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# Hyperconjugative Control by Remote Substituents of Diastereoselectivity in the Oxygenation of Hydrocarbons

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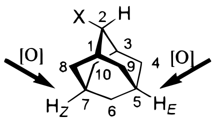
## ABSTRACT



X=$CH_2OCOCH_3$, $NHCOCH_3$, $OCOCH_3$, F, $OSO_2CH_3$, $OSO_2C_6H_4CH_3$, $ONO_2$, $NH_3^+$

**The oxidation of 2-substituted adamantanes (2) with TFDO (1) is reported. The data show a stereodifferentiation of the chemical environments induced by remote electron-withdrawing substituents which produces remarkable *Z*/*E* diastereoselectivity in the oxidation of the tertiary $C_5$–H and $C_7$–H bonds. The results show a bell-shaped correlation between the *Z*/*E* stereoselectivity and the substituent constant $\sigma_I$, which is interpreted in terms of hyperconjugative stabilization of the diastereomeric transition states.**

Interpreting the effect of remote substituents on the diastereoselectivity in chemical reactions by stereoelectronic factors is an important subject in the field of organic chemistry.[1] Many studies have been conducted on diastereoselectivity in addition and elimination reactions as a consequence of the different degrees of stabilization of transition states by hyperconjugation.[2] Examples include studies of the selectivity of reactions[3] such as ketone reduction and olefin epoxidation. However, to the best of our knowledge, reports on the effects of remote substituents on the reactivity of unactivated C−H $\sigma$-bonds are scarce,[3d] most likely due to the lack of reactivity of hydrocarbons which necessitates the use of drastic or unusual reaction conditions.[4] Recently, methyl(trifluoromethyl) dioxirane (TFDO) (**1**) has been revealed to be an efficient reagent[5] for *electrophilic*[6] oxygen atom insertion into unactivated C−H bonds of hydrocarbons under *very mild*

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conditions. These characteristics make this reaction a powerful tool for investigating the effects of remote substituents on the reactivity of unactivated C−H $\sigma$-bonds in hydrocarbons.

In this Letter, we report the stereoselective oxidation of 2-substituted adamantanes (**2**) with TFDO (**1**)[7] (see Scheme 1).[8] The observed selectivity is interpreted in terms of hyperconjugative stabilization of the transition states. The results are collected in Tables 1, and the plot of ln *Z/E* versus Charton's preferred[9] $\sigma_I$ substituent parameters is shown in Figure 1. The data show that the stereodifferentiation of the chemical environments induced by a remote electron-withdrawing substituent produces remarkable *Z*/*E* diastereoselectivity in the oxidation of the tertiary $C_5$−H and $C_7$−H bonds in compounds **2**. Only the oxygenation of the tertiary C−H bonds was observed. Protonation prevents any oxygenation reaction at the nitrogen atom in compound **2h**.[5c] The results show a bell-shaped correlation (see Figure 1) between the *Z*/*E* stereoselectivity and the substituent constant[9] $\sigma_I$. This surprising correlation for an electrophilic process[6] can be interpreted in terms of hyperconjugative stabilization of the diastereomeric transition states and reveals the simultaneous operation of Cieplak's and Ahn's hyperconjugation.[2c−e]

**Scheme 1**

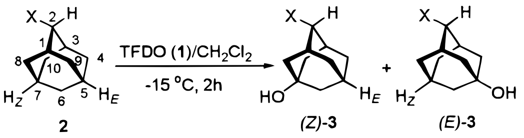

**Table 1.** Diastereoselective Oxidation of 2-Substituted Adamantanes **2** with TFDO (**1**) in Dichloromethane at −15 °C[a]

| 2 | X | $\sigma_I$[b] | (*Z*)-**3** /(*E*)-**3** ratio[c] |
|---|---|---|---|
| **a** | $CH_2OCOCH_3$ | 0.15 ± 0.012 | 1.006 ± 0.0217 |
| **b** | $NHCOCH_3$ | 0.28 ± 0.005 | 1.538 ± 0.0168 |
| **c** | $OCOCH_3$ | 0.38 ± 0.0140 | 2.504 ± 0.0554 |
| **d** | F | 0.54 ± 0.0080 | 2.572 ± 0.0145 |
| **e** | $OSO_2CH_3$ | 0.55 ± 0.013 | 2.534 ± 0.0156 |
| **f** | $OSO_2C_6H_4CH_3$ | 0.58[d] | 2.365 ± 0.0510 |
| **g** | $ONO_2$ | 0.66[d] | 2.030 ± 0.0452 |
| **h**[e] | $NH_3^+$ | 1.07[d,f] | 0.914 ± 0.0284 |

