

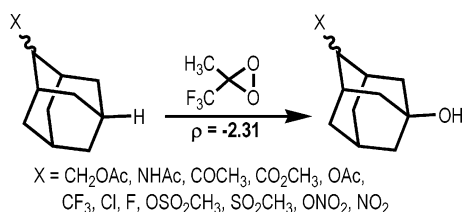
## Oxygenation of Alkane C–H Bonds with Methyl(trifluoromethyl)dioxirane: Effect of the Substituents and the Solvent on the Reaction Rate

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The mechanism of the oxygenation of alkane C–H bonds with methyl(trifluoromethyl)dioxirane (**1a**) is studied through the effect of the substituent and solvent on the rate of oxygenation of 2-substituted adamantanes (**2**). The results suggest a remarkable electron deficiency at the reacting carbon atom in the transition state leading to the regular oxygenation products. The linearity of the Hammett plot reveals that the reaction mechanism does not change within a range of 0.15–0.67 units of  $\sigma_1$ . A change in the solvent does not affect the distribution of the products, indicating a through-bond transmission of the substituent effect as the origin of the deactivation of the substrate.

### Introduction

Dioxiranes **1** are three-membered cyclic peroxides that can efficiently oxygenate saturated C–H bonds<sup>1</sup> under mild conditions. Methyl(trifluoromethyl)dioxirane (**1a**) is the most effective reagent known in these reactions that take place under very mild conditions and with high selectivity, even on deactivated substrates.<sup>2</sup>

The mechanism of the oxygenation reaction has been the subject of controversy (Scheme 1). Most of the experimental evidence regarding this process supports a reaction mechanism that involves an electrophilic attack

of the dioxirane on the reacting C–H bond, which leads to O-transfer reaction products through a concerted oxenoid transition state (path a, Scheme 1).<sup>3</sup> However, the formation of epoxides and alkyl acetates in the reaction of dimethyldioxirane (**1b**) with hydrocarbons

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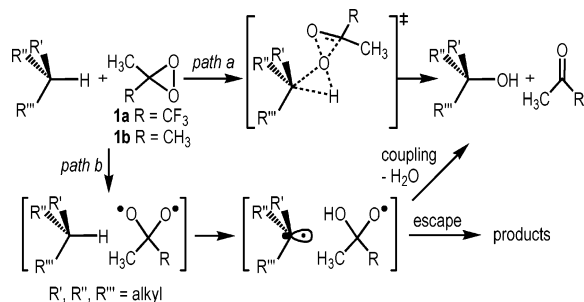
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**SCHEME 1. Mechanistic Pathways for the Oxygenation of Alkane C–H Bonds by Dioxiranes 1**



under an inert atmosphere has led other authors<sup>4</sup> to propose an alternative radical-mediated mechanism for these reactions (path b, Scheme 1). In this mechanism, the substrate-induced homolysis of the peroxidic O–O bond of the dioxirane is followed by a rate-determining H-abstraction from the substrate by the dioxyl biradical. The coupling of the radical pair within the solvent cage (oxygen-rebound) produces the regular oxygenation products, while the escape of the alkyl radical to the solution gives rise to the minor products, esters, and epoxides. Theoretical calculations<sup>5</sup> support both alternative reaction mechanisms as feasible reaction pathways for the oxygenation of saturated C–H bonds with dioxiranes. Raouk et al.<sup>5c</sup> also suggested that both concerted and stepwise mechanisms could arise from the splitting of the reaction pathway after a common transition state.

However, in our study<sup>6</sup> of the reaction of saturated hydrocarbons with dimethyldioxirane (**1b**), we found differences in the kinetic isotopic effects for regular oxygenation products (alcohols and ketones) and radical-derived products (esters and epoxides). These results strongly suggest a distinct mechanistic origin for each type of product and support the notion that the concerted reaction pathway leads to the oxygenation of saturated C–H bonds while the molecule-induced homolysis of the dioxirane leads to the minor radical-derived products. The findings obtained by Schreiner et al.<sup>7</sup> on the reaction of propellanes with dimethyldioxirane also support the notion that the molecule-induced homolysis pathway plays a minor role in the oxygenation of alkanes with dioxiranes.

