# H-Bonding Interactions in the Epoxidation of Alkenylammonium Salts with Dimethyldioxirane and *m*-Chloroperbenzoic Acid: A Kinetic Study

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The epoxidation rate constants for the reaction of allylic and homoallylic primary and quaternary ammonium salts with DMDO (**1b**) and *m*-CPBA (**2**), as well as the stereochemical outcome of these reactions, were determined. The presence of an ionic functional group in the substrate complicates the kinetic study of the reaction. However, $k_0$ can be determined from the $k_{obs}$ values measured in solutions with different ionic strengths. The order of magnitude of the rate constants is the same for the epoxidation of primary and quaternary homoallylic ammonium salts, while primary allylic ammonium salts react more than 10 times faster than their quaternary counterparts. High *syn*-diastereoselectivity is achieved in the epoxidation of the primary allylic salt **3aH**$^+$ while the quaternary allylic ammonium salt **5a**$^+$ gives equimolecular (*m*-CPBA) or predominantly *anti* (DMDO) mixtures of diastereomers. These results are consistent with the existence of hydrogen bond interaction between the protic substrates and the oxidant.

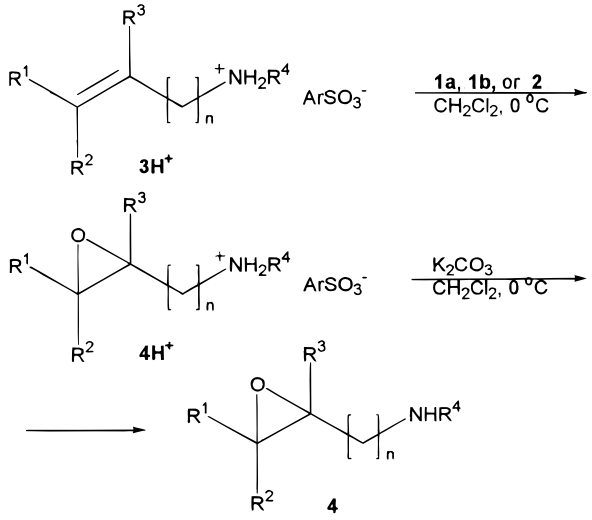
## Introduction

Methyl(trifluoromethyl)dioxirane (TFDO) (**1a**) and dimethyldioxirane (DMDO) (**1b**) are widely used in the selective oxidation of many substrates, especially in the hydroxylation of nonactivated C−H bonds of hydrocarbons and the epoxidation of C=C double bonds.[1]These reactions have been successfully extended to the oxidation of functionalized compounds when the substituents are not able to react with dioxiranes or have been adequately protected against oxidation. We have previously shown that primary and secondary aliphatic amines and alkenylamines react with TFDO (**1a**), DMDO (**1b**), and *m*-chloroperbenzoic acid (*m*-CPBA) (**2**) exclusively at the hydrocarbon chain when the amine nitrogen is protected upon protonation with arenesulfonic acids.[2] For instance, this methodology allows for the selective epoxidation of C=C double bonds of arenesulfonates of alkenylammonium **3H**$^+$ under mild conditions with excellent yields (see Scheme 1), allowing for the conversion of alkenylamines into epoxyalkylamines **4**.[2b]

In the course of our comparative study[2b] of the epoxidation of alkenylammonium salts **3H**$^+$ with compounds **1** and **2**, we observed that the electron-withdrawing character of the ammonium group results in an important deactivation of the olefin toward epoxidation and, consequently, that the epoxidation of salts **3H**$^+$ requires reaction times much longer than usual in the epoxidation of simple olefins. This effect decreases with the distance between the olefin and the ammonium group. Outstanding features of the oxidation of alkenylammonium salts **3H**$^+$ with DMDO (**1b**) and *m*-CPBA (**2**) are the high *syn*-distereoselectivity achieved and the enhanced reactivity shown by 2-cyclohexenylammonium *p*-chlorobenzenesulfonate (**3aH**$^+$) (see Scheme 2).

To explain these findings, we suggested[2b] that hydrogen bonding between the acid ammonium group protons, in a pseudoequatorial position, and a peroxide oxygen

**Scheme 1**

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(1) (a) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811. (b) Adam, W.; Hadjiaropoglou, L. P. *Top. Curr. Chem.* **1993**, *164*, 45. (c) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (d) Adam, W.; Hadjiaropoglou, L. P.; Curci, R.; Mello, R. In *Organic Peroxides*; Ando, W., Ed.; Wiley: New York, 1992; Chapter 4, pp 195−219.

(2) (a) Asensio, G.; Gonzalez-Nuñez, E.; Bernardini, C. B.; Mello, R.; Adam, W. *J. Am. Chem. Soc.* **1993**, *115*, 7250. (b) Asensio, G.; Mello, R.; Boix-Bernardini, C.; Gonzalez-Nuñez, E.; Castellano, G. *J. Org. Chem.* **1995**, *60*, 3692.

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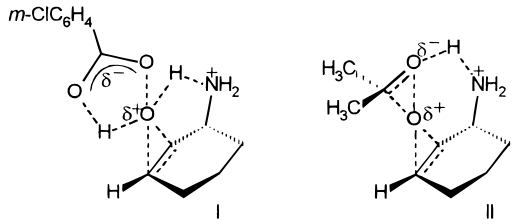
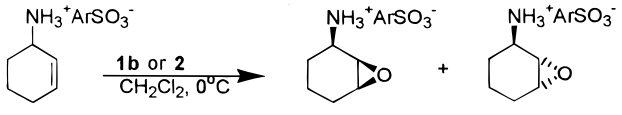



**Figure 1.** Model of hydrogen bonding in the epoxidation of allylic alkenylammonium salt **3aH**$^+$ with *m*-CPBA (**I**) and DMDO (**II**).