[a] Initial 3:2 molar ratio 2:1. [b] $\sigma_I$ values from ref 9. [c] From VPC analysis; values are the average of at least three independent runs. [d] Standard error not reported. [e] Counteranion *p*-chlorobenzenesulfonate. Reaction was carried out in 2,2,2−trifluoroethanol. [f] $\sigma_I$ value corresponds to the trimethylammonium group.

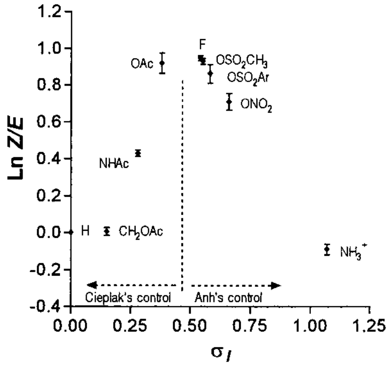

**Figure 1.** Plot of ln (*Z*)-**3**/(*E*)-**3** vs Charton's preferred $\sigma_I$ values (from ref 9). Data are average of at least three independent runs. Error bars represent the standard deviation.

The diastereoselectivity in addition and elimination reactions has been explained[2,3] by considering that hyperconjugation can lower the energy of the transition state sufficiently to be reflected in the observed product ratios. Three types of hyperconjugative interactions have been advanced. Felkin's[2b] hyperconjugative effect represents the destabilization of the transition state due to repulsion between the incipient $\sigma_{\neq}$ bond and syn-periplanar $\sigma$ orbitals (**4**). On the other hand, Ahn's[2c] (**5**) and Cieplak's[2d,e] (**6**) attractive interactions between the $\sigma_{\neq}$ and $\sigma_{\neq}$* orbitals of the newly formed bond and the antiperiplanar $\sigma$* and $\sigma$ orbitals, respectively, contribute to the stabilization of the transition state. The effects of the remote substituents on the observed diastereoselectivity will reflect, among other factors, their ability to modify the relative energies of the adjacent orbitals interacting with the nascent bond, and its transmission will depend on the relative orientation of the interacting bonds in the transition state.[2] Similar considerations should be made to account for our results on diastereoselectivity induced by remote substituents in the C−H bond oxyfunctionalization of hydrocarbons. Felkin's torsional barrier (**4**) should be derived mostly from interactions with the $C_{4,6,9}$−H and

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(8) **Experimental Procedure.** Oxidations with TFDO (**1**) were performed by adding an aliquot of a ketone-free $CH_2Cl_2$ solution of TFDO (**1**) to a $CH_2Cl_2$ solution of the substrate **2** with a substrate/oxidant molar ratio of 3:2. The final concentration of **2** was 0.05 M in all cases. All runs were carried out at −15 °C until dioxirane **1** was totally consumed (2 h). Reaction mixtures were analyzed by gas chromatography, and products were identified by comparison with authentic samples. Spectral data for compounds **2** and **3** are given in Tables 2 and 3. Experimental details are given as Supporting Information.

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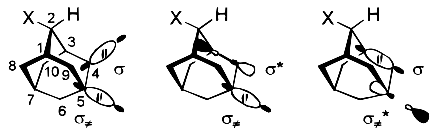
**Table 2.** $^{13}$C NMR and HRMS Data for *Z* Isomers of Compounds **3**[a]

