Probing for Steric and Electronic Effects in Diastereoselective Dioxirane Epoxidations Compared to the Oxygen Transfer by Peroxy Acids

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The spiro transition state for the oxygen transfer by dioxiranes is substantiated by the fact that no enhanced steric effects are observed when dioxiranes with alkyl groups of different size are employed, as manifested by the same (within the experimental error) diastereoselectivities in the epoxidation of 2-menthene and 1,3-dimethylcyclohexene for different dioxiranes. The π-facial selectivity (*anti* attack) in the epoxidation of the acetate and the methyl and trimethylsilyl ether derivatives of 2-cyclohexenol derives from steric interactions, whereas a pronounced electronic effect (electrostatic repulsion) is held responsible for the high *anti* selectivity of peroxides such as ascaridol and 3-hydroperoxycyclohexene. Quite generally, dioxiranes display only slightly higher diastereoselectivities than *m*CPBA in sterically controlled epoxidations of cycloalkenes.

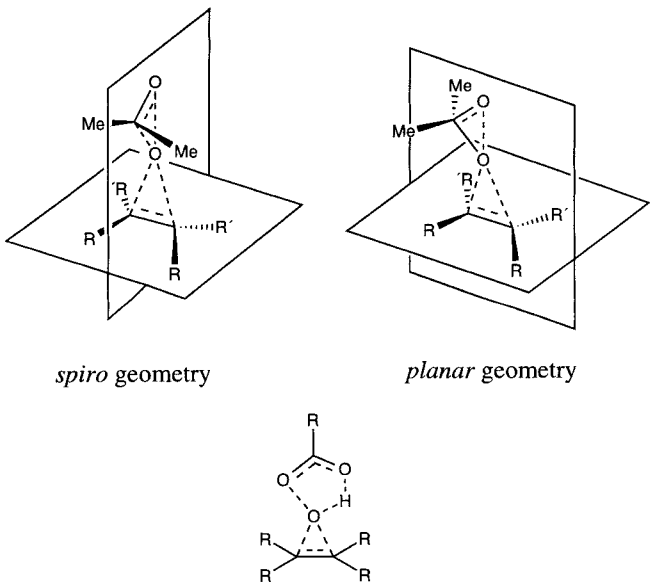
Introduction

Dioxiranes, especially the isolated dimethyldioxirane (DMD)[1], have proven to be useful oxidants for a diversity of oxyfunctionalizations of organic and organometallic substrates[2]. The epoxidation of olefins under extremely mild conditions is of particular interest due to its well-established synthetic value. Thus, even highly sensitive epoxides have been prepared for the first time by the convenient DMD route[3].

Numerous investigations have also been performed to elucidate the reaction mechanism of the DMD epoxidation and a concerted electrophilic attack of the dioxirane on the alkene double bond (S_N2 reaction of a π nucleophile on the peroxide bond) is the consensus[4]. Also inverse α- and β-secondary isotope effects for the epoxidation of DMD with alkenes support a concerted mechanism[5]. Additionally, relative epoxidation rates of differently substituted alkenes showed a remarkable dependence on steric interactions. Specifically, that the reactivity of *cis* alkenes is about an order of magnitude higher than that of their *trans* analogues suggests a spiro transition state geometry for the DMD approach on the double bond, in which the plane of the three-membered peroxide ring is orthogonal to the π bond (Figure 1)[6].

The proximity of the two dioxirane methyl groups to the oxygen atom that is being transferred, which is dictated by the tetrahedral structure of the dioxirane (Figure 1), allows the DMD to respond to the substitution pattern of the alkene. In contrast, for peracids such as *m*CPBA, no steric discrimination between the spiro and planar geometries is expected since the substituent R is too far away to interact sterically with the alkene substituents (Figure 1). Thus, it was shown for peracids that, rather than steric effects, the

