Pure & Appl. Chem., Vol. 67, No. 5, pp. 811–822, 1995.
Printed in Great Britain.

Dioxirane oxidations: Taming the reactivity–selectivity principle

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Abstract: Dioxiranes (**1**), a new class of powerful oxidants, have been employed to carry out a variety of synthetically useful transformations. Dioxirane reactivity appears to be earmarked by the propensity for easy electrophilic O-atom transfer to nucleophilic substrates, as well as for O-insertion into "unactivated" hydrocarbon C-H bonds. For a number of substrates of varying electron-donor power, ranging from α,β-unsaturated carbonyls, to alkenes to sulfoxides to sulfides, the reactivity of dimethyldioxirane (**1a**) exceeds that of peroxybenzoic acid by a factor of the order of 10^2; upon increasing substrate nucleophilicity, kinetic data show that the selectivity is not diminished, and actually appears to be enhanced. Despite its exceptional reactivity, high regio- and stereoselectivities can be attained in oxyfunctionalizations at hydrocarbon C-H bonds using the powerful methyl-(trifluoromethyl)dioxirane (**1b**); this has been applied to accomplish remarkably high regio- and stereoselective epoxidations and oxyfunctionalizations of target molecules. In these reactions, stringent steric and stereoelectronic requirements for O-insertion seem to dictate selectivity; adoption of an FMO model provides a likely rationale.

INTRODUCTION

The stage for the extensive developments of dioxirane chemistry nowadays witnessed was set by the discovery, first reported in 1979 *(1a)*, that the reaction of simple ketones with potassium caroate $KHSO_5$ at a pH close to neutrality provides an easy access to dioxiranes (**1**). Kinetic, stereochemical and ^{18}O-labeling data stringently indicated the involvement of dioxiranes in these reactions *(1)*.

Later, the feat *(2a)* of isolation of a few dioxiranes from the caroate/ketone system allowed authentic representatives of this family of peroxides to become fully characterized spectroscopically *(2)*. Then, the availability of dioxiranes in the isolated as well as *in situ* form spurred an intensive utilization of these powerful oxidants to carry out a variety of synthetically useful oxidations under mild conditions *(3)*.

1

(**1a**: $R^1 = R^2 = CH_3$
1b: $R^1 = CH_3$; $R^2 = CF_3$)

Some of the established transformations *(3)* performed by dioxiranes are summarized by the rosette in Figure 1. These include the oxidation of chloride ion to the hypochlorite ion (transformation 1), of pyridine to its N-oxide (transformation 2), of sulfides to sulfoxides or of sulfoxides to sulfones (transformation 3), epoxidation of alkenes (transformation 4), and oxidation of alkynes (transformation 5); the latter reaction is envisaged to proceed via an oxirene intermediate. Also, oxidations amounting to O-insertion into C-H bond of aldehydes (transformation 6), of secondary or primary alcohols (transformation 7), of acyclic and cyclic ethers (transformation 8), and of Si-H bond of silanes (transformation 9) have been described *(3)*.

The efficient oxyfunctionalization of simple, "unactivated" C-H bonds of alkanes (transformation 10) under extremely mild conditions *(3,4)* undoubtedly counts to date among the highlights of dioxirane chemistry.

† In partial fulfillment of the requirements for the Ph.D. Degree.

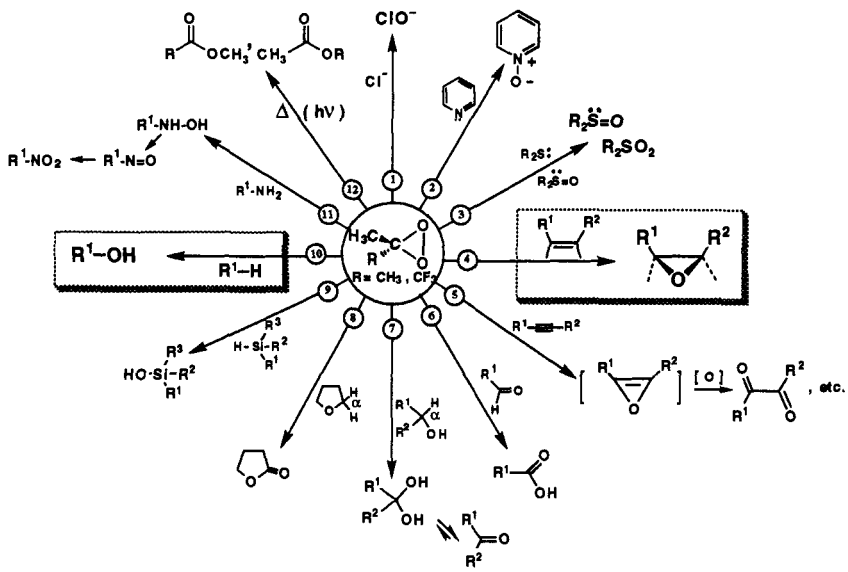


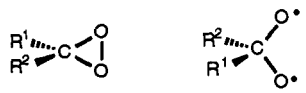
Fig. 1. Some primary transformations using dioxiranes

Dioxiranes have also been used for a rapid and quantitative oxidation of primary amines to nitro compounds (transformation 11); a stepwise process involving hydroxylamines and nitroso compounds was postulated, since both are oxidized by dimethyldioxirane to their nitro derivatives *(3c)*.

