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Theoretical Investigations of Substituent Effects in Dimethyldioxirane Epoxidation Reactions

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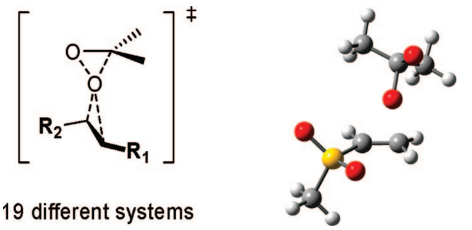
Received April 3, 2008



A detailed theoretical study of dimethyldioxirane-mediated epoxidations with a variety of differently substituted alkenes **3**−**21** is presented. Transition structures and activation barriers were determined in the gas phase and in acetone as solvent with the B3LYP/6-311+G(d) level of theory. Substituent effects were elucidated by frontier orbital analyses of the reacting species as well as by natural bond orbital (NBO) analysis of the transition structures. Epoxidations with alkenes carrying electron-donating groups such as OMe or NHAc commonly tend to have low activation energies and early transitions states, whereas using alkenes with electron-withdrawing moieties such as CN, SO_2Me, CO_2Me, CF_3, CHO, and Cl higher activation barriers and late transition states are observed. In all cases a net charge transfer (CT) from the alkene to the dioxirane was observed substantiating the electrophilic character of dimethyldioxirane.

Introduction

Epoxides are versatile substrates in the synthesis of a variety of compounds with vicinal functional groups such as 1,2-diols and 1,2-amino alcohols.[1] For the generation of epoxides starting from alkenes several methods are known, e.g., catalytic reactions such as the Sharpless[2] or Jacobsen epoxidation,[3] and the use of peroxycarboxylic acids.[4] However, the use of peroxycarboxylic acids has the disadvantage that acidic carboxylic acids are formed in the epoxidation process which can induce unwanted side reactions. Thus, sensitive epoxides such as those of enol ethers tend to polymerize in the presence of acids. On the other hand, when employing dioxiranes for the epoxidation this problem does not occur since ketones are formed as the second product.[5] In the most simple case when using dimethyldioxirane (DMDO, **1a**) acetone is formed as the only byproduct, which is neutral and can easily be removed from the reaction mixture. Therefore, DMDO, either generated in situ[6] or isolated as a solution,[7] is often used as the reagent of choice for the synthesis of highly sensitive epoxides such as glycal epoxide **2**. These compounds have become powerful building blocks in carbohydrate synthesis,[8] as shown in Scheme 1.

Since its first usage in synthetic organic chemistry by Murray, Adam, and Baumstark more than two decades ago,[5–7] dimethyldioxirane has become a popular epoxidizing reagent of unusual synthetic utility. Moreover, not only electron-rich but also some

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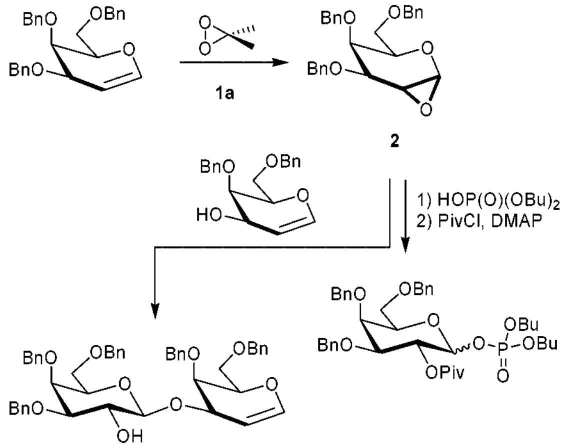
SCHEME 1



electron-poor alkenes have been successfully epoxidized utilizing dioxiranes.[16] The *syn*-stereospecific nature, kinetic investigations, and H/D isotope effects[9] as well as computational studies by Bach and Houk have revealed that DMDO-mediated epoxidations are concerted processes and proceed via a *spiro*-configured transition state.[10,11] Such a geometrical preference can easily be understood by considering the relevant frontier orbitals of dioxirane and the alkene moiety (Figure 1). Whereas the interaction (a) between π(C−C) and σ*(O−O) is symmetrical with respect to the O−O axis, the transfer of electron density from the lone pairs (n_p) to the π(C−C) orbital reaches its maximum when the system has a *spiro* geometry (b).

