Oxidation of Primary Amines by Dimethyldioxirane: Ab Initio Model Studies

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We performed ab initio studies of the initial step in dimethyldioxirane (DMDO) oxidation of primary amines, i.e., transfer of the first oxygen atom. The activation barrier for oxygen transfer from DMDO to methylamine is 17.7 kcal/mol (in vacuum) calculated at the MP2/6-311+G** level. The reaction is exothermic: −13.0 kcal/mol (MP2/6-311+G**). The transition structure occurs at an N···O distance of 1.702 Å and shows characteristics of being late along the reaction pathway. Polar solvents substantially decrease the reaction barrier with an even more remarkable decrease (to about 10% of its original value) observed when solvent molecules are hydrogen-bonded to the peroxy oxygens. DMDO displays characteristics of a typical electrophile in the reactions studied here.

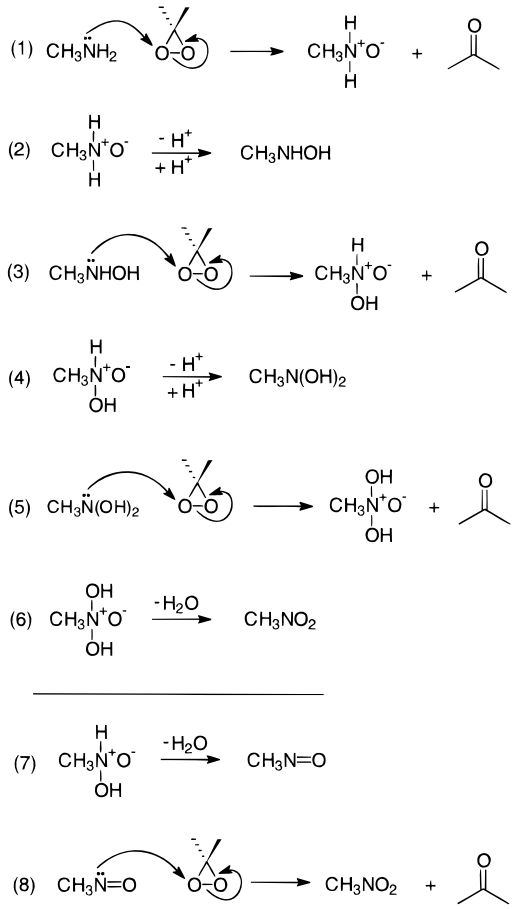
Introduction

The chemistry of dioxiranes (e.g., **1**−**3**) has attracted significant scientific interest due to the powerful and often unique ability of these compounds to transfer an oxygen atom to a wide variety of substrates. Probably the most intensively studied and reported reaction is the dioxirane epoxidation of alkenes.[1−3] However, dioxiranes can also oxidize carbon−hydrogen bonds in hydrocarbons[4,5] as well as atoms containing lone pairs in compounds such as sulfides and sulfoxides[6] and primary[7] and secondary[8] amines.

1 R = H
2 R = F
3 R = CH_3

Oxidation of primary amines (or isocyanates, *vida infra*) by dimethyldioxirane (DMDO, **3**) in acetone is an attractive synthetic route to nitro compounds that are difficult to synthesize by direct nitration methods. In particular, DMDO oxidation of an amino group is an especially attractive synthetic route to nitro derivatives of cage carbon compounds such as adamantane[9] and cubane.[10] Often, the starting compound for DMDO oxidation is an isocyanate;[10] however, the reaction between isocyanates and DMDO takes place in a wet acetone solution and presumably progresses *via* oxidation of the amino group formed upon hydrolysis of the isocyanate.[11]

Scheme 1



The detailed reaction mechanism of dioxirane oxidations remains largely unknown since the chemistry of dioxiranes has not been thoroughly studied. Our work represents the first attempt to address the question of the mechanism of oxidation of primary amines by DMDO. The present work also contributes to the understanding of dioxirane oxidation chemistry in general, since several of the effects observed are general to dioxiranes and are in no way limited to amine oxidation.