Although the mechanism of the "autodecomposition" of dioxiranes (i.e. their fate in the absence of any substrate) is still object of debate, rearrangement into esters (transformation 12) represents a main pathway *(3)*. In fact, although the thermal reactions of dimethyldioxirane (hereafter DMDO) (**1a**) are rather complex, methyl acetate is normally the main decomposition product *(5)*. Also, methyl trifluoroacetate is produced in the thermal or photochemical decomposition *(6)* of methyl(trifluoromethyl)dioxirane (hereafter TFDO) (**1b**).

Because of their versatile reactivity, dioxiranes are today widely adopted as a new class of efficient oxygen-transfer reagents, selective (chemo-, regio- and stereo-) in their action, bland toward the oxidation product, and capable of performing under mild, strictly neutral conditions.

Despite the rapid proliferation of dioxirane applications in synthesis *(3)*, comparatively few investigations appear to have been directed toward establishing their reaction mechanisms. For instance, in some mechanistic studies *(7)* the gathering of unambiguous evidence concerning dioxirane electrophilic character appears to have been hindered by the dichotomy existing between them and bis(oxyl) diradicals **2**. The latter represent a class of elusive entities that have so-far escaped direct observation.



1 **2**

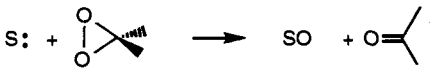
Whenever substrates were tested (e.g., $(EtO)_3P$, $(EtO)_2S$) that — in a parallel with 1,2-dioxetane chemistry *(8)* — might have yielded at low temperatures (-50 °C) insertion products (i.e., cyclic phosphoranes or sulfuranes) these were not observed *(9)*. Actually, theoretical studies *(10)* confirmed that dioxirane **1** is the lowest energy form of $R^1R^2CO_2$ isomers; calculations indicate that the diradical **2** is at least 15 kcal mol^{-1} higher. In view of the rather low activation barrier estimated (1-2 kcal mol^{-1}) for the reclosure, the strained dioxirane **1** has kinetic stability, and persists in the absence of oxidizable substrates. Just the unimolecular rearrangement of dioxirane into ester (transformation 12) seems to demand the intermediacy of the diradical form **2**; such

preliminary conversion, in fact, would be essential for a symmetry-allowed process *(3)*. However, the thermal decomposition of dioxiranes — as experimentally determined in solution — is not significant at 25 °C (E_a = 23-25 kcal/mol) *(9,11)*. Hence, the unimolecular rearrangement into esters still requires a sizable activation energy, in spite of the high exothermicity of this process ($\Delta H \geq$ -80 kcal/mol).

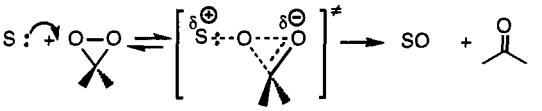
REACTION MECHANISMS

Electrophilic oxygen-atom transfers

It was noted that the most characteristic and distinctive feature of dioxiranes consists in their propensity for easy O-atom transfer to a variety of donor substrates (S:), yielding oxidation products SO and ketone (eq 1).



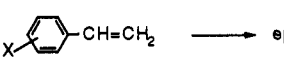
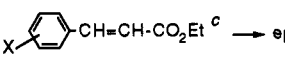
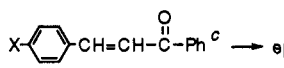
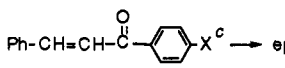
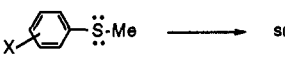
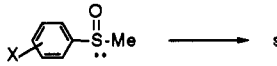
(1)



(2)

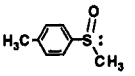
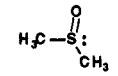
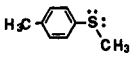
The conversion of pyridine into pyridine N-oxide by the dioxirane generated *in situ* (from cyclohexanone and caroate) is among the first examples to be reported by Edwards *et al.*; a careful kinetic analysis of the various steps that obtain in the *in situ* oxidizing system was carried out *(12)*. A positive Hammett ρ value of about +2 has been estimated *(3a)* for the oxidation of an electron-donor dye by a series of substituted aryl methyl dioxiranes generated *in situ*; this is that expected on grounds of the dioxirane behaving as the electron donor.

TABLE 1. Hammett "Rho" Values of Some Dioxirane Reactions

Entry	Reaction	Dioxirane	Solvent	T, °C	ρ	ref.
1	 epoxide	1a	acetone	23	-0.90 [a,b]	15
2	 epoxide	1a	acetone	20.5	-1.53	16
3	 epoxide	1a	acetone	30.	-1.03 [a,b]	17
4	 epoxide	1a	acetone	30.	-0.18 [a,b]	17
5	 sulfoxide	1a	acetone	20.5	-0.77 [d]	13
6	 sulfone	1a	acetone	20.5	-0.76 [e]	13
7		1a	$CHCl_3$	0	-1.0	14
8		1b	$CHCl_3$	0	-0.35	14

[a] Value of ρ^+; cf., epoxidation by peracetic acid in AcOH (25 °C) gives ρ^+= -1.2, and ρ = -1.6. [b] Carefully dried (Na_2SO_4) dioxirane solution. For substituted styrenes (entry 1), the ρ^+ value is -1.0 in slightly moist (0.15 mole fraction H_2O) acetone (ref. 15). [c] *E* stereoisomer. [d] Cf., for oxidation of sulfides X-C_6H_4-SPh by H_2O_2 (MeOH, 25.0 °C),ρ = -1.2 (ref. 21). [e] Oxidation by peroxybenzoic acid $PhCO_3H$ in dioxane at 25.0 °C yields ρ = - 0.55 (ref. 21).