Amid these conflicting reports,<sup>3–7</sup> we have established<sup>8</sup> that the electronic character of the substituent and its

relative position with respect to the reacting C–H bond also have significant effects on the rate and selectivity of this reaction. Thus, in our study<sup>8b</sup> on the oxygenation of the tertiary C–H bonds of a 2-substituted adamantane model with methyl(trifluoromethyl)dioxirane (**1a**), we found that the *Z/E* selectivity depended on the electron-withdrawing ability of the substituent. The plot of  $\ln Z/E$  versus  $\sigma_I$  of the substituents,<sup>9</sup> within a range of 0.15–1.07 units of  $\sigma_I$ , showed two correlation lines with opposite slopes, which were explained<sup>8b</sup> in terms of long-range hyperconjugative interactions of the reaction center with the remote substituent. However, within the mechanistic context, these data raise the question as to whether the change in the slope observed could indicate a change in the reaction mechanism induced by the increasing electron-withdrawing ability of the remote substituent. The validity of our interpretation<sup>8</sup> of the dependence of *Z/E* selectivity on the electron-withdrawing ability of the remote substituent requires that we verify that the reaction mechanism remains unchanged along a series of substituents.

In an earlier report, Murray et al. studied<sup>10</sup> the effect of the substituents on the oxygenation rate of 1-substituted adamantanes with dimethyldioxirane (**1b**) and found evidence to support an electrophilic mechanism. However, the range of substituents used was relatively narrow (0.15–0.47 units of  $\sigma_I$ ), and some substituents remarkably deviated from the trend because the model substrate allowed through-space interaction between the substituent and the reacting center in the transition state. These data do not allow us to conclude that the reaction mechanism is consistent along a broader range of electron-withdrawing substituents with the more reactive methyl(trifluoromethyl)dioxirane (**1a**). Furthermore, the literature contains little systematic experimental data concerning the specific influence of the substituents and the solvent on the oxygenation of saturated substrates with methyl(trifluoromethyl)dioxirane (**1a**).

We report here the effect of the substituents on the rate of the oxygenation of substituted saturated hydrocarbons with methyl(trifluoromethyl)dioxirane (**1a**). The study was performed for a series of 2-substituted adamantanes, a model substrate that avoids through-space interaction of the substituent with the reacting center, with a series of electron-withdrawing substituents covering a range of 0.15–0.67 units of  $\sigma_I$ .<sup>9</sup> The Hammett plot shows a straight line with a negative slope that suggests a significant electronic deficiency at the substrate in the transition state and indicates that the reaction mechanism remains unchanged along the whole series of substituents. The kinetic solvent effect found in the oxygenation of 2-adamantyl acetate (**2e**) with methyl(trifluoromethyl)dioxirane (**1a**) is significant and makes it possible to disregard a radical-mediated mechanism as the main pathway to the regular oxygenation products in these reactions. The absence of any significant influence of the solvent on the *Z/E* isomer ratio allows us to also disregard the through-space transmission of the substituent effect.

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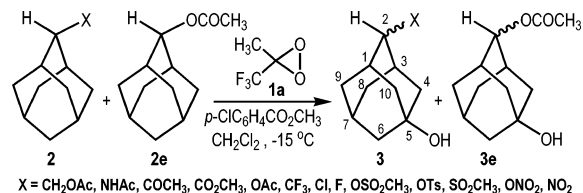
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**SCHEME 2.** Determination of the Relative Rates  $k_X/k_{OAc}$  in the Oxidation of Substrates **2** with Dioxirane **1a****TABLE 1.** Relative Rates and Effect of the Solvent on Diastereoselectivity in the Oxygenation of Substrates **2** with Methyl(trifluoromethyl)dioxirane (**1a**)