Oxidation of primary amines to nitro compounds is a multistep process believed to involve subsequent transfer of three oxygen atoms from DMDO to the nitrogen atom.[7] Steps 1−6 (Scheme 1) represent one possible mechanism where three identical transfers of oxygen occur from

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DMDO to the amine, hydroxylamine, and dihydroxylamine, with final loss of water, to give nitromethane from methylamine. In each oxidation step, the amine nitrogen acts as the nucleophile and DMDO the electrophile. In the alternative mechanism (steps 1−3, then 7 and 8, Scheme 1), the loss of water after the second oxygen transfer produces the nitroso compound; the nitroso nitrogen would then act either as a nucleophile to attack DMDO or as an electrophile that is attacked by DMDO for the final oxygen atom transfer. At this point there is not enough evidence to support one of these two alternative mechanisms in preference to the other. Modeling studies are under way in our group to elucidate a preferred mechanism (i.e., steps 4−6 vs steps 7 and 8).

In the present work we modeled only the initial step, transfer of the first oxygen atom from DMDO to methylamine. We located the transition state structure for this reaction at various levels of ab initio theory in the gas phase, as well as in several dielectric medium representations of solvents. In addition, we investigated the catalytic activities of hydrogen-bond-donor molecules, water and methanol, on the reaction barrier. Subsequent steps of the mechanism involving transfer of the second and third oxygen atoms from DMDO are presently under investigation. However, we anticipate (based on preliminary calculations) that these subsequent transfer reactions have similar characteristics to the first oxygen atom transfer process as studied here.

Dioxirane is a challenging molecular system for quantum mechanical methods due to the nature of the O−O bond in the three-membered ring.[12] Our results (*vida infra*) indicate that dioxirane systems can be successfully modeled using only moderately expensive methods such as MP2 and B3LYP coupled with moderate size basis sets.

Methods

All calculations were performed with the Gaussian 94 suite of programs.[13] Stationary points (energy minimum, all positive eigenvalues of the Hessian matrix, and transition state, one negative eigenvalue of the Hessian matrix) on the potential energy surface were fully optimized using second-order Møller-Plesset (MP2), and density functional theory (DFT) methods. Basis sets from moderate, 6-31G*, to moderately large, 6-311+G**, were employed. Since DFT evaluation of vibrational frequencies is computationally inexpensive and provides accurate values, vibrational zero-point energies (ZPE) were calculated exclusively at the B3LYP/6-31G* level and were used to correct energies at all levels of theory applied here. The effects of dielectric solvent were simulated with the SCIPCM model[14] as implemented in Gaussian 94.[13] We encountered numerous convergence problems performing geometry optimizations with the SCIPCM field present; therefore only single point energy calculations were performed with this model, i.e., geometries were not optimized in the dielectric medium. An isodensity value of 0.0002 was used in the SCIPCM calculations; we found this value provided for good SCF convergence in the systems studied. We note that while absolute energies change with the isodensity level used, we did not observe such a dependence on the relative energies. Analysis of electronic properties and molecular orbitals was performed via natural bond orbital (NBO) analysis.[15]

Results

DMDO (**3**), is the primary dioxirane used synthetically; therefore, we use it here to model the reaction with a prototypical primary amine, methylamine (**4**). Experimental structures of DMDO or other dialkyl dioxiranes have not been reported. Therefore, we tested the performance of various levels of theory for two other members of the dioxirane family, namely dioxirane (H_2CO_2, **1**) and difluorodioxirane (F_2CO_2, **2**), which have been the subject of detailed experimental structural studies.[16−18]