TABLE 2. Second-order rate constants for the oxidation of some electron-donor substrates by dimethyldioxirane (DMDO) **1a** and by peroxybenzoic acid (PBA) in CH_2Cl_2[a] at 25.0 °C.

Entry	Substrate	k_2 ($M^{-1}s^{-1}$) [b]		$\left(\frac{k^{DMDO}}{k^{PBA}}\right)$
		DMDO	PBA	
1		0.11×10^{-2}	–	–
2	$CH_3(CH_2)_7C{\equiv}C{-}(CH_2)_2CH_3$	3.9×10^{-2}	–	–
3		1.4	1.9×10^{-2}	74.
4		3.9	3.5×10^{-2}	111.
5		26.	$8. \times 10^{-2}$	325.
6		1.1×10^{2} [c]	0.33	333.
7		8.9×10^{3} [d]	25. [d]	356.

[a] Unless noted otherwise. [b] In most of the cases, rate constant values were obtained from second-order rate-law integrated plots that were linear to over 80% reaction; unless noted otherwise, kinetics were performed by following oxidant consumption by a titrimetic (iodometry) technique (cf., ref. 4). Initial concentrations of reagents generally varied from 1.5×10^{-2} to 0.5×10^{-3} M. Estimated error ranged from 2% to 20% (for the faster kinetics). [c] In acetone/CH_2Cl_2 ca. 1:1, from stopped-flow kinetics experiments carried out by shot-injection in a mixing chamber of aliquots (1 mL) of DMDO and sulfide solutions that were from 0.08 to 0.10 M; the decay of DMDO concentration with time was monitored spectrophotometrically at 334 nm during ca. 850 ms, at 0.1 ms time intervals. [d] From competition experiments (experimental procedure, cf. ref. 4) , wherein p-tolyl methyl sulfide and excess (from 30 to 100 times) dimethylsulfoxide were allowed to react with DMDO; GC analysis (Freon A112 internal standard) allowed to determine the concentrations of oxidized products, i.e. p-Tol-SO-CH_3 and Me_2SO_2, hence the relative rate $k_r = (k^{TolSMe} / k^{Me_2SO})$. From this, and the rate constant value for the oxidation of dimethylsulfoxide (entry 6), the absolute rate constant for p-tolyl methyl sulfide was estimated.

As for reactions involving dioxiranes *isolated* in solution of the parent ketone, the kinetics were found to obey a clean overall second-order rate-law (order one each in dioxirane and substrate) in almost every case that they were studied *(3)*. In fact, rate studies on the substituent effect in dioxirane oxidation of sulfides and of sulfoxides *(13,14)*, as well as epoxidations *(15)*, all yielded negative ρ values, which indicates electrophilic oxidation. For α,β-unsaturated carbonyl compounds such as ethyl cinnamates *(16)* and chalcones *(17)* (entry 2 and 3, Table 1), the estimated ρ values show that the electronic requirements at the β-carbon are essentially identical to that in substituted styrenes (entry 1). Both electrophilic and nucleophilic epoxidation of α,β-unsaturated carbonyl substrates should involve substantial bonding at the β-carbon in the transition state (hereafter, t.s.); however, the electronic requirements would be opposite. For instance, in the nucleophilic epoxidation of chalcone by alkaline hydrogen peroxide (HOO^-) in MeOH at 30 °C, a ρ value of +0.92 was found *(18)*.

Based on his thianthrene 5-oxide (*SSO*) mechanistic probe *(7)*, Adam suggested that dioxiranes could display chiefly *nucleophilic* O-transfer toward certain substrates such as sulfoxides *(7)* or α,β-unsaturated carbonyl compounds *(19)*. This claim has been recently withdrawn *(20)*. In fact, it turned out that the high

(X_{SO} = 0.85) nucleophilic oxidation parameter measured *(7)* for isolated DMDO (cf., X_{SO} = 0.87 for carbonyl oxide t-Bu(Me)C^+-O-O^-) was due to an artifact; the corrected values for DMDO and TFDO came to X_{SO} = 0.13 and 0.10, respectively *(20)*; this might have been expected for oxidants displaying indeed strong electrophilic character (cf., X_{SO} = 0.06 for H_2O_2, $HClO_4$).

Kinetic data in Table 2 illustrate the reactivity of dioxiranes toward a few standard substrates of widely varying electron-donor power. The observed order of reactivity toward DMDO (**1a**), i.e. α,β-unsaturated carbonyls < alkynes < alkenes < heteroaromatic nitrogen base < sulfoxides << sulfide, is that expected *(21)* on grounds of the substrate behaving as the nucleophile toward the peroxide O-O bond. For instance, based on second-order rate constant values, p-tolyl methyl sulfoxide is over 300 times less reactive than its parent sulfide (entry 5 and 7); 2-cyclohexen-1-one (an electron-poor olefin) is almost 130 times less reactive toward DMDO (**1a**) than is cyclohexene (entry 1 and 3). These facts stringently indicate that in these reactions electrophilic oxygen is being transferred from dioxirane to substrate, as in oxidations with peroxyacids in neutral or acidic media *(21)*.