Figure 1. Transition state geometries of the DMD and peracid epoxidations



spiro geometry

planar geometry

planar or *spiro* geometry

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nucleophilicity of the double bond is the decisive factor for the epoxidation rate. While for peracids each additional alkyl group enhances the rate by about an order of a magnitude due to the increased nucleophilicity of the alkene, for the sterically more demanding DMD it is much less because every additional substituent also increases the unfavorable steric interactions. Therefore, relative rates are not indicative to test the transition state geometry for peracids, as manifested for *cis-*, *trans-*, and *gem*-disubstituted alkenes, which are epoxidized equally fast irrespective of their substitution pattern[7]. Hence, it is difficult to assess experimentally whether the spiro or planar butterfly-type transition state geometry applies for the peracid epoxidation[8]. Also theoretical work does not unequivocally resolve this query, although most computations on peracid epoxidations concur with the spiro transition state for the oxygen transfer, as exemplified in the peroxyformic acid reaction with ethylene[9].The most recent calculation is consistent with the planar geometry, but predicts a non-concerted mechanism[10].

Since diastereoselectivity has been employed as a sensitive mechanistic probe for steric and electronic effects in photooxygenations[11], a similar study should be helpful in assessing such effects in DMD epoxidations of appropriate olefins. Moreover, a comparison of the steric demand between DMD and peracids would be valuable for mechanistic insight. Indeed, the power of this mechanistic tool has been demonstrated in the latest work on diastereoselective epoxidations of allylic alcohols by DMD, in which it was found that the hydroxy group exerts a stabilizing effect through hydrogen bonding on the DMD transition state and, thereby, controls the π-facial selectivity[12]. The diastereoselectivities for DMD were in most cases somewhat lower than for *m*CPBA; this was ascribed to the less effective hydrogen bonding and a slightly larger dihedral angle in the transition state for DMD. In view of this success, it was of interest to employ diastereoselectivity to assess the structural details of the transition state geometry of the oxygen transfer by employing differently substituted dioxiranes and alkenes. For the latter substrates, the epoxidations were conducted also with the peracid *m*CPBA for comparison.

The dioxirane derivatives **1a–d** were selected for the diastereoselective epoxidations of the cycloalkenes **2a, b**. Similar work has been performed with dioxiranes generated in situ, but with conflicting results. For example, a pronounced effect was observed for such dioxiranes on the π-facial selectivity of the epoxidation of 1,3-dimethylcyclohexene (**2b**)[13], but for steroids the steric influence was comparatively small[14]. To sort out this discrepancy, solutions of *isolated* dioxiranes, which are readily available by extraction[15], were to be employed to circumvent the direct oxidation by Caroate in the in situ process[16]. In this way, the exclusive oxidation by dioxirane would be assured, uncontaminated by oxygen transfer from other potential oxidants.

Additional stereochemical data should be valuable to decide a priori the reagent of choice for the diastereoselective epoxidation of chiral olefins in preparative applications by assessing if effects other than hydroxy direction determine the sense and extent of diastereoselectivity. For the purpose of probing steric effects in the alkene substrates, the set of cyclic alkenes **2a–c** with no further functionalities was chosen, since steric interactions are well defined therein. In addition to diastereoselectivity, the substrates **2d,e** allow the determination of the regioselectivity for the DMD versus *m*CPBA epoxidations. The cyclic enone **2f** permits the testing of the effect of carbonyl conjugation, and the functionalized allylic substrates **2g–i**, derivatives of 2-cyclohexenol, were selected to determine electronic effects other than hydrogen bonding on the stereochemical course. The cyclic substrates **2j,k** were of interest to find out the stereocontrolling features of peroxide functionalities. The diastereoselectivities for the epoxidation of olefins **2a–k** by the dioxiranes **1a–d** are reported here.