The occurrence of discrete radicals during the course of the reaction was ruled out on the basis of carefully designed experiments[12] and computational means.[13] The latter revealed that a hydrogen bonding interaction in the transition state leads to a substantially decreased activation barrier for epoxidations with dioxirane.[14] Recently, a biphilic (electrophilic/nucleophilic) dichotomy of dioxirane reactivity similar to that of peracids was discussed by high-level theoretical means.[15] However, in a recent experimental study such a view could be confirmed neither by linear free energy relationships (Hammett plots) nor by cyclic voltammetry of dioxiranes.[16]

Despite intensive theoretical investigations of epoxidation reactions with dimethyldioxirane (DMDO, **1a**), an in-depth computational study of substituent effects with respect to transition state geometries and activation barriers has not been performed.

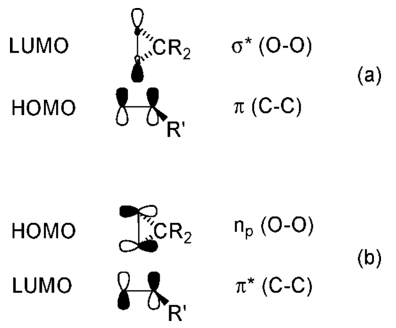


FIGURE 1. Most important interactions of the frontier molecular orbitals of dioxirane and alkene explaining the *spiro* geometry of the transition state.

TABLE 1. Comparison of Basis Sets for the Epoxidation of 4 with DMDO (1a)[a]

method and basis set	$E_A^{\text{gas phase}}$
B3LYP/6-31G	67.4
B3LYP/6-31G(d)	68.5
B3LYP/6-311G(d)	66.8
B3LYP/6-31+G(d)	65.3
B3LYP/6-311+G(d)	62.6

[a] The activation energies in the gas phase are given in kJ/mol.

Computational Details

All calculations were carried out with the Gaussian 03 software package.[17] Geometry and energy optimizations were performed at the B3LYP/6-311+(G)d level of theory without any symmetry constraints.[18,19] It is known that Hartree−Fock (HF) methods are inadequate to describe dioxiranes; methods that incorporate electronic correlation energy, at least to some extent, are necessary to correctly describe dioxiranes.[20] High-level computations have shown that Becke's three-parameter hybrid functional together with the correlation functional of Lee, Yang, and Parr (B3LYP)[18] allows an accurate description of the examined dioxirane epoxidations.[10,11,13–15] In our initial attempts we varied the basis sets of Pople's 6-31G family with and without polarization and diffuse functions (Table 1).

Frequency calculations were undertaken to confirm the nature of the stationary points, yielding one imaginary frequency (NImag = 1) for transition states (TS) with largest contributions from internal coordinates involved in the reaction and none (NImag = 0) for minima. All optimizations were performed without any constraints (C_1 symmetry). All energies were corrected for zero point. For the evaluation of solvent effects the self-consistent reaction field (SCRF) theory, using the PCM-united atom topological model (UAHF, radii of interlocking spheres),[21] was employed as implemented in Gaussian 03. Natural bond orbital (NBO) analyses[22] with the B3LYP/6-311+G(d) density have been used to analyze the major interactions in terms of localized orbitals. A

