Epoxidation by Dimethyldioxirane: Effects of Intramolecular and Intermolecular Interactions

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Received August 11, 1997. Revised Manuscript Received December 2, 1997

Abstract: The Density Functional Theory B3LYP/6-31G* method is used to provide a detailed understanding of the origins of intra- and intermolecular (solvent) effects on the epoxidation of C−C double bonds by dimethyldioxirane (DMDO) in a model system, 2-methyl-2-butene. We found that the presence of hydrogen bond donor substituents, such as hydroxyl and amino groups, at the allylic position on the olefin leads to substantially decreased activation barriers for epoxidation. This effect is observed exclusively when a hydrogen bond interaction is present between the hydroxyl or amino substituent and the attacking DMDO molecule, and is not caused by inductive electronic effects of the substituents. An even more significant lowering of the activation barrier is seen when DMDO forms a hydrogen bond with methanol (representing a hydrogen bond donor solvent) in the transition state. Solvent polarity, studied using the SCIPCM model, influences the epoxidation barrier to a much smaller degree than do hydrogen bonding interactions.

Introduction

Dioxiranes offer a powerful and often unique ability to transfer an oxygen atom to a wide variety of substrates, including carbon−hydrogen bonds in hydrocarbons[1] and atoms containing lone pairs, such as sulfides and sulfoxides[2] and primary[3] and secondary amines.[4] However, the most intensively studied and reported reaction is dioxirane epoxidation of carbon−carbon double bonds.,[5,6] Control of regioselectivity and stereoselectivity by conformation and substituents in the alkene system, and by solvent used in the reaction, is the subject of much recent attention. Baumstark and co-workers observed the greater reactivity of cis-alkenes in the dimethyldioxirane (DMDO) epoxidation of the cis/trans pairs of alkenes.[5] They also documented highly accelerated epoxidation rates upon addition of water to DMDO in acetone.[6] Murray and Gu reported rates of DMDO epoxidation of ethylcinnamate and cyclohexene in a number of binary solvent systems.[7] Solvents with hydrogen bond donor capacity increase reaction rates, whereas the opposite effect, i.e., a decrease in reaction rates, was seen for solvents with hydrogen bond acceptor capacity.[7] A pronounced dependence of epoxide diastereoselectivity on substituent has been recently reported in DMDO epoxidations of cyclohexenes. In addition, a strong solvent influence on this stereoselectivity has been also observed.[8] Adam and Smerz have documented similar substituent and solvent effects in regio- and diastereselective epoxidation of allylic alcohols by DMDO.[9] The observed control of regio- and stereoselectivity is postulated to occur primarily through hydrogen bonding interactions with the hydroxyl substituents of allylic alcohols and/or with molecules of a protic solvents.[8,9]

The present computational study elucidates the atomistic details of intra- and intermolecular interactions affecting reactivity and selectivity in DMDO epoxidations of alkenes. The transition-state barriers for DMDO epoxidation of 2-methyl-2-butene and its derivatives are significantly lowered in the presence of a hydrogen bonding interaction with DMDO provided by substituents present in the alkene system or hydrogen bond donor solvents such as methanol. Reaction barriers are also decreased, although to a smaller extent, in the presence of polar solvents. Our results provide an elegant explanation of experimentally observed substituent and solvent effects in dioxirane epoxidations.

Computational Methods

Dioxiranes are challenging problems for ab initio calculations. Hartree−Fock methods are inadequate for dioxiranes; methods that incorporate electronic correlation energy, at least to some extent, are required to correctly describe dioxiranes.[10] We used the B3LYP/6-31G* density functional method herein, which we previously successfully applied to dioxiranes in our study of DMDO oxidations of primary amines.[11] This method was used in other computational studies of dioxirane systems;[12−15] it also reproduced well (and much better than MP2/6-31G*) the experimental transition states in the epoxidation of alkenes by peracids.[14,16] However, in some other epoxidations, such as by oxaziridine, both B3LYP/6-31G* and MP2/6-31G* give unsymmetrical transition-state structures.[16]

Whereas there is convincing evidence that the B3LYP/6-31G* model reproduces well transition-state geometries as well as trends in activation