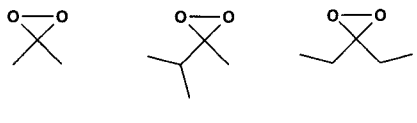
Results and Discussion

The results for the dioxiranes **1a–d** (Table 1) clearly show that the diastereoselectivity in the epoxidations of the alkenes **2a,b** does not depend significantly on the size of the dioxirane substituents[17]. Within the error limits, the same d.r. values were observed for the cycloalkenes **2a** and **2b** (Table 1, entries 1–5 and 6–8), except for the **1d/2b** combination (entry 9). Thus, no further steric strain between the alkyl groups of the dioxirane and the substrates is exerted, which is in accord with the spiro geometry. As Figure 1 displays, for this oxygen transfer trajectory the alkyl substituents of the dioxirane point away from those of the alkene substrate. In contrast, for the planar transition state, an increase in diastereoselectivity would be expected for dioxiranes with larger alkyl groups due to the proximity of the dioxirane substituents and the alkene. Similar steric effects should also hold true for a recently suggested diradical attack on the π bond[18], for which the end-on trajectory applies with an angle of ca. 109°[3g,30].

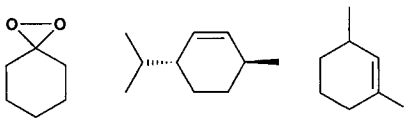
Also the temperature effect on the diastereoselectivity of the DMD epoxidation of 2-menthene (**2a**) is small; a temperature difference of ca. 100 °C causes an increase in the d.r. value from 78:22 to 84:16 (Table 1, entry 1, 2). Thus, for preparative purposes, it is doubtful whether control of the diastereoselectivity can be achieved by variation of the dioxirane substituents or the temperature. In the spiro geometry (Figure 1), the substituents of the dioxirane are just too far away from the chirality centers in the substrate to provide effective steric interactions, except when very bulky dioxiranes are used, but these are to date not preparatively accessible.

Nevertheless, that steric effects also operate in the spiro transition state is evidenced in Table 1 by the appreciable diastereoselectivity for the two substrates **2a** (d.r. ca. 80:20) and **2b** (d.r. ca. 72:28, except dioxirane **1d**). Thus, the preferred *anti* π-facial attack expresses the minimized steric interactions between the substrate and dioxirane alkyl groups, as exemplified in the transition state (Figure 2) for 2-menthene (**2a**). The approach from the methyl-bearing π face in the half-chair conformation is favored over the side with the isopropyl group. Moreover, such steric discrimination

Table 1. Diastereoselectivities of the epoxidations of 2-menthene (**2a**) and 1,3-dimethylcyclohexene (**2b**) with dioxiranes **1a–d**



1a **1b** **1c**



1d **2a** **2b**

entry	substrate	oxidant (conditions)	conversion[a] [%]	d.r. (*trans/cis*)	Lit.: d.r. (in situ)[b]
1	**2a**	**1a**, acetone, 4 h	>95	78:22	
2	**2a**	**1a**, acetone, 4 h, –78 °C	>95	84:16	
3	**2a**	**1b**, 3-methylbutanone, 24 h	19[c]	81:19	
4	**2a**	**1c**, 3-pentanone, 24 h	58	82:18	
5	**2a**	**1d**, cyclohexanone, 24 h	14[c]	80:20	
6	**2b**	**1a**, acetone, 4 h	>95	72:28	86:14
7	**2b**	**1b**, 3-methylbutanone, 4 h	24[c]	70:30	
8	**2b**	**1c**, 3-pentanone, 4 h	95	72:28	
9	**2b**	**1d**, cyclohexanone, 4 h	85	80:20	91:9
10	**2b**	$KHSO_5$, acetone, MeOH, H_2O, $NaHCO_3$, 4 h	73[d]	74:26	86:14
11	**2b**	$KHSO_5$, MeOH, H_2O, $NaHCO_3$, 4 h	15	62:38	75:25

[a] Run at ca. 20 °C, determined by GC analysis (error ±2% of the stated values) unless noted otherwise; mass balances >90%, yields >95% (normalized to 100% conversion). – [b] Ref.[13]. – [c] 0.3 equiv. of dioxirane. – [d] Determined by ^{1}H-NMR analysis of characteristic signals (error ±5% of the stated values).

is slightly more effective for 2-menthene (**2a**) than for 1,3-dimethylcyclohexene (**2b**) since isopropyl versus methyl interactions are more pronounced than methyl versus hydrogen ones in the latter (d.r. ca. 72:28). Consequently, variation of the substrate structure appears to be more effective in expressing steric interactions than such variation of dioxiranes. This is demonstrated in the selectivity data of Table 2 for DMD versus *m*CPBA with a variety of substrates **2**, for which steric and electronic effects have been examined[25]. The diastereoselectivity results in Table 2 exhibit a consistently higher diastereoselectivity for DMD as epoxidizing agent than for *m*CPBA[26]. Nevertheless, the difference is quite small, despite the fact that dioxiranes have been claimed to be considerably more sensitive towards steric interactions[4,27] than peracids[28].