**Scheme 2**




| | *syn*:*anti* |
|---|---|
| **1b** | 90:10 |
| **2** | 99:1 |

atom was involved in the transition state (see Figure 1). In the case of oxidation with *m*-CPBA (**2**), a similar although less intense effect has been invoked to explain the diastereoselectivity in the epoxidation of allylic olefins substituted by alcohol, amide, and carbamate groups.[3] The intensity of this effect in the case of ammonium salts should be related to the greater acidity of the ammonium proton. Furthermore, acceleration of epoxidation should result from stabilization of the transition state due to the hydrogen bridge. However, these results could also be explained by considering other stereoelectronic effects, such as, for instance, ion−dipole or dipole−dipole interactions. Recent theoretical calculations[4] have shown that in DMDO epoxidations hydrogen bond donor substituents at the allylic position on the olefin lead to substantially decreased activation barriers, an effect observed exclusively in the presence of hydrogen bond interactions between the substrate and the attacking DMDO molecule. To better understand the mechanism of the epoxidation of olefins, we report here our comparative study on the reactivity of primary and quaternary allylic and homoallylic alkenylammonium salts with DMDO (**1b**) and *m*-CPBA (**2**). In this study, the stereochemical outcome of the epoxidation of the cyclic quaternary allylic salt (2-cyclohexenyl)trimethylammonium *p*-chlorobenzenesulfonate (**5a**$^+$) with DMDO (**1b**) and *m*-CPBA (**2**) as well as the epoxidation rate constants for the reaction of allylic and homoallylic primary and quaternary ammonium salts **3aH**$^+$, *cis*-3-hexenylammonium *p*-chlorobenzenesulfonate (**3bH**$^+$), **5a**$^+$, and (*cis*-3-hexenyl)-trimethylammonium *p*-chlorobenzenesulfonate (**5b**$^+$) were determined.

## Results

**Determination of Stereoselectivity in the Epoxidation of the Quaternary Ammonium Salt 5a$^+$.** The reaction of **5a**$^+$ with DMDO (**1b**) and *m*-CPBA (**2**) gave a mixture of the stereoisomeric epoxides *syn*- and *anti*-**6a**$^+$.

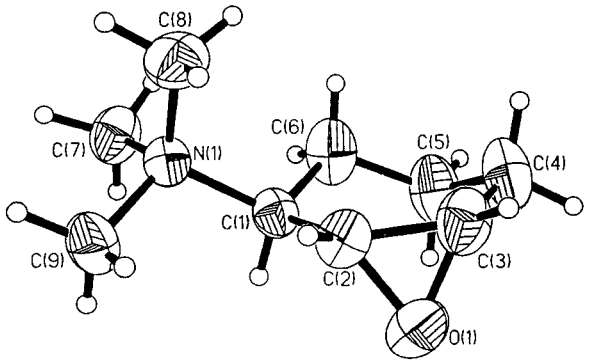
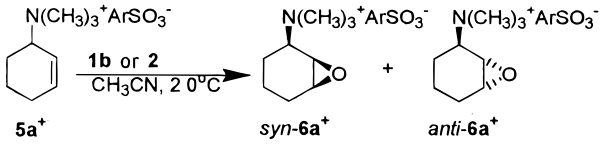



**Figure 2.** X-ray structure of compound *anti*-**6a**$^+$ showing the *trans* stereochemistry. The anion has been omitted for simplicity. Displacement ellipsoids are drawn at the 50% probability level.

**Scheme 3**




| | time | conversion % | *syn*-**6a**$^+$ | *anti*-**6a**$^+$ |
|---|---|---|---|---|
| **1b** | 48 h | 100 | 20 | 80 |
| **2** | 18 d | 37 | 50 | 50 |

The *syn*/*anti* ratio was 1:4 in the oxidation with DMDO (**1b**) (Scheme 3). Crystallization of the crude reaction mixture from acetonitrile enabled the isolation of pure *anti*-**6a**$^+$, the structure of which was determined by X-ray diffraction and $^1$H and $^{13}$C NMR analyses (Figure 2). The *syn*/*anti* ratio and the conversion of **5a**$^+$ were determined by $^1$H NMR analysis of the crude reaction mixture by integration of the peak areas corresponding to the methylammonium groups, which show different chemical shift values ($\delta$ **5a**$^+$ = 3.00 ppm, $\delta$ *syn*-**6a**$^+$ = 3.13 ppm and $\delta$ *anti*-**6a**$^+$ = 3.16 ppm). The $^1$H NMR spectrum of the epoxide *anti*-**6a**$^+$ shows unresolved multiplets at $\delta$ = 3.34 and 3.41 ppm corresponding to the epoxide H(2) and H(3) hydrogen atoms. The signal corresponding to H(1) appears at $\delta$ = 3.54 ppm and is coupled to the vicinal methylene protons ($J$ = 11.5 Hz and $J$ = 5.9 Hz) but is not coupled to the epoxide H(2) hydrogen. In the case of the epoxide *syn*-**6a**$^+$, $^1$H NMR analysis of the crude reaction mixture corresponding to epoxidation with DMDO (**1b**) only gives a clear view of the H(1) hydrogen, which appears downfield ($\delta$ = 3.85 ppm), coupled to H(2). The signals corresponding to H(2) and H(3) overlap signals corresponding to the isomer *anti*-**6a**$^+$ and could not be assigned.

The reaction of the allylic quaternary ammonium salt **5a**$^+$ with *m*-CPBA (**2**) was extremely slow. After 18 days under our usual reaction conditions, only 55% conversion of peracid and 37% conversion of substrate could be attained. In this case, isolation of the epoxides could not be achieved, but NMR analysis of the crude mixture revealed a *syn*-**6a**$^+$/*anti*-**6a**$^+$ ratio of ca. 1:1, indicating that the epoxidation with peracid is not selective.

**Kinetic Study of the Epoxidation of Primary and Quaternary Allylic and Homoallylic Alkenylammonium Salts with DMDO (1b) and *m*-CPBA (2).** The

(3) (a) Hovejda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (b) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63. (c) Kocovsky, P.; Stary, F. *J. Org. Chem.* **1990**, *55*, 3236.

(4) Miaskiewicz, K.; Smith, D. A. *J. Am. Chem. Soc.* **1998**, *120*, 1872.

kinetics[5] of the epoxidation of olefins with dioxiranes and peracids have been widely studied, and it is well established that these are second-order reactions, first-order with regard to alkene and peroxide. It is expected that the epoxidation of alkenylammonium salts obeys a similar kinetic law. However, the presence of an ionic functional group in the substrate in the latter case complicates the kinetic study of the reaction. In the presence of solute−solute or solute−solvent electrostatic interactions, solute activity $a$ and concentration have different values, and the solution does not exhibit ideal behavior. The kinetic law of any reaction is related to the activities of the species involved, but not to their concentrations. However, when a reaction occurs between neutral species, they can be considered to exhibit near-ideal behavior in solution, and hence it is valid to approximate the value of the activity using the value of the concentration. When a reaction occurs between ions, this approximation cannot be used. Thus, for a second-order reaction,

$$v = ka_Aa_B = k_0f_Af_B[A][B] = k_{obs}[A][B] \qquad (1)$$

were $f_A$ is the activity coefficient of solute A and $k_{obs} = k_0f_Af_B$.

