

On the Reactivity of C(sp³)–H σ -Bonds: Oxygenation with Methyl(trifluoromethyl)dioxirane

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The reactivity of C–H σ -bonds of a series of 2-substituted adamantanes **2** towards methyl(trifluoromethyl)dioxirane (**1**) shows a consistent dependence on the electron-withdrawing ability, either inductive or by resonance, of the substituent. The results are interpreted in terms of the ability of the substrate molecule to delocalize the electronic perturbation of the reacting center at the beginning of the reaction path. The model shows that the electronic demand from the reacting C–H σ -bond is transmitted along the substrate through a chain of hyperconjugative interactions, the relative inten-

sities of which depend on the σ -bonds involved. The substrate molecule simultaneously provides positive and negative stabilizing hyperconjugative interactions to the reacting center, their balance defining the geometry of the system at the beginning of the reaction path. The model constitutes a new experimental approach to measurement of the perturbation induced by substituents with significant resonance contributions on an adjacent C–H σ -bond.

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Introduction

C(sp³)–H σ -bonds, the commonest σ -bonds in organic compounds, are involved in a variety of fundamental processes of organic chemistry^[1] such as H-atom abstraction, tautomeric and acid-base equilibria, elimination and oxidation reactions, and also the hyperconjugative stabilization of reactive species such as radicals or carbocations. C(sp³)–H σ -bonds of hydrocarbons are chemically inert towards most conventional reagents, but it is known that the presence of substituents in saturated systems induces changes in the electronic structures of the adjacent C–H σ -bonds, which then become suitable targets for free radicals or for electrophilic, nucleophilic, or basic reagents. It is well known, for instance, that tertiary C–H σ -bonds react more rapidly than secondary ones, and that these in turn react more rapidly than primary C–H σ -bonds in H-abstraction reactions, an experimental fact that is interpreted in terms of the hyperconjugative stabilization exerted by the adjacent alkyl groups on the carbon-centered radical intermediates. It is also well known that electron-withdrawing substituents increase the acidities of adjacent C–H σ -bonds, which then react with bases in deprotonation or elimination reactions. In addition, electron-releasing substituents activate adjacent C–H σ -bonds towards electrophiles in such a way that,

for instance, alcohols are much easier to oxidize than hydrocarbons.

The effect of substituents on the relative reactivities of remote C–H σ -bonds, however, has been much more difficult to assess, as the chemical inertness of saturated substrates poses a major difficulty to the achievement of selective reactions at these positions. The scarcity of systematic studies on this subject has the consequence that there is poor understanding of the way in which a saturated substrate responds to the electronic demand originating from a reacting C–H σ -bond and of the influence of substituents on the reaction path. The development of efficient C–H σ -bond activation reactions^[2] is a subject of major interest in fundamental and synthetic organic chemistry and, in this context, understanding of those factors governing the relative reactivity of C–H σ -bonds has become a significant target of chemical research.

Methyl(trifluoromethyl)dioxirane (**1**) is an efficient tool with which to bridge this gap, since it is able to insert an O-atom efficiently into a C–H σ -bond under very mild conditions.^[3] Dioxirane **1** is also highly selective and sensitive to substituents in substrate molecules, which influences the rates and the regio- and stereoselectivities of these oxygenation reactions.^[3,4] These characteristics prompted us to apply the oxygenation of C–H σ -bonds with methyl(trifluoromethyl)dioxirane (**1**) to suitable saturated substrates as a unique probe with which to monitor the influence of substituents on the reactivities of remote C–H σ -bonds.

Our work has allowed us to establish^[4k,4m,5] that electron-withdrawing substituents deactivate saturated substrates towards dioxirane **1** and direct the oxygenation to

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the C–H σ -bonds furthest from the substituent. The linear and negative slope ($\rho = -2.31$) observed^[5c] in the Hammett plot of the relative rates of reaction of a series of 2-substituted adamantanes (**2**) against the electron-withdrawing abilities of the substituents gave evidence not only of the electrophilic character of dioxirane **1** in these reactions, but also of its sensitivity towards the deactivation of the C(sp³)–H σ -bonds caused by remote substituents. The observed distance-dependent deactivation of alkyl chains was interpreted^[4k,4m,5] as a result of the through-bond transmission of the inductive substituent effect by a successive polarization of adjacent σ -bonds.

The reactivities of C–H σ -bonds in saturated substrates also depend on the relative positions and orientations of the remote substituents.^[5] In previous papers we have reported that monooxygenations of a series of 2-substituted adamantanes^[5a] **2** and substituted cyclohexanes^[5b] **3** (Figure 1) with dioxirane **1** showed significant differences in the relative reactivities of the diastereotopic C⁵–H and C⁷–H σ -bonds and the C–H_{ax} and C–H_{eq} σ -bonds, respectively. These results provided evidence of a long-range and strongly directional substituent effect that, superposing on the undifferentiated through-bond inductive deactivation, distinctly modifies the electronic characters of the remote C–H σ -bonds. The results were interpreted^[5a,5b] in terms of hyperconjugative interactions^[6] operating in the stabilization of the diastereomeric reacting systems. The relative reactivities of the diastereotopic C–H σ -bonds were then attributed to the abilities of the remote substituents to modulate the relative intensities of these interactions at each reacting position.

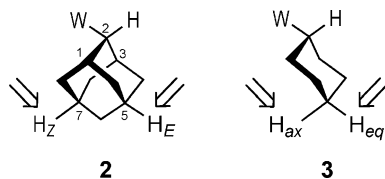
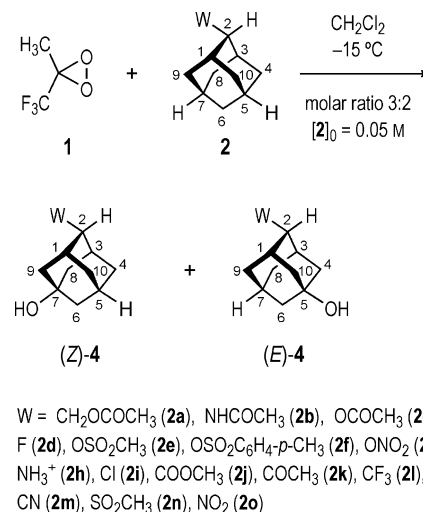


Figure 1. 2-Substituted adamantane and monosubstituted cyclohexane models **2** and **3**.

In a previous communication we reported a bell-shaped correlation between *Z/E* stereoselectivities and the substituent constants (σ_f) for compounds **2a–h**.^[5a] Here we report a thorough study of the substituent effects on the relative reactivities of C⁵–H and C⁷–H σ -bonds in 2-substituted adamantanes (**2**) towards methyl(trifluoromethyl)dioxirane (**1**). The distinct reactivities of the tertiary C(sp³)–H σ -bonds are interpreted in terms of the different abilities of remote C²–H and C²–W σ -bonds to provide hyperconjugative stabilization to the *Z* and *E* reacting systems as a response of the substrate molecules to the electronic demands exerted by interaction with the electrophilic dioxirane **1**. Quantitative application of orbital interaction principles explains the experimental facts and establishes the dependence of the hyperconjugative abilities of C²–H σ -bonds on the electronic characters of the adjacent W substituents.

Results

Our study of the oxygenation of 2-substituted adamantanes **2** with methyl(trifluoromethyl)dioxirane (**1**) at -15°C covered 15 electron-withdrawing substituents: namely, CH₂OAc (**2a**), NHCOCH₃ (**2b**), OCOCH₃ (**2c**), F (**2d**), OSO₂CH₃ (**2e**), OSO₂C₆H₅CH₃ (**2f**), ONO₂ (**2g**), NH₃⁺ (**2h**), Cl (**2i**), COCH₃ (**2j**), COOCH₃ (**2k**), CF₃ (**2l**), CN (**2m**), SO₂CH₃ (**2n**), and NO₂ (**2o**) (Scheme 1). Isomeric alcohols (*Z*)-**4** and (*E*)-**4** were prepared by treatment of the corresponding substrates with dioxirane **1** (Scheme 1). The reaction products were isolated by column chromatography and characterized by ¹³C NMR spectroscopy.^[5c] The structures of (*Z*)-**4e** (OMs), (*E*)-**4e** (OMs), (*Z*)-**4i** (Cl), (*Z*)-**4j** (COCH₃), (*Z*)-**4n** (SO₂CH₃), and (*E*)-**4n** (SO₂CH₃) were ascertained by X-ray diffraction.^[5c] This preparative work enabled us to establish suitable GC analysis conditions for each pair of isomeric alcohols (*Z*)-**4** and (*E*)-**4** and to determine their retention times unequivocally. GC analyses of compounds **4c** (OAc), **4e** (OMs), **4f** (OTs), and **4h** (NH₃⁺) were performed on their trifluoroacetylated derivatives (for details see Exp. Sect.).