On the other hand, the observed second-order rate law suggests that the t.s. of the rate-determining step must contain both reagents (eq. 2). For cyclohexene epoxidation by DMDO (**1a**) in aprotic solvents, the activation parameters range from $\Delta H^{\neq}$ = 5.0 kcal mol^{-1} and $\Delta S^{\neq}$ = -41. cal $K^{-1}mol^{-1}$ for $CDCl_3$ solvent to $\Delta H^{\neq}$ = 7.4 kcal mol^{-1} and $\Delta S^{\neq}$ = -35. cal $K^{-1}mol^{-1}$ for acetone *(16)*. For epoxidation of a less reactive alkene such as chalcone PhCH=CH-C(:O)Ph, Baumstark found $\Delta H^{\neq}$ = 9.5 kcal mol^{-1} and $\Delta S^{\neq}$ = -40. cal $K^{-1}mol^{-1}$ in acetone *(17)*. Also analogous to peroxyacids, dioxirane epoxidations are found to be highly *syn* stereospecific *(3)*. This, and the large and negative $\Delta S^{\neq}$ values recorded, convincingly point to a rather concerted bond-making bond-breaking process.

In the epoxidation of simple alkenes, this would give rise to a t.s. bearing much similarity to the well known "Bartlett's butterfly" t.s. envisaged in epoxidations by organic peroxyacids *(21)*. However, with respect to peroxyacids, higher rates are expected in the dioxirane case, since the driving force for O-transfer by the three-membered ring peroxide would also encompass relief of ring-strain and favorable enthalpy change associated with the formation of a strong C=O π-bond (eq 2). Actually, rate data in Table 2 allow one to estimate that the reactivity of dimethyldioxirane (**1a**) exceeds that of a standard peroxyacid (such as peroxybenzoic acid $PhCO_3H$) by a factor ranging to over 10^2 (entries 3 -7).

For the more reactive TFDO (**1b**) a further increase in rate of over 10^2 might be expected; for instance, a k_2 value of 0.75 ± 0.05 $M^{-1}s^{-1}$ has been measured *(9)* for the epoxidation of 2-cyclohexen-1-one by **1b** in CH_2Cl_2 at 10.0 °C (compare with entry 1, Table 2). More relevant, kinetic data in Table 2 indicate that on going from cyclohexene to p-tolyl methyl sulfoxide to p-tolyl methyl sulfide — i.e., upon considerably increasing substrate nucleophilicity — the *selectivity is not diminished*; instead, it even appears to be enhanced, in violation of the reactivity/selectivity principle (RSP) *(22)*.

Selectivity in epoxidations

The most studied chemical transformation employing dioxiranes relates to their ability to convert various alkenes into the corresponding epoxides. Since dioxiranes are inert toward the epoxide produced and are capable of performing even at low temperatures and under neutral conditions, it becomes feasible to isolate some extremely labile epoxides, which could be just postulated as reactive intermediates previous to the discovery of these new oxidants *(3)*. To mention one example, Crandall *(23)* employed DMDO in the low-temperature epoxidation of many allenes to their spiro dioxides. On account of their extreme sensitivity toward hydrolysis, several previous efforts to obtain these labile diepoxides had failed.

As mentioned above, dioxiranes perform *syn* stereospecific O-transfer to the alkenes; *Z*-alkenes give

Z-epoxides and *E*-alkenes give *E*-epoxides. Also, it is normally found that *Z*-alkenes are more reactive than their *E*-stereomers *(3)*. Akin to peroxyacids, a concerted t.s. has been postulated for dioxirane epoxidations. It is of interest to speculate regarding the possible geometry of the t.s. in dioxirane epoxidations. Extremes are depicted in Figure 2, which have a spiro and a planar orientation.

Rate data are helpful in discriminating between the two limiting t.s. geometries. In fact, the trend of relative reactivity for epoxidation of substituted alkenes by dimethyldioxirane (**1a**) is qualitatively similar to that found for epoxidation by organic peroxyacids, i.e. $R_2C{=}CR_2 > R_2C{=}CHR > RCH{=}CHR \cong R_2C{=}CH_2 > RCH{=}CH_2$. With peroxyacids, the electron-donating effect brought by each additional unencumbered alkyl substituent increases the reactivity by roughly one order of magnitude. With DMDO, the epoxidation rate appears to be much less sensitive to electronic effects exercised by the number of alkyl substituents. For instance, 1,2-dimethylcyclohexene was found to be only 1.2-fold more reactive than 1-methylcyclohexene toward **1a** *(15)*.