Figure 2. Preferred transition state for the dioxirane epoxidation of 2-menthene (**2a**)

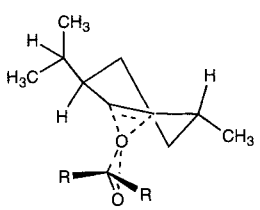
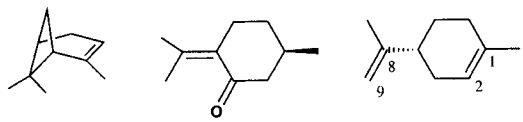
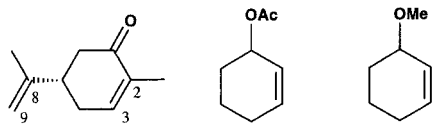


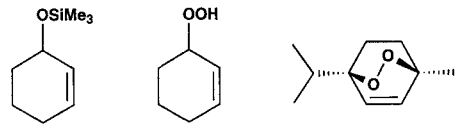
Table 2. Diastereoselectivities of the epoxidations of olefins **2a–k** by DMD (**1a**) and *m*CPBA



2c **2d** **2e**



2f **2g** **2h**



2i **2j** **2k**

entry	olefin	diastereoselectivity[a] (*trans/cis*) DMD[b]	*m*CPBA
1	**2a**	78:22	72:28
2	**2b**	72:28	54:46
3	**2c**	>95:5	>95:5[c]
4	**2d**	65:35	58:42
5	**2e**	67:33[d] (1,2) 50:50 (8,9)	50:50[c] (1,2) /
6	**2f**	55:45[f]	50:50[f]
7	**2g**	72:28 (66:34)[g]	57:43[h]
8	**2h**	75:25[f] (78:22)[f]	70:30[j]
9	**2i**	88:12 (87:13)[k]	76:24
10	**2j**	91:9 (84:16)[f]	43:57
11	**2k**	> 95:5	60:40[m]

[a] Determined by ^{1}H-NMR analysis of the crude reaction mixtures (error limit ±5% of the stated values), mass balances, conversions and yields >95%. – [b] DMD (1.0 equiv.), acetone, ca. 20 °C, 2–8 h. – [c] Ref.[20]. – [d] Regioselectivity 80:20 for 1,2- versus 8,9-epoxides. – [e] Regioselectivity 93:7 for 1,2- versus 8,9-epoxides, ref.[21]. – [f] Regioselectivity >95:5 for 8,9- versus 2,3-epoxides. – [g] Ref.[12a]; besides epoxidation, 5% of 2-cyclohexenone was formed. – [h] Ref.[23]. – [i] Besides epoxidation, 19% of 2-cyclohexenone was formed. – [j] Ref.[22]. – [k] Ref.[12a]; besides epoxidation, 10% of 2-cyclohexenone was formed. – [l] Ref.[25]; besides epoxidation, 9% of 2-cyclohexenone was formed. – [m] Ref.[24].

Thus, as already discussed in regard to the dioxirane variation (Table 1), for the *cis*-disubstituted (**2a**) and trisubstituted (**2b**) alkenes, the preferred approach of the dioxirane proceeds through a spiro transition state with its substituents oriented to the less substituted side of the double bond (Figure 1). The attack proceeds from the sterically less encumbered π face of the substrate (Figure 2). When the substrate is sterically as loaded as α-pinene (**2c**), for both DMD and *m*CPBA the attack occurs exclusively opposite to the *gem*-dimethyl group (Table 2, entry 3). In contrast, the low diastereoselectivities for both DMD and *m*CPBA with the electron-poor enone **2d** (Table 2, entry 4) signal that the methyl group is too far away to exercise effective π-facial control in the oxygen transfer.