Scheme 1. Oxygenation of 2-substituted adamantanes **2** with methyl(trifluoromethyl)dioxirane (**1**).

The oxygenation reactions addressed towards determination of the relative reactivities of C⁵–H and C⁷–H σ -bonds were each performed at -15°C by addition of an aliquot of a dichloromethane solution of methyl(trifluoromethyl)dioxirane (**1**) to a solution of the substrate **2** in the same solvent (Scheme 1). The initial **2/1** molar ratio was 3:2, with an initial concentration $[2]_0 = 0.05\text{ M}$. Crude reaction mixtures were directly analyzed by GC, except in those cases in which derivatization of the reaction products was required (for details see Exp. Sect.). The results shown in Table 1 are each the average of at least three independent experiments.

The oxygenations of substrates **2** in all cases took place exclusively at the tertiary C⁵–H and C⁷–H σ -bonds. GC–MS analyses of the reaction mixtures showed no evidence of the characteristic products originating from the radical-

Table 1. *Z/E* Selectivity in the oxygenation of 2-substituted adamantanes **2** with methyl(trifluoromethyl)dioxirane (**1**).^[a]

2	W (X/Z)	<i>Z/E</i> ^[b]
a ^[c]	CH ₂ OCOCH ₃	1.006 ± 0.022
b ^[c]	NHCOCH ₃	1.538 ± 0.017
c ^[c]	OCOCH ₃	2.504 ± 0.055
d ^[c]	F	2.572 ± 0.014
e ^[c]	OSO ₂ CH ₃	2.534 ± 0.016
f ^[c]	OSO ₂ C ₆ H ₄ - <i>p</i> -CH ₃	2.365 ± 0.051
g ^[c]	ONO ₂	2.030 ± 0.045
h ^[c]	NH ₃ ⁺ ^[d]	0.914 ± 0.028
i	Cl	1.994 ± 0.021
j	COOCH ₃	1.469 ± 0.040
k	COCH ₃	1.281 ± 0.021
l	CF ₃	1.328 ± 0.000
m	CN	1.143 ± 0.014
n	SO ₂ CH ₃	1.340 ± 0.036
o	NO ₂	1.927 ± 0.005

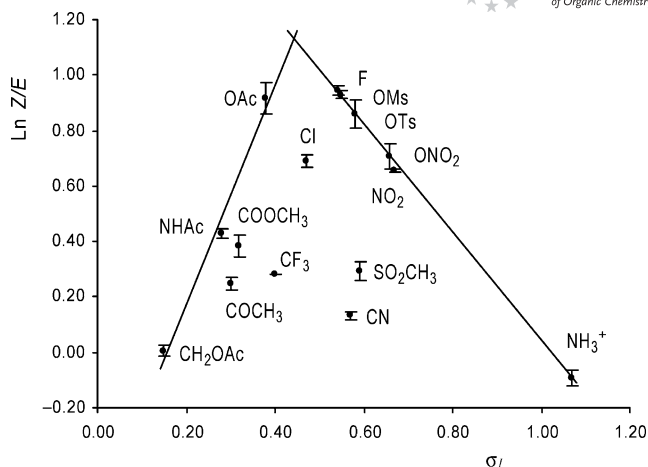
[a] Reactions were each carried out at -15 °C in dichloromethane with an initial **2/1** molar ratio of 3:2. [b] From VPC analysis; values are each the average of at least three independent runs. [c] Data from ref.^[5a] [d] The counteranion was *p*-chlorobenzenesulfonate. The reaction was carried out in 2,2,2-trifluoroethanol.

triggered decomposition of dioxirane **1**, such as trifluoroacetic or acetic acid esters or chlorinated products.^[7] As previously described,^[4m] protonation efficiently prevented any oxygenation at the nitrogen atom in compound **2h**.

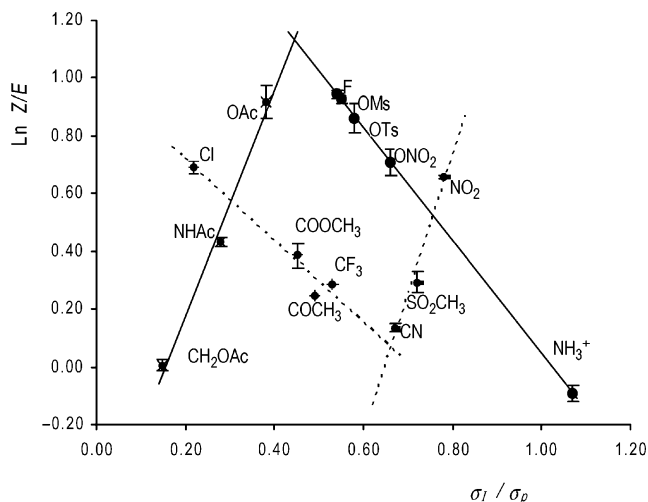
The data show that substituents at C² induce stereodifferentiation of the remote tertiary C⁵-H and C⁷-H σ -bonds, which results in the diastereoselective oxygenation of compounds **2** (Table 1). In order to visualize the effects of the electron-withdrawing abilities of the W substituents on the relative reactivities of the remote C-H σ -bonds, we plotted $\ln Z/E$ versus σ_I of the substituent^[8] (Figure 2). At first glance, the data in the plot show no further coherence, rather a general preference for the oxygenation of the C⁵-H σ -bonds to provide the corresponding *Z*-hydroxylated products (*Z*)-**3**. In fact, substituents with similar electron-withdrawing abilities give different values of *Z/E* selectivity: for instance, 1.143 for CN ($\sigma_I = 0.59$) and 2.365 for OSO₂C₆H₄-*p*-CH₃ ($\sigma_I = 0.58$).

However, a closer examination of the data allowed us to observe that the *Z/E* selectivities for substrates **2a–h** showed a consistent dependence on the σ_I values of the substituents, with two lines of complementary slopes (Figure 2). In this case, the *Z/E* selectivity initially increases as the electron-withdrawing ability of the substituent increases, and the reverse trend is observed after a maximum value has been reached (Figure 2). This result contradicts the intuitive expectation for a C⁵-H σ -bond becoming progressively more reactive than C⁷-H σ -bond as σ_I of the W substituent increases.

Conversely, the *Z/E* selectivity data for substrates **2i–o** did not show any definite trend when plotted against the σ_I values of the substituents. Significantly, the *Z/E* selectivity data that correlate with the σ_I values of the W substituents correspond to substrates (**2a–h**) carrying inductive electron-withdrawing groups (X-type) at C², while the data that fail to correlate with the σ_I values correspond to substrates **2i–**

Figure 2. *Z/E* Selectivity in the oxygenation of 2-substituted adamantanes **2** with dioxirane **1** vs. σ_I values.^[8] Error bars represent standard deviation.

o bearing substituents with low-energy empty orbitals that can interact with adjacent filled orbitals (*Z*-type). All these substituents are able to withdraw electron density by resonance. This observation prompted us to plot $\ln Z/E$ against σ_p ^[9] for substrates **2i–o** (Figure 3). In this instance, the plot showed a V-shaped correlation with two lines of complementary slopes opposite to those observed in the plot of $\ln Z/E$ against σ_I for substrates with X substituents **2a–h**. Thus, *Z/E* selectivity initially decreases as the σ_p value of the substituent increases, and the reverse trend is observed after a minimum value has been reached (Figure 3). The results show that *Z*-type substituents at C² induce lower *Z/E* selectivity than X-type substituents with similar σ_I values (Figure 2).