The epoxidation of alkenylammonium salts with dioxiranes requires the interaction of a cation and a neutral molecule, and weak ion−dipole electrostatic interactions preclude the approximation of ideal behavior. In this case, the use of the concentrations of the reagents instead of their activities would give values of $k_{obs}$ that would not be useful for a comparative study of the reactivity of different substrates or oxidants. It is difficult to determine activity coefficients since the electrostatic interactions depend on the solvation of the reagents, and this in turn depends on their structure and the ionic strength ($u$) of the solution. However, the approximation of Brönsted et al.[6] allows the determination of $k_0$ from the $k_{obs}$ values determined in solutions with different ionic strengths. For a general reaction (2), eq 3, where $b$ is a coefficient characteristic of the solute, predicts that the logarithm of the rate constant for a reaction between an ion and a neutral molecule is proportional to the ionic strength of the solution.[6a]

$$A + B \rightarrow [X]^{\ddagger} \rightarrow \text{products} \qquad (2)$$

$$\log k_{obs} = \log k_0 + (b_A + b_B - b_X)u \qquad (3)$$

This approximation is valid for dilute solutions which follow the Debye−Hückel law. In any case, the association of ions can affect the reaction rate in several ways, the most important of which is lowering of the ionic strength of the solution and modification of electrostatic solute−solute or solute−solvent interactions.

On the basis of the above considerations, a kinetic study of reactions between ionic substrates and neutral reagents can be performed by measuring the rate constant $k_{obs}$ at different ionic strengths. If log $k_{obs}$ is plotted against $u$, according to eq 3, log $k_0$ can be obtained.

In the epoxidation of alkenylammonium salts **3aH**$^+$, **3bH**$^+$, **5a**$^+$, and **5b**$^+$ with DMDO (**1b**) and *m*-CPBA (**2**), these approximations could be successfully applied. The measurements were performed with dilute acetonitrile solutions of salts **3H**$^+$ and **5**$^+$ to minimize the formation of ion pairs. Tetramethylammonium perchlorate and tetramethylammonium *p*-chlorobenzenesulfonate were selected to modify the solution ionic strength, since both are quite soluble in acetonitrile and inert toward oxidation. Absolute oxidation rates were measured at 20 °C under second-order conditions with the same initial concentrations of alkenylammonium salt and peroxide; the consumption of peroxide was determined by iodometric titration of a measured volume of the reaction mixture. The ionic strength of the solutions was fixed in each experiment by using different initial concentrations of the additional quaternary ammonium salt (ca. 0.001−0.015 M). A DMDO (**1b**) ca. 0.08 M acetone solution or a *m*-CPBA (**2**) ca. 0.1 M acetonitrile solution, previously thermostated, was poured at time zero over a solution containing the corresponding alkenylammonium salt (**3H**$^+$ or **5**$^+$) and the additional quaternary ammonium salt ($Me_4NClO_4$ or $Me_4NArSO_3$) in acetonitrile. Aliquots of this solution were taken and titrated periodically by iodometry. Linear plots of 1/[S] against time were obtained in each experiment according to the kinetic equation $1/[S] = 1/[S]_0 + k_{obs}t$, with a correlation coefficient of $\gamma = 0.99$ and at up to over 70% conversion of peroxide. The values of $k_{obs}$ ($M^{-1}$ $s^{-1}$) were determined from the slope of the correlation line. The results are summarized in Table 1. Linear diagrams with good correlation coefficients that allow us to calculate $k_0$ ($M^{-1}$ $s^{-1}$) were obtained when log $k_{obs}$ was plotted against the ionic strength ($u$) of the solution according to the equation $\log k_{obs} = \log k_0 + bu$ (12) (see Figures 3 and 4). The results are shown in Table 1. The linear correlation found between log $k_{obs}$ and the ionic strength ($u$) indicates that the system follows the Debye−Hückel law under the reaction conditions used. Moreover, the same $k_0$ value was found under different ionic strengths with any of the tetramethylammonium salts added, thus validating the approximation used. The salt effect ($b$) is not easy to rationalize since it is a composite of several simultaneous factors (see eq 3 and Table 1). Moreover, the alkenylammonium salt will experiment anion exchange with the added salt and hence different aggregate species will participate in the reactions and different charge distributions will appear in the transition states.

A kinetic study of the oxidation of **5a**$^+$ with *m*-CPBA (**2**) could not be performed due to the long reaction time. Measurement of the decrease in the peracid concentration was impaired in this case by decomposition of the peracid at room temperature over time.

## Discussion

From the above results, different trends can be considered for the stereochemical and kinetic outcome of the epoxidation of primary and quaternary alkenylammonium salts with either DMDO (**1b**) or *m*-CPBA (**2**). On one hand, a high *syn*-diastereoselectivity is achieved in the epoxidation of the primary allylic salt **3aH**$^+$, while the quaternary allylic ammonium salt **5a**$^+$ gives equimolecular (*m*-CPBA) or predominantly *anti* (DMDO) mix-

(5) (a) Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311. (b) Baumstark, A. L.; Vasquez, P. C.; *J. Org. Chem.* **1988**, *53*, 3437. (c) Murray, R. W.; Gu, D. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2203.

(6) (a) Frost, A. A.; Pearson, R. G. In *Kinetics and Mechanism*, 2nd ed.; J. Wiley & Sons: New York, 1961; p 147ff. (b) King, E. L. In *How Chemical Reactions Occur*; W. A. Benjamin, Inc.: New York, 1963. (c) Laider, K. L. In *Chemical Kinetics*, 2nd ed.; McGraw-Hill Inc.: New York, 1965; Chapter 9.