For the pair of related diolefinic substrates **2e**, **f** (Table 2, entries 5 and 6), the observed regioselectivities display typical electronic effects due to the nucleophilicities of the double bonds. In diolefin **2e**, the trisubstituted ring double bond should be more reactive than the external disubstituted one, while in diolefin **2f** the situation is reversed in view of the electron-poor enone double bond. Indeed, the regioselectivities in Table 2 (entries 5 and 6) nicely corroborate this expectation, more so for *m*CPBA than DMD, since electronic effects dominate for the former. Thus, for the diolefin **2e** both *m*CPBA (97:7) and DMD (80:20) preferentially form the ring epoxides, but for **2f** both oxidants give exclusively (>95:5) the 8,9-epoxide.

The lower diastereoselectivity in the ring epoxidation of **2e** (67:33) versus **2b** (72:28) in Table 2 (entries 2 and 5) reveals again the importance of steric effects in DMD epoxidations. Although both substrates possess the 1-methylcyclohexene unit, in the derivative **2e** the homoallylic isopropenyl group is less effective for steric discrimination than the allylic methyl substituent in **2b**, because the former is too far away from the reaction center.

Surprisingly, electronic effects appear to be of minor importance in the epoxidation of the functionalized acetyl, methyl and trimethylsilyl derivatives of 2-cyclohexenol **2g–i** (Table 2, entries 7–9). This is most definitively evident in the π-facial selectivities of *m*CPBA. If electrostatic repulsions were to operate, the more electronegative acetoxy substituent would be expected to discriminate between the two π faces of the ring, which should be manifested in a higher diastereoselectivity (prefered *anti* attack) than for methoxy or trimethylsilyloxy substituents. In fact, the reverse trend applies, which follows the steric bulk of these substituents in the order **2i** (76:24) > **2h** (70:30) > **2g** (58:42). As expected, for *m*CPBA the steric effect is relatively small, but for DMD somewhat more appreciable, i.e. **2i** (88:12) > **2h** (75:25) > **2g** (72:28). The importance of steric effects in DMD epoxidations is further evidenced quantitatively in the E_s correlation[25].

Unusual is the high *anti* diastereoselectivity in the DMD epoxidation of the hydroperoxide **2j** and the endoperoxide **2k** compared to *m*CPBA (Table 2, entries 10 and 11, i.e. >90:10 for the former)[29]. That hydrogen-bonding effects do not apply for the hydroperoxy derivative **2j** is convincingly demonstrated by the *anti* π-facial selectivity. Instead of only steric factors, for these peroxidic substrates we suggest that electrostatic effects (dipole–dipole repulsions) operate on the approaching dioxiranes, as already proposed to rationalize the stereochemical outcome in other instances[25,30].

In accordance with the overwhelming majority of previous work on DMD epoxidations[2g], we reiterate that dioxirane epoxidations of alkenes proceed by a concerted electrophilic (oxenoid) oxygen transfer[31]. The diastereoselectivities of the epoxidation of substrates **2a** and **2b** with differently substituted dioxiranes corroborate well the established spiro mechanism of DMD epoxidations[4,6]. Recently reported enantioselective epoxidations by C_2-symmetric dioxiranes also support the spiro geometry for dioxirane attack[32].

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Experimental Section

General: ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC 200 spectrometer by using $CDCl_3$ as internal standard. Potassium iodide-starch paper (Merck) was used for peroxide tests. Dimethyldioxirane (**1a**) was prepared according to our described procedure[1b]; the differently substituted dioxiranes **1b–d** were obtained and used as solution in the corresponding ketone as detailed in the literature procedure[15]. Starting materials **2a**[33], **2b**[34], **2g**[35], **2h**[35], **2i**[20], **2j**[36], and **2k**[37] were made according to literature-known procedures; the relative configuration of the products was determined by comparison of the spectral data with those given in the literature for **3a**[38], **3b**[13], **3c**[26], **3d**[39], **3e**[40], **3f**[41], **3g**[35], **3h**[35], **3i**[20], and **3j**[21] or by independent preparation according to literature procedures. The commercial compounds **2c**, **2d**, **2e** and **2f** were used as received; solvents were purified and dried by reported standard methods.

