# General and theoretical aspects of the peroxide group

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I. INTRODUCTION

Since dioxygen (O₂) is the second most abundant molecule in the atmosphere, it should not be too surprising that O–O bonds play such a major role in our lives. In a great many instances dioxygen is the source of the oxygen atoms used in the formation of peroxy compounds. The peroxy linkage is vital to both the incorporation of oxygen in the human body by biochemical syntheses and biochemical decomposition of molecules in our metabolism. It also is a major player in oxidative degradation, combustion, atmospheric and stratospheric chemistry, as well as in smog reactions. Thus, both the formation and decomposition of compounds containing the O–O bond pervade our lives in many ways and a thorough understanding of the mechanistic nuances of such chemical processes are of vital importance to us all.

More than two decades have passed since the last critical review in this Patai series was presented by Cremer¹. This comprehensive review considered mainly the conformational aspects, physical properties, molecular orbitals of relatively small peroxy compounds such as XO₂, X₂O₂, peroxides, peroxyacids and ozonides (X = H, C, N, O and F). At that time, the peroxy systems were considered to be among the most difficult functional groups for computational treatment² owing to the very nature of the oxygen–oxygen bond. In fact, early theoretical studies on the conformational properties of hydrogen peroxide presented difficulties in just computing the O–O rotational barrier³ in HO–OH; processes involving O–O bond cleavage were treated with great caution. Many of these difficulties were simply a manifestation of the level of theory available at that time and the speed and sophistication of the computers available. The most commonly available method of calculation was Hartree–Fock theory (HF) and it soon became obvious that such single reference methods were not adequate for calculations involving the numbers of electron lone-pairs inherent to the O–O bond.

In the past decade more efficient code and faster computers have allowed the use of electron-correlated methods of calculation and this has opened this area of theoretical chemistry to a wide range of research groups. The present sequel will be focused mainly on recent theoretical studies on a variety of oxidative processes involving oxygen atom transfer. We will include an extensive description of the very recent chemistry of peroxynitrous acid (HO–ONO), dioxiranes, peracids and alkyl hydroperoxides. Since chemically realistic molecular systems can now be treated at an adequate level of electron-correlated
theory, new and exciting mechanistic details of oxidation chemistry can be gleaned from such computations that simply were not available to earlier investigators.

II. BACKGROUND AND HISTORICAL PERSPECTIVE

During the formative years of the development of theoretical procedures for the treatment of oxidative processes involving the peroxy moiety, the Hartree–Fock level of theory was most often applied. There were essentially no serious efforts to treat the O–O bond at the extended Huckel level or by the semiempirical CNDO/2 or INDO methods. In fact, most such semiempirical methods are not specifically parameterized even today for the O–O bond. When the earlier versions of the Gaussian suite of programs (G-70) were widely distributed among academic institutions, the use of ab initio calculations for mechanistic studies became widespread although most researchers were still restricted to the use of a minimal basis set (STO-3G). This 1970 version had basis sets with s and p functions only and no gradient optimization methods or electron-correlation corrections were available. As Gaussian 80 and G82 became even more widely distributed, second-order Möller–Plesset perturbation theory (MP2) with the ability to handle d functions came into limited use with SCF gradients and MP2 first derivatives. Although the Gaussian suite of programs was widely used, other codes such as Gamess, ACES, MOLPRO, CADPAC, Jaguar etc. were added to the arsenal of the theoretical chemist. In fact, many such programs became sufficiently ‘user friendly’ that a number of experimentalists became adept at doing theoretical calculations to augment their laboratory experiments.

As Gaussian 92 became more widely available to the general research population, standard protocol was to use MP2 or higher-order Möller–Plesset theory up to MP4 to calculate the electron-correlation correction. However, the computational expense involved still typically mandated that the geometry be optimized at the HF level. While the use of HF theory proved satisfactory in some smaller systems, it also often led to major errors in the overall energetics of reactions, especially where lone-pair electrons were involved. The size of the practical basis set had expanded to 3-21G and many applications employed the 6-31G basis set and some even with d-functions on all heavy atoms [6-31G* or 6-31G(d)]. Minimal basis sets such as STO-3G were no longer publishable by the late 1970s while 4-31G basis sets were still acceptable for publication in major journals up to the late 1980s. By the mid 1980s the 6-31G(d) basis set had become the standard for most applications unless the size of the system was prohibitive.