**Table 1. Kinetic Measurement of the Oxidation of Allylic and Homoallylic Alkenyl *Ammonium* Salts $3H^+$ and $5a^+$ with DMDO (1b) and *m*-CPBA (2) in the Presence of $Me_4N$-*p*-$ClC_6H_4SO_3$ or $Me_4NClO_4$ in Acetonitrile at 20.0 ± 0.1 °C**

| run | salt | $Me_4NX$ | peroxide | $[S]_0 \times 10^2$ (M) | $[Me_4NX]_0 \times 10^2$ (M) | $u \times 10^2$ (M) | $k_{obs} \times 10^2$ ($M^{-1}$ $s^{-1}$) | $k_0 \times 10^2$ ($M^{-1}$ $s^{-1}$) | *b* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **3aH**$^+$ | $ArSO_3^-$ | DMDO | 0.50 | 0.52 | 1.02 | 3.902 | | |
| 2 | **3aH**$^+$ | $ArSO_3^-$ | DMDO | 0.50 | 1.03 | 1.53 | 3.974 | | |
| 3 | **3aH**$^+$ | $ArSO_3^-$ | DMDO | 0.50 | 1.50 | 2.00 | 4.070 | 3.6 ± 0.2 | 2.6 ± 0.6 |
| 4 | **3aH**$^+$ | $ArSO_3^-$ | DMDO | 0.50 | 1.83 | 2.33 | 4.244 | | |
| 5 | **3aH**$^+$ | $ClO_4^-$ | DMDO | 0.50 | 0.51 | 1.01 | 3.790 | | |
| 6 | **3aH**$^+$ | $ClO_4^-$ | DMDO | 0.52 | 1.03 | 1.55 | 3.880 | | |
| 7 | **3aH**$^+$ | $ClO_4^-$ | DMDO | 0.52 | 1.96 | 2.48 | 4.020 | 3.6 ± 0.4 | 2 ± 1 |
| 8 | **3aH**$^+$ | $ClO_4^-$ | DMDO | 0.50 | 2.49 | 2.99 | 4.087 | | |
| 9 | **3aH**$^+$ | $ClO_4^-$ | DMDO | 0.52 | 3.04 | 3.56 | 4.181 | | |
| 10 | **3aH**$^+$ | $ArSO_3^-$ | *m*-CPBA | 0.50 | 0.01 | 0.51 | 0.969 | | |
| 11 | **3aH**$^+$ | $ArSO_3^-$ | *m*-CPBA | 0.50 | 0.48 | 0.98 | 0.982 | 0.942 ± 0.006 | 2.0 ± 0.2 |
| 12 | **3aH**$^+$ | $ArSO_3^-$ | *m*-CPBA | 0.50 | 0.98 | 1.48 | 1.009 | | |
| 13 | **3aH**$^+$ | $ClO_4^-$ | *m*-CPBA | 0.50 | 0.18 | 0.68 | 0.917 | | |
| 14 | **3aH**$^+$ | $ClO_4^-$ | *m*-CPBA | 0.50 | 0.50 | 1.00 | 0.613 | 0.942 ± 0.009 | -1.5 ± 0.4 |
| 15 | **3aH**$^+$ | $ClO_4^-$ | *m*-CPBA | 0.50 | 1.09 | 1.59 | 0.890 | | |
| 16 | **5a**$^+$ | $ArSO_3^-$ | DMDO | 0.50 | 0.52 | 1.02 | 0.376 | | |
| 17 | **5a**$^+$ | $ArSO_3^-$ | DMDO | 0.50 | 1.00 | 1.49 | 0.391 | 0.27 ± 0.04 | 12 ± 5 |
| 18 | **5a**$^+$ | $ArSO_3^-$ | DMDO | 0.50 | 1.50 | 2.00 | 0.500 | | |
| 19 | **5a**$^+$ | $ClO_4^-$ | DMDO | 0.50 | 0.50 | 0.99 | 0.281 | | |
| 20 | **5a**$^+$ | $ClO_4^-$ | DMDO | 0.50 | 1.01 | 1.50 | 0.291 | 0.27 ± 0.01 | 2 ± 1 |
| 21 | **5a**$^+$ | $ClO_4^-$ | DMDO | 0.50 | 1.48 | 1.97 | 0.294 | | |
| 22 | **3bH**$^+$ | $ArSO_3^-$ | DMDO | 0.50 | 0.49 | 0.93 | 83.64 | | |
| 23 | **3bH**$^+$ | $ArSO_3^-$ | DMDO | 0.50 | 1.00 | 1.50 | 92.60 | 71 ± 2 | 7.5 ± 0.7 |
| 24 | **3bH**$^+$ | $ArSO_3^-$ | DMDO | 0.50 | 1.52 | 2.02 | 99.87 | | |
| 25 | **3bH**$^+$ | $ClO_4^-$ | DMDO | 0.50 | 0.49 | 0.99 | 78.30 | | |
| 26 | **3bH**$^+$ | $ClO_4^-$ | DMDO | 0.51 | 1.01 | 1.52 | 81.72 | 71.1 ± 0.8 | 4.1 ± 0.4 |
| 27 | **3bH**$^+$ | $ClO_4^-$ | DMDO | 0.50 | 1.47 | 1.97 | 86.02 | | |
| 28 | **3bH**$^+$ | $ArSO_3^-$ | *m*-CPBA | 0.50 | 0.51 | 0.56 | 0.785 | | |
| 29 | **3bH**$^+$ | $ArSO_3^-$ | *m*-CPBA | 0.50 | 0.97 | 1.47 | 0.794 | 0.77917 ± 0.00005 | 0.571 ± 0.002 |
| 30 | **3bH**$^+$ | $ArSO_3^-$ | *m*-CPBA | 0.50 | 1.58 | 2.08 | 0.801 | | |
| 31 | **3bH**$^+$ | $ClO_4^-$ | *m*-CPBA | 0.50 | 1.02 | 1.52 | 0.652 | | |
| 32 | **3bH**$^+$ | $ClO_4^-$ | *m*-CPBA | 0.50 | 1.60 | 2.10 | 0.606 | 0.76 ± 0.01 | −4.7 ± 0.4 |
| 33 | **3bH**$^+$ | $ClO_4^-$ | *m*-CPBA | 0.50 | 0.49 | 0.99 | 0.068 | | |
| 34 | **5b**$^+$ | $ArSO_3^-$ | DMDO | 0.50 | 0.10 | 0.60 | 20.45 | | |
| 35 | **5b**$^+$ | $ArSO_3^-$ | DMDO | 0.50 | 0.49 | 0.99 | 21.33 | 19.05 ± 0.09 | 5.0 ± 0.1 |
| 36 | **5b**$^+$ | $ArSO_3^-$ | DMDO | 0.50 | 1.07 | 1.57 | 22.88 | | |
| 37 | **5b**$^+$ | $ClO_4^-$ | DMDO | 0.50 | 0.52 | 1.02 | 20.15 | | |
| 38 | **5b**$^+$ | $ClO_4^-$ | DMDO | 0.50 | 1.01 | 1.51 | 20.47 | 19.1 ± 0.3 | 2.0 ± 0.4 |
| 39 | **5b**$^+$ | $ClO_4^-$ | DMDO | 0.50 | 1.48 | 1.98 | 21.09 | | |
| 40 | **5b**$^+$ | $ArSO_3^-$ | *m*-CPBA | 0.50 | 0.11 | 0.61 | 0.933 | | |
| 41 | **5b**$^+$ | $ArSO_3^-$ | *m*-CPBA | 0.50 | 0.51 | 1.01 | 0.100 | 0.0845 ± 0.004 | 7.2 ± 0.2 |
| 42 | **5b**$^+$ | $ArSO_3^-$ | *m*-CPBA | 0.50 | 0.99 | 1.49 | 0.108 | | |
| 43 | **5b**$^+$ | $ClO_4^-$ | *m*-CPBA | 0.50 | 0.13 | 0.63 | 0.087 | | |
| 44 | **5b**$^+$ | $ClO_4^-$ | *m*-CPBA | 0.50 | 0.54 | 1.04 | 0.089 | 0.0847 ± 0.0002 | 2.1 ± 0.1 |
| 45 | **5b**$^+$ | $ClO_4^-$ | *m*-CPBA | 0.50 | 1.05 | 1.55 | 0.091 | | |