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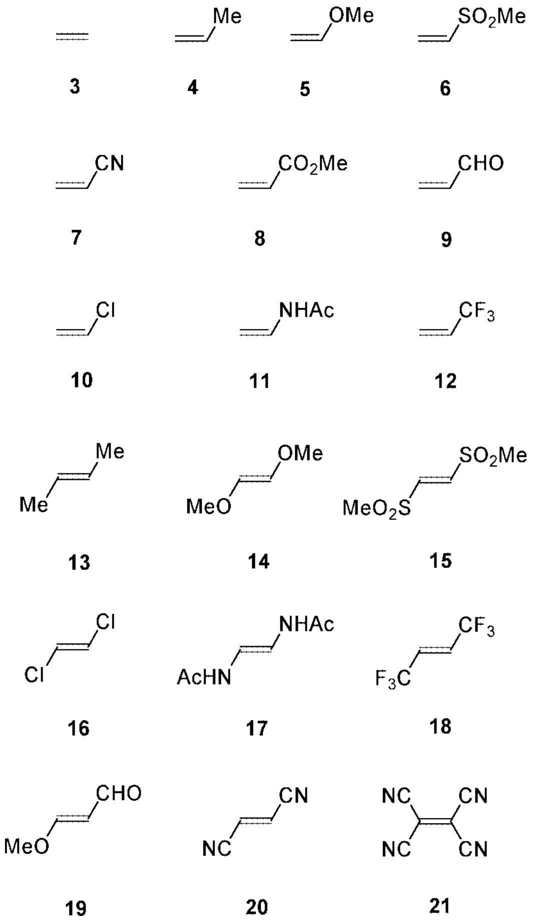


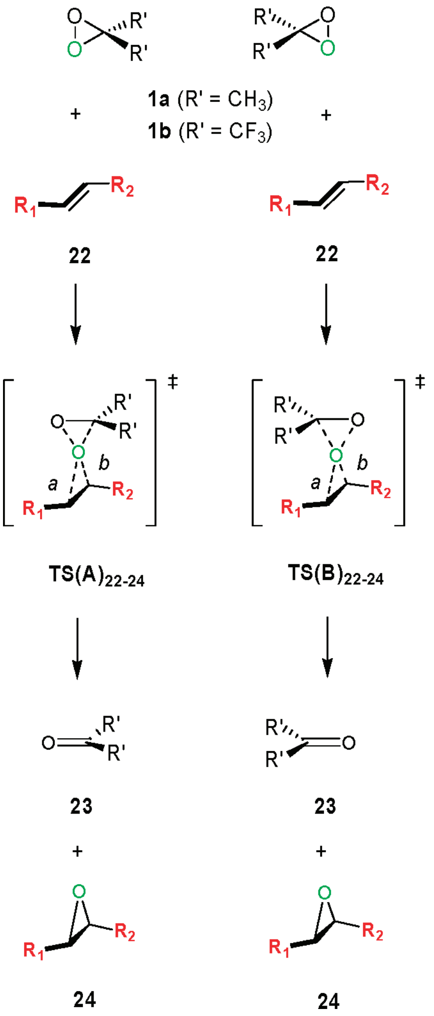
FIGURE 2. Different alkene model systems **3**–**21** investigated in this study.

natural population analysis (NPA) and resulting Wiberg bond indices (WBI)[23] were used for detailed study of the electronic structure and bonding of the optimized transition structures. Molecular orbital energy levels (HOMO and LUMO) were computed on the HF/6-311+G(d) level of theory based on the B3LYP optimized geometry.

Results and Discussion

For a systematic discussion of the particular influences of different substituents R attached to the alkene moiety we chose 19 model systems shown in Figure 2. Nine of them are monosubstituted (**4**–**12**), and the remaining substrates carry two (**13**–**20**, in a trans arrangement) or more than two substituents (**21**). We used neutral (Me), electron-donating (OMe, NHAc) as well as electron-withdrawing substituents (SO_2Me, CO_2Me, Cl, CHO, CN, CF_3). In particular, such a substitution pattern allows an examination of the major orbital interactions in the transition state. We refrained from elucidating substituent effects for moieties such as free amino groups, sulfides, or phosphanes that easily undergo oxidation of the heteroatom by dioxiranes. For all systems shown in Figure 2 we examined the transition states $\mathbf{TS}_{22-24}$ and their corresponding activation energies of the epoxidation by dimethyldioxirane (DMDO) to yield the corresponding epoxide **24** and acetone **23a** as a second product as shown in Scheme 2.[24]