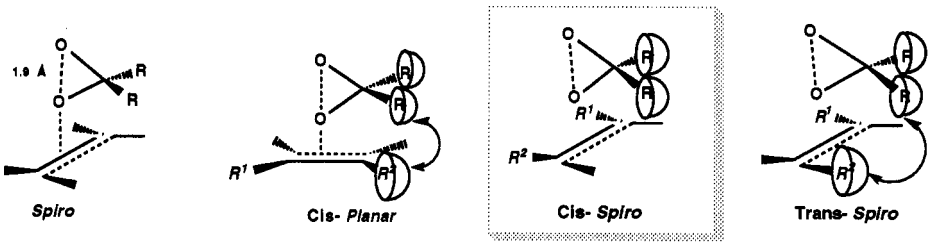
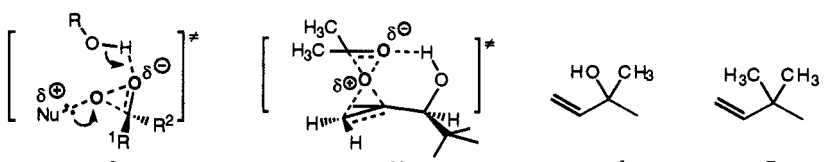


Fig. 2. Transition state geometries for dioxirane epoxidations

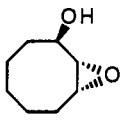
However, in dioxirane epoxidations the steric interactions appear to be more important than in the peroxyacid case, as several trans alkenes were found to be ca. 8-fold less reactive than their cis stereomers. This finding argues in favor of a spiro geometry of the t.s.; in fact, it is possible to rationalize the observed cis/trans selectivity on ground of a spiro arrangement, since in this case one side of the cis-alkenes can be approached preferentially by the reagent (Figure 2). Instead, for both cis- and trans-alkenes one severe steric repulsion can not be avoided in a planar arrangement. Thus, as originally proposed by Baumstark *(15)*, a spiro arrangement in the t.s. seems to be favored; however, calculations show that the energy difference between the two extreme geometries considered might turn out to be quite small *(10c)*.

It is found that protic solvents enhance the rate of dioxirane epoxidations; for instance, Baumstark *(15)* found that addition of water to acetone solvent increases the rate of epoxidation of p-methoxystyrene by DMDO (**1a**). Perhaps the most systematic study to-date on solvent effects in dioxirane epoxidations has been carried out by Murray, who reported *(16)* that in protic solvents MeOH and AcOH the rate of cyclohexene epoxidation by DMDO at 25 °C is respectively 5 and 7.5 times faster than in acetone.



Akin to O-transfer from simple peroxides (H_2O_2, t-BuOOH) to nucleophilic substrates *(21)*, a rationale can be found envisaging participation of the hydroxylic solvent (ROH) as a third particle in the t.s., for example as shown in **3**.

The advantage gained by this solvent participation consists in the fact that endothermic charge separation (cf., eq 2) is significantly diminished. In the case of epoxidation of some allylic alcohols, it was envisaged *(24)* that a similar participation could be exerted *intramolecularly* by the OH functionality, e.g. as in **3'**; however, this seems at odd with rate data. In fact, rate constants reported by Baumstark *(15b)* show that epoxidation of allylic alcohol 3-methyl-1-buten-3-ol (**4**) with DMDO occurs about twice *slower* than epoxidation of its non-hydroxylic counterpart **5**.



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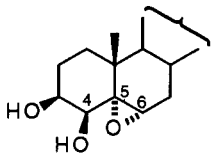

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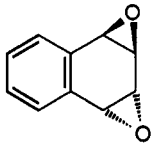
Furthermore, DMDO epoxidation of allylic alcohols possessing sufficient conformational rigidity was found to proceed with *anti* stereoselectivity. For some early examples *(25)*, epoxidation of 2-cycloocten-1-ol and of 4β-hydroxycholesterol gave the corresponding trans-epoxyalcohol **6** and the 5,6α-epoxide **7**, respectively with 99% and >80% stereoselectivity.

Various polycyclic aromatic hydrocarbons can be transformed into arene oxides by dioxiranes *(3)*. For instance, phenanthrene could be epoxidized to its 9,10-oxide in 83% yield by using DMDO (**1a**) during several hours at 22 °C. By comparison, the more reactive TFDO (**1b**) converts phenanthrene, to an extent of over 80% at -20 °C within less than 5 min, to afford the 9,10-oxide in 93% yield *(2c)*. Also using this powerful dioxirane, during 15 min at -20 °C naphthalene could be quantitatively and stereoselectively converted *(26)* into its *anti*-1,2;3,4-dioxide (**8**).

In these, as well as several other examples recorded *(27)*, the remarkable *anti* stereoselectivities observed suggest that this should be determined by an intermolecular dipolar directing effect exercised by a polar substituent present in the substrate (e.g., the 1,2-epoxide ring first introduced in the naphthalene case above) over the incoming dioxirane, for example as sketched in **8**. In fact, the available evidence *(3)* indicates that dioxiranes are highly polar species (cf., $\mu = 2.5$ D for the parent dioxirane H_2CO_2). Therefore, along with steric effects, electrostatic effects (as dipole-dipole interactions) in the t.s. might become an important factor in discriminating between *anti* and *syn* attack by the dioxirane (favoring an *anti* approach in the cases presented above).



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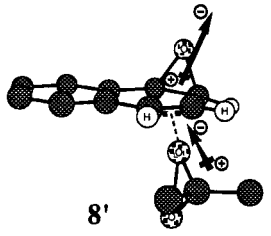
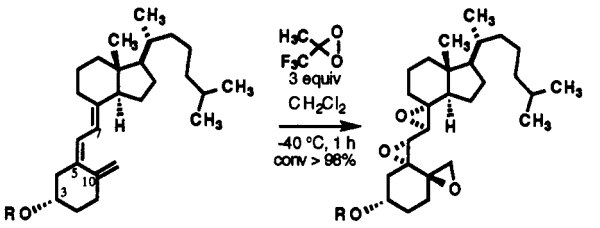


8'

In dioxirane oxidations, a favorable conjunction of steric and dipolar interaction effects, coupled with stringent stereoelectronic requirements in the t.s., may result in outstanding regio- and/or stereoselectivities. Examples came from our studies on dioxirane oxidations in the cholestane steroid series *(28)*, featuring biomimetic, highly selective oxyfunctionalizations. On the line of selective oxidation of natural targets, in a recent work *(29)* we have shown that remarkable selectivities can be attained in applying dioxiranes (**1b**) to the oxyfunctionalization of vitamin D_3 and of its 3-acyl derivatives.