2 (X)	Z attack %				
	$\sigma_1^a$	$k_{\text{rel}}^b$	$\text{CCl}_4^c$	$\text{CH}_2\text{Cl}_2^c$	$\text{CF}_3\text{CH}_2\text{OH}$
<b>2a</b> ( $\text{CH}_2\text{OAc}$ )	0.15	3.435	50.0	50.1 <sup>d</sup>	50.9
<b>2b</b> ( $\text{NHAc}$ )	0.28	1.503		60.6 <sup>d</sup>	60.0
<b>2c</b> ( $\text{COCH}_3$ )	0.30	1.646	54.8	56.2	56.4
<b>2d</b> ( $\text{COOCH}_3$ )	0.32	1.466	57.5	59.5	60.0
<b>2e</b> ( $\text{OAc}$ )	0.38	1.000	71.0	71.5 <sup>d</sup>	71.6
<b>2f</b> ( $\text{CF}_3$ )	0.40	0.931	56.9	57.0	57.7
<b>2g</b> ( $\text{Cl}$ )	0.47	0.541	65.6	66.6	67.0
<b>2h</b> ( $\text{F}$ )	0.54	0.463	70.8	72.0 <sup>d</sup>	72.9
<b>2i</b> ( $\text{OSO}_2\text{CH}_3$ )	0.55	0.425	72.1	71.7 <sup>d</sup>	72.2
<b>2j</b> ( $\text{CN}$ )	0.57	0.345	50.2	53.3	54.4
<b>2k</b> ( $\text{OTs}$ )	0.55		72.1	71.7 <sup>d</sup>	72.2
<b>2l</b> ( $\text{SO}_2\text{CH}_3$ )	0.59	0.316	55.2	57.3	58.9
<b>2m</b> ( $\text{ONO}_2$ )	0.66	0.233	65.6	67.0 <sup>d</sup>	68.2
<b>2n</b> ( $\text{NO}_2$ )	0.67	0.208	64.3	65.8	66.2
<b>2o</b> ( $\text{NH}_3^+$ )	1.07				47.7 <sup>d</sup>

<sup>a</sup> Data from ref 9. <sup>b</sup> Measured in dichloromethane; the values are the averages of at least three independent runs, and the standard deviations are within 0.106 and 0.012. <sup>c</sup> The data are limited by the solubility of the substrates **2** in the selected solvent. <sup>d</sup> Data from ref 8a.

## Results

The effect of the substituents on the relative rate of oxygenation with methyl(trifluoromethyl)dioxirane (**1a**) was determined for a series of 2-substituted adamantanes (see Scheme 2). The relative reaction rates were determined by competition experiments between 2-adamantyl acetate (**2c**) and the substrates **2** with methyl(trifluoromethyl)dioxirane (**1a**, Scheme 2). Reactions were carried out at  $-15^\circ\text{C}$  under an air atmosphere by adding an aliquot of a dichloromethane solution<sup>11</sup> of the dioxirane **1a** to a solution containing a mixture of the corresponding substrate **2**, 2-adamantyl acetate (**2e**) and methyl para-chlorobenzoate as an internal standard. In all cases, the initial concentration of the reagents was 0.05 M with a molar ratio of 1:1:1. The relative rates were obtained from the areas of the starting materials in GC analysis, and the values are the averages of at least three independent experiments. The calibration curves for the different substrates and the internal standard were determined before the GC analysis (see Experimental Procedures). The results are shown in Table 1. The relative rate for substrate **2o** (X =  $\text{NH}_3^+$ ) was not measured since it is insoluble in dichloromethane. The values obtained for substrate **2k** (X =  $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_3$ ) showed a large error due to the irregular response of the substrate under the GC analysis conditions and thus are not included in the table.

In all cases, the reactions gave only products that resulted from the oxygenation of the distant tertiary

**TABLE 2.** Absolute Rate Constants for Reaction of **2e** with **1a** in Different Solvents

solvent	$E_T^{N^a}$	$k_2$ ( $\text{M}^{-1} \text{s}^{-1}$ )
$\text{CCl}_4$	0.052	$0.0518 \pm 0.022$
$\text{CH}_2\text{Cl}_2$	0.309	$0.0796 \pm 0.015$
$\text{CH}_3\text{CN}$	0.46	$0.1703 \pm 0.010$
$\text{CF}_3\text{CH}_2\text{OH}$	0.898	$0.0954 \pm 0.008$

<sup>a</sup> Data from ref 17.

$\text{C}_5\text{-H}$  or  $\text{C}_7\text{-H}$  bonds, with not even traces of oxygenation at the tertiary  $\text{C}_1\text{-H}$  or  $\text{C}_3\text{-H}$  bonds or at the methylene bridges. A change in the solvent (carbon tetrachloride, dichloromethane, and 2,2,2-trifluoroethanol) did not significantly affect these results (Table 1). The experimental details concerning the synthesis and characterization of the reaction products are provided in the Experimental Procedures. The reactions take place with a high conversion of the substrates into the corresponding oxygenated products indicating the absence of free radicals in the course of the reaction.<sup>11</sup> Also, the GC-MS analysis of the reaction mixtures showed the absence of the characteristic products derived from the radical pathways (esters or halogenated derivatives).