SCHEME 2



These investigations were performed in the gas phase as well as in acetone as solvent because DMDO is commonly used as a dilute solution in acetone. Calculated activation energies are shown in Table 2. One observes activation barriers for the gas phase reaction ranging from 28 (for the doubly OMe substituted ethene, **14**) to 107 kJ/mol (for the tetracyanoethylene, **21**). As anticipated, in the case of the monosubstituted alkene derivatives electron-donating moieties decrease the activation energies, whereas strongly electron-withdrawing groups cause an increase. Such an effect can be seen more dramatically for the disubstituted congeners (e.g., **5** and **14** versus **12** and **18**). Of course, the larger steric hindrance in the disubstituted alkenes may counterbalance this trend to some extent (**11** versus **17**). The push–pull-substituted derivative **19** shows a behavior in between that of electron-rich and electron-poor substrates. Comparing the activation barriers in the gas phase with those in acetone solution one realizes that DMDO epoxidations in solution commonly proceed more easily than those in the gas phase. For the monosubstituted systems **4**–**12** differences

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(24) For alkenes with $R_1 = R_2$ the transition states **TS(A)** and **TS(B)** are homomorphic. For alkenes with $R_1 \neq R_2$ the transition states **TS(A)** and **TS(B)** are diastereomorphic; only the transition structure with the lower energy of both is considered. In all cases with $R_1 \neq R_2$ the transition state **TS(B)** is favored over **TS(A)**.

TABLE 2. **Activation Energies (Gas Phase and Acetone Solution) Derived by B3LYP/6-311+G(d) for the Epoxidation of Alkenes 3−21 with DMDO 1a**[a]

system	R_1	R_2	$E_A^{\text{gas phase}}$	E_A^{solution}
3	H	H	73.2	61.8
4	Me	H	62.6	39.3
5	OMe	H	47.0	26.4
6	SO_2Me	H	93.5	76.3
7	CN	H	82.3	68.0
8	CO_2Me	H	75.7	61.6
9	CHO	H	76.2	62.5
10	Cl	H	77.3	53.9
11	NHAc	H	41.3	27.4
12	CF_3	H	87.3	68.9
13	Me	Me	60.0	47.8
14	OMe	OMe	28.1	18.6
15	SO_2Me	SO_2Me	81.3	94.0
16	Cl	Cl	86.9	79.6
17	NHAc	NHAc	47.8	39.5
18	CF_3	CF_3	97.1	93.9
19	OMe	CHO	65.7	47.0
20	CN	CN	99.3	117.5
21[b]	CN	CN	107.3	114.8

[a] All energy values are corrected for zero-point and given in kJ/mol. [b] Tetracyanoethylene is used as alkene.

TABLE 3. **Activation Energies (Gas Phase and Solution) Derived by B3LYP/6-311+G(d) for the Epoxidation of Alkenes 3−7, 10, 12, 16, 19, and 20 with HFDO 1b**[a]

system	R_1	R_2	E_A	$\Delta E_A^{\text{DMDO-HFDO}}$	E_A^{solvent}	$\Delta E_A^{\text{DMDO-HFDO solvent}}$
3	H	H	16.1	57.1	8.7	53.1
4	Me	H	1.6	60.9	2.5	36.8
5	OMe	H	[b]	[b]	[b]	[b]
6	SO_2Me	H	48.2	45.3	63.2	30.8
7	CN	H	37.4	44.9	46.2	21.9
10	Cl	H	16.6	60.7	18.1	35.7
12	CF_3	H	39.3	48.1	42.4	26.6
16	Cl	Cl	35.7	51.2	24.5	55.1
19	OMe	CHO	7.9	57.8	24.1	23.0
20	CN	CN	77.4	24.9	90.1	27.4

[a] All energy values are corrected for zero-point and given in kJ/mol. [b] The transition state was not found.