tures of diastereomers. Moreover, the rate constant $k_0$ for the epoxidation of the primary allylic ammonium salt **3aH**$^+$ is greater than that corresponding to the epoxidation of its quaternary counterpart **5a**$^+$. The same trend is observed, although to a lesser extent, in the epoxidation of the homoallylic ammonium salts **3bH**$^+$ and **5b**$^+$. The results concerning the stereochemistry of the epoxidation of **3aH**$^+$ and **5a**$^+$ are significant. It is well-known that reactions with dioxiranes show a high steric demand. Therefore, we would expect that epoxidation of the primary allylic salt **3aH**$^+$ with DMDO (**1b**) would yield mainly the *anti* epoxide, as does the quaternary allylic salt **5a**$^+$. To account for the different stereochemical outcomes of these reactions, one could invoke an increase in ion−dipole interactions between the ammonium group and DMDO (**1b**) to address the formation of the epoxide to the *syn* diastereoface in the case of the oxidation of **3aH**$^+$ and argue an increase in steric hindrance due to the bulkier quaternary ammonium group in **5a**$^+$ to justify the formation of the *anti* epoxide in this case. However, our kinetic study shows a value of $3.6 \times 10^{-2}$ $M^{-1}$ $s^{-1}$ for the rate constant $k_0$ in the epoxidation of **3aH**$^+$ with DMDO (**1b**), while $k_0$ is only $0.27 \times 10^{-2}$ $M^{-1}$ $s^{-1}$ in the reaction of **5a**$^+$ [$k_0$(**3aH**$^+$)$_{DMDO}$/$k_0$(**5a**$^+$)$_{DMDO}$ = 13.3], indicating that the primary ammonium group not only exerts a directing effect in the diastereoselection of the dioxirane attack but also accelerates the reaction rate; i.e., it stabilizes the transition state leading to the *syn*-epoxide from **3aH**$^+$. A similar, yet smaller, effect on the reaction rate is observed in the epoxidation of primary (**3bH**$^+$) and quaternary (**5b**$^+$) homoallylic ammonium salts; in this case, the ratio of $k_0$(**3bH**$^+$)$_{DMDO}$/$k_0$(**5b**$^+$)$_{DMDO}$ is 3.72. The stereochemistry of the epoxidation of the cyclic alkenylammonium salts as well as the acceleration of the reaction by the primary ammonium group strongly suggests the involvement of a hydrogen bridge between the ammonium protons and the dioxirane oxygen atom that is believed to develop a negative charge[4,5c] in the epoxidation transition state (Figure 1). The rate constants in the epoxidation of primary and quaternary homoallylic ammonium salts are on the same order of magnitude. In contrast, primary allylic ammonium salts react more than 10 times faster than their quaternary counterparts. This difference can be attributed to the lower reactivity of the allylic C=C double bond induced by the proximity of the deactivating ammonium group. Moreover, formation of the hydrogen bond requires a six-membered ring arrangement in the case of allylic salts,

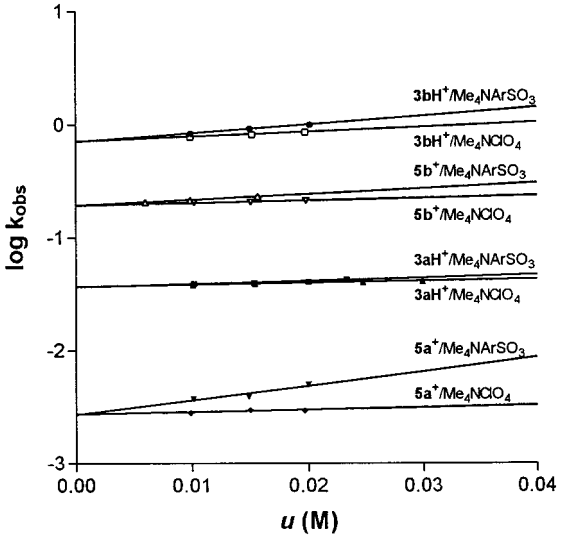



**Figure 3.** Plot of log $k_{obs}$ vs ionic strength ($u$) in the epoxidation of alkenylammonium salts with DMDO (**1b**) in acetonitrile al 20 °C. Ionic strength modified by addition of tetramethylammonium salts as stated. For numerical data, see Table 1.