The G92 program marked the introduction of density functional theory (DFT) although general skepticism prevented its more general use until the G94 code became available. During the early 1990s it was possible to optimize the geometry of some systems using the electron-correlated MP2 method and this recipe coupled with an MP4 energy correction became the most generally accepted method to study systems up to eight heavy atoms (nonhydrogen atoms). This general protocol was accepted by all but the most rigorous theoreticians to be at least adequate. However, this was not a panacea since calculations of transition structures involving the problematic O–O bond and related molecules sometimes led to structural problems even with the MP2 method. This problem was exacerbated by the fact that analytical second derivative calculations were not yet available, so the optimized structure could not be characterized by a frequency calculation as a minimum (all real frequencies) or a first-order saddle point (a transition state with one imaginary frequency).

In the mid-nineties more highly correlated methods such as CCSD and QCISD became available through distribution of the ACES and Gaussian 94 programs. Geometry optimization with these more cpu intensive programs was restricted for the most part to six heavy atoms. About this time multiconfigurational self-consistent-field (MCSCF) or
complete active space (CASSCF) methods became the rage. Such calculations were highly touted as being very accurate and especially good for fairly small biradicaloid systems where more than one reference state was anticipated. However, while this may be true for highly symmetrical alkenes and dienes, the choice of the active space actually used in more complex systems is highly subjective and can lead to serious problems. A cautionary note typically accompanies the suggested use of these multireference methods; these are not the ‘black box’ calculations so typically available today. During these earlier years most practitioners preferred to use the Gamess\textsuperscript{7b} code for MCSCF calculations since it was faster than Gaussian. However, a major drawback of these CAS methods existed in that a second-level electron-correlation correction to the total energies was essential in order to be able to compute relative energies of saddle points on a reaction surface.

The implementation of Gaussian 98 and the introduction of much faster computers coincided with the rise of the G1, G2 and CBS-Q methods, another milestone in computational chemistry, since chemical accuracy was now available for compounds up to six heavy atoms. Currently, the G3 and CBS-Q methods can treat systems up to ten heavy atoms without too much difficulty, affording bond energies in most cases within 1–2 kcal mol\textsuperscript{−1} accuracy.

It was not until the introduction and widespread use of density functional theory (DFT) that reliable calculations on larger molecules became possible. This method is much faster than MP2, implicitly corrects for at least part of the electron correlation and also provides geometries and overall energetics in many cases comparable to those of higher-level methods. The B3LYP variant of the DFT code has proven to be especially tractable for systems as large as fifty heavy atoms even with a respectable size basis set. In many applications now being reported a 6-311+G(d,p) or 6-311+G** basis set is applied to the more difficult problems. The plus basis (+) is especially useful for the peroxy moiety since its function is to better describe anions or electron lone-pairs through the introduction of a large p-orbital on each heavy atom. In addition to the d-orbitals on each heavy atom (d), polarization functions (p) are included on each hydrogen atom to provide a better description of secondary- and hydrogen-bonding interactions. Today the B3LYP variant of DFT calculations is the method of choice for most investigators working on practical theoretical problems of oxidative chemistry. Direct comparison of B3LYP data with that of other methods by a number of investigators has proven its general applicability.

The scientific community has also been particularly fortunate that the software required to locate such complex minima and transition structures has kept pace with the accompanying explosion in hardware. It is now common place for individual investigators to have in their own laboratory a multiprocessor computer of equal computing power to the regional supercomputer laboratories of just a decade ago. However, without the more advanced code for locating such complex molecules we could not take advantage of such hardware developments. A decade ago most geometry optimization methods used the algorithm developed by Schlegel\textsuperscript{10} and introduced in the early Gaussian versions as the ‘Berny algorithm’. Today, with such added options as modredundant optimization (redundant coordinate optimization\textsuperscript{11}) the number of gradient cycles required to locate the minimum-energy geometry of a saddle point is more than cut in one-half. The author of this review, an experimentalist, published his first theoretical paper on electrophilic addition to alkenes using extended Huckel theory in 1970\textsuperscript{12a}. He has had the good fortune to watch the evolution of theoretical chemistry to the point where one can now do a systematic theoretical study of alkene epoxidation with peracids and dioxiranes on chemically relevant molecules. At present, state-of-the-art calculations modeling enzymatic reactions are feasible. It is from this backdrop that we now present the more successful theoretical studies on several new and emerging areas of oxidative chemistry involving the O–O bond.
III. BOND DISSOCIATION ENERGIES OF SELECTED PEROXO COMPOUNDS