($E_A^{\text{gas phase}} - E_A^{\text{solution}}$) in the range of 14−23 kJ/mol are encountered, which renders the solution phase reactions to occur about 300 to 10 000 times faster (at 298 K) than the gas-phase transformations. These differences are smaller for the disubstituted analogues (3 to 18 kJ/mol); however, according to the calculations in three cases with alkenes with strongly electron-withdrawing groups (**15**, **20**, and **21**) the gas-phase epoxidation proceeds more easily than the reaction in solution.

For 10 of the 19 model systems (**3**−**7**, **10**, **12**, **16**, **19**, **20**) we also scrutinized the transition states for the epoxidation with hexafluorodimethyldioxirane (HFDO, **1b**) as the most powerful epoxidizing agent of the dioxirane family. Due to its relative instability commonly not hexafluorodimethyldioxirane, but methyl(trifluoromethyl)dioxirane is used. However, to elucidate the effect of the fluorine more easily we used for comparison hexafluorodimethyldioxirane in our investigations. Table 3 gives an overview of the activation energies obtained with HFDO, in the gas phase and in solution. A comparison with the DMDO reactions reveals that the activation energies with the fluorine-substituted dioxirane are tremendously decreased, by about 25 to 60 kJ/mol for the gas phase. An analysis of the values in solution, however, shows that the activation barriers for the HFDO mediated epoxidation in solution are higher than those in the gas phase (except for **3** and **16**), which stands in sharp contrast to the results obtained for DMDO. These trends are also visualized for the gas phase in Figure 3.

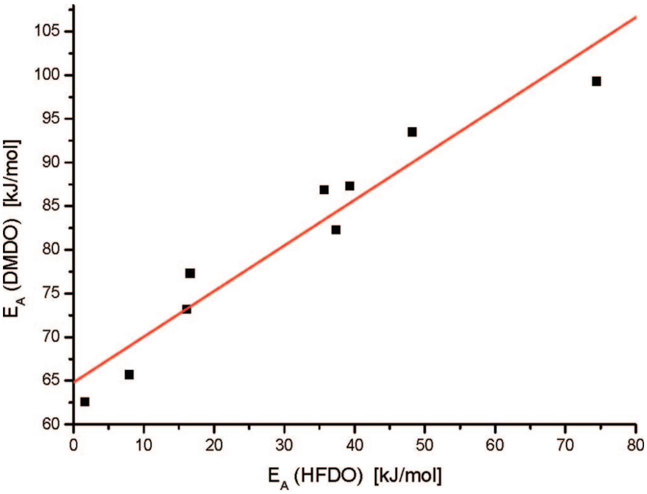

FIGURE 3. Relation between the activation energies E_A in epoxidation reactions by DMDO and by HFDO in the gas phase (top) and in acetone solution (bottom). Linear regression gives the following: $E_A(\text{DMDO}) = 64.8(\pm 2.0)\ \text{kJ/mol} + 0.52(\pm 0.05) \times E_A(\text{HFDO})$.