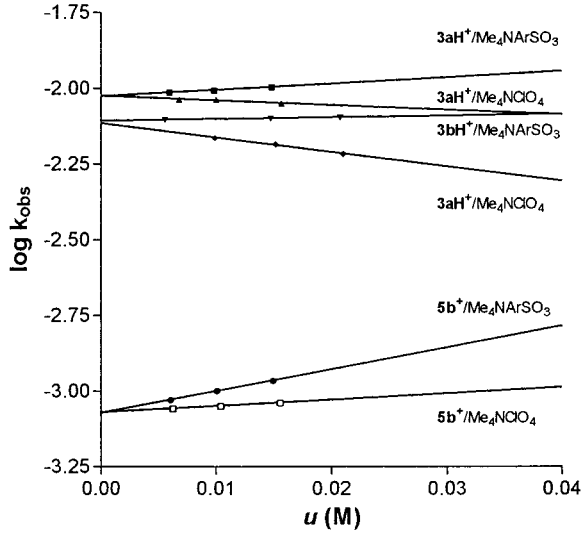



**Figure 4.** Plot of log $k_{obs}$ vs ionic strength ($u$) in the epoxidation of alkenylammonium salts with *m*-CPBA (**2**) in acetonitrile al 20 °C. Ionic strength modified by addition of tetramethylammonium salts as stated. For numerical data, see Table 1.

and a less-favorable seven-membered ring for homoallylic salts. Entropic factors also do not favor the creation of a hydrogen bond in the case of homoallylic salts due to the linear nature of **3bH**$^+$. Overall, the effect of the hydrogen bond on the stability of the transition state must be weaker for homoallylic ammonium salts than for allylic ammonium salts.

The steric course of the epoxidation of allylammonium salts **3aH**$^+$ and **5a**$^+$ with *m*-CPBA (**2**) is in good agreement with previous reports concerning the epoxidation of olefins carrying substituents with acidic hydrogen atoms.[3] The high diastereoselectivity achieved in the epoxidation of **3aH**$^+$ is in contrast with the lack of selectivity in the epoxidation of **5a**$^+$. The steric demand of the transition state for epoxidation with *m*-CPBA (**2**) is less than that with DMDO (**1b**) (see Figure 1), and therefore the epoxidation with *m*-CPBA (**2**) can proceed on the *syn* stereoface even in the presence of the bulky quaternary ammonium group. On the other hand, the primary ammonium salt **3aH**$^+$ is much more reactive than its quaternary counterpart **5a**$^+$, and this is particularly interesting considering that the electron-withdrawing effects of the ammonium and tetramethylammonium groups are comparable. However, while the epoxidation of **3aH**$^+$ is a relatively fast reaction ($k_{0,m-CPBA} = 0.942 \times 10^{-2}$ M$^{-1}$ s$^{-1}$), the reaction of the peracid with **5a**$^+$ is so slow that it competes with its thermal decomposition at room temperature. These results strongly suggest that the primary ammonium group exerts a directing effect on the attack of the peroxide and may stabilize the transition state leading to epoxidation.

The rate of the epoxidation of homoallylic ammonium salts **3bH**$^+$ and **5b**$^+$ with *m*-CPBA (**2**) follows the same trend observed for allylic salts; i.e., the primary salt ($k_0 = 0.7 \times 10^{-2}$ M$^{-1}$ s$^{-1}$) reacts faster than the quaternary salt ($k_0 = 0.0845 \times 10^{-2}$ M$^{-1}$ s$^{-1}$). As observed in the epoxidation with DMDO (**1b**), the deactivating effect of the ammonium group is in this case less than that in the oxidation of allylic ammonium salts [$k_0$(**3bH**$^+$)$_{m-CPBA}$/$k_0$(**5b**$^+$)$_{m-CPBA}$ = 9.0], indicating that the deactivating effect of the ammonium group decreases with the distance to the C=C double bond. In contrast, while epoxidation of the primary allylic ammonium salt [$k_0$(**3aH**$^+$)$_{m-CPBA}$ = 0.942 M$^{-1}$ s$^{-1}$] proceeds faster than that of the primary homoallylic salt [$k_0$(**3bH**$^+$)$_{m-CPBA}$ = 0.76 M$^{-1}$ s$^{-1}$], the rates of the epoxidation of the quaternary salts follow the expected trend. These observations clearly show that in the epoxidation with *m*-CPBA (**2**) the hydrogen bond has less of an effect in the case of the homoallylic salt. Several possible factors can explain this behavior, such as the different charge separation in the transition state for each substrate or the entropic factor associated with the restriction of the degrees of freedom of the homoallylic substrate in the transition state due to formation of the hydrogen bond, a situation that does not exist in the case of a cyclic allylic substrate bearing an ammonium group in a pseudoequatorial orientation.

In conclusion, the epoxidation rate enhancement observed in the reaction of allylic and homoallylic primary ammonium salts if compared with their quaternary counterparts as well as the *syn* diastereoselectivity observed clearly support the involvement of a hydrogen bond interaction between the acidic substituent and the peroxide oxygen in the transition state.

## Experimental Section

**General**. All solvents and reagents were purified by standard procedures, and solvents were freshly distilled prior to use. Acetonitrile was previously treated with $Na_2CO_3$ at room temperature for 24 h and used immediately after distillation over $CaH_2$. Acetone DMDO (**1b**) solutions were dried over $MgSO_4$ prior to use. Dilute solutions of DMDO (**1b**) are not known to decompose violently, but the usual precautions for handling peroxides should be applied, including the use of a shield. All reactions should be performed in a fume hood to avoid exposure to the volatile oxidant.[7] Tetramethylammonium *p*-chlorobenzoate was prepared by anion exchange by treating the corresponding chloride with silver(I) *p*-chlorobenzoate. Salts **3aH**$^+$ and **3bH**$^+$ were prepared as described.[2b]

(7) Crandall, J. K. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; Vol. 3, pp 2061−2064

**X-ray** data collection was carried out using a Siemens P4 single-crystal diffractometer controlled by XSCANS version 2.1[8] software. Omega scans were used for data collection, at speeds of 10−60 deg per minute. Three standard reflections were measured after every 97 reflections; no systematic decrease in standard intensities was observed. Data reduction included profile fitting and an empirical absorption correction; maximum and minimum transmissions, 0.869 and 0.834.