The chemistry of peroxides is to a first approximation simply dictated by the fact that the bond energy of the generic O−O bond is quite low. Consequently, many reactions of the peroxo moiety are thermally induced since it is assumed that O−O bond cleavage can be accomplished at relatively low temperatures. This is something of an enigma since homolysis produces alkoxyl radicals (RO•) that are not especially stable. However, the lack of thermodynamic stability of most peroxides is also at the root of a major problem; difficulty in isolation and characterization of a great many peroxo compounds means that the accuracy of O−O bond dissociation energies (BDE) is sometimes questionable. Molecules possessing an O−O bond, which is electronically challenged with four pairs of lone-pair electrons, pose an interesting theoretical puzzle. Just what is responsible for the relatively weak O−O bond? Since by nature the oxygen radicals that result from O−O bond cleavage are less stable than many typical radicals, including carbon radicals, one could anticipate a much stronger O−O bond.13

Average bond energies (kcal mol\(^{-1}\)) of oxygen atoms bound to carbon (C−O ≈ 84), nitrogen (N−O ≈ 53) and fluorine (F−O ≈ 44) are all presumed to be substantially greater than that of oxygen bound to itself. Consequently, a relatively low bond energy (O−O ≈ 34 kcal mol\(^{-1}\)) has typically been ascribed to a generic peroxide.1 The unusual reactivity of peroxides is generally attributed to weakness of the O−O bond linkage and hence the ease with which it is homolytically cleaved. The kinetics of the thermal decomposition of a number of peroxides has been studied, and these bond dissociation enthalpies (BDE) have been used to derive O−O bond strengths. It was concluded that the strength of the O−O bond in dialkyl peroxides is about 37 (±1) kcal mol\(^{-1}\) and is independent of the alkyl group. The BDE of the O−O bond in diacyl peroxides was estimated by this method to be only 30 (±1) kcal mol\(^{-1}\). Established estimates of the amount of energy required to cleave homolytically a generic peroxide ZO−OY ranges from 47 for hydrogen peroxide down to about 29 kcal mol\(^{-1}\) for dialkyl peroxodicarbonates (Table 1).14 A more accurate value has recently been determined for H\(_2\)O\(_2\), which corresponds to 50.5 kcal mol\(^{-1}\) for the BDE at 298.15

It has been assumed that the enthalpy for homolysis of related peroxides such as ZO−OY can be derived from the mean BDE for ZO−OZ and YO−OY. For example, the enthalpy for O−O dissociation in peroxyacetic acid (ΔH\(_{298}^\circ\)) 38.5 kcal mol\(^{-1}\) has been derived from the enthalpies of HO−OH (47 kcal mol\(^{-1}\)) and CH\(_3\)COO−OCOCH\(_3\) (30 kcal mol\(^{-1}\)). It was the use of this relatively low BDE for diacyl peroxides to predict O−O bond energies that led to the low estimate for peracids. One major source of discrepancy between the accepted experimental O−O bond energies and theoretical values lies in the fact that the experimental O−O bond energies for diacyl peroxides are in error. The bond dissociation enthalpies used to derive the O−O bond energies were predicted on the basis of the assumption that a unimolecular one-step O−O bond dissociation was involved. The mechanism of O−O bond cleavage in diacyl peroxides is more complex than had been assumed initially and \(^{18}\)O oxygen scrambling was shown by Bach and coworkers to be quite facile by a unique ‘peroxo Oxy-Cope’ rearrangement.16a

A variety of bond dissociation enthalpies at 298 K have been calculated at the G2MP2, CBS-Q and G2 levels of theory and a summary of typical O−O BDEs are presented in Table 1. It becomes immediately obvious that the estimate of the O−O BDE of a generic peroxide should be increased by 10 kcal mol\(^{-1}\) to ca 44 kcal mol\(^{-1}\).