The influence of the solvent on the reaction rate of 2-adamantyl acetate (**2e**) with methyl(trifluoromethyl)dioxirane (**1a**) was determined in 2,2,2-trifluoroethanol, dichloromethane, acetonitrile, and carbon tetrachloride. The reactions were carried out at  $-15.0 \pm 0.1^\circ\text{C}$ , under second-order conditions ( $[\mathbf{1a}]_0 = [\mathbf{2e}]_0 = 0.016 \text{ M}$ ) by adding an aliquot ( $-15.0 \pm 0.1^\circ\text{C}$ ) of a ketone-free dichloromethane solution of methyl(trifluoromethyl)dioxirane (**1a**) to a mixture of equimolar amounts of the substrate **2e** and the internal standard (methyl para-chlorobenzoate) in the selected solvent. The ratios 2,2,2-trifluoroethanol/dichloromethane, acetonitrile/dichloromethane, and carbon tetrachloride/dichloromethane were ca. 11:1 in all cases. The kinetic constants were obtained from the plots of  $1/[\mathbf{2e}]$  versus  $kt$ , which were linear up to a substrate conversion of ca. 70%. The values shown in Table 2 are the averages of at least three independent runs.

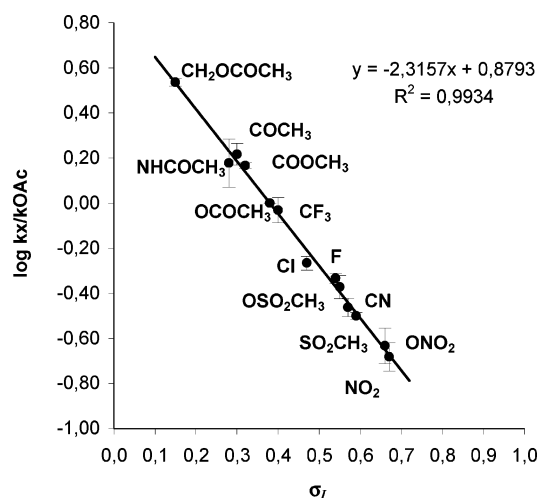
## Discussion

The plot of  $\log k_X/k_{OAc}$  versus  $\sigma_1$  of the substituents (Figure 1) shows that the rate of the oxygenation reaction progressively decreases as the electron-withdrawing ability of the substituent ( $\sigma_1$ ) increases. This dependence is consistent along the range of 0.15–0.67 units of  $\sigma_1$ , indicating that the mechanism of the reaction does not change along the whole series of substituents.

The large and negative slope of this Hammett plot ( $\rho = -2.31$ ) is consistent with a reaction mechanism involving a strongly electron-demanding transition state, in agreement with the electrophilic character of the dioxirane (**1a**). The plot of the data versus  $\sigma_Q$  values<sup>12</sup> yields again a straight line with a slope ( $-0.47$ ,  $R^2 = 0.9865$ ) that is comparable to the  $\rho$  values obtained for some reactions that proceed through carbocation intermedi-

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**FIGURE 1.** Relative rates of reaction of substrates **2** with dioxirane **1a** vs Charton's preferred<sup>9</sup>  $\sigma_I$  constants ( $\log k_X/k_{OAc} = -2.3157\sigma_I + 0.8793$ ,  $R^2 = 0.9934$ ). The values are the averages of at least three independent experiments.

ates,<sup>13</sup> such as the solvolysis of 4-substituted 2-adamantyl para-toluensulfonates ( $\rho = -0.53$ ), 7-substituted 2-norbornyl para-toluensulfonates ( $\rho = -0.72$ ), and tertiary alkyl chlorides ( $\rho = -0.71$ ). Murray et al. reported<sup>10</sup> a slope of  $-0.371$  in the plot of the rate constants of the oxygenation of 1-substituted adamantanes with dimethyldioxirane (**1b**) versus  $\sigma_Q$  substituent constants,<sup>12</sup> which is in agreement with the less electrophilic nature of this dioxirane as compared with methyl(trifluoromethyl)dioxirane (**1a**). The models used in these studies place the substituent one bond closer to the reacting carbon atom than our model substrate **2**. The results are also in good agreement with the effect of the substituents on the rate of oxygenation of saturated hydrocarbons with peracids.<sup>14</sup>