Hartree−Fock (HF) ab initio models are totally incapable of correctly describing the geometry and properties of the dioxirane group.[19] Therefore, we turned our attention to the DFT and MP2 methods. We tested four DFT functionals, BLYP, B3PW91, B3LYP, and SVWN, and found the B3LYP functional performing decisively the best for geometries of **1** and **2** (only results from B3LYP calculations are presented here). The B3LYP and MP2 geometries of **1**−**2** and **3**, calculated with the 6-31G* and 6-311+G** basis sets, are collected in Table 1, together with the available experimental geometries for **1** and **2**. Agreement with experimental values is good; MP2/6-311+G** geometries agree with experiment within measurement error. The agreement with experimental geometries is as good (and sometimes even better) than that observed with high level correlated methods.[12,20−23] The main difference observed between B3LYP and MP2 geometries is in the O−O bond distance: B3LYP underestimates this bond length whereas MP2 slightly overestimates it. The basis set seems to have a negligible effect on B3LYP geometries; however, a clear improvement is seen in MP2 geometries by increasing the basis set from 6-31G* to 6-311+G**. Both B3LYP and MP2 also provide values for the dipole moment of **1** in good agreement with experiment. The B3LYP/6-31G* value is 2.38 D compared to experimentally determined value of 2.48(7) D.[16] We note that the applicability of the B3LYP functional to the geometry, vibrational properties, and energetics in **2** has already been suggested by Kraka et al.,[21] whereas sufficiently good performance of the MP2 method for ground-state **1** and its oxygen-transfer reactions has been indicated by Bach et al.[22]

Relative energies of the reactive complex, i.e., a stationary point formed by the reactants before reaching the TS, products, and transition structures (TS) for the oxidation of methylamine by DMDO are collected in Table 2. Structures of the reactive complex and TS are

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Table 1. Calculated and Experimental Geometrical Parameters of Dioxirane, Difluorodioxirane, and Dimethyldioxirane[c]

	C−O (Å)	O−O (Å)	C−H/C−F/C−C (Å)	O−C−O (deg)	H−C−H/ F−C−F/ C−C−C (deg)
			Dioxirane (H_2CO_2)		
MP2/6-31G*	1.399	1.531	1.090	66.4	116.5
B3LYP/6-31G*	1.391	1.507	1.093	65.6	116.1
MP2/6-311+G**	1.389	1.521	1.089	66.4	117.0
B3LYP/6-311+G**	1.388	1.503	1.090	65.6	116.8
experiment[a]	1.388(4)	1.516(3)	1.090(2)	66.2(2)	117.3(2)
			Difluorodioxirane (F_2CO_2)		
MP2/6-31G*	1.357	1.587	1.330	71.6	108.6
B3LYP/6-31G*	1.352	1.555	1.326	70.2	109.0
MP2/6-311+G**	1.346	1.577	1.322	71.7	108.6
B3LYP/6-311+G**	1.345	1.552	1.326	70.5	108.9
experiment[b]	1.348(8)	1.578(1)	1.317(6)	71.7(5)	108.8(7)
			Dimethyldioxirane $(CH_3)_2CO_2$		
MP2/6-31G*	1.409	1.534	1.502	65.9	118.1
B3LYP/6-31G*	1.403	1.506	1.510	64.9	118.0
MP2/6-311G**	1.399	1.525	1.503	66.0	117.7
B3LYP/6-311+G**	1.401	1.501	1.507	64.8	117.8

[a] Reference 15. [b] Reference 17. [c] Experimental geometry for dimethyldioxirane is not available.

Table 2. Energies (ZPE included) (kcal/mol) of stationary Points on the Reaction Pathway Relative to Energies of Isolated Substrates, i.e. DMDO and Methylamine

	reactive complex	transition state	products
MP2/6-31G*	−5.38	20.6	−5.47
MP2/6-311+G**	−3.85	17.7	−13.0
B3LYP/6-31G*	−2.66	14.4	−9.61
B3LYP/6-311+G**	−1.07	12.2	−18.9

illustrated in Figure 1, with detailed geometrical parameters for the TS collected in Table 3. MP2 and B3LYP give similar descriptions of the TS geometries and activation barriers, although there are small quantitative differences between the two methods.