The bond dissociation energy of hydrogen peroxide has been accurately predicted by high-level ab initio theory.16 It was disclosed very early that Hartree–Fock theory, in the absence of electron-correlation correction, simply cannot be applied to problems involving O−O bond dissociation. For example, the predicted O−O bond energy in peroxyformic acid is only 1.0 kcal mol\(^{-1}\) by Hartree–Fock theory, whereas at the
### Table 1. Calculated O−O bond dissociation energies (ΔH$_{298}$, kcal mol$^{-1}$) at different levels of theory$^a$. Bond dissociation energies in the last column (BDE$_{exp.}$, kcal mol$^{-1}$) are experimental$^{15,18}$

<table>
<thead>
<tr>
<th>Compound</th>
<th>B3LYP/6-31+G(d,p)</th>
<th>G2MP2</th>
<th>G2</th>
<th>CBS-Q</th>
<th>BDE$_{exp.}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO−OH</td>
<td>51.40</td>
<td>50.45</td>
<td>50.72</td>
<td>50.5</td>
<td></td>
</tr>
<tr>
<td>CH$_3$O−OH</td>
<td>37.5</td>
<td>46.04</td>
<td>44.96</td>
<td>44.65</td>
<td></td>
</tr>
<tr>
<td>CH$_3$O−OCH$_3$</td>
<td>28.7</td>
<td>40.68</td>
<td>39.43</td>
<td>38.52</td>
<td>37.8</td>
</tr>
<tr>
<td>(CH$_3$)$_3$CO−OH</td>
<td>36.7</td>
<td>48.30</td>
<td>45.00$^b$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tricyclic Flavin hydroperoxide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32.7</td>
</tr>
<tr>
<td>(CH$_3$)$_3$CO−OC(CH$_3$)$_3$</td>
<td></td>
<td></td>
<td></td>
<td>45.20</td>
<td></td>
</tr>
<tr>
<td>H(C=O)O−OH</td>
<td>49.16</td>
<td>48.41</td>
<td>47.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=O)O−OH</td>
<td>22.83</td>
<td>21.96</td>
<td>20.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$(C=O)O−OH</td>
<td>48.32</td>
<td>47.55</td>
<td>47.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CF$_3$(C=O)O−OH</td>
<td>48.90</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$(C=O)O−O(C=O)CH$_3$</td>
<td>37.89</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_2$=C(CH$_3$)O−OH</td>
<td>22.73</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H$_3$SiO−OH</td>
<td>52.46</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H$_3$SiO−OSiH$_3$</td>
<td>55.45</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CH$_3$)$_3$SiO−OH</td>
<td>53.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CH$_3$)$_3$SiO−OSi(CH$_3$)$_3$</td>
<td>54.81</td>
<td>56.83</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ For a more complete discussion including additional citations, see References 16–20.

$^b$ Calculated by the G3 method.

$^c$ The BDE value for tricyclic flavin hydroperoxide is taken from Reference 20c.

MP4/MPI/6-31G* level ΔE values for HO−OH and HCO$_2$−OH are predicted to be 49.2 and 50.7 kcal mol$^{-1}$, respectively$^{17}$. The fact that these two BDEs are significantly higher than the accepted average bond energy of 34 kcal mol$^{-1}$ prompted a systematic theoretical study of O−O bond energies by Bach and his group$^{16}$.

It is also noteworthy that both peroxynitrous acid and isopropenyl hydroperoxide have exceptionally low O−O BDE while silyl peroxides have systematically higher BDEs$^{16b}$. The pronounced decrease in the O−O bond energy of CH$_3$O−OCH$_3$ relative to HO−OH obviously reflects the greater stability of the CH$_3$O radical as compared to the HO radical. The substituent effects on the O−O bond enthalpy appear to be nearly additive since the G2 mean O−O bond enthalpy for dimethyl peroxide and hydrogen peroxide yields a BDE of 45.0 kcal mol$^{-1}$, equal to the G2 value for O−O bond energy in methyl hydroperoxide. These data should prove to be a worthwhile addition to the literature on this topic since it is the O−O bond energies that control much of the chemistry of peroxides.

Early theoretical studies on the epoxidation reaction were carried out at the MP2 level of theory and were mainly concerned with just identification of transition structures$^{17}$. However, as the field matured it became necessary to also reproduce accurate activation barriers for these oxygen atom transfer reactions. It soon became evident that the B3LYP method typically underestimates the O−O BDE as noted for selected examples in Table 2. At a relatively high level of theory$^{16}$, with an adequate basis set, it is possible to get bond strengths in quite good agreement with experiment$^{15,18}$. It is especially relevant to point this out because this DFT variant is the most commonly applied method for calculations involving oxidation mechanisms. The B3LYP method has been used successfully in a variety of the procedures involving O−O cleavage and affords activation barriers in good agreement with experiment$^{12b,19,20}$. For example, the calculated activation barrier for the m-chloroperoxybenzoic acid epoxidation of cyclohexene agrees within 1 kcal mol$^{-1}$ with the experimental value$^{19d}$. DFT theory has also been used to calculate the O−O BDE in a series of fluoro-substituted peroxides$^{23}$ and it has been applied to the optimization of
1. General and theoretical aspects of the peroxide group