For instance, reaction of 3β-acetyl vitamin D_3 (**9a**) with TFDO (**1b**) in CH_2Cl_2 at -40 °C displayed outstanding diastereoselectivity, in that just the corresponding all-*R* triepoxide **10a** was formed in 85% isolated yield (eq 3); X-ray crystallographic analysis allowed to determine unambiguously the 5*R*,6*R*,7*R*,8*R*,10*R* stereochemistry *(29)*.

In reacting with **1b** under the identical conditions, vitamin D_3 itself (**9b**) also gave the corresponding all-*R* triepoxide **10b** (72% isolated yield); here, chemoselectivity is demonstrated by the fact that the unmasked secondary alcohol moiety at C-3 was left unaffected.



9
(**9a** : R = Ac ;
9b : R = H)

10
(**10a** : R = Ac ; yield 85% (isol)
10b : R = H)

(3)

In the above reaction, it is remarkable that just one out of the possible diastereoisomers — i.e., the 5,6(β);7,8(β);10,19(α)-triepoxide — is isolated in good yield (eq 3).

Apparently, the series of *three* consecutive epoxidations at the triene system of substrate proceeds with a *high degree of stereocontrol* (>90%) *(29)* . Stepwise epoxidation experiments indicate that the sequence initiates with epoxidation at the more electron-rich unsaturated $\Delta^{7,8}$ moiety; this should be forced to occur at the β face, due to effective steric shielding by the flagpole 18α-CH_3. However, once granted obligatory initial formation of the 7,8(β)-epoxide, further stringent stereoelectronic and intermolecular dipolar directing effects, exercised over the incoming oxidant by the epoxide functionalities sequentially introduced must dictate the stereocontrolled synthesis of just one out of the remaining four possible diastereoisomers.

From the previous examples it is evident that the dioxirane epoxidations can display remarkable selectivity indeed.

Selectivity of oxygen-atom insertions into C-H bonds of alkanes

It was mentioned that a distinctive feature of dioxirane reactivity consists in their ability to yield O-atom insertions into alkane and cycloalkane C-H bonds *under extremely mild conditions*, so that even simple "unactivated" hydrocarbons can be oxyfunctionalized *(3)*. However, it was noted that these oxidations require reaction times of hours and excess oxidant when DMDO is employed *(30)*. By contrast, the more powerful TFDO (**1b**) is capable of carrying out these transformations often in a matter of minutes and with unchanged selectivity (**4**). Some examples are collected in Figure 3.

Such transformations are indeed rare for peroxides without the help of enzymes and/or metal catalysts. For instance, remarkable is the practically complete conversion of cyclohexane into cyclohexanone by **1b** (Figure 3, transformation 1) in over 95% yield, at -20 °C during ca. 20 min *(4)*. Kinetic data for this representative oxyfunctionalization at 0 °C in CH_2Cl_2 are: $k_2 = 2.9 \times 10^{-2}$ M^{-1} s^{-1}, $\Delta H^{\neq} = 13.7$ kcal mol^{-1}, $\Delta S^{\neq} = -15$ cal $K^{-1}mol^{-1}$, and ($k_H/k_D = 2$). When secondary alcohols are the reaction products, these are further oxidized to the corresponding ketones. Actually, it turns out that dioxiranes are reagents useful also in the conversion of alcohols into carbonyl compounds *(31)*.

In these alkane oxyfunctionalizations, high secondary vs. primary and tertiary vs. secondary selectivities (R_S^t from 15 to over 250) are customarily observed *(4)* (Figure 3). Valuable is the selective bridgehead hydroxylation of adamantane by TFDO (**1b**) to afford the tetrahydroxyadamantane (transformation 4) *(32)*. In this reaction, kinetic data show that **1b** is more reactive than DMDO (**1a**) by a factor of over 700. In spite of this, *the high selectivity for tertiary bridgehead C-H hydroxylation remains unchanged.*

Also, the high regio- and stereoselectivities recorded *(30)* with **1a** are not lost when using the more reactive dioxirane **1b**. For instance, using TFDO (**1b**) in the selective oxyfunctionalization at tertiary C-H of stereomeric 1,2-dimethylcyclohexanes, as well as of trans- and cis-decalin (transformation 5), the reaction