We also calculated activation barriers at the B3LYP/6-31G* level in the presence of dielectric medium with four different values of dielectric constant (ϵ) ranging from 5 to 40 (Table 4). The effect of hydrogen-bond donors on the DMDO−methylamine oxidation was modeled by locating a TS in the presence of a single water or methanol molecule interacting with DMDO. The calculated TS structures and energies in the presence of these two hydrogen-bond-donor molecules are presented in Figure 2 with the geometrical parameters listed in Table 5.

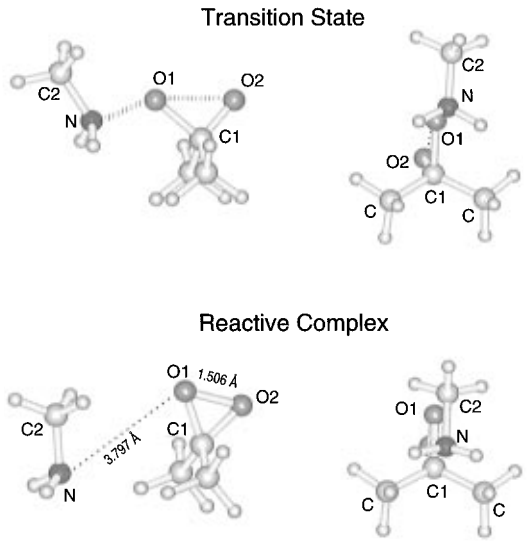

Figure 1. Calculated (B3LYP/6-31G*) structures of the transition state and reactive complex in the oxygen transfer reaction from DMDO to methylamine. Each structures is shown as two views that are approximately 90° rotated from each other.

Discussion

Molecules containing the dioxirane ring are a very challenging problem for quantum mechanical models and require inclusion of correlation energy.[19] High levels of theory, such as multiconfigurational SCF, configuration interaction, and coupled cluster methods, usually coupled with large basis sets, are frequently employed for studies of dioxirane systems.[12,20−23] Such expensive levels of theory are still impractical for large molecular systems (such as the TS and complexes studied here). Therefore, we have sought less advanced computational models that can provide reasonable quality results for dioxirane systems at acceptable computational cost. We find that both MP2 and B3LYP methods coupled with moderately sized basis sets can be successfully applied for dioxirane systems relatively inexpensively, given recent improvements in hardware and software technologies.

The gas phase reaction barrier for the oxygen transfer from DMDO to methylamine is rather high, 17.7 kcal/mole at MP2/6-311+G**. Barriers calculated at the B3LYP level are about 5 kcal/mol lower than those calculated at the MP2 level with the same basis set. The TS for the oxygen transfer to methylamine occurs at the N···O distance of 1.7 Å (both MP2 and B3LYP), although the TS geometry does not give much indication about the relative position of the transition state along the reaction pathway. The O−O and the C−O1 bonds are significantly stretched (cf. Table 4), while the C−O2 bond undergoes substantial shortening such that it is <0.1 Å longer in the TS than in acetone (formed from **3** after oxygen atom transfer). On the other hand, flattening of the tetrahedral C1 (that becomes sp^2 and planar in acetone) is not observed at all in the TS. Breaking of both the O1−O2 and C−O1 bonds, as well as formation of the N−O1 bond, are involved in the transition state. Contributions from these internal coordinates dominate the eigenvector with a negative eigenvalue (i.e., the reaction coordinate) and are −0.4887, −0.3675, and 0.6436, respectively (B3LYP/6-31G*). NBO analysis shows that the N−O bond is already present in the TS,

Table 3. Geometrical Parameters of the TS for an Oxygen Atom Transfer from DMDO to Methylamine Calculated[a]

