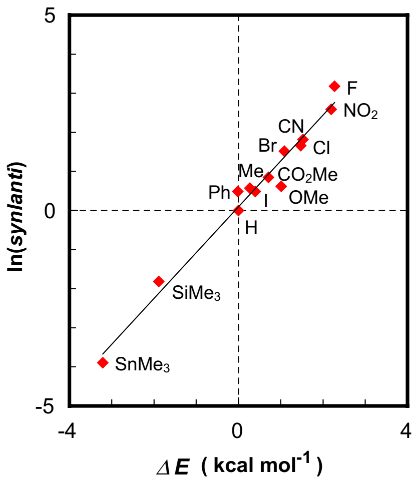


Figure 2. Correlation between the energy difference between *Z*- and *E*-5-substituted 2-adamantyl cations ($\Delta E = E_E - E_Z$)[6] and observed stereoselectivity ($\ln(syn/anti)$).[5]

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