The theoretical descriptions<sup>5</sup> of the transition structures for alkane oxidation with dioxiranes define a highly asynchronous and polar transition state for the concerted electrophilic O-atom insertion mechanism, in which the reacting carbon atom develops a significant electron deficiency. Conversely, the transition state for H-atom abstraction from the substrate by the dioxy radical, which is the rate-determining step of the alternative radical-mediated mechanism, shows a much lower dipole moment and also a lower charge density at the reacting carbon atom.<sup>5</sup> It is known<sup>15</sup> that reactions involving radical intermediates are less sensitive to remote substituent effects than ionic processes. Thus, the data reported<sup>16</sup> on the relative rates of hydrogen abstraction

for a series of 2-substituted adamantanes by triplet biacetyl correlate with the  $\sigma_I$  of the substituent with slopes of  $-1.4$  and  $-1.8$  for syn and anti C–H  $\sigma$ -bonds, respectively. However, these data were interpreted in terms of the electric field model for transmission of the inductive substituent effect.<sup>16</sup>

Therefore, the high sensitivity of the oxygenation of 2-substituted adamantanes with methyl(trifluoromethyl)dioxirane (**1a**) to the electron-withdrawing ability of the remote substituent, placed in a distance of four  $\sigma$ -bonds from the reacting center, is consistent with an electrophilic concerted O-atom insertion mechanism as the main route to the regular oxygenation products in these reactions.

The effects of the substituents on the relative reaction rates (Figure 1) evidence their relative abilities to diminish the electron density of the substrate molecule. The reactions take place at the tertiary C–H bonds that are furthest from the substituent at C2, which are the less-deactivated positions with regard to the electrophilic oxygenation. These results are in agreement with previous data reported on the effect of the substituents on the regioselectivity of the oxygenation of C–H bonds with dioxirane **1a**.<sup>2b,d,e,8b</sup> The effect of the substituents shows a nondirectional character and weakens with distance, suggesting a through-bond mode of transmission of the inductive electron-withdrawing effect. In this way, the substituent withdraws electron density from the entire substrate through successive polarization of the adjacent bonds. The intensity of this effect will depend on the electron-withdrawing ability of the substituent. Since the relative reactivity of the diastereotopic C–H bonds is scarcely affected by the polarity and dielectric constant of the solvent (Table 1), neither the different reactivity of the substrates in the oxygenation reaction nor the diastereoselectivity of the reaction can be attributed to the through-space mode of transmission of the inductive effect of the substituent. These results support our previous interpretation<sup>8</sup> of the effect of remote substituents on the diastereoselectivity of the oxygenation reaction in terms of hyperconjugative through-bond transmission of the substituent effect.

The kinetic solvent effect on the reaction rate is modest, although significant. The relative reaction rates found in carbon tetrachloride, dichloromethane, acetonitrile, and 2,2,2-trifluoroethanol were 1:1.54:1.84:3.29, which indicates that an increase in the polarity and hydrogen-bond donor (HBD) ability of the solvent enhances the reaction rate. This trend indicates increasing charge separation upon going from the reactants to the transition state.<sup>17</sup> Since both 2-adamantyl acetate (**2e**) and methyl(trifluoromethyl)dioxirane (**1a**) are polar hydrogen-bond acceptors, an increase in the polarity of the solvent increases the solvation of the reactant molecules and lowers their free energy. Thus, the experimental data indicate that the lowering of the transition-state free energy due to solvation is greater than that of the reagents and support a significant increase in the dipole moment and charge separation upon going from the reactants to the transition state.<sup>17</sup>

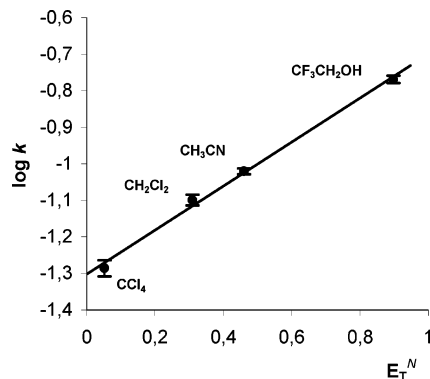
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**FIGURE 2.** Correlation of  $\log k_2$  with  $E_T^N$  for the reaction of **2e** with **1a** ( $\log k_2 = 0.6028E_T^N - 1.3025$ ,  $R^2 = 0.9958$ ).