	N···O1 (Å)	O1−O2 (Å)	C1−O1 (Å)	C1−O2 (Å)	C1−O1···N (deg)	O1···N−C2 (deg)	O2−C1−O1···N (deg)[b]
MP2/6-31G*	1.6814	1.9793	1.4960	1.3038	123.1	104.6	180.0
MP2/6-311+G**	1.7028	1.9652	1.4656	1.3100	121.2	104.7	180.0
B3LYP/6-31G*	1.7104	2.0113	1.5255	1.2981	121.9	106.1	180.2
B3LYP/6-311+G**	1.7643	1.9812	1.5069	1.3085	121.9	105.4	180.0

[a] Numbering of atoms as in Figure 1. [b] The A−B−C−D dihedral denotes the dihedral angle formed by the A−B−C and the B−C−D planes.

Table 4. Energies (relative to reactants) of Transition State and Reactive Complex (ZPE included) Calculated with the SCIPCM Model of Dielectric Medium

dielectric constant used in calculations	common solvent with a close value of ϵ[a]	transition state (kcal/mol)	reactive complex (kcal/mol)
5.0	CCl_4 ($\epsilon = 2.24$)	7.09	−1.67
10.0	CH_2Cl_2 ($\epsilon = 9.08$)	5.42	−1.47
20.0	acetone ($\epsilon = 20.7$)	4.43	−1.39
40.0	CH_3CN ($\epsilon = 36.02$)	3.93	−1.27

[a] CRC Handbook of Chemistry and Physics, 68th edition, CRC Press: Cleveland, OH, 1987−88.

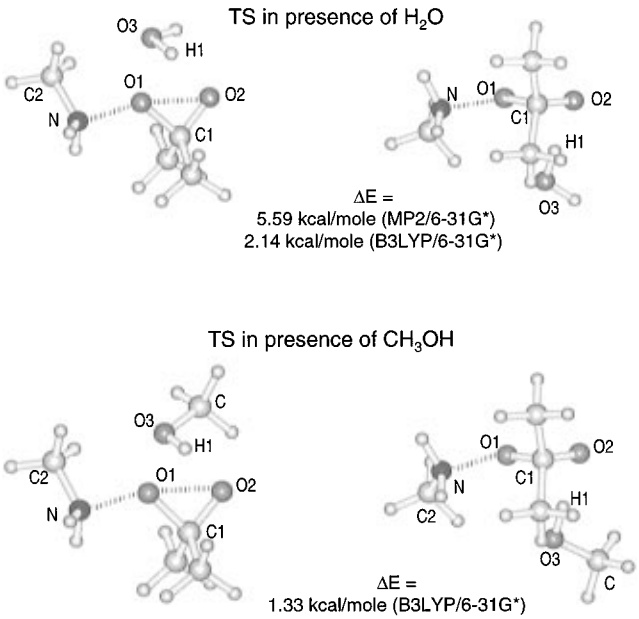

Figure 2. Calculated (B3LYP/6-31G*) structures of the transition state in the presence of hydrogen-bonded water and methanol molecules. Two views, approximately rotated by 90° from each other, are shown for each structure.

although with a high antibonding contribution (bonding/antibonding occupancy of 1.984/0.372), whereas O−O bonding is almost totally absent in the TS. This may indicate that the TS is rather late along the reaction pathway. The C−O1 bond still present in the TS shows an antibonding contribution increased to 0.188 from 0.047 in **3** (based on NBO analysis).

The question of the nucleophilicity versus electrophilicity of dioxirane has been widely debated[2,24,25], and requires a short discussion here as well. Figure 3 shows a schematic depiction of DMDO attacking methylamine with lone pairs on oxygen and nitrogen atoms shown. DMDO approaches the amine nitrogen exactly along the direction of the nitrogen lone pair and leads to the O1−N bonding character in the TS. Substantial electron charge

Table 5. Geometrical Parameters of Transition Structures Calculated in the Presence of Hydrogen-Bonded Water and Methanol Molecules[a]

	TS in the presence of	
	H_2O	CH_3OH
N···O1 (Å)	1.7921	1.7902
O1−O2 (Å)	1.9202	1.9200
C1−O1 (Å)	1.4684	1.4696
C1−O2 (Å)	1.3330	1.3336
H1···O1 (Å)	2.2378	2.2390
H1···O2 (Å)	1.9466	1.9064
C1−O1···N (deg)	121.6	121.5
O3−H1···O2 (deg)	167.1	168.0

[a] Numbering of atoms as in Figure 2.