TABLE 2. Comparison of the calculated barriers (kcal mol$^{-1}$) for the oxidation of alkenes, dimethyl sulfide, trimethylamine and trimethylphosphine with peroxynitrous acid, peroxyformic acid and dimethyldioxirane (DMDO)

<table>
<thead>
<tr>
<th>Reactants</th>
<th>Peroxynitrous acid (20.3)$^a$</th>
<th>Peroxyformic acid (46.9)$^a$</th>
<th>DMDO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene</td>
<td>18.3$^b$</td>
<td>18.8$^b$</td>
<td>19.4$^c$</td>
</tr>
<tr>
<td>Propylene</td>
<td>15.5$^b$</td>
<td>16.0$^b$</td>
<td></td>
</tr>
<tr>
<td>Dimethyl sulfide</td>
<td>9.6 (6.9)$^d$</td>
<td>6.6$^e$</td>
<td>9.4$^e$</td>
</tr>
<tr>
<td>Trimethylamine</td>
<td>5.3 (1.6)$^d$</td>
<td>0.9$^e$</td>
<td>6.3$^e$</td>
</tr>
<tr>
<td>Trimethylphosphine</td>
<td>1.5 (−0.1)$^d$</td>
<td>0.5$^e$</td>
<td>1.0$^e$</td>
</tr>
</tbody>
</table>

$^a$ The O−O bond energies ($D_o$) calculated with G2 theory are given in parentheses.

$^b$ At the QCISD(T)/6-31G*//QCISD/6-31G* level.

$^c$ The barrier for ethylene epoxidation with DMDO was calculated at the QCISD(T)//QCISD(full)/6-31G* level. The barrier for ethylene oxidation with the parent dioxirane is lower (16.6 kcal mol$^{-1}$ at the same level).

$^d$ At the QCISD(T)/6-31G*//MP2/6-31G* level, the barriers calculated at the MP4/6-31G*//MP2/6-31G* level are shown in parentheses.

$^e$ At the MP4/6-31G*//MP2/6-31G* level.

IV. THE CHEMISTRY OF PEROXYNITROUS ACID

A. Historical Overview

It has now been more than a decade since Beckman and his collaborators$^{22}$ first disclosed their observations that the combination of two relatively unreactive, yet biologically relevant free radicals, superoxide anion and nitric oxide, would produce a new highly reactive physiologically important reagent. The interaction of these two presumably innocuous species appears to be diffusion controlled and produces a thermally stable peroxy anion, peroxynitrite (equation 1)$^{23}$.

$$\text{O}_2^- + \cdot\text{NO} \rightarrow \cdot\text{ON}=\text{O}$$  \hspace{1cm} (1)

$$\cdot\text{O}−\text{ON}=\text{O} + \text{H}^+ \rightarrow \text{HO−ON}=\text{O} \rightarrow \cdot\text{OH} + \cdot\text{NO}_2$$ \hspace{1cm} (2)

At physiological pH the anion will be partially protonated (pKa 6.8)$^{23}$ to produce a new and potent biological oxidizing agent, peroxynitrous acid, the first such peroxy acid known to be produced in vivo. This highly reactive oxidizing agent has a half-life of less than a second at 37°C. Although HO−ONO decomposes at physiological pH, its nitrite anion is stable in base solution for months. Peroxynitrite anion (−O−ON=O) is 36 kcal mol$^{-1}$ higher in energy than its nitrate isomer (−O−NO$_2$).