Ingold et al. established<sup>18</sup> that the kinetic solvent effects observed in hydrogen-abstraction reactions are related in many cases to the hydrogen-bond acceptor (HBA) ability of the solvent since the approaching radical must replace the solvent molecule in the substrate-solvent HBD–HBA complex before the hydrogen-abstraction process can occur. Thus, the rate of hydrogen-atom abstraction from a C–H bond by a reactive radical<sup>18</sup> is insensitive to a change in the solvent, according to the poor HBD ability of the substrate and the absence of any significant increase in charge separation upon going from the reactants to the transition state. On these grounds, the stepwise radical mechanism should be insensitive to the solvent since the formation of the dioxy radical takes place by interaction of the molecules of substrate and dioxirane that are already within the solvent cage. On the other hand, the effect of the solvent on the substrate-induced homolysis step would hardly account for the observed kinetic solvent effect since in this case the charge separation on going from the reactants to the transition state would be even lower than in the H-abstraction step. Therefore, the kinetic solvent effect found in the oxygenation of 2-adamantyl acetate (**2e**) with methyl(trifluoromethyl)dioxirane (**1a**) would be more consistent with a concerted electrophilic O-atom transfer mechanism than with a stepwise radical mechanism.

In any analysis of solvent effects on chemical reactions, it is customary to seek a linear relation between a solvent parameter and the logarithm of the rate constant (i.e., a linear free energy relationship). Among the different empirical solvent parameters described, the rate constants for the oxygenation of **2e** with **1a** yield a fairly good correlation ( $R^2 = 0.996$ ) with the Dimroth–Reichardt  $E_T^N$  solvent polarity parameter,<sup>19</sup> with a positive slope of 0.603 (Figure 2). This solvent parameter is not a macroscopic property of the bulk solvent but probes the cybotactic region<sup>20</sup> of the solvent in which the order

of the solvent molecules has been affected by the solute. The  $E_T^N$  parameter thus measures the specific Lewis acidity of the solvent in addition to its dipolarity, polarizability, and cohesion forces, which are the effects that the cybotactic region has on the model solute molecules.

Murray et al. reported<sup>21</sup> that the rate constants for the oxygenation of *cis*-1,2-dimethylcyclohexane with dimethyldioxirane (**1b**) show a good correlation with the Kamlet–Taft  $\alpha$  parameter.<sup>22</sup> Significantly, these data do not correlate with the  $E_T^N$  parameter, while our data fail to correlate with the Kamlet–Taft  $\alpha$  values or any of the solvent parameters which, like  $\alpha$ , specifically measure the HBD ability of the solvent.<sup>17</sup> These observations reveal that the oxygenation of saturated C–H bonds with dimethyldioxirane (**1b**) is more sensitive to the specific HBD ability of the solvent than the reaction with the more electrophilic methyl(trifluoromethyl)dioxirane (**1a**). These results agree with the more localized and basic character developed by the dimethyldioxirane (**1b**) oxygen atom in the transition state, with respect to that developed by the oxygen atom in methyl(trifluoromethyl)dioxirane (**1a**), in which the negative charge is delocalized through the strong electron-withdrawing trifluoromethyl group. Also, methyl(trifluoromethyl)dioxirane (**1a**) induces a more intense charge separation in the transition state than dimethyldioxirane (**1b**). The solvation of the transition state for oxygenation with methyl(trifluoromethyl)dioxirane (**1a**) becomes more sensitive to the nonspecific dipole–dipole, dipole–induced dipole, and dispersion forces that solvate the charge separation induced by the interaction between the substrate and the electrophile. The correlation of the rate constants found for the oxygenation of 2-adamantyl acetate (**2e**) with methyl(trifluoromethyl)dioxirane (**1a**) with the Dimroth–Reichardt  $E_T^N$  parameter of the solvent results from the relative abilities of the solvents to provide these types of solvating interactions.