| X | $C_{1,3}$ | $C_2$ | $C_{4,9}$ | $C_5$ | $C_6$ | $C_7$ | $C_{8,10}$ | HRMS[b] |
|---|---|---|---|---|---|---|---|---|
| $CH_2OCOCH_3$ | 36.97 | 41.72 | 39.73 | 67.91 | 45.60 | 30.46 | 31.90 | $CI^+$ (223.1334) 223.1330[c] |
| $NHCOCH_3$ | 35.03 | 54.07 | 39.97 | 67.83 | 46.10 | 31.11 | 35.90 | $EI^+$ (209.1416) 209.1417[c] |
| $OCOCH_3$[c] | 34.35 | 74.73 | 39.31 | 67.11 | 44.88 | 29.18 | 34.59 | $EI^+$ (210.1256) 210.1253[c] |
| F | 35.33 | 93.24 | 39.25 | 67.21 | 44.55 | 29.09 | 34.05 | $EI^+$ (170.1107) 170.1100 |
| $OSO_2CH_3$ | 34.72 | 83.13 | 38.90 | 66.87 | 44.46 | 28.80 | 35.66 | $EI^+$ (246.0926) 246.0920 |
| OTs | 35.42 | 83.52 | 38.97 | 66.95 | 44.48 | 28.89 | 34.80 | $EI^+$ (322.1239) 322.1238 |
| $ONO_2$ | 33.48 | 84.00 | 39.46 | 66.99 | 44.38 | 29.13 | 34.80 | $EI^+$ (213.1001) 213.1001 |
| $NH_3^+$[d] | 35.14 | 55.34 | 38.74 | 67.36 | 45.77 | 30.67 | 36.52 | $EI^+$(168.1388) 168.1372 |
| $OCOCH_3$[c]<br>$C_5$: $OCOCF_3$ | 34.81 | 74.04 | 35.25 | 85.38 | 40.17 | 29.58 | 34.41 | $CI^+$ (264.0973) 264.0962[c] |
| $NHCOCF_3$<br>$C_5$: $OCOCF_3$ | 34.32 | 52.48 | 35.03 | 84.46 | 40.46 | 29.49 | 35.03 | $EI^+$ (359.0956) 359.0957[c] |

[a] $^{13}$C NMR at 52.80 MHz, chloroform-$d_1$, $\delta$ (ppm). Only representative signals are reported. [b] (Calcd) found. [c] Data correspond to the mixture of isomers. [d] Spectra recorded in methanol-$d_4$.

$C_{6,8,10}$−H bonds for *E* or *Z* oxygen insertion, respectively (see Figure 2). However, adamantane geometry does not allow any significant hyperconjugative interaction between the $C_2$−X bond and the interacting C−H bonds. Therefore, the *Z*/*E* selectivity induced by $C_2$ substituents should be attributed to the relative stabilization of the corresponding transition states by Ahn (**5**) and Cieplak's (**6**) orbital interactions of the nascent bond with the $C_{1,8}$ and $C_{3,10}$ bonds or the $C_{1,9}$ and $C_{3,4}$ bonds, respectively (see Figure 2). The energy of these bonds will be modulated in each case by hyperconjugative interaction either with the $C_2$−H bond or the $C_2$−X bond, and the observed selectivity will reflect these interactions. The effect of remote substituents on the energy of the empty $\sigma_{CC}$* and occupied $\sigma_{CC}$ orbitals, which are able to stabilize the transition state by hyperconjugative interaction with the nascent bond orbitals, is depicted in Figure 3. As the electron-withdrawing ability of the substituent ($\sigma_I$) increases, the $\sigma_{\neq}-\sigma_{CC}$* energy gap progressively decreases, while the $\sigma_{CC}-\sigma_{\neq}$* energy gap increases. Therefore, as $\sigma_I$ increases, Ahn's transition-state stabilization is more intense and Cieplak's interaction becomes progressively weaker. According to this analysis, *Z* TS's will be stabilized by long-distance hyperconjugative interactions with $C_2$−H bonds, the intensity of which will remain roughly constant in the series, while *E* TS's will receive distinct hyperconjugative stabilization from the corresponding $C_2$−X bond. Since the slope of the lines corresponding to the energy of the $\sigma_{CC}$ and $\sigma_{CC}$* versus the substituent constant $\sigma_I$ are different, there is a $\sigma_I$ value for which the global hyperconjugative stabilization by the substituent is minimum. This point would correspond to a maximum in the *Z*/*E* selectivity.