There were initially two proposals put forth to account for the powerful oxidizing capacity of peroxynitrous acid. Beckman and coworkers$^{22}$ suggested that peroxynitrite dissociation produced a strong oxidant able to initiate many reactions currently used that imitated the action of hydroxyl radical. It was also proposed that this new oxidant could actually be the hydroxyl radical according to equation 2. The first and perhaps simplest explanation advanced for the atypical reactivity of this peroxy acid was O−O bond homolysis to produce the nitrogen dioxide radical ($\cdot\text{NO}_2$) and hydroxyl radical ($\cdot\text{OH}$) as the proximate oxidant$^{24}$. Hydroxyl radical is generally recognized as the most reactive of all biologically relevant ‘oxy radicals’. However, initial reports by Koppenol and coworkers$^{25}$
precluded the formation of \( ^\ast \text{OH} \) from the decomposition of \( \text{HO}^-\text{ONO} \) based upon thermodynamic calculations and kinetic measurements. The measured activation parameters for peroxynitrite decomposition (\( \Delta H^\neq = 18 \pm 1 \text{ kcal mol}^{-1} \) and \( \Delta S^\neq = 3 \pm 2 \text{ eu} \)) suggested that the entropy of activation was too small to be consistent with the \( ca \ 12 \text{ cal mol}^{-1} \text{ K}^{-1} \) typically observed for \( \text{O}^-\text{O} \) bond homolysis in peroxides\(^{25} \).

The second proposal is a bit more imaginative and arises from the above arguments that \( \text{O}^-\text{O} \) bond homolysis is much too slow to be involved in oxidations by peroxynitrate. Pryor and coworkers\(^{23,26} \) invoked the intermediacy of a metastable form of peroxynitrous acid (\( \text{HO}^-\text{ONO}^* \)) in equilibrium with its ground state. This so-called ‘excited state’ of peroxynitrous acid has, to date, eluded detection or characterization by the experimental community. However, recent high-level theoretical calculations by Bach and his collaborators\(^{27} \) have presented plausible evidence for the intermediacy of such a short-lived species with a highly elongated \( \text{O}^-\text{O} \) bond and have confirmed its involvement in the oxidation of hydrocarbons (see below). The discovery\(^{23–26} \) of this novel series of biologically important oxidants has fostered a new area of research in both the experimental and theoretical communities. In this chapter we will describe many of the more pertinent theoretical studies on both the physical properties and chemical reactivity of peroxynitrous acid.

B. Peroxynitrite Anion and Peroxynitrous Acid. Ground State Properties

Initially, McGrath and Powland\(^{28} \) calculated various \( \text{HO}^-\text{ONO} \) conformers at the HF/6-31G(d) and MP2/6-31G(d) levels. They concluded that there are a total of eight conformers of \( \text{HO}^-\text{ONO} \), but realistically only the three most stable conformers were important. Subsequent calculations by Jin and collaborators\(^{29} \) at the B3LYP/6-311+G(d,p) level concurred with these findings and studied the overall potential energy surface (PES) for \( \text{HO}^-\text{ONO} \) isomerization. The nomenclature presented in Figure 1 is the same as that developed earlier by McGrath and Powland\(^{28b} \).

The different rotational isomers of peroxynitrous acid \( \text{ONO}^-\text{OH} \) are labeled by their respective dihedral angles (\( <\text{ONO}^-\text{O} \)) and (\( <\text{NO}^-\text{OH} \)) designated 0, 30, 60, 90 and

![Diagram](https://via.placeholder.com/150)

FIGURE 1. Equilibrium structures of \( \text{HO}^-\text{ONO} \) conformers
180° as cis, gauche, perp and trans, respectively. For example, the conformer with cis ONO−O and trans NO−OH is denoted by (cis,trans). Jin and coworkers29 confirmed the earlier eight conformers of HO−ONO (Figure 1) to be stationary points. The three stable conformers are (cis,cis), (cis,perp) and (trans,perp), respectively, all have real vibrational frequencies29, while the other five different conformers, (cis,gauche), (cis,trans), (trans,cis), (trans,trans) and (perp,perp), are treated as transition states because these structures all have an imaginary frequency.

Of the three stable conformers of HO−ONO, the (cis,cis) conformer with a five-membered hydrogen-bonded ring lies lower in energy than the others. Three different channels in the isomerization process of HO−ONO were found. The (cis,perp) is a bridge transferring from (trans,perp) to the (cis,cis) conformer29.

The calculated barrier heights of these channels indicate that the (trans,perp) conformer can be more easily observed than the (cis,cis) and (cis,perp) conformers by experiment. However, as is noted below, at higher levels of theory the cis,perp appears to be the global minimum.

In earlier theoretical studies Shen and coworkers used Hartree–Fock self-consistent-field (HF) calculations with different basis sets to study water complexes of anionic ONO−O−30. Two stable ONO−O− isomers, cis and trans, formed hydrogen bonds with H2O molecules at different positions. Second-order Møller–Plesset perturbation theory (MP2) with a