General Procedure for the Epoxidations of Alkenes by Dimethyldioxirane: The alkene **2** was dissolved in acetone and 1.0–1.1 equiv. of dimethyldioxirane (0.05–0.10 M solution in acetone) was rapidly added at ca. 20°C. The solution was stirred at this temperature until the peroxide test (KI/HOAc) was negative. The solvent was removed in vacuo (20°C, 20–100 Torr) to afford a mixture of the corresponding epoxides **3** in high purity. Only for the substrates **2g**, **2h** and **2i** were small amounts of the corresponding 2-cyclohexanone **4** obtained (cf. Table 2).

General Procedure for the Epoxidations of Alkenes by mCPBA: The *m*CPBA (1.0–1.4 equiv.) was dissolved in CH_2Cl_2 (ca. 20 ml) and 1.0 equiv. of alkene **2** (0.5–1.0 mmol) was added at ca. 20°C. The solution was stirred at this temperature for 3–12 h. The reaction mixture was filtered, and the filtrate was washed with $NaHCO_3$ solution (3 × ca. 10 ml) and brine (1 × ca. 10 ml) and dried ($MgSO_4$). The solvent was removed in vacuo (20°C, 20–100 Torr) to afford mixtures of the corresponding epoxides with identical (within the error limit ±5%) d.r. values as reported in the literature (cf. Table 2).

Oxidation of 2-Cyclohexen-1-yl Hydroperoxide (**2j**) *with DMD:* According to the general procedure, a 0.081 M solution of dimethyldioxirane (9.90 ml, 0.80 mmol) in acetone was added to 92.0 mg (0.80 mmol) hydroperoxide **2j**. The solution was stirred at ca. 20°C for 2 h and the solvent was removed (20°C, 20 Torr) to yield 101 mg (>95%) of a 9:91 mixture of the 2-cyclohexenone derivative and the two diastereomeric epoxides 2-hydroperoxy-7-oxabicyclo[4.1.0]heptane [(*1S*,2R*,6S**)-**3j**:(*1R*,2R*,6R**)-**3j** = 9:91] as a colorless oil. The two diastereomers were separated from the enone by low-temperature (−10°C) column chromatography on silica gel (63% yield) with 2:1 Et_2O/PE as eluent. (*1S*,2R*,6S**)-**3j**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.04–1.97 (m, 6H, 3-H), 3.26–3.32 (m, 1H), 3.46–3.53 (m, 1H), 4.30–4.35 (m, 1H), 9.77 (br. s, 1H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.8 (t), 22.8 (t), 22.9 (t), 52.0 (d), 54.0 (d), 80.2 (d). – (*1R*,2R*,6R**)-**3j**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.04–1.97 (m, 6H, 3-H), 3.21 (br. s, 1H), 3.36–3.38 (m, 1H), 4.17 (dd, J_1 = 8.9 Hz, J_2 = 6.2 Hz, 1H), 9.77 (br. s, 1H).

– ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.4 (t), 24.1 (t), 24.5 (t), 53.0 (d), 53.2 (d), 78.9 (d). – IR (CCl_4): $\tilde{\nu}$ = 3600–3050, 2990, 2970, 1690, 1670, 1460, 1430, 1380, 1250, 1120, 1080, 1050, 1030, 980, 950 cm^{-1}. – $C_6H_{10}O_3$ (130.1): calcd. C 55.37, H 7.74; found C 55.08, H 8.05.

The configuration of the product was determined by reduction of the diastereomeric mixture of epoxy hydroperoxides **3j** with Ph_3P (NMR scale), which afforded the corresponding known epoxy alcohols (*1R*,2R*,6S**)- and (*1S*,2R*,6R**)-7-oxabicyclo[4.1.0]heptan-2-ol[42] quantitatively in a 10:90 *syn*:*anti* ratio.

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