**4** **5** **6**

**Figure 2.**

On these bases, the experimental data collected in Table 1 and Figure 1 reveal that the total hyperconjugative stabilization provided by the $C_2$−H bond to the *Z* TS is stronger than that provided by the $C_2$-X bond, leading preferentially in the oxidation to the *Z*-alcohol. However, the selectivity trend on the branch with positive slope in the plot is dominated by Cieplak's hyperconjugation of the $C_2$−H bond, while the branch with negative slope reveals the progressive onset of Ahn's hyperconjugation. The observed results fit nicely with the trend predicted by the analysis of Figure 3 considering only hyperconjugative interactions. The use of a more sensitive experimental probe perhaps could reveal to what degree electrostatic interactions may contribute to the transition-state stabilization.[1]

In conclusion, the remote substituent effect observed on the C−H bond reactivity of 2-substituted adamantanes (**2**) in the electrophilic oxygenation by TFDO can be successfully explained on the basis of the distinct hyperconjugative

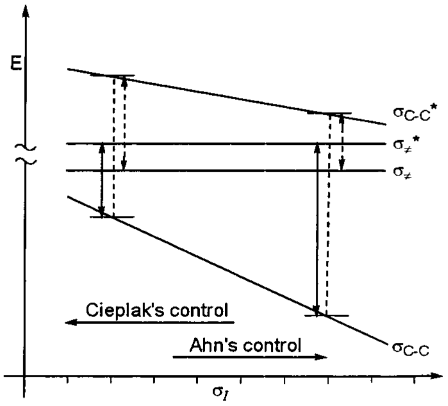


**Figure 3.** Variation of the hyperconjugative contributions ($\sigma_{\neq}-\sigma_{CC}$*) and ($\sigma_{CC}-\sigma_{\neq}$*) as a function of the $\sigma_I$ value of the hyperconjugating substituent resulting from the more intense substituent effect on filled orbitals.

**Table 3.** $^{13}C$ NMR and HRMS Data for *E* Isomers of Compounds **3**[a]

| X | $C_{1,3}$ | $C_2$ | $C_{4,9}$ | $C_5$ | $C_6$ | $C_7$ | $C_{8,10}$ | HRMS[b] |
|---|---|---|---|---|---|---|---|---|
| $CH_2OCOCH_3$ | 31.39 | 41.99 | 45.91 | 68.12 | 45.63 | 30.14 | 30.28 | $CI^+$ (223.1334) 223.1329 |
| $NHCOCH_3$ | 35.03 | 54.60 | 45.21 | 67.83 | 46.10 | 31.06 | 31.15 | $EI^+$ (209.1416) 209.1417[c] |
| $OCOCH_3$[c] | 33.23 | 75.51 | 43.12 | 67.11 | 44.88 | 29.37 | 30.15 | $EI^+$ (210.1256) 210.1253[c] |
| F | 34.33 | 94.16 | 42.52 | 67.45 | 45.09 | 29.52 | 30.03 | $EI^+$ (170.1107) 170.1101 |
| $OSO_2CH_3$ | 34.72 | 83.13 | 38.90 | 66.87 | 44.46 | 28.80 | 35.66 | $EI^+$ (246.0926) 246.0930 |
| OTs | 34.32 | 84.23 | 43.19 | 66.97 | 44.95 | 29.17 | 29.73 | $EI^+$ (322.1239) 322.1240 |
| $ONO_2$ | 32.45 | 84.67 | 43.18 | 67.18 | 44.81 | 29.20 | 30.18 | $EI^+$ (213.1001) 213.0997[c] |
| $NH_3^+$ | 34.21 | 55.90 | 44.62 | 67.23 | 45.72 | 30.77 | 29.88 | $EI^+$ (168.1388) 168.1342[c] |
| $OCOCH_3$[c]<br>$C_5$:$OCOCF_3$ | 30.01 | 74.52 | 38.99 | 84.88 | 40.40 | 29.78 | 33.62 | $CI^+$ (264.0973) 264.0962[c] |
| $NHCOCF_3$<br>$C_5$:$OCOCF_3$ | 33.23 | 52.77 | 39.62 | 84.17 | 40.23 | 29.67 | 29.94 | $EI^+$ (359.0956) 359.0957[c] |

[a] $^{13}C$ NMR at 52.80 MHz, chloroform-$d_1$, $\delta$ (ppm). Only representative signals are reported. [b] (Calcd) found. [c] Data correspond to the mixture of isomers. [d] Spectra recorded in methanol-$d_4$.

stabilization of diastereomeric transition states by long-range interactions. This effect has been evaluated for the first time based on the outstanding selectivity shown by TFDO when reacting with saturated hydrocarbons.

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**Supporting Information Available:** Experimental details for the synthesis and characterization of compounds **2** and **3**. This material is available free of charge via the Internet at http:/pubs.acs.org.

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