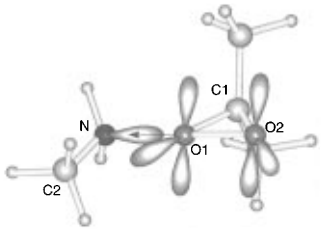

Figure 3. The transition state structure with lone pairs on the amine nitrogen and DMDO oxygens shown. Each oxygen atom of DMDO has a p-orbital and an sp hybrid lone pair orbital. DMDO attacks the amine nitrogen in the transition state exactly along the nitrogen's lone pair.

transfer of −0.589 (NBO analysis) from methylamine to DMDO is seen in the TS. In addition, intermolecular interactions decreasing the energy of the LUMO on DMDO lead to a dramatic decrease in the activation barrier (*vida infra*). All these facts indicate that the DMDO attack on primary amines is purely electrophilic in nature.

It is interesting to note that ab initio calculated transition structures for oxygen transfer from **1** to other substrates, such as ethylene[21] and hydrogen sulfide,[24] are similar to the TS reported here for primary amine oxidation in terms of both geometry and energy. The barrier of 17.6 kcal/mol was calculated for the gas-phase oxidation of ethylene by **1** at the RQCISD(T)/6-31G*//MP2/6-31G* level.[21] An MP2/6-31G* barrier of 26.8 kcal/mole for oxygen transfer from **1** to H_2S has been reported.[24] Both of these values are close to the barriers calculated here for the reaction of **3** with **4**, especially when slight differences in the level of theory and/or oxidant (**1** vs **3**) are considered. The dioxirane C−O and O−O distances observed in the transition structures for all three oxygen transfer reactions, i.e. with ethylene, H_2S, and **4**, are within 0.1 Å of each other. This observed similarity in TS for oxygen transfer regardless of substrate may indicate that the activation barriers to oxygen atom transfer from dioxiranes is controlled, to a large extent, by the strengths of the C−O and O−O bonds in the dioxirane system. However, we also note here that a substantially lower reaction barrier of 11.7 kcal/mol

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(MP2/6-31G*) has been reported for oxygen transfer to hydrogen sulfoxide.[24]

Substantial solvent effects have been observed experimentally in epoxidation reactions by dioxiranes.[2,3,26−28] Similar effects have not been reported so far in the oxidation of amines, probably not because they do not exist, but because oxidation the of amines has received less attention. In the present study, we examined the potential solvent effect on oxygen transfer from **3** to **4** through two approaches: (1) performing the calculation in the presence of a dielectric constant representative of the solvent medium, and (2) performing the calculation in the presence of an explicit hydrogen-bond donor. The activation barrier is substantially lowered in the dielectric medium (Table 4) and shows significant decrease, with an increasing value of ϵ. This seems to be an obvious result of stabilization of the highly polar (8.1 D, B3LYP/6-31G*) TS relative to the starting materials. An even more dramatic effect on the barrier is seen with explicit solvent molecules hydrogen-bonded to **3**. The barrier is just 1−2 kcal/mol (B3LYP/6-31G*) in the presence of water or methanol interacting with DMDO (Figure 2). Without the ZPE contribution the barrier is even slightly negative at the B3LYP level. The hydrogen-bond profoundly affects the LUMO (primarily antibonding O−O) in complexes formed between **3** and water or methanol (Figure 4), decreasing its energy by as much as 9 kcal/mol in the complex with water and 10 kcal/mol in the complex with methanol. If DMDO's electrophilicity is a decisive reactivity factor (*vida supra*), such a substantial drop in the LUMO energy will result in a decreased activation barrier, as observed here.