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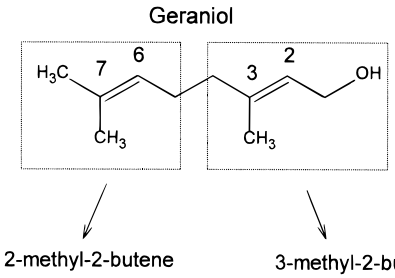
S0002-7863(97)02800-X CCC: $15.00
Published on Web 03/04/1998

Scheme 1



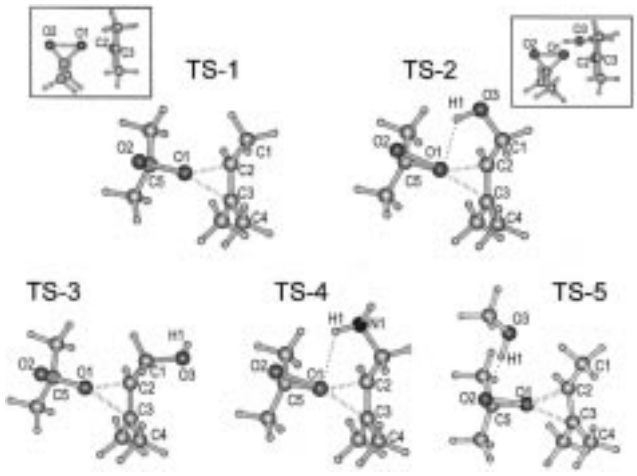


Figure 1. B3LYP/6-31G* transition-states structures for DMDO epoxidation of the double bond in 2-methyl-2-butene (TS-1), 3-methyl-2-buten-1-ol (TS-2 and TS-3), 1-amino-3-methyl-2-butene (TS-4), and 2-methyl-2-butene in the presence of methanol (TS-5). Small boxed inserts for TS-1 and TS-2 show an alternative view of the structure.

barriers in various epoxidation reactions and in oxidations by dioxirane, it should be kept in mind that absolute values of B3LYP/6-31G* activation barriers in such reactions are underestimated by as much as 4−5 kcal/mol when compared with QCISD, CCSD, MP4, and MP2 calculations.[11,14] However, such underestimation is of little concern in this work, where the relative values of transition-state barriers are primarily explored. For the same reason, the 6-31G* basis set is adequate for the present study, although a larger basis set with polarization functions on hydrogens would be more suitable to reproduce more precisely the energetics of the hydrogen bond interactions as present in some of the molecular systems studied here.

All calculations were performed using Gaussian 94.[17] Our model systems, the reaction between DMDO and 2-methyl-2-butene or its hydroxy or amino derivatives, were inspired by and simulate the epoxidation of geraniol by DMDO studied experimentally by Adam and Smerz[9] as illustrated in Scheme 1. Transition-state (TS) structures were calculated for DMDO epoxidation of 2-methyl-2-butene (TS-1), 3-methyl-2-buten-1-ol (TS-2 and TS-3), 1-amino-3-methyl-2-butene (TS-4), and 2-methyl-2-butene in the presence of methanol (TS-5), as illustrated in Figure 1. Vibrational frequencies calculated for all the studied systems confirmed the nature of the stationary points (energy minimum, all positive frequencies; transition states, one imaginary frequency with largest contributions from internal coordinates involved in the reaction).

Effects of dielectric solvent were simulated using the SCIPCM model[18] as implemented in Gaussian 94[17] using an isodensity value of 0.0005. SCIPCM calculations were single-point calculations; i.e., geometry was taken from the gas-phase calculations and was not re-optimized using the dielectric model. Analysis of electronic properties and molecular orbitals was performed via natural bond orbital (NBO) analysis.[19]

Results and Discussion

Calculated TS structures are illustrated in Figure 1. Activation energies and enthalpies, as well as selected geometrical parameters of the TS structures, are collected in Table 1.

Geometric changes on going from reactant to TS are primarily found in DMDO; the alkene geometry is only slightly perturbed. We observed substantial lengthening of the C5−O1 and O1−O2 bonds in DMDO. The second C−O bond, i.e., C5−O2, undergoes significant shortening toward the forming C═O bond in acetone, a product in the reaction. The alkene undergoes only a small lengthening of the double bond and a slight distortion from planarity in the TS.