Figure 3. *Z/E* selectivity in the oxygenation of 2-substituted adamantanes **2** with dioxirane **1** vs. σ_I ^[8] (line) and σ_p ^[9] (dashed line) for X- and Z-series of substituents, respectively. Error bars represent standard deviations.

The experimental data on the oxygenation of 2-substituted adamantanes **2** with methyl(trifluoromethyl)dioxirane (**1**) indicate a definite and systematic influence of the elec-

tronic characters, either inductive or resonance, of the W substituents on the relative reactivities of the remote C⁵–H and C⁷–H σ -bonds.

Discussion

Reaction Mechanism

Within a mechanistic context, the question could be raised as to whether the change of slope in the plot of *Z/E* selectivity versus the parameter quantifying the electronic effect of the substituent is indicative of a change in the reaction mechanism^[10,11] induced by the increasing electron-withdrawing abilities of the W substituents. However, we have previously reported^[5c] that the Hammett plot for the oxygenation of 2-substituted adamantanes **2** with methyl(trifluoromethyl)dioxirane (**1**) showed a linear correlation ($\rho = -2.31$), consistent throughout a series of substituents ranging from 0.15 to 0.67 units of σ_I . The experimental data allow a change in the reaction mechanism to be disregarded as the origin of the inversion of slope found in the dependence of *Z/E* selectivity on the electronic characters of the substituents.

The major experimental evidence presently available^[10] on the oxygenation of alkane C–H bonds with methyl(trifluoromethyl)dioxirane (**1**) supports a concerted “oxenoid” O-atom insertion mechanism as the main reaction pathway (Figure 4).

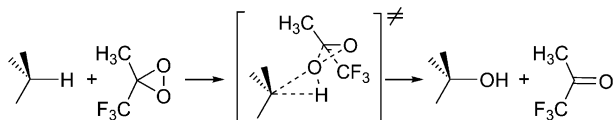


Figure 4. Concerted O-atom insertion mechanism for the oxygenation of C–H σ -bonds with methyl(trifluoromethyl)dioxirane (**1**).

Theoretical calculations^[12] indicate an asynchronous and early transition state in which the breaking of the C–H σ -bond and the forming of the O–H σ -bond are significantly more advanced than the forming of the C–O σ -bond. Raouk et al. showed^[12b] that electron-releasing substituents enhance the hydride-transfer characters of the transition states, which show higher positive charge densities at the reacting carbon atoms, longer C–H and C–O distances, and more advanced formation of the O–H σ -bonds than those found for nonsubstituted substrates. Conversely, electron-withdrawing substituents favor tighter transition states with lower positive charge densities at the reacting carbon atoms, shorter C–H and C–O bond lengths, and longer O–H distances, in agreement with the electrophilic character of dioxirane **1**.

However, Sarzi-Amadè et al.^[12a] stated that: “... *concerted TSs for alkane hydroxylations are seriously flawed by the drawback of wave function instability (as a result of their significant diradicaloid character) and, consequently, cannot be definitely considered genuine transition structures. Actually, no TSs could be located by the more adequate UB3LYP method. This is a real pity as the concerted mechanism con-*

vincingly explains the most important experimental observations.” Since theoretical methods, at the present state of the art and technique, cannot provide definite help in interpreting the reactivities of C–H σ -bonds of saturated substrates towards methyl(trifluoromethyl)dioxirane (**1**), our attempt to explain the experimental results rests on the powerful tools to interpret chemical reactivity provided by perturbation theory.^[13]

Transmission of the Substituent Effect

The experimental data are indicative of a long-range and strongly directional substituent effect that, superposing on the undifferentiated through-bond inductive effect (A, Figure 5), distinctly activates C⁵–H and C⁷–H σ -bonds towards the electrophilic dioxirane **1**. Both through-space^[14,15] and hyperconjugative^[16] modes of transmission of the substituent effect would fit this description (B, C and D, Figure 5).

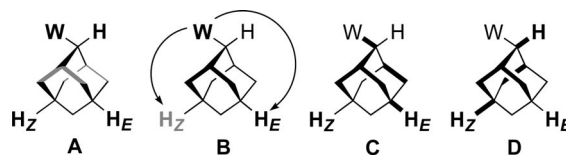


Figure 5. Inductive (A), electrostatic (B), and hyperconjugative (C and D) effects in the 2-substituted adamantane model **2**.

Electric fields associated with substituents have successfully justified the relative reactivities of diastereotopic positions in a variety of organic reactions, particularly in those involving charged reagents or intermediates.^[15] However, we have previously reported^[5c] that changing the solvent (CCl₄, CH₂Cl₂, CH₃CN, CF₃CH₂OH) in oxygenations of 2-substituted adamantanes **2** with dioxirane **1** does not significantly modify the *Z/E* selectivity found for X-type and Z-type substituents.^[5c] The insensitivity of these reactions to drastic changes in both polarity and dielectric constant of the reaction medium strongly suggests that, in this instance, the different reactivities of C⁵–H and C⁷–H σ -bonds cannot be attributed to electrostatic effects derived from the substituents (B, Figure 5).

The hyperconjugative transmission of the substituent effect^[16] (C and D, Figure 5) has a strongly directional character since it takes place through the overlap of filled and empty orbitals of adjacent *antiperiplanar* σ -bonds throughout the substrate molecule (C and D, Figure 5).

Qualitative models for interpreting the diastereoselectivities of chemical reactions on the basis of perturbation theory^[13] assume that the slope of the energy profile at the earliest reaction pathway stages determines (or is directly related to) the energy of the transition state. These models interpret the relative reactivities of two diastereotopic positions in terms of the distinct abilities of their corresponding chemical environments to modulate the energy of the reacting system through hyperconjugative interactions at the beginning of the reaction pathway. These concepts^[13] are applicable only to that part of the reaction path that includes a rather small deformation of the initial structures,

and this restriction obviously deters investigation in the vicinity of transition states whose structures significantly differ from those of the reactants.

The Beginning of the Reaction Path

The reactions of methyl(trifluoromethyl)dioxirane (**1**) with alkane C–H σ -bonds start with the interaction of the low-lying σ^*_{OO} antibonding orbital of the electrophile with the bonding σ_{CH} local orbital of the C–H σ -bond (Figure 6). Electron delocalization between frontier orbitals promotes the weakening of both C–H and O–O σ -bonds and causes a narrowing of the energy gap between their filled and empty orbitals (σ_{CH} , σ^*_{CH}) and (σ_{OO} , σ^*_{OO}), respectively.^[13g] The lowering in energy of the σ^*_{CH} orbital (LUMO of the C–H σ -bond) promotes its interaction with the nonbonding n_{O} orbital of the oxygen atom (HOMO of dioxirane **1**), and thus initiates the O–H σ -bond-forming process required for the concerted O atom insertion to take place (Figure 6).

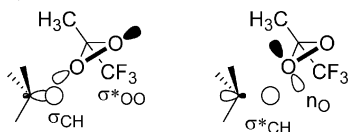


Figure 6. Orbital interactions of dioxirane **1** with a C–H σ -bond.

It is worth noting that the H-shift from carbon to oxygen atoms in the concerted O-atom insertion is not a proper hydride-transfer process, but instead has a mixed-in proton-transfer character deriving from the electron deficiency generated at both carbon and hydrogen atoms in the process of electron delocalization from substrate to electrophile. In a true hydride-transfer process the system would adopt a linear arrangement of carbon, hydrogen, and oxygen atoms and the frontier orbital interaction would transfer electron density from C–H into O–H σ -bonds without contributing to C–O σ -bond formation. Conversely, in the concerted O-atom insertion into a C–H σ -bond by dioxirane **1**, the substrate molecule holds its bonding electrons as they are transferred from the C–H to the C–O σ -bonds while the H-shift takes place through a different bonding interaction between oxygen and hydrogen atoms. The concerted character of the reaction is then better depicted (Figure 7) as a hybrid of resonance structures that represent elemental hydride-transfer (**I**), carbanion-transfer (**II**), and proton-transfer (**III**) processes.