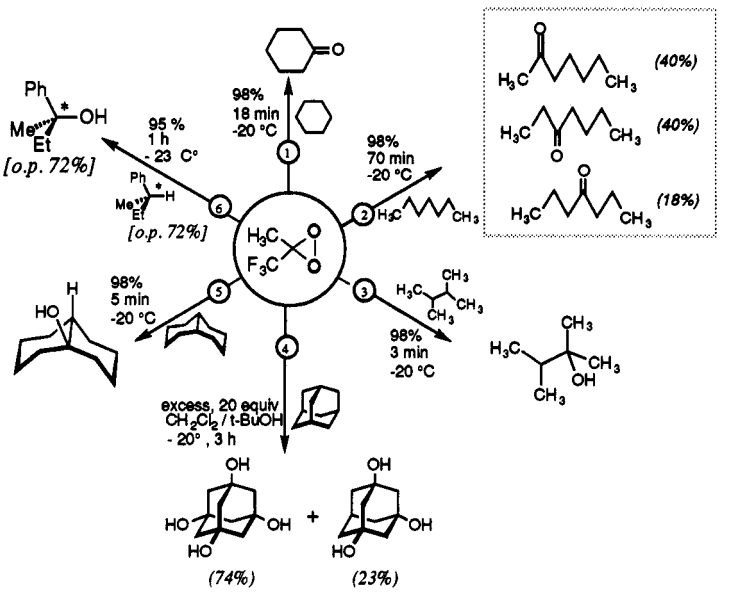
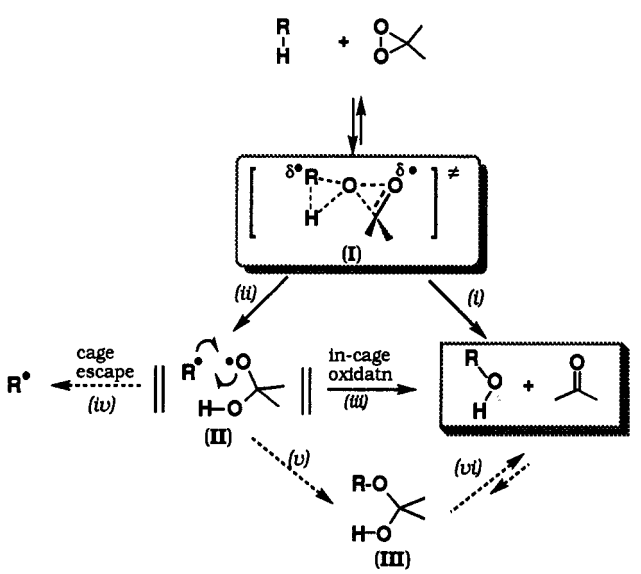


Fig. 3 Efficient oxyfunctionalization of alkanes using methyl(trifluoromethyl)dioxirane (**1b**)

is *completely stereospecific* with retention *(4)*. Furthermore, optically active 2-phenylbutane could be cleanly converted *(33)* into 2-phenyl-2-butanol in over 90% yield, and with *complete retention of configuration* employing dioxirane **1b** (transformation 6).

In the dioxirane oxyfunctionalization of alkanes, selectivity, stereochemical evidence, *and kinetics* all point to a rather concerted "oxenoid" mechanism of insertion *(4)*, having no *distinct* radical nor carbenium ion character (Scheme 1).

Scheme 1



Indeed, these oxidations were found to obey second-order kinetics (first-order each in dioxirane and in alkane), yielding integrated second-order rate-law plots that were linear to over 80% substrate conversion in most cases *(4,30)*. The clean second-order kinetics and the observed lack of sizable interference by oxygen suggest that a *chain* process involving free radicals should not be operative. Also at odds with a

purely radical process involving H-abstraction would be the high stereoselectivities recorded (see above).

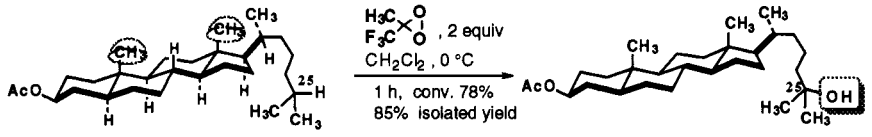
Again on grounds of the simple second-order overall kinetics (order one in substrate) and the H/D kinetic isotope effect determined, a preliminary equilibrium involving ring-opening of dioxirane to its bis(oxyl) diradical **1** ⇄ •O-CR_2-O• (**2**) (with the latter then serving as the active species) should be excluded *as the rate-determining step*. Moreover, theoretical calculations *(10)*, and experimental evidence *(6,9,11)* indicate that this event is disfavored energetically, since dioxirane ring opening to bis(oxyl) diradicals •O-CR_2-O• (**2**) should be up-hill by at least 15 kcal mol^{-1}.

However, one can not exclude that some diradical character develops in the t.s. (Scheme 1). In fact, while the dioxirane O-O bond is being broken, significant widening of the O-C-O angle from 60° to nearly 107° occurs *(10c)*, so that t.s. asymmetry might serve to relax the energy requirements of O-atom insertion.

Actually, pursuing a possible analogy between dioxirane oxidation and metalloporphyrin hydrocarbon oxygenations *(34)*, one might even envisage that — *after the t.s. of the slow step* — the formation of the alcohol be mediated by caged radical-pairs (**II**) (path *ii* , Scheme 1); then, in-cage oxidation (amounting to oxygen rebound) would lead to products (path *iii*). According to this sequence, the high stereoselectivities recorded might be accommodated, provided one makes the *assumption* that in-cage collapse of the radical pair to products occurs faster than loss of configuration of caged R•. Of course, once radical-pairs **II** are produced (from t.s. **I** via *ii*), both species R• and •O-CR_2-OH might diffuse out of the cage. In alkane oxyfunctionalization by TFDO (**1b**) we found no indication of freely diffusing alkyl radicals; for instance, at variance with oxygenations of alkanes by metalloporphyrins *(34)* or by ozone *(35)* , no substantial amounts of chlorinated products R-Cl (derived by reaction of R• with $CHCl_3$ or CH_2Cl_2 solvent) were detected.