The structure was determined by Patterson methods and initially refined using the SHELXTL PC version 5.1[9] software package, which was also used for the figure. All 22 hydrogen atoms appeared in a difference map, and each was introduced in an ideal position, riding on the atom to which it was bonded; each was refined with an isotropic temperature factor 20% greater than that of the other ridden atom. All other atoms were refined with anisotropic thermal parameters. Final refinement on F2 was carried out using SHELXL 93.[10]

**Iodometric Titration of DMDO (1b) and *m*-CPBA (2).** To a 100-mL Erlenmeyer flask containing 10 mL of 10% aqueous KI and 5 mL of a 2:3 mixture of acetone and acetic acid cooled at 0 °C was added an aliquot (usually 0.1 mL) of a solution of DMDO (**1b**) or *m*-CPBA (**2**) in the appropriate solvent. $I_2$ was formed immediately and was titrated with an aqueous $Na_2S_2O_3$ solution (usually ca. 0.01 N).[11]

**Tetramethylammonium *p*-Chlorobenzenesulfonate**. To a stirred suspension of $Ag_2O$ (2.32 g, 10 mmol) in water was added *p*-chlorobenzenesulfonic acid (4.40 g, 20 mmol) slowly at room temperature to give a white precipitate of silver *p*-chlorobenzenesulfonate. After 1 h of vigorous stirring, a water solution (20 mL) of tetramethylammonium chloride (2.19 g, 20 mmol) was added and a white precipitate of AgCl appeared; the stirring was continued for one additional hour and the solid was then filtered out, and the resulting clear solution was evaporated under vacuum to yield a white solid which was crystallized from acetonitrile and characterized as tetramethylammonium *p*-chlorobenzenesulfonate (3.29 g, 62%): $^1$H NMR ($D_2O$, 250 MHz) $\delta$ 3.13 (s, 12H), 7.50 (d, $J$ = 8.6 Hz, 2H), 7.72 (d, $J$ = 8.6 Hz, 2H); $^{13}$C NMR ($D_2O$, 62.5 MHz) $\delta$ 56.17, 56.23, 56.29, 128.08, 130.08, 135.15, 148.95.

**2-Cyclohexenyltrimethylammonium *p*-Chlorobenzenesulfonate (5a$^+$)**. To a round-bottom flask equipped with a thermometer and a condenser (−30 °C) containing 11.8 g (200 mmol) of trimethylamine cooled to −40 °C was added a solution of 6.44 g (40 mmol) of 3-bromocyclohexene in 30 mL of $CH_2Cl_2$ dropwise under stirring. The reaction mixture was allowed to warm to rt and maintained for 6 h. The excess trimethylamine was distilled off, and the resulting white solid was washed with cold $CH_2Cl_2$ and dried under vacuum to give 7.30 g (83% yield) of 2-cyclohexenyltrimethylammonium bromide. To a suspension of 2.32 g (10 mmol) of $Ag_2O$ in ca. 40 mL of water at rt was added 3.85 g (20 mmol) of *p*-chlorobenzenesulfonic acid portionwise. After 1 h under vigorous stirring, a solution of 4.40 g (20 mmol) of 2-cyclohexenyltrimethylammonium bromide in 20 mL of water was added. After 1 h under vigorous stirring, the mixture was filtered and the water was distilled off under reduced pressure. The resulting solid was recrystallized from $CH_3CN$ to give 4.65 g (70% yield) of 2-cyclohexenyltrimethylammonium *p*-chlorobenzenesulfonate (**5a**$^+$): $^1$H NMR ($D_2O$, 250 MHz) $\delta$ 1.60−1.85 (m, 3H), 2.05 (m, 2H), 2.15 (m, 1H), 3.00 (s, 9H), 4.04 (m, 1H), 5.79 (m, 1H), 6.29 (m, 1H), 7.50 (d, $J$ = 8.4 Hz, 2H), 7.72 (d, $J$ = 8.5 Hz, 2H); $^{13}$C NMR ($D_2O$, 62.5 MHz) $\delta$ 16.73, 19.29, 20.36, 46.76, 46.82, 46.89, 63.12, 114.59, 123.61, 125.60, 135.31, 137.57, 148.29.

**(*cis*-3-Hexenyl)trimethylammonium *p*-Chlorobenzenesulfonate (5b$^+$).** To a round-bottom flask equipped with a thermometer and a condenser (−30 °C) containing 5.8 g (100 mmol) of trimethylamine cooled to −15 °C was added a solution of 3.43 g (10 mmol) of *cis*-3-hexenyl *p*-chlorobenzenesulfonate in 30 mL of $CH_2Cl_2$ dropwise under stirring. The reaction mixture was allowed to react at this temperature for 24 h, and the appearance of a white precipitate was observed. Then the excess trimethylamine and solvent were distilled off under vacuum, and the resulting white solid was washed with ether, filtered, and crystallized from $CH_3CN$. It was characterized as (*cis*-3-hexenyl)trimethylammonium *p*-chlorobenzenesulfonate (**5b**$^+$), 2.90 g (87% yield): $^1$H NMR ($CDCl_3$, 250 MHz) $\delta$ 0.95 (t, $J$ = 7.47 Hz, 3H), 2.0(m, 2H), 2.45 (q, $J$ = 7.45 Hz, 2H), 3.30 (bs, 9H), 3.42 (t, $J$ = 7.40 Hz, 2H), 5.15 (m, 1H), 5.52 (m,1H), 7.31 (d, $J$ = 8.45 Hz, 2H), 7.78 (d, $J$ = 8.45 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) $\delta$ 13.87, 20.63, 21.50, 53.11, 66.0, 121.12, 127.36, 128.20, 135.00, 136.32, 146.00.