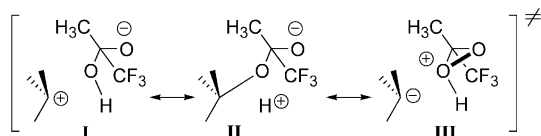


Figure 7. Resonance structures describing the concerted character of O-atom insertion into a C–H σ -bond with dioxirane **1**.

Incipient Bond

Loosened bonds arising from incipient bond-forming and bond-breaking processes at the beginning of the reac-

tion path promote hyperconjugative interactions between the reacting center and its chemical environment, and these contribute significantly to the total energy of the reacting system. These interactions are generally analyzed in terms of the *incipient bond*,^[6,17] which in our concerted model reaction would represent the progressive reorganization of bonding electrons from the C–H to the C–O σ -bonds.

In accordance with the asynchronous character^[12] of this formal hydride-transfer process, electron delocalization between reactant molecules promotes an initial loss of bonding between carbon and hydrogen atoms that is not fully compensated by C–O σ -bond formation. Therefore, as the reacting system starts to move along the reaction path, the energy gap between the bonding (σ_{inc}) and antibonding (σ^*_{inc}) orbitals of the so defined incipient bond decreases and their interactions with adjacent bonds progressively strengthen.

On the other hand, an increase in the electron-withdrawing ability of the substituent diminishes both the electron delocalization between reactants and the loss of bonding character of the incipient bond. Consequently, for a given degree of advance of the reacting system, the energy gap between the bonding and antibonding orbitals of the incipient bond is broader for the more strongly electron-withdrawing substituent.

Hyperconjugative Interactions

Three types of hyperconjugative interactions can be envisaged as the reacting system starts to move along the reaction path (Figure 8). The structure of the 2-substituted adamantane model (**2**) permits Anh's [σ_{inc} , σ_{CC}^*] and Cieplak's [σ^*_{inc} , σ_{CC}] hyperconjugative interactions^[6] between filled and empty orbitals of the incipient bond and their corresponding *antiperiplanar* C–C σ -bonds (see **A** and **C** in Figure 8). Conversely, the geometry of the system prevents Felkin's destabilizing interaction^[17] [σ_{inc} , σ] (torsional strain) (**F**, Figure 8) between filled orbitals of the incipient bond and *synperiplanar* adjacent bonds from being significant enough to differentiate the diastereotopic reacting positions.

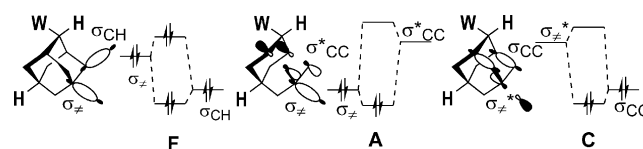


Figure 8. Felkin's [σ_{inc} , σ_{CH}] (**F**), Anh's [σ_{inc} , σ_{CH}^*] (**A**), and Cieplak's [σ^*_{inc} , σ_{CH}] (**C**) hyperconjugative interactions in the 2-substituted adamantane model (**2**).

Both Ahn's and Cieplak's stabilizing interactions^[6] (**A** and **C** in Figure 8) strengthen as the reacting system progresses along the reaction path, and both favor the initial loosening of bonds required for the reaction to advance towards the transition state.^[13g] The involvement of these interactions is restricted to the earliest stages of the reaction path, where the concepts of qualitative perturbation theory still apply.

The Substituent Effect

Anh's and Cieplak's hyperconjugative interactions^[6] imply either placing electrons into antibonding σ_{CC}^* orbitals or removing electron density from bonding σ_{CC} orbitals, and consequently they promote the loosening of the C–C σ -bonds *antiperiplanar* to the incipient bond as well as the narrowing of the energy gap between their bonding and antibonding orbitals. These perturbed C–C σ -bonds can then interact efficiently with the next *antiperiplanar* σ -bonds and transmit the electronic demand from the reacting center one step further. The diastereotopic C^5-H_Z and C^7-H_E reacting σ -bonds are connected through the adjacent *antiperiplanar* C–C σ -bonds to the C^2-H and C^2-W bonds, respectively, which then respond to the perturbation according to the relative energies of their bonding and antibonding orbitals. In this way, remote substituents receive the electronic demand from the reacting centers through chains of hyperconjugative interactions that, starting at the incipient bond, extend along the whole substrate molecule.

In order to simplify our approach we will consider that C^2-H and C^2-W σ -bonds perturb their corresponding antiperiplanar C–C σ -bonds and, in this way, modulate the hyperconjugative interactions with the *Z* and *E* incipient bonds, respectively.

According to the principles of orbital interaction, the energies of the bonding and antibonding orbitals of a C–W σ -bond – σ_{CW} and σ_{CW}^* – decrease as the electronegativity of the W substituent^[13a,16] increases, and this perturbation is hyperconjugatively transmitted to the adjacent *antiperiplanar* C–C σ -bonds. The higher the electron-withdrawing ability of the substituent at C^2 , the lower the energies of the adjacent σ_{CC} and σ_{CC}^* orbitals become (Figure 9). This effect is more intense on filled orbitals and, consequently, Cieplak's interaction decreases faster than Anh's interaction increases (Figure 9).

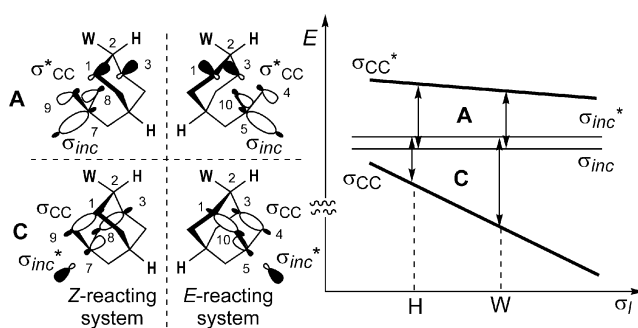


Figure 9. Effect of increasing electron-withdrawing ability of W substituents on Anh's [σ_{inc} , σ_{CC}^*] (A) and Cieplak's [σ_{inc}^* , σ_{CC}] (C) hyperconjugative interactions for the *Z* and *E* reacting systems.

In the case of 2-substituted adamantanes (**2**), the effect of the C^2-H and C^2-W σ -bonds on the energies of the bonding and antibonding orbitals of the C^1-C^9/C^3-C^8 and C^1-C^{10}/C^3-C^4 σ -bonds, respectively, determines the intensity of Anh's and Cieplak's hyperconjugative interactions for the reacting systems at positions $C^5(Z)$ and $C^7(E)$, respectively (Figure 9). Therefore, the *Z/E* selectivity of the

reaction is determined by the relative ability of the C^2-H σ -bond to stabilize the *Z* reaction pathway in relation to that of the C^2-W σ -bond to stabilize the *E* reaction pathway.

According to the σ_I value of the H substituent, Anh's stabilization of the *Z* reacting system is the weakest of the whole series, while Cieplak's is the strongest. If the electronic character of the C^2-H σ -bond does not change throughout the series of substituents (Figure 9), nor does the hyperconjugative stabilization of the *Z* reacting system. Then, as the electron-withdrawing ability of the W substituent increases, Anh's interaction [σ_{inc} , σ_{CC}^*] strengthens and leads to an increase in the stabilization of the *E* reacting system. Therefore, Anh's model predicts a consistent decrease in the *Z/E* selectivity throughout the series (Figure 9). Conversely, Cieplak's model, [σ_{inc}^* , σ_{CC}], predicts a decreasing stabilization of the *E* reacting system and a steady increase in the *Z/E* selectivity throughout the series of substituents (Figure 9).

The Model

The experimental data (Figure 3) show that the relative reactivities of C^5-H and C^7-H σ -bonds depend on the electronic characters of the W substituents in a more complex way than predicted by the straightforward application of Anh's or Cieplak's models of hyperconjugative interactions^[6] (Figures 2 and 3).