None the less, dioxirane reactions are known which suggest that under certain conditions leakage to radical pathways becomes feasible (possibly via caged pairs **II**). Indeed, this seems to take place in the DMDO oxidation of substituted benzaldehydes *(36)* and of cyclic ethers *(37)* .

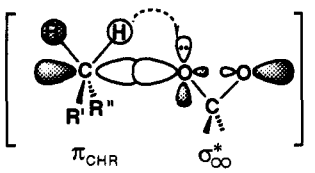
Whatever the mechanistic details of dioxirane O-insertions into alkane C-H bonds, the synthetic outcome of this transformation is undeniable. For instance, it is remarkable that the selectivities recorded for dioxirane O-insertion into tertiary vs. secondary C-H bonds of cyclic and polycyclic hydrocarbons also apply to more complex frameworks such as in steroidal substrates *(28,29)*. In addition, apparently dioxiranes are capable of discriminating among several tertiary C-H functionalities and yield amazing site-selectivity. Thus, we were able to achieve the direct, high-yield oxyfunctionalization at C-9 of prednisone acetate *(28a)*, at C-25 of vitamin D_3 derivatives *(29)*, as well as at the side-chain C-25 of several 5α-cholestanes *(28b)* (e.g., eq 5). Normally, such site-selective oxy-functionalizations require rather elaborate methods *(38)*.



3β-acetoxy-5α-cholestane (5)

This site-selective oxyfunctionalization at side chain C-25 of cholestane derivatives is puzzling and points to enhanced steric and/or stereoelectronic availability of these centers to dioxirane O-insertion as compared to the other tertiary C-H positions available in these target molecules. An FMO approach is helpful in understanding the possible origin of the high selectivities witnessed in these cases. In fact, Bach and co-workers *(39)* have recently performed careful *ab initio* calculations in support of a frontier MO theory that provides a distinctive rationale for both the stereospecificity and the stereoselectivity of O-insertion into hydrocarbon C-H bond by electrophiles and peroxides.

In this FMO analysis, the electrophilic attack is directed along the peroxide O-O bond axis toward the relevant carbon atom of the substrate, so that the dioxirane electrophilic oxygen approaches a filled C-H fragment orbital containing both a carbon 2p orbital and a hydrogen atom. The latter is then favorably oriented to be shifted to the approaching oxygen atom, which employs an electron pair to serve as migration terminus while the O-O bond is being broken. For DMDO attack at a generic tertiary C-H, this should produce a t.s. geometry such as **11**; here we use the filled π_{CHR} fragment orbital of the hydrocarbon in juxtaposition with the dioxirane empty $\sigma^*_{O\text{-}O}$ orbital, since Bach's calculations suggest that this produces a preferred orientation of approach. In this orientation, the least hindered t.s. would be that with R'= R"= CH_3.



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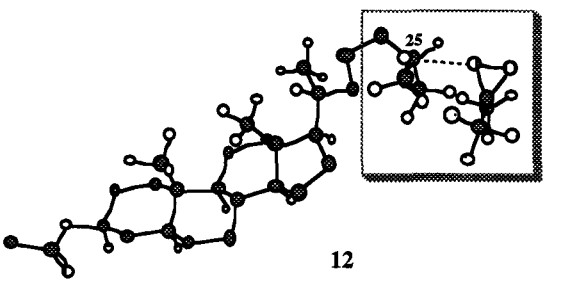

12

The application of this model of O-insertion to the tertiary C^{25}-H of 3β-acetoxy-5α-cholestane (cf., eq 5) is sketched in **12**. It is seen that this is the only tertiary C-H site bearing a gem-dimethyl center; all other tertiary C-H would present some additional steric hindrance to optimum stereoalignment for dioxirane attack.

CONCLUSIONS

From the compendium above it is evident that using dioxiranes — a new class of strong oxidants — can be remarkably advantageous in organic synthesis. The high ranking selectivities recorded using dioxiranes seem to be dictated by stringent steric and stereoelectronic requirements for O-transfer.

Thus, even using the powerful TFDO (**1b**), high regio-, stereo-, and site-selective oxyfunctionalizations can be attained, despite its exceptional reactivity. To shed light on the origin of this phenomenon in detail undoubtedly poses a stimulating challenge for the community of mechanistic chemists. However, a detailed discussion on this novel and intricate aspect of dioxirane chemistry, still posing several mechanistic incognita, is still premature at the time this article is being written. Suffice here to say that dioxirane oxidations appear to be another case of violation of the reactivity-selectivity principle (RSP); it reinforces current views *(22)* that the RSP has only limited applicability and should be used with caution.

ACKNOWLEDGMENT

We thank the Ministry of University, Scientific and Technological Research of Italy (MURST 40), and the CNR - Progetto Strategico "Tecnologie Chimiche Innovative" (Rome, Italy) for partial financial support. We are indebted to professor J. O. Edwards (Brown University, Providence, R.I.) for many helpful discussions, and Dr. L. Carbonaro (Università di Pisa, Italy) for advise and assistance in performing stopped-flow kinetics experiments.

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