The most important geometrical parameters of the transition states are listed in the Supporting Information. In addition to relevant distances we also focused on two further parameters introduced by Deubel for such transfer reactions.[15] The first one is the extent of reaction ξ in the transition state and allows an evaluation of early or late transition states on the reaction coordinate.[25] The ξ values may range between $\xi = 0$ (for starting materials) and 1 (for products). A second useful parameter is the extent of asymmetry χ;[25] it provides a measurement for the deviation from the highly symmetrical (orthogonal) attack of the dioxirane on the C═C bond ($\chi = 0$). A comparison of the monosubstituted systems clearly shows early transition states for strongly electron-donating groups such as OMe and NHAc (see Supporting Information). This behavior is in line with the small activation barriers encountered for these systems. Late transition states are the result of electron-withdrawing moieties attached to the alkene (e.g., **6**, **7**, **12**). Again differences in steric bulk between the different substituents may slightly change the expected order. Also for the doubly substituted systems a general trend in ξ is not observable. All DMDO epoxidation reactions (except the one with tetracyanoethylene) show highly distorted transition structures indicating an asynchronous bond formation. Simple molecular orbital considerations reveal a larger coefficient of the HOMO of the alkene for the terminal (nonsubstituted) carbon atom regardless of being substituted by an electron acceptor or an electron donor. Assuming that the $\text{HOMO}_{\text{alkene}}-\text{LUMO}_{\text{dioxirane}}$ interaction is the predominant one (see the next paragraph) it is an immediate consequence that

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(25) (a) For the definition of the extent of reaction ξ in the transition state according to Deubel: $\xi = [d(\text{O1−O2,TS}) - d(\text{O1−O2,re})]/[d(\text{O1−O2,TS}) - d(\text{O1−O2,re}) + d(\text{O1−(C═C2),TS}) - d(\text{O1−(C1═C2),pr})]$. O1 is the proximal oxygen atom being transferred whereas O2 is the distal oxygen atom. C1 is the terminal carbon atom of the C═C bond and C2 is the vicinal carbon atom. The d(O1−O2) values are the O1−O2 distances in the transition states (TS) and in the reactants (re), respectively. d(O1−(C1═C2)) is the minimum distance between the O1 atom and the C═C bond in the TS and in the product (pr), respectively. (b) For the definition of the extent of asymmetry χ in the transition state according to Deubel: $\chi = [d(\text{O1−C1,TS}) - d(\text{O1−C2,TS})]/d(\text{C1−C2,TS})$. The d(X−Y) values are the distances between the atoms X and Y in the transition states.

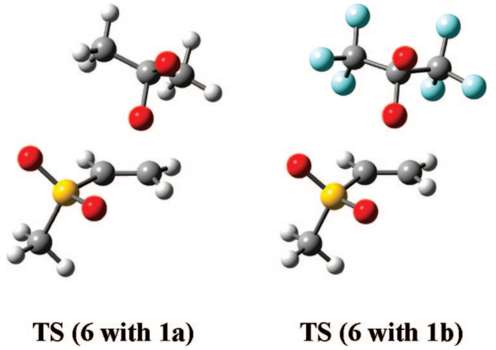

FIGURE 4. Transition states for the epoxidation of alkene **6** with dimethyldioxirane **1a** (left side) and hexafluorodimethyldioxirane **1b** (right side).

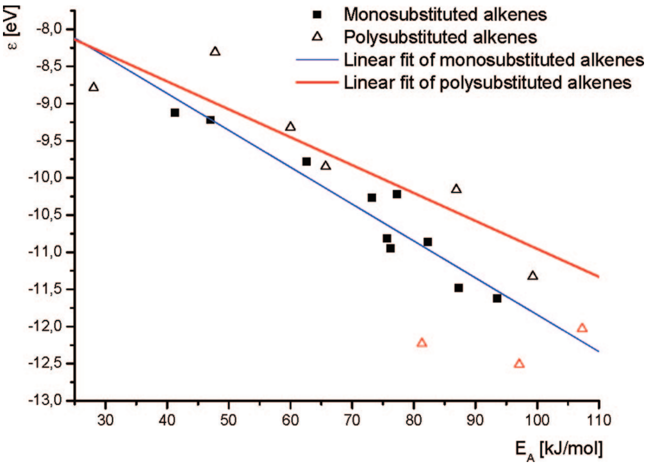

FIGURE 5. Relation between the activation energy E_A in DMDO epoxidation and the HOMO energy of the respective alkene. Linear regression gives for monosubstituted alkenes ε(HOMO) [eV] = $-6.88(\pm0.40) + 0.050(\pm0.005) \times E_A$ [kJ/mol] and for disubstituted alkenes ε(HOMO) [eV] = $-7.20(\pm0.61) + 0.038(\pm0.009) \times E_A$ [kJ/mol].