The NBO-derived atomic charge on the oxygen atoms in **3** increases (i.e., become less negative) in the hydrogen-bonded complexes, changing from −0.302 in **3** to −0.290 in the complex with water and −0.296 in the complex with methanol. However, this effect is rather small and probably not significant when compared to lowering the energy of the LUMO.

The effects of solvent dielectric and hydrogen-bonding observed in our calculations provide an elegant explanation for the strong solvent effects seen in dioxirane epoxidations. Baumstark and Vasquez[2] observed that added water increased the reaction rate by an order of magnitude for methoxystyrene oxidation by **3**. In the most comprehensive study of solvent effects on DMDO epoxidations, Murray and Gu[27] reported reaction rates in a wide range of solvent varying by an order of magnitude. Their analyses showed a strong relationship between reaction rate and the hydrogen-bonding properties of the solvent, with hydrogen-bond-donor solvents increasing the reaction rate and hydrogen-bond-acceptor solvents decreasing it. Although in the recent study by Adam and Smerz[28] the reaction rates have not been measured, hydrogen-bonding between **3** and hydrogen-donor solvents such as methanol was used to explain the regioselectivity observed in the epoxidation of geraniol and the π-facial selectivity leading to diastereoselectivity

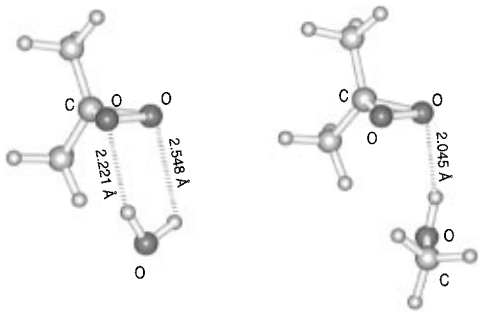

Figure 4. Calculated (B3LYP/6-31G*) structures of the complex formed between DMDO and water and between DMDO and methanol. Energies of interaction with DMDO (ZPE corrected) are −6.93 and −8.60 kcal/mol for methanol and water, respectively.

for the epoxidation of chiral allylic alcohols. All these experimental studies suggest the hydrogen-bond-donor properties of the solvent as the dominant factor influencing reaction rates in DMDO epoxidations.

Our calculations show that solvent polarity should also affect the reaction rate. However, the effects of solvent polarity on the activation barrier are substantially smaller than those seen upon a hydrogen-bonding interaction of **3** with solvent molecules. Thus, the influence of solvent polarity can become obscured by the more dominant effects of solvent's hydrogen-bonding capabilities and may be difficult to measure.

Conclusions

(1) The activation barrier for oxygen transfer from DMDO to methylamine is 17.7 kcal/mol (in vacuum) calculated at the MP2/6-311+G** level. The reaction is exothermic: −13.0 kcal/mol (MP2/6-311+G**). The TS occurs at an N···O distance of 1.702 Å and shows characteristics of being late along the reaction pathway.

(2) Polar solvents decrease the reaction barrier, as shown in B3LYP/6-31G* calculations with the dielectric medium included via the SCIPCM model.

(3) Hydrogen-bond donors, such as water and methanol, form hydrogen-bonded complexes with the O−O moiety of DMDO. This interaction has a remarkable effect on the activation barrier, decreasing it an order of magnitude, from 14.4 kcal/mol to just 1.33 kcal/mol in the presence of hydrogen-bonded methanol (B3LYP/6-31G*). This decrease of the reaction barrier is due to the lowered energy of the LUMO on DMDO.

(4) DMDO behaves as 100% electrophile in the oxygen transfer to amine nitrogen.

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Supporting Information Available: A list of energies and Cartesian coordinates for selected molecular species studied here (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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