All TS structures are asymmetric with respect to C(alkene)···O(dioxirane) distances; the C2···O1 distance is substantially shorter than the C3···O1 distance, as expected, because C2 and C3 are not equivalent. C3 is sterically more hindered. The presence of amino or hydroxyl substituents on the alkene causes increased asymmetry in the C···O distances, e.g., with 2-methyl-2-buten-1-ol, C2···O1 is shorter by as much as 0.35 Å than C3···O1.

Both intra- and intermolecular interactions have a profound effect on activation energies. The hydroxyl group at C1, in a conformation that allows for it to interact with the attacking DMDO, brings down the activation enthalpy from 13.6 kcal/mol to 7.2 kcal/mol. This is not an electronic effect, i.e., changes in electronic density distribution within the alkene, but is clearly due to direct interaction between DMDO and the OH group. When the OH group is rotated away from DMDO, such that it cannot interact with DMDO, the activation barrier returns to 13.2 kcal/mol. The interaction between OH and DMDO has the form of hydrogen bonding, although the hydrogen bond angle of 120° is quite far from an optimal linear configuration.

The observed decrease in activation enthalpy is not limited to 3-methyl-2-buten-1-ol. An amino group at C1 has a similar interaction with DMDO and decreases the activation enthalpy. However, the decrease is smaller when compared to the hydroxyl group (to 10.3 vs 7.2 kcal/mol) which is explained by a weaker hydrogen bonding interaction as evidenced by a longer N···H distance and even less favorable angle. One may expect similar effects on the reaction barrier with other substituents that possess hydrogen bond donor capability.

An even more profound effect than observed with hydrogen bond donor substituents is observed in the presence of methanol − the "external" hydrogen bond donor. The activation enthalpy is just 2.7 kcal/mol when methanol is hydrogen bonded to DMDO in TS-5. Methanol is geometrically less constrained than substituents on the alkene and thus forms a stronger

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Table 1. Activation Energies ($\Delta E^{\ddagger}$, Uncorrected for Zero-Point Energy), Activation Enthalpies ($\Delta H^{\ddagger}_{298}$), and Selected Geometrical Parameters of the Calculated Transition-State Structures. Annotation of Transition States and Atoms as in Figure 1

	TS-1 (2-methyl-2-butene)	TS-2 (3-methyl-2-buten-1-ol)	TS-3 (3-methyl-2-buten-1-ol)	TS-4 (1-amino-3-methyl-2-butene)	TS-5 (2-methyl-2-butene with methanol)
$\Delta E^{\ddagger}$ (kcal/mol)	13.6	6.74	13.0	10.0	0.81
$\Delta H^{\ddagger}_{298}$ (kcal/mol)	13.6	7.23	13.2	10.3	2.69
O1···C2 (Å)	1.946	1.938	1.909	1.944	2.046
O1···C3 (Å)	2.194	2.275	2.258	2.246	2.261
O1−O2 (Å)[a]	1.879	1.856	1.873	1.861	1.833
C5−O1 (Å)[b]	1.482	1.475	1.479	1.474	1.453
C5−O2 (Å)[b]	1.329	1.340	1.331	1.338	1.355
C3−C2 (Å)[c]	1.385	1.383	1.385	1.383	1.379
H1···O1 (Å)		2.112	4.349	2.318	2.453
H1···O2 (Å)		2.525	5.901	2.700	1.865
O3/N1−H1···O1/O2 (deg)		120.1[d]		110.6[e]	168.7[f]
C1−C2−C3−C4 (deg)[g]	11.5	10.0	13.9	10.1	8.7

[a] 1.506 Å in DMDO. [b] 1.403 Å in DMDO. [c] 1.342 Å in 2-methyl-2-butene. [d] O3−H1···O1. [e] N1−H1···O1. [f] O3−H1···O2. [g] 0.0° (planar) in 2-methyl-2-butene.