**2,3-Epoxycyclohexyltrimethylammonium *p*-Chlorobenzenesulfonate (6a$^+$). Procedure A.** To a stirred solution of 2-cyclohexenyltrimethylammonium *p*-chlorobenzenesulfonate (66.4 mg, 0.2 mmol) in 3 mL of $CH_3CN$ at 20 °C was added an aliquot of a 0.08 M acetone solution of DMDO (**1b**) (5 mL, 0.4 mmol). The reaction was stirred at rt for 48 h, at which point iodometric titration showed that the peroxide was consumed. The solvent was removed under vacuum, and the solid residue was analyzed by $^1$H NMR, which showed total conversion of the starting material into the corresponding 2,3-epoxycyclohexyltrimethylammonium *p*-chlorobenzenesulfonate (**6a**$^+$) as a diastereomeric mixture (*syn*/*anti* 20:80): $^1$H NMR ($CD_3CN$, 250 MHz) $\delta$ 1.2−1.5 (m, 2H), 1.5−1.9 (m, 2.5H), 1.9−2.1 (m, 1.5H), 3.14 (s, 1.8H), 3.16 (s, 7.2H), 3.32 (m, 1H) 3.44 (d, 0.8H), 3.53 (m, 1H), 3.90 (dt, $J$ = 10.6, 5.2, 1.6 Hz, 0.2H); $^{13}$C NMR ($CD_3CN$, 62.5 MHz) $\delta$ 15.59, 19.85, 20.73, 21.95, 22.10, 23.69, 49.45, 50.09, 52.00, 52.07, 52.12, 52.48, 52.54, 52.60, 53.93, 54.57, 70.01, 70.06, 70.11, 71.93, 71.99, 72.54, 128.31, 128.89, 135.11, 147.22. Recrystallization from $CH_3CN$ enabled us to isolate the *anti* isomer, which was fully characterized by X-ray diffraction. $^1$H NMR ($CD_3CN$, 250 MHz): $\delta$ 1.31 (m, 2H), 1.6−1.8 (m, 2H), 1.95 (m, 2H), 3.22 (d, $J$ = 1.6 Hz, 1H), 3.44 (d, $J$ = 1.7 Hz, 1H), 3.53 (dd, $J$ = 11.5, 6.0 Hz, 1H). $^1$H NMR ($CD_3CN$, 250 MHz): $\delta$ 15.59, 21.95, 23.68, 50.09, 52.00, 52.07, 52.13, 52.94, 70.03, 70.07, 70.11, 128.31, 128.89, 135.11, 147.22.

**Procedure B**. To a stirred solution of 2-cyclohexenyltrimethylammonium *p*-chlorobenzenesulfonate (166 mg, 0.5 mmol) in 9 mL of $CH_3CN$ at 20 °C was added an aliquot of a 0.5 M acetonitrile solution of *m*-CPBA (**2**) (2 mL, 1.0 mmol) dropwise. After 18 days at rt, the peroxidic titer showed 55% consumption of the peroxide. The solvent was removed under vacuum, and the crude reaction product was analyzed by $^1$H NMR. The spectroscopic analysis showed 37% conversion of the substrate to give the corresponding 2,3-epoxycyclohexyltrimethylammonium *p*-chlorobenzenesulfonate as a diastereomeric mixture (*syn*/*anti* 50:50).

***cis*-3,4-Epoxyhexyltrimethylammonium *p*-Chlorobenzenesulfonate (6b$^+$).** To a stirred solution of (*cis*-3-hexenyl)-trimethylammonium *p*-chlorobenzenesulfonate **(5b$^+$)** (68.0 mg, 0.2 mmol) in 5 mL of $CH_3CN$ at 0 °C was added an aliquot of a 0.08 M acetone solution of DMDO (**1b**) (2,5 mL, 0.2 mmol). The mixture was allowed to stand under stirring overnight at which point iodometric titration showed that the peroxide was consumed. The solvent was removed under vacuum, and the solid residue was analyzed by $^1$H NMR, which showed total conversion of the starting material into the corresponding *cis*-3,4-epoxyhexenyltrimethylammonium *p*-chlorobenzenesulfonate (**6b**$^+$): $^1$H NMR ($CDCl_3$, 250 MHz) $\delta$ 1.00 (t, $J$ = 7.38 Hz, 3H), 1.48 (m, $J$ = 7.34 Hz, 2H), 1.75 (m, 1H), 2.25 (m, 1H), 2.90 (m, 2H), 3.28 (bs, 9H), 3.60 (m,1H), 3.85 (m, 1H), 7.33 (d, $J$ = 6,69 Hz, 2H), 7.79 (d, $J$ = 6.55 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 62.5 Mz) $\delta$ 10.50, 21.08, 22.72, 53.25, 53.45, 53.65, 58.61, 64.30, 127.35, 128.26, 135.30, 145.10.

**Kinetic Measurements. General Procedure.** The absolute reaction rates for the oxidation of alkenylammonium salts **3H**$^+$ and **5**$^+$ with DMDO (**1b**) and *m*-CPBA (**2**) in acetonitrile

(8) Siemens Industrial Automation Incorporated Analytical Instrumentation Business Unit 6300 Enterprise Lane, Madison, WI 52719-1173.

(9) Siemens Analytical X-Ray Instruments, Inc., 6300 Enterprise Lane, Madison, WI 52719-1173.

(10) Sheldrick, G. M. SHELXL-93, program for the refinement of crystal structures, University of Göttingen, Germany, 1993.

(11) (a) Adam, W.; Asensio, G.; Curci, R.; Gonzalez-Nuñez, M. E.; Mello, R. *J. Am. Chem. Soc.* **1992**, *114*, 8345. (b) Kolthoff, I. M. In *Treatise on Analytical Chemistry*; John Wiley & Sons: New York, 1978.

were determined in a thermostatic bath at 20.0 ± 0.1 °C under second-order conditions, using concentrations of peroxide and substrate of ca. 0.005 M. The ionic strength of the solutions was adjusted using the quaternary ammonium salts $Me_4NArSO_3$ or $Me_4NClO_4$ in initial concentrations of 0.001−0.005 M. To a solution of the ammonium salt **3H**$^+$ or **5**$^+$ (0.155 mmol) and $Me_4NArSO_3$ or $Me_4NClO_4$ (0.031−0.465 mmol) in acetonitrile (ca. 29 mL) that had been thermostated at 20.0 ± 0.1 °C was added an aliquot of a ca. 0.08 M acetone solution of DMDO (**1b**) (2.0 mL, 0.155 mmol) or a 0.08 M solution of *m*-CPBA (**2**) in acetonitrile (2.0 mL, 0.155 mmol) that had been previously thermostated at 20.0 ±0.1 °C. The final volume was ca. 31.0 mL, and the molar ratio of substrate:peroxide was 1:1. Peroxide consumption was monitored periodically by iodometric titration (2.0 mL aliquots). From the kinetic equation $1/[S_0] + k_{obs}t$, the plot of of 1/[S] vs $t$ allowed us to obtain the rate constant $k_{obs}$ ($M^{-1}$ $s^{-1}$) for each ionic strength $u$, where [S] is the remaining peroxide concentration. The plots were linear at up to 70% conversion of the peroxide. The plots of log $k_{obs}$ vs ionic strength $u$ were linear with good correlation coefficients. From the equation $\log k_{obs} = \log k_0 + bu$, the values of $k_0$ ($M^{-1}$ $s^1$) were extrapolated to ionic strength $u = 0$. The results are shown in Figures 3 and 4 and in Table 1.

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**Supporting Information Available:** X-ray structural information on *anti*-**6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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