TABLE 4. Wiberg Bond Indices (WBI) for Bonds *a* and *b* (for Definition, See Scheme 2) and Charge Transfer (CT) Based on the B3LYP/6-311+G(d) Density of the Transition State[a]

			DMDO epoxidation		HFDO epoxidation	
system	R_1	R_2	WBI	CT	WBI	CT
3	H	H	0.35/0.35	0.391	0.23/0.23	0.352
4	Me	H	0.37/0.28	0.409	0.18/0.13	0.279
5	OMe	H	0.38/0.15	0.416	[c]	[c]
6	SO_2Me	H	0.47/0.31	0.279	0.33/0.28	0.394
7	CN	H	0.47/0.24	0.271	0.34/0.20	0.377
8	CO_2Me	H	0.43/0.27	0.312		
9	CHO	H	0.44/0.26	0.280		
10	Cl	H	0.44/0.23	0.383	0.27/0.13	0.363
11	NHAc	H	0.39/0.13	0.421		
12	CF_3	H	0.42/0.32	0.344	0.30/0.27	0.395
13	Me	Me	0.27/0.33	0.413		
14	OMe	OMe	0.17/0.22	0.383		
15	SO_2Me	SO_2Me	0.30/0.48	0.240		
16	Cl	Cl	0.26/0.42	0.356	0.23/0.29	0.474
17	NHAc	NHAc	0.24/0.30	0.486		
18	CF_3	CF_3	0.30/0.47	0.257		
19	OMe	CHO	0.21/0.40	0.440	0.09/0.21	0.334
20	CN	CN	0.29/0.49	0.239	0.26/0.36	0.382
21[b]	CN	CN	0.36/0.36	0.140		

[a] CT from alkene to dioxirane is given in electron units. [b] Tetracyanoethylene is used as alkene. [c] Transition state was not found.

the epoxide bond to the terminal carbon is formed first. For HFDO-mediated epoxidations we observe larger distances *a* and *b* than for the corresponding DMDO epoxidations. The extent of asymmetry χ is significantly smaller than that for the reactions with DMDO. Figure 4 compares two transition structures using the SO_2Me substituted alkene **6** with DMDO **1a** (left side) and HFDO **1b** (right side). Even on a qualitative basis, one observes in the latter case a much less asymmetric transition state.

On the basis of the B3LYP optimized geometries of the various alkenes and the two epoxidizing reagents we performed HF calculations to obtain HOMO and LUMO energies of the corresponding species. With these data in hand (see Supporting Information),[26] we evaluated the dominant orbital interactions.

We observe high-lying HOMOs for alkenes with electron-donating groups such as OMe and NHAc (−8.3 to − 9.5 eV), whereas strongly electron-withdrawing groups such as SO_2Me, CN, and CF_3 result in a decrease of the HOMO energy (−10.0 to −12.5 eV). Assuming a predominant interaction of the HOMO of the alkene with the LUMO of the dioxirane (electrophilic attack of the alkene by the dioxirane), a significant lower lying HOMO should result in an increase of the activation energy. Figure 5 compares the HOMO energies of alkenes **3**−**21** with the activation barriers for the epoxidation with DMDO in the gas phase. As anticipated, a high-lying HOMO is prone to donate its electrons to the low-lying LUMO of the dioxirane that is an unoccupied σ^* (O−O) orbital (cf. Figure 1). In three cases **15**, **20**, and **21**—these are the systems carrying at least two strongly electron-withdrawing groups—the energy difference between the LUMO of the alkene with the HOMO of the dioxirane is only slightly larger than the dominant $\text{HOMO}_{\text{alkene}}-\text{LUMO}_{\text{dioxirane}}$ interaction. In Figure 5 these systems are shown as red triangles and do significantly deviate from regression. Of course, such a regression can only take into account one major parameter and as long as a second one is important, deviations result.