Thus, the experimental data available<sup>2,6,7</sup> on the oxygenation of alkane C–H bonds with dioxiranes **1** configure a mechanistic picture in which the formation of the regular oxidation products (alcohols and carbonyl compounds) takes place through an electrophilic O-atom insertion mechanism, while the radical-derived products arise from the substrate-induced homolysis of dioxirane **1** and the escape of the radical pair from the solvent cage. The alkyl radical formed reacts with either the dioxirane **1** (an extremely efficient spin-trap),<sup>11</sup> to give the corresponding esters and the radical-chain decomposition of the peroxide,<sup>11</sup> or the solvent, to give chlorinated products. The distinct kinetic isotopic effect found<sup>6</sup> for each type of product indicates that after the initial interaction between substrate and dioxirane **1**, the process splits into two reaction pathways with different transition states leading to the O–O bond-homolysis and the O-atom insertion, respectively. The incidence of each process depends on the structure of the dioxirane **1**, dimethyldioxirane (**1b**) being more prone to homolysis than the more electrophilic methyl(trifluoromethyl)dioxirane (**1a**).

In summary, we have found that the relative rate of oxygenation of 2-substituted adamantanes (**2**) with

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methyl(trifluoromethyl)dioxirane (**1a**) consistently decreases as the electron-withdrawing effect of the remote substituent increases. The data support a concerted electrophilic O-atom insertion as the main reaction pathway leading to the regular oxygenation products, which does not change along the whole series of substituents tested. The kinetic solvent effect also suggests a significant increase in charge separation upon going from the reactants to the transition state. The distribution of the reaction products is not affected by the polarity or the dielectric constant of the solvent, indicating that through-bond transmission of the inductive effect of the substituent is the origin of deactivation of the substrate.

## Experimental Procedures

**Determination of the Relative Rates of Oxygenation of 2-Adamantane Derivatives (2) by Methyl(trifluoromethyl)dioxirane (1a). General Procedure.** To a stirred 0.1 M solution (2 mL) of substrate **2**, 2-adamantyl acetate (**2e**) and methyl para-chlorobenzoate in dichloromethane, thermostated at  $-15 \pm 0.1$  °C was added an aliquot (2 mL) of a thermostated 0.1 M solution of methyl(trifluoromethyl)dioxirane (**1a**) in dichloromethane.<sup>11</sup> The initial concentration of the reagents was 0.05 M, and the initial molar ratio **2:2e:1** was 1:1:1 in all cases. The reaction was carried out under air and protected from the light for 2 h. The reaction mixtures were directly analyzed by GC. The substrate conversions were obtained from the areas of the starting materials at  $t = 0$  and after the reaction was complete, by applying the equation

$$k_X/k_{OAc} = f_X [(A_X/A_{ST})_0 - (A_X/A_{ST})_t] / f_{OAc} [(A_{OAc}/A_{ST})_0 - (A_{OAc}/A_{ST})_t]$$

The factors  $f_X$  for the different substrates were determined by analyzing a series of standard solutions of the substrate and the internal standard, over the concentration range from 0.01 to 0.1 M. The values, obtained from the slopes of the plots of  $[2]/[ST]$  versus  $A_2/A_{ST}$ , were  $f_{2a} = 0.942$ ,  $f_{2b} = 1.204$ ,  $f_{2c} = 0.845$ ,  $f_{2d} = 0.758$ ,  $f_{2e} = 0.715$ ,  $f_{2f} = 0.914$ ,  $f_{2g} = 0.713$ ,  $f_{2h} = 0.597$ ,  $f_{2i} = 1.616$ ,  $f_{2j} = 0.800$ ,  $f_{2l} = 1.485$ ,  $f_{2m} = 1.103$ , and  $f_{2n} = 0.958$ . The values of the relative rate of reaction were the averages of at least three independent experiments.