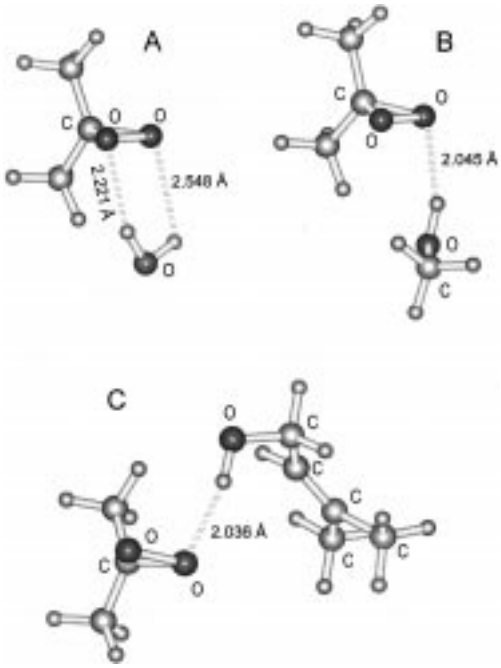

Figure 2. B3LYP/6-31G* structure of hydrogen bonded complexes formed between DMDO and water (A), methanol (B), and 2-methyl-2-butene (C).

hydrogen bond interaction (the H1···O1 distance is just 1.865 Å and the O3−H1···O1 angle is 168.7°) with DMDO.

In these epoxidation reactions, DMDO is the electrophile and the alkene π system is the nucleophile. The TS geometries provide optimal interaction between frontier orbitals, i.e., the LUMO of DMDO and the HOMO of the alkene. Hydrogen bonding interactions with the dioxirane exert their effect on the reaction barrier by lowering the DMDO LUMO (primarily antibonding O−O) energy. The LUMO energy is decreased by 0.0165 au in the complex between DMDO and methanol (Figure 2A) compared to isolated DMDO. A similar effect is seen when water interacts with DMDO (Figure 2B) and in the hydrogen bonded complex formed with 2-methyl-2-butene (Figure 2C). In these cases, the DMDO LUMO energy decreases by 0.0145 and 0.0115 au, respectively. Although it has been suggested that the hydroxyl group in allylic alcohols should lower the nucleophilicity of the double bond through inductive electron withdrawal, we do not find the hydroxyl group exercising any meaningful electronic effect on the HOMO (π C═C orbital) of the allylic alcohol. The HOMO energy is −0.248 au in 3-methyl-2-buten-1-ol versus −0.244 au in 2-methyl-2-butene; the HOMO occupancies are 1.935 and 1.944, respectively. In addition, the atomic partial charges on C2 and C3 do not change significantly with the introduction of the hydroxyl group at C1. As a result, our calculations indicate that the inductive effect of the OH group in allylic alcohol is very small, if any, and the primary mechanism by which this group may affect the reaction barrier for epoxidation is through a direct interaction with DMDO in the TS.

Table 2. Transition-State Activation Energies ($\Delta E^{\ddagger}$) Calculated in the Presence of Dielectric Medium Using the SCIPCM Model

dielectric constant ϵ in SCIPCM calculations	common solvent with a close value of ϵ	TS−1 $\Delta E^{\ddagger}$ (kcal/mol)	TS−2 $\Delta E^{\ddagger}$ (kcal/mol)
gas phase	gas phase	13.6	6.74
10	CH_2Cl_2 ($\epsilon = 9.08$)	9.98	6.47
20	acetone ($\epsilon = 20.7$)	9.53	6.41
40	CH_3CN ($\epsilon = 36.02$)	9.26	6.37

Solvent polarity affects the activation barrier for epoxidation of 2-methyl-2-butene (TS-1), as revealed by calculations using the SCIPCM model (Table 2). $\Delta E^{\ddagger}$ for TS-1 decreases from 13.6 kcal/mol in the gas phase to 9.3 kcal/mol when a dielectric constant of 40 is used. The decrease in the activation barrier reflects the polarity (μ = 4.22 D) of TS-1 (for comparison: μ_{DMDO} = 2.89 D, $\mu_{2-methyl-2-butene}$ = 0.18 D). The solvent-induced decrease in $\Delta E^{\ddagger}$ for TS-1 is substantially smaller than observed with hydrogen bonding interactions (Table 1). It is also smaller than the decrease found previously for the DMDO oxidation of methylamine, where a very polar (μ = 8.06 D) TS structure was formed.[11] In contrast to TS-1, the activation barrier for TS-2 is almost unperturbed by the presence of polar solvents, despite its large dipole moment of 5.23 D. We explain this based on the stronger solvation of the substrate, 3-methyl-2-buten-1-ol (μ = 1.63 D).