To get further insights into the principal interactions natural bond orbital (NBO) analyses were undertaken. It is notable that the π(C=C) → σ^*(O−O) interaction is the major one in all systems. This result is in line with the calculated HOMO−LUMO data provided (see the Supporting Information). In all cases, even for alkenes with strongly electron-withdrawing groups, the $\text{HOMO}_{\text{alkene}}-\text{LUMO}_{\text{dioxirane}}$ interaction is energetically favored over the $\text{LUMO}_{\text{alkene}}-\text{HOMO}_{\text{dioxirane}}$ interaction. Wiberg bond indices (WBI) were calculated; they further corroborate the view of early and late transition states (Table 4). Charge transfer (CT) data estimated from NPA charges clearly show that electron donation occurs from the alkene to the dioxirane. Electron-poor substrates donate less charge than electron-rich ones; however, we could not identify a single system in which the alkene moiety obtains a net charge from the oxidant. Thus, all alkenes are attacked in an electrophilic manner, which stands in contrast to the recent hypothesis of a nucleophilic reactivity of dimethyldioxirane.[15]

Conclusion

Dioxirane-mediated epoxidation reactions of a variety of differently mono-, di-, and tetrasubstituted alkenes were evalu-

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(26) The calculated HOMO energies are in the same range as those derived experimentally by photoelectron (PE) spectroscopy: (a) For various substituted alkenes, see: Houk, K. N.; Munchausen, L. L. *J. Am. Chem. Soc.* **1976**, *98*, 937–946. (b) For ionization energies of dioxiranes, see: Gleiter, R.; Schang, P.; Adam, W.; Eggelte, H. J.; Erden, I.; Bloodworth, A. J. *J. Electron Spectrosc. Relat. Phenom.* **1980**, *19*, 223–230.

ated by computational means with use of the B3LYP/6-311+G(d) level of theory. Gas-phase reactivities as well as solvent effects were examined for epoxidations with DMDO and HFDO. In general, the observed activation barriers strongly depend on the nature of the substituent. Electron-donating substituents cause a decrease of the activation energies and induce early transition states whereas electron-withdrawing groups increase the barriers. Depending on the electronic bias of the substituents one observes a range of 28 to 107 kJ/mol for the gas-phase DMDO-mediated epoxidations. In acetone solution these values are tremendously decreased except for the most powerful electron-withdrawing groups such as CN and SO_2Me. The activation barriers for HFDO-mediated epoxidations are much smaller than those obtained for DMDO; however, when going from the gas phase to an acetone solution these values are increased (except for ethylene **3** and dichloroalkene **16**). With HFDO we observed very early transition states and smaller values of asymmetry than for the corresponding DMDO-mediated transformations. Investigations of the frontier orbitals have shown that the key stabilizing interaction is the $\mathrm{HOMO}_{\mathrm{alkene}}$ with the $\mathrm{LUMO}_{\mathrm{dioxirane}}$. This view was further corroborated by NBO analyses. The recently published hypothesis of a biphilic dichotomy[15] of dioxirane reactivity was not substantiated. An examination of the net charge transfer reveals in all cases electron donation from the alkene to the dioxirane.

Acknowledgment. This research was supported by the Deutsche Forschungsgemeinschaft (Emmy Noether Fellowship to D.B.W.) and the Fonds der Chemischen Industrie. A.D. is grateful to the Studienstiftung des deutschen Volkes for a graduate fellowship. The authors thank Prof. Lutz F. Tietze for useful advice and generous support of the work.

Supplementary Information Available: Cartesian coordinates and total energies for all calculated compounds and transition states, relevant interatomic distances of the transition states and HF based orbital energies of starting materials, and full ref 17. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800692Z