If the *Z/E* selectivity is considered to arise from the balance between the relative ability of the C^2-H σ -bond to stabilize the *Z* reaction pathway in relation to that of the C^2-W σ -bond to stabilize the *E* reaction pathway, the existence of two correlation lines with opposite slopes for each series of substituents indicates that the two hyperconjugative interactions alternate in the control of the diastereoselectivity depending on the electron-withdrawing ability of the W substituent. Since the energies of bonding and antibonding orbitals of the C–C σ -bonds involved in the hyperconjugative interactions progressively decrease as σ_I of the W substituent increases (Figure 9), the data strongly suggest that both hyperconjugative interactions operate simultaneously in the stabilization of each diastereomeric reaction pathway.

Simultaneous operation of Anh's and Cieplak's models implies that the stabilization received by the reacting system corresponds to the sum of the two types of hyperconjugative interactions. Cieplak's interaction – [σ_{CC} , σ_{inc}^*] – represents electron donation from the substrate to dioxirane **1**, stabilizing the developing positive charge at the reacting carbon atom and enhancing the hydride-transfer character of the reacting system (**I**, Figure 7). Anh's interaction – [σ_{inc} , σ_{CC}^*] – balances these effects, since it helps the substrate molecule to hold the electron density shifting from the C–H to the C–O σ -bonds. In this way, it promotes C–O σ -bond formation and enhances the proton-transfer character of H-shift from carbon to oxygen atoms (**II**, **III**, Figure 7). Cieplak's and Anh's hyperconjugative interactions distinctly stabilize the resonance forms that describe

the concerted O-atom insertion reaction (Figure 7) and their relative intensities determine the geometry of the reacting system.

With regard to *Z* substituents, they exert both inductive and resonance electron-withdrawing effects that are quantified by σ_I and σ_p , respectively. Therefore, the hyperconjugative character of the C–*Z* σ -bond, associated with the inductive electron-withdrawing ability of the *Z* substituent, superposes with the perturbation of the adjacent C²–H σ -bond associated with the presence of a low-energy empty *p*, *d*, π^* or σ^* orbital.^[18] This characteristic allows substituents such as Cl or CF₃ to be included in this class. In this instance, changes in the *Z/E* selectivity could be attributed to variations in the hyperconjugative stabilization received by the *Z* reacting system from the remote C²–H σ -bond.

The X-Series

The model applies straightforwardly to the series of X-substituted substrates **2** (Figure 9, W = X). In this case, the *Z/E* selectivity arises from the variable stabilization of the *E* reacting system provided by the C²–X σ -bond while the stabilization of the *Z* reacting system provided by the C²–H σ -bond is mostly invariant in this series. Actually, an increase in the electron-withdrawing ability of the X substituent modifies the relative energies of both the σ_{CH} and σ_{CH}^* orbitals of the C²–H σ -bond, but, as these changes would not be comparatively as large as the changes in the relative energies of the σ_{C-X} and σ_{C-X}^* orbitals of the C²–X σ -bond within the same range of σ_I values, the stabilization of the *Z* reacting system can be considered roughly invariant throughout the series of substituents.

The branch with a positive slope in the plot of *Z/E* selectivity versus σ_I of X substituents corresponds to the progressive loss of Cieplak's stabilization of the *E* reacting system, which is not fully compensated by the slow increase in Anh's stabilization (Figure 9, W = X). This trend reaches a point of minimum stabilization for the *E* reacting system, which corresponds to the maximum *Z/E* selectivity in this series of substituents. The branch with a negative slope corresponds to increasing stabilization of the *E* reacting system provided by Anh's interaction, which is dominant in this region (Figure 9, W = X). Significantly, the slopes of these branches are different, according to the distinct effect that the substituent has on the filled and empty orbitals of the interacting C–C σ -bonds.

The Z-Series

Z/E selectivity in the oxygenation of 2-substituted adamantanes (**2**) bearing *Z* substituents at C² shows a significant dependence on the resonance effect of the electron-withdrawing group. This result indicates that the reacting C⁵–H σ -bond receives the effect from the remote *Z* substituent through the modification of the electronic character of the adjacent C²–H σ -bond. The interaction^[13] of filled σ_{CH} and empty σ_{CH}^* orbitals of the C²–H σ -bond with the low-

energy vacant orbital associated with the adjacent *Z* substituent lowers the energy of both the bonding and the anti-bonding C²–H σ -bond orbitals (Figure 10). If σ_p is considered to represent the relative energy of the low-energy vacant orbital associated with the *Z* substituent, the higher σ_p is, the lower the energy of the vacant orbital interacting with the C²–H σ -bond orbitals, and the more intense the interaction. Perturbation of C–H σ -bonds by adjacent resonance substituents (either electron-withdrawing or electron-releasing) is well known in organic chemistry. For instance, this perturbation is responsible for the increased acidity of hydrogen atoms at the α -position to the *Z* substituent,^[13a] since in this case lowering the energy of the antibonding σ_{CH}^* orbital of the C–H σ -bond facilitates an interaction with the filled orbital of the base.

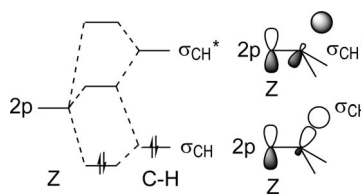


Figure 10. Interaction of the low-energy empty orbital of a *Z* substituent with the filled and the empty orbitals of the adjacent C–H σ -bond.

The effect of the *Z* substituent on the adjacent C²–H σ -bond can be represented as a formal variation in the electron-withdrawing ability of the hydrogen atom [$\sigma_I(H_Z)$], since such a perturbation would also result in a lowering in energy of both σ_{CH} and σ_{CH}^* orbitals. However, we must keep in mind that the parameter $\sigma_I(H_Z)$ is just a formal value that actually represents the perturbation exerted by the resonance contribution of the *Z* substituent on the adjacent C²–H σ -bond.

The model of simultaneous operation of Anh's and Cieplak's hyperconjugative interactions throughout the *Z*-series involves having to consider that the *Z* reacting system in this instance receives variable stabilization from the remote C²–H σ -bond (Figure 11). The correlation line with a negative slope corresponds to a region where $\sigma_I(H_Z)$ is lower than $\sigma_I(Z)$, although it progressively increases as σ_p of the *Z* substituent increases (*Z*₁ substituent in Figure 11). This region is mainly controlled by Cieplak's hyperconjugative interaction; here the $\sigma_I(H_Z)$ and $\sigma_I(Z)$ values progressively converge and the trend shows that the C²–H bond's ability to provide hyperconjugative stabilization to the *Z* reaction path decreases when compared to the C²–*Z* bond's ability to stabilize the *E* transition state (*Z*₁ substituent in Figure 11). Selectivity reaches a minimum when $\sigma_I(H_Z)$ and $\sigma_I(Z)$ are the same. The correlation line with a positive slope appears when $\sigma_I(H_Z)$ exceeds $\sigma_I(Z)$ (*Z*₂ substituent in Figure 11). This region is mainly controlled by Anh's hyperconjugative interaction; here the $\sigma_I(H_Z)$ and $\sigma_I(Z)$ values progressively diverge as σ_p of the *Z* substituent increases. The data show that the C²–H bond's ability to provide Anh-type stabilization to the *Z* reaction path is increasingly higher than that of C²–*Z* σ -bond for the *E* reaction path.

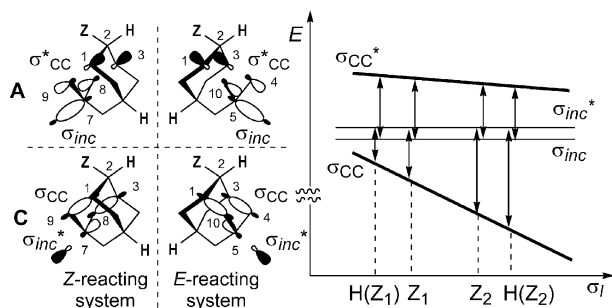


Figure 11. Anh's $[\sigma_{inc}, \sigma_{CC}^*]$ (A) and Cieplak's $[\sigma_{inc}^*, \sigma_{CC}]$ (B) hyperconjugative interactions for a Z_1 substituent (with low σ_I and σ_p) as well as a Z_2 substituent (with high σ_I and σ_p) along with those of their adjacent α -hydrogen atoms.

Application of PMO Theory

The rate constants for the oxygenation of C^5 -H and C^7 -H σ -bonds of 2-substituted adamantanes **2** can be expressed in terms of the hyperconjugative stabilization (ΔE) received by the Z and E reacting systems at the beginning of the reaction path in relation to a reference reacting system devoid of stabilization (ΔG_0) [Equation (1)].

$$\ln k_Z/k_E \propto \Delta G_E - \Delta G_Z = (\Delta G_0 - \Delta E_E) - (\Delta G_0 - \Delta E_Z) = \Delta E_Z - \Delta E_E \quad (1)$$

Principles of orbital interaction^[13] establish that the stabilization of the bonding combination of two interacting orbitals depends directly on the overlap integral (S) and inversely on the difference in energy of the orbitals involved. If we consider that the Z and E reacting systems simultaneously receive Cieplak's and Anh's stabilizations (Figure 9) from remote C^2 -H and C^2 -W σ -bonds, respectively, we obtain Equation (2) and Equation (3),

$$\Delta E_Z = [2 k^2 S_{C(H)}(\epsilon_{inc}^* - \epsilon_{CC})] + [2 k^2 S_{A(H)}(\epsilon_{CC}^* - \epsilon_{inc})] \quad (2)$$

$$\Delta E_E = [2 k^2 S_{C(W)}(\epsilon_{inc}^* - \epsilon_{CC})] + [2 k^2 S_{A(W)}(\epsilon_{CC}^* - \epsilon_{inc})] \quad (3)$$

where ϵ_{CC} , ϵ_{CC}^* , ϵ_{inc} , and ϵ_{inc}^* represent the energies of the interacting orbitals σ_{CC} , σ_{CC}^* , σ_{inc} , and σ_{inc}^* , and S_C and S_A are the overlap integrals for Cieplak's and Anh's hyperconjugative interactions, respectively. By considering $S_{C(H)} = S_{C(W)} = S_{A(H)} = S_{A(W)}$, and by substituting 2 and 3 into Equation (1), we obtain [Equation (4)],

$$\ln k_Z/k_E \propto S' \{ [1/(\epsilon_{inc}^* - \epsilon_{CC})]_H + [1/(\epsilon_{CC}^* - \epsilon_{inc})]_H \} - \{ [1/(\epsilon_{inc}^* - \epsilon_{CC})]_W + [1/(\epsilon_{CC}^* - \epsilon_{inc})]_W \} \quad (4)$$

where S' is the proportionality constant, which comprises all the invariant magnitudes derived from the different equations applied. This expression can be parameterized from a simplified energy diagram that shows the dependence of the relative energy of the interacting orbitals on the electron-withdrawing ability of the remote substituent (Figure 12). In this diagram, the dependence of the energies of σ_{inc} and σ_{inc}^* orbitals on σ_I of the remote substituent is represented as two opposing parabolas, since for a given

degree of advance of the reacting system the energy gap between the bonding and antibonding orbitals of the incipient bond is broader for the more strongly electron-withdrawing substituent. On the other hand, the energies of the σ_{CC} and σ_{CC}^* orbitals are represented as linear functions of σ_I of the W substituent, with intercepts H and H^* and slopes k_c and k_a , respectively (Figure 12).

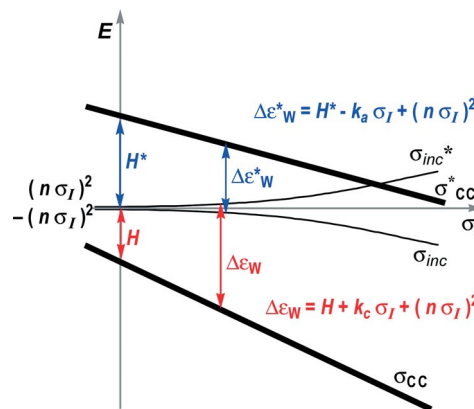


Figure 12. Relative energies of orbitals involved in hyperconjugative stabilizing interactions versus the electron-withdrawing ability (σ_I) of the substituent.

According to the diagram (Figure 12), the energy gaps for Anh's and Cieplak's interactions for a given remote substituent W – $[\sigma_{inc} - \sigma_{CC}^*]$ and $[\sigma_{CC} - \sigma_{inc}^*]$, respectively – are Equation (5) and Equation (6),

$$\Delta \epsilon_W = (\epsilon_{inc}^* - \epsilon_{CC}) = H + k_c \sigma_I + [n \sigma_I(W)]^2 \quad (5)$$

$$\Delta \epsilon_W^* = (\epsilon_{CC}^* - \epsilon_{inc}) = H^* - k_a \sigma_I + [n \sigma_I(W)]^2 \quad (6)$$

where H and H^* represent the energy gaps for Cieplak's and Anh's interactions, respectively, for $\sigma_I = 0$ (Figure 12). Thus, the equation that represents the Z/E selectivity of the reaction in terms of the simultaneous operation of Cieplak's and Anh's hyperconjugative interactions in the diastereomeric reaction pathways becomes Equation (7).

$$\ln k_Z/k_E \propto S' \{ (1/[H + k_c \sigma_I(H) + (n \sigma_I(H))^2]) + (1/[H^* - k_a \sigma_I(H) + (n \sigma_I(H))^2]) \} - \{ (1/[H + k_c \sigma_I(W) + (n \sigma_I(W))^2]) + (1/[H^* - k_a \sigma_I(W) + (n \sigma_I(W))^2]) \} \quad (7)$$

It is worth noting that the parameter σ_I is used to define the relative energies of the interacting orbitals of the incipient bond and the adjacent C-C σ -bonds. In this context, $\sigma_I(H)$ is a formal value that allows the perturbation of the C^2 -H σ -bond exerted by the adjacent W substituents to be introduced.

Equation (7) expresses the relative reactivities of C^5 -H and C^7 -H σ -bonds as a function of σ_I of the remote substituent, either H or W, in terms of six invariant parameters: namely, H , k_c , n , H^* , k_a , and the proportionality constant S' . This equation can be resolved by iterative methods, pro-

vided that enough experimental data are available. Experimentally determined *Z/E* selectivity data for the series of 2-substituted adamantanes with X-type substituents are particularly suitable for this calculation since, in this instance, the electronic character of the C²–H σ -bond [$\sigma_I(\text{H}_X)$] can be assumed to be roughly invariant along the series.

The calculation was performed on the experimentally determined values of *Z/E* selectivity for the substituents X = CH₂OAc, OAc, OSO₂C₆H₄CH₃, and NH₃⁺ by using the Solver implemented in Microsoft Excel[®] software. The system was restricted by requiring that $H^* \geq H$ and $k_c \geq k_a$, in accordance both with the electrophilic character of the reaction on the saturated substrate and with the stronger effect of the substituents on the filled orbitals. The iterative numerical calculation performed by the Solver led to different sets of valid solutions for Equation (7). The set with the smallest values was: $H = 3.6539 \times 10^{-4}$, $H^* = 3.6629 \times 10^{-4}$, $k_c = 3.5172 \times 10^{-5}$, $k_a = 3.5171 \times 10^{-5}$, $n = 1.8101 \times 10^{-3}$, and $S' = 8.2676$. We made no further attempt to optimize these results. The model described here predicts that *Z/E* selectivity should be unity when the σ_I values for H and W are the same. As the experimental data show that $\ln Z/E \approx 0$ for X = CH₂OCOCH₃ with $\sigma_I = 0.15$ (**2a**), then $\sigma_I(\text{H}_X)$ for the series of X substituents should carry a value of ca. 0.15, which would be in agreement with the perturbation exerted by the X substituent on the C²–H σ -bond. Figure 13 shows the plot of Equation (7) for $\sigma_I(\text{H}) = 0.15$ and the experimentally determined *Z/E* values found for the X-type substituents.

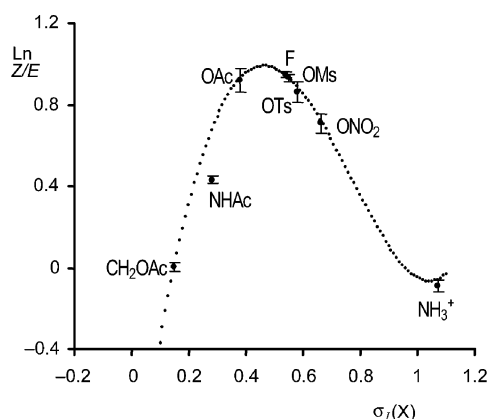


Figure 13. Plots of Equation (7) for $\sigma_I(\text{H}_X) = 0.15$ and of $\ln Z/E$ vs. $\sigma_I(X)$ for the oxygenation of 2-substituted adamantanes **2a–h** with dioxirane **1**.

When $\sigma_I(\text{H}_Z)$ of the hydrogen atom is allowed to vary, Equation (7) gives rise to a 3-D plot which represents the relative reactivities of the C⁵–H and C⁷–H σ -bonds of the 2-substituted adamantanes (**2**) towards methyl(trifluoromethyl)dioxirane (**1**) as a function of the electronic character of each substituent at C² (Figure 14). The different sets of solutions for Equation (7) provide similar wave-shaped plots for this dependence.

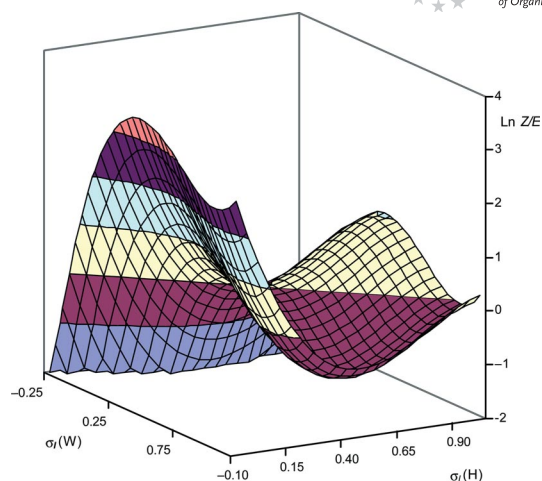


Figure 14. Plot of $\ln Z/E$ vs. $\sigma_I(W)$ and $\sigma_I(\text{H}_Z)$, according to Equation (7).

Figure 14 shows that the model combining the concepts of the simultaneous operation of Anh's and Cieplak's interactions and the variable hyperconjugative character for the C²–H σ -bond depending on the adjacent substituent correctly explains the observed experimental data. Thus, the model predicts different profiles for the dependence of *Z/E* selectivity on the electronic character of the substituent for the series of X and Z substituents (Figure 14). In fact, the plot shows a U-shaped dependence of *Z/E* selectivity on the formal $\sigma_I(\text{H}_Z)$ of the hydrogen atom, which according to our model is related to $\sigma_p(Z)$ of the Z substituent.

Dependence of $\sigma_I(\text{H}_Z)$ on $\sigma_p(Z)$

Formal $\sigma_I(\text{H}_Z)$ values for C²–H can be calculated for different Z substituents by substituting the experimentally observed *Z/E* selectivity data for the Z-series – $\sigma_I(Z)$ – and the previously calculated parameters in Equation (7). The $\sigma_I(\text{H}_Z)$ values thus obtained are those required for the experimentally observed value of $\ln Z/E$ to fit in the surface shown in Figure 14. These values are collected in Table 2.

Table 2. $\sigma_I(\text{H}_Z)$ values calculated for Z substituents from Equation (7).

(Z)- 2	$\sigma_I(Z)^{[a]}$	$\sigma_p(Z)^{[b]}$	$\sigma_I(\text{H}_Z)$
Cl (2i)	0.47	0.22 (0.24)	0.200
COOCH ₃ (2j)	0.32	0.45 (0.44)	0.221
COCH ₃ (2k)	0.30	0.49 (0.47)	0.234
CF ₃ (2l)	0.40	0.53 (0.53)	0.284
CN (2m)	0.57	0.67 (0.70)	0.655
SO ₂ CH ₃ (2n)	0.59	0.72 (0.73)	0.705
NO ₂ (2o)	0.67	0.78 (0.81)	0.950

[a] Data from ref.^[9] [b] Data from Shorter;^[9] data in brackets are from Exner.^[19]

Parent Equation (7) was constructed by considering only the inductive electron-withdrawing ability of the remote W substituent, either X- or Z-type, $\sigma_I(W)$, and resolved from the experimentally determined values of *Z/E* selectivity for

the X substituents series. In this sense, calculated formal $\sigma_I(H_Z)$ values do not contain any reference to σ_p of the Z substituent except for the concept of variable $\sigma_I(H_Z)$ of the hydrogen atom derived from the principles of orbital interaction that were applied for developing the model. In order to gain a deeper insight into this relationship, we have to consider those principles in detail and verify whether the experimentally obtained values fit them.

By assuming that the energy of the bonding σ_{CH} of the C–H σ -bond depends directly on $\sigma_I(H_Z)$ (Figure 12) we obtain Equation (8),

$$\varepsilon(\sigma_{CH})_Z = \varepsilon(\sigma_{CH})_0 - A \sigma_I(H_Z) \quad (8)$$

where $\varepsilon(\sigma_{CH})_Z$ and $\varepsilon(\sigma_{CH})_0$ represent the energies of bonding orbitals for a C–H σ -bond modified by the adjacent Z substituent and an unperturbed C–H σ -bond, respectively, and A is a proportionality constant.

On the other hand, the orbital interaction theory establishes^[13] that the energy of the bonding orbital resulting from interaction between bonding and antibonding orbitals of an unperturbed C–H σ -bond with the low-energy vacant orbital of the Z substituent (Figure 10) is Equation (9),

$$\varepsilon(\sigma_{CH})_Z = \varepsilon(\sigma_{CH})_0 - \{H^2/[\varepsilon(Z) - \varepsilon(\sigma_{CH})_0]\} \quad (9)$$

where $\varepsilon(Z)$ represents the energy of the low-energy vacant orbital of the Z substituent and H is the energy integral corresponding to the orbital interaction. By equating Equations (8) and (9), we obtain Equation (10),

$$\sigma_I(H_Z) = A'/[\varepsilon(Z) - \varepsilon(\sigma_{CH})_0] \quad (10)$$

where A' represents invariant magnitudes and proportionality constants. By expressing $\varepsilon(Z)$ as directly proportional to σ_p , we obtain Equation (11),

$$\sigma_I(H_Z) = A'/[\varepsilon(Z)_0 - B \sigma_p(Z)] - \varepsilon(\sigma_{CH})_0 \quad (11)$$

where $\varepsilon(Z)_0$ represents the energy of the low-energy vacant orbital of a Z substituent with $\sigma_p = 0$, and B is a proportionality constant. By grouping invariant magnitudes and making $B' = B/[\varepsilon(Z)_0 - \varepsilon(\sigma_{CH})_0]$ we obtain Equation (12),

$$\sigma_I(H_Z) = A'/[1 - B' \sigma_p(Z)] \quad (12)$$

A' and B' were determined numerically by using our calculated values for $\sigma_I(H_Z)$ (Table 2) and reported data on $\sigma_p(Z)$; we found that $A' = 0.1080$ and $B' = 1.1584$. Plots of $\sigma_I(H_Z)$ values and Equation (12) versus $\sigma_p(Z)$ are shown in Figure 15.

Since calculated $\sigma_I(H_Z)$ values carry no reference to $\sigma_p(Z)$ of the Z substituent, the goodness of the correlation line depends on the set of $\sigma_p(Z)$ values selected. Thus, the plot of $\sigma_I(H_Z)$ values versus $A'/[1 - B' \sigma_p(Z)]$ with use of the $\sigma_p(Z)$ values collected by Exner^[19] provides a good linear correlation ($R_2 = 0.9853$) with slope 1.0442 and intercept at 0.0069 for all Z substituents except for NO_2 . On the other hand, our data indicate that $\sigma_p(\text{Cl})$ should be 0.40, while tabulated values range between 0.22–0.24. In addition, the $\sigma_p(Z)$ values reported by Exner^[19] for CN (0.70) and NO_2 (0.81) differ slightly from those required for perfect fitting in our plots, which are 0.72 and 0.77, respec-

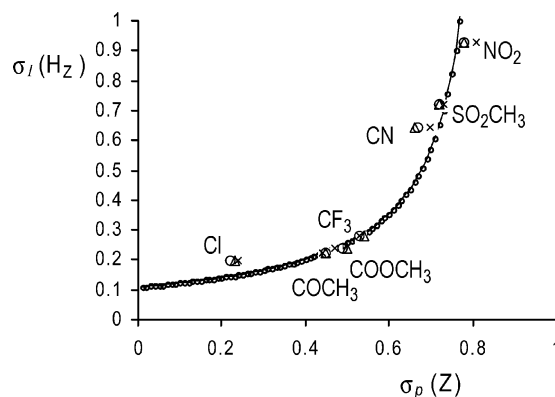


Figure 15. Plot of $\sigma_I(H_Z)$ and $A'/1 - B'\sigma_p$ ($A' = 0.108$ and $B' = 1.158$ determined numerically) vs. Shorter^[19] (O), Exner^[19] (X), and Taft^[20] (Δ) sets of σ_p .

tively. It is noteworthy that the $\sigma_I(H_Z)$ values were obtained from experimental *Z/E* selectivity data found in the oxygenation of 2-substituted adamantanes (**2**) with methyl(trifluoromethyl)dioxirane (**1**) by applying fundamental principles of the perturbation theory, and that $\sigma_I(Z)$ and $\sigma_p(Z)$ were obtained from acid ionization equilibrium constants in water for model aliphatic and aromatic carboxylic acids, respectively. In this context, the data shown in Figure 15 are significant and indicate that the empirical parameters σ_I and σ_p contain valuable information on the electronic characters of the substituents which is consistent throughout a broad variety of chemical and electronic properties of organic compounds.^[21]

The results shown in Table 2 and Figure 15 quantify the perturbation of a C–H σ -bond exerted by an adjacent Z-functional group by means of $\sigma_I(H_Z)$, a formal value which represents the relative energies of the bonding and antibonding orbitals of the perturbed C–H σ -bond (Figure 12). Increasing values of $\sigma_I(H_Z)$ imply lower energies for both σ_{CH} and σ_{CH}^* orbitals, in agreement with the well known activation of σ -bonds towards basic reagents exerted by adjacent Z substituents. Notably, these features of functional group interaction have been revealed by the relative rates of oxygenation of C⁵–H and C⁷–H σ -bonds of 2-substituted adamantanes (**2**) with methyl(trifluoromethyl)dioxirane (**1**). In this context, $\sigma_I(H_Z)$ values quantify the acidities of C–H σ -bonds adjacent to Z substituents without interference originating from the solvation of ion pairs or from the changes of solvents and bases commonly associated with the methods used to determine the pK_a values of carbon acids.^[22]

Conclusions

The relative reactivities of the C⁵–H and C⁷–H σ -bonds of 2-substituted adamantanes **2** towards methyl(trifluoromethyl)dioxirane (**1**) show a consistent dependence on the electron-withdrawing abilities, either inductive or by resonance, of the W substituents that cannot be attributed to

changes in the reaction mechanism. The results are interpreted in terms of the relative abilities of the C²–H and C²–W σ -bonds to provide hyperconjugative stabilization to the Z and E reacting centers, respectively, at the beginning of the reaction pathway. The electronic demand from the reacting C–H σ -bonds is transmitted along the substrate molecule through chains of electron-releasing and electron-withdrawing hyperconjugative interactions, both operating simultaneously. In this way, the remote C²–H and C²–W σ -bonds receive perturbation from the Z and E reacting centers, respectively, and provide differentiated hyperconjugative stabilization according to their electronic characters. The experimental data reveal that electron-withdrawing substituents with low-energy empty orbitals, strongly perturb the hyperconjugative abilities of their adjacent C²–H σ -bonds. The experimental results fit nicely to the trends predicted by the orbital interaction theory, which allows the effects of Z-substituents on the electronic characters of the adjacent C–H σ -bonds to be determined. Consequently, the role of the hydrogen atom as a reference substituent should be taken with care. Our results have revealed the exquisite sensitivity of methyl(trifluoromethyl)dioxirane (**1**) to subtle electronic effects operating in the substrate molecules and the deep insight into chemical reactivity provided by perturbation theory.

Experimental Section

Solvents were purified by standard procedures^[23] and distilled before use. Methyl(trifluoromethyl)dioxirane^[24] (**1**) in ketone-free dichloromethane solution was prepared as described^[7] and the peroxide contents of the solutions were determined by iodometric titration.^[25] Solvents were removed under vacuum at 0 °C in all cases. 2-Substituted adamantyl derivatives **2** were prepared by reported procedures.^[5c] The Z and E isomers of 5-hydroxy-2-adamantyl derivatives (**3**) were prepared by oxidation with methyl(trifluoromethyl)dioxirane (**1**) and unequivocally characterized as described previously.^[5c] ¹H and ¹³C NMR spectra of compounds **4** are reported as Supporting Information in ref.^[5c].

Determination of the Z/E Selectivity in the Oxidation of 2-Substituted Adamantanes **2 by Methyl(trifluoromethyl)dioxirane (**1**):** General procedure. An aliquot of a methyl(trifluoromethyl)dioxirane (**1**) solution in dichloromethane (initial **2**/**1** molar ratio 3:2) was added in one portion to a stirred solution of **2** in dichloromethane (0.05 M), cooled to –15 °C. The reaction was maintained at –15 °C in the dark for 2 h, and then the solvent was evaporated under vacuum to remove the unreacted peroxide. The residue was redissolved in the same volume of dichloromethane, and the solution was analyzed by glc. The products were identified by comparison with authentic samples.^[5c] The Z/E selectivity was determined from the peak areas corresponding to each isomer. The samples were analyzed at least three times by glc. The Z/E selectivity values reported are each the average of at least three independent experiments. In the case of compounds **2c**, **2e**, **2f**, and **2h**, the crude reaction mixtures were quantitatively trifluoroacetylated by the procedures reported below.

Quantitative Trifluoroacetylation of **4c:** Once the reaction of **2c** with methyl(trifluoromethyl)dioxirane (**1**) was complete, the solvent was removed under vacuum and the residue was redissolved in dichlo-

romethane (2 mL) and cooled to 0 °C. The solution was then added dropwise to a cooled solution of trifluoroacetic anhydride (5 equiv.) in dichloromethane (1.5 mL). The reaction mixture was allowed to stand at 0 °C and protected from moisture for 18 h. The mixture was treated with anhydrous potassium carbonate (5 equiv. with respect to trifluoroacetic anhydride) for 3 h. The mixture was diluted with dichloromethane, and the solids were filtered off. The efficiency of the trifluoroacetylation was monitored by glc with use of methyl *p*-chlorobenzoate as an internal standard. The same procedure was applied for **4e** and **4f**.

Quantitative Trifluoroacetylation of **4h:** Once the reaction of **4h** with methyl(trifluoromethyl)dioxirane (**1**) was complete, the solvents were removed under vacuum. The residue was redissolved in acetonitrile (substrate concentration ca. 0.05 M) and treated with five equiv. of anhydrous potassium carbonate at room temperature for 48 h. The mixture was cooled to 0 °C and was then added dropwise at 0 °C to a stirred solution of trifluoroacetic anhydride (10 equiv.) in dichloromethane (2 mL). After 48 h the mixture was treated with solid anhydrous potassium carbonate (5 equiv.) for 3 h. The solvents were removed under vacuum, and the residue was redissolved in dichloromethane (10 mL). The solids were filtered off and the solution was analyzed by glc. The efficiency of this trifluoroacetylation procedure was monitored by glc with methyl *p*-chlorobenzoate as an internal standard.

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