**Kinetic Measurements. General Procedure.** To a stirred 0.0175 M solution (4 mL) of 2-adamantyl acetate (**2e**) and 0.0148 M of the internal standard (methyl para-chlorobenzoate) in the selected solvent (2,2,2-trifluoroethanol, dichloromethane, acetonitrile, or carbon tetrachloride), thermostated at  $-15 \pm 0.1$  °C, was added an aliquot (0.35 mL) of a thermostated 0.2 M solution of methyl(trifluoromethyl)dioxirane (**1a**) in dichloromethane (solvent/dichloromethane 11.4:1,  $C_{t=0} = 0.016$  M). The reaction mixture was sampled (0.2 mL) every ca. 10 s, and the aliquots were quenched at 0 °C with 0.05 mL of tetramethylethylene and 0.01 g of sodium carbonate in 0.2 mL of dichloromethane. The reaction mixtures were analyzed by GC, and substrate conversion was obtained from the areas of the starting materials. The rate constant  $k_2$  was obtained from the slope of the plot of  $[1/C_t - 1/C_0]$  versus  $t$ . The results are the averages of at least three independent runs.

**Synthesis of (Z)- and (E)-5-Hydroxy Derivatives (3). General Procedure.** To a stirred solution of 0.15 g (0.88 mmol) of **2g** in 4.8 mL of the selected solvent cooled at  $-15$  °C was added 5.8 mL of a 0.15 M dichloromethane solution of methyl(trifluoromethyl)dioxirane (**1a**). The reaction was al-

lowed to stand at  $-15$  °C for 2 h in the dark. The solvent was removed under vacuum, and the products were separated by column chromatography (silica gel, hexane/ethyl acetate 2:1). The isomer (Z)-2-chloro-5-hydroxy-adamantane [(Z)-**3g**] was eluted first, and the isomer [(E)-**3g**] was eluted last.

The oxidation of 2-adamantylammonium para-chlorobenzenesulfonate (**2o**) was carried out by adding an aliquot of a dichloromethane methyl(trifluoromethyl)dioxirane (**1a**) solution to the ammonium salt dissolved in 2,2,2-trifluoroethanol. After 2 h, the reaction was treated with 5 equiv of anhydrous potassium carbonate and allowed to stand for 48 h at room temperature with stirring. The solids were filtered off, the solvent was removed under vacuum, and the residue was chromatographed on silica gel with a mixture of ethyl acetate/methanol (98:2  $\rightarrow$  0:100). A ca. 20:80 Z/E mixture of both isomers **3o** was eluted first, and a ca. 80:20 Z/E mixture was eluted last.

The diastereoselectivity of the reaction was determined by GC analysis of an aliquot of the crude reaction mixture sampled before chromatographic separation. The products were identified by comparison with authentic samples. In the case of compounds **2e**, **2i**, and **2k**, samples of the crude reaction mixtures were quantitatively trifluoroacetylated before the GC analysis. For compound **2o**, the reaction mixture was treated with sodium carbonate before treatment with trifluoroacetic anhydride.

In the cases of substrates **2c**, **2l**, **2m**, and **2n**, only the (Z)-**3** isomers could be isolated in pure form by column chromatography, and the (E)-**3** isomers were characterized in a (E)-enriched mixture. For substrate **2a**, only the (E)-**3a** isomer could be isolated in pure form by column chromatography, and (Z)-**3a** was characterized in a (Z)-enriched mixture. The (Z)- and (E)-isomers of **3b**, **3d**, **3e**, and **3o** could not be separated by column chromatography and were characterized in a ca. 75:25 (Z)-isomer-enriched mixture.

The (Z)- and (E)-isomers of the 5-hydroxylated products (**3**) were characterized by <sup>13</sup>C NMR spectroscopy. The extensive available data<sup>23</sup> on the <sup>13</sup>C NMR spectra of substituted 2,5-adamantane derivatives show characteristic patterns for each isomer, which allows a straightforward identification. Tables 1 and 2 (Supporting Information) show <sup>13</sup>C NMR data for compounds (Z)-**3** and (E)-**3**. Once the (Z)- and (E)-isomers were fully characterized, retention times in GC were unequivocally assigned. The structures of compounds (Z)-**3g**, (Z)-**3i**, (E)-**3i**, (Z)-**3c**, (Z)-**3l**, and (E)-**3l** were confirmed by X-ray diffraction analyses (Supporting Information).

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**Supporting Information Available:** Synthetic procedures for compounds **2**. Spectroscopic characterization of (Z)- and (E)-5-hydroxy derivatives **3**. X-ray crystal data for compounds (Z)-**3g**, (Z)-**3i**, (E)-**3i**, (Z)-**3c**, (Z)-**3l**, and (E)-**3l**. <sup>13</sup>C NMR spectra for compounds **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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