The calculated effects of intra- and intermolecular interactions on activation barriers correlate very well with available experimental observations. For example, our calculated enthalpy of activation $\Delta H^{\ddagger}$ of 9.9 kcal/mol for TS-1 in dielectric of ϵ = 20 agrees well with the experimentally determined $\Delta H^{\ddagger}$ of 7.4 kcal/mol for epoxidation of cyclohexene by DMDO in acetone.[7] Murray and Gu measured reaction rates of epoxidation of cyclohexene and ethyl *trans*-cinnamate by DMDO in binary solvent mixtures and applied a Kamlet−Taft equation to analyze origins of solvent effects.[7] Their analysis indicates that by far the most important facet contributing to the solvent effect is the solvent's hydrogen bond donor properties; reaction rates increase with increased donor properties. A solvent's polarity

appeared to be the least important term in the Kamlet−Taft equation; however, a small increase of reaction rates was found with increasing polarity. We observe exactly the same effects computationally, where a dramatic lowering of the activation barrier is seen with hydrogen bonding donating methanol, while a much smaller decrease in the barrier is seen with increasing polarity of the solvent.

Our results are also in qualitative agreement with the experimental work on DMDO epoxidation of geraniol performed by Adam and Smerz.[9] As suggested by their results, competing hydrogen bond interactions between the hydroxyl group present in geraniol and hydrogen bond donor solvents, such as methanol, is primarily responsible for the observed regiospecificity of the reaction. The lowest yields of the 6,7 epoxide (cf. Scheme 1) have been measured in methanol as solvent.[9] Our results indicate that DMDO hydrogen bonding in the TS with methanol is much stronger than with the allylic hydroxyl group, which explains the regioselectivity. In the absence of hydrogen donor solvents, the importance of the internal hydrogen bond increases and, consequently, the yield of the 2,3 epoxide increases. However, our simple and mainly gas-phase model does not provide for quantitative agreement with experimental yields. Whereas Adam and Smerz observed increased yields of the 2,3 epoxide in acetone and CCl_4 compared to methanol, the overall preference for epoxidation of the 6,7 double bond of geraniol was still seen in acetone and CCl_4. This preference was explained by the authors as due to the lowered nucleophilicity of the 2,3 double bond due to electron withdrawing by the hydroxyl group. Our calculations show no indication of such lowered nucleophilicity in the allylic alcohol.[20] It is also possible that decreased reactivity of allylic alcohols is due to solvations effects in either the ground state or the transition state. DMDO oxidations are always performed in the presence of some amount of unavoidable acetone; as a result the reaction medium is always at least binary. We note that the study by Murray and Gu indicates a complex pattern of solvent effects on DMDO epoxidations with hydrogen bonding acceptor and self-organizing properties of solvent at least as important as solvents polarity.[7] Our simple model calculations, while providing convincing evidence for importance of hydrogen bonding interactions and lesser importance of solvent polarity on reaction barriers, cannot fully account for all competing interactions that can affect the reaction in the liquid phase.

Conclusions

We calculated an activation enthalpy of 13.6 kcal/mol for the epoxidation of 2-methyl-2-butene by DMDO in the gas phase at the B3LYP/6-31G* level. In a dielectric medium with $\epsilon = 20$, $\Delta H^{\ddagger}$ is 9.6 kcal/mol, which agrees well with the experimental value of 7.4 kcal/mol for epoxidation of cyclohexene in acetone. In the related allylic alcohol, 3-methyl-2-buten-1-ol, the gas-phase activation barrier is substantially lowered to 7.2 kcal/mol due to a hydrogen bonding interaction between the hydroxyl group of the alcohol and DMDO. This interaction decreases the energy of the LUMO on DMDO.

We observed a dramatic lowering of the reaction barrier to just 2.7 kcal/mol when methanol interacts (via hydrogen bonding) with DMDO at the transition state for epoxidation of the alkene. By comparison, increasing the polarity of the solvent only slightly decreases the epoxidation barrier. This effect is much less profound than seen for hydrogen bonding interactions.

Supporting Information Available: Absolute energies for five substrates and five transition states, and Cartesian coordinates of optimized structures for 2-methyl-2-butene, 3-methyl-2-buten-1-ol, 1-amino-3-methyl-2-butene, and all five transition states (6 pages). See any current masthead page for ordering information and Web access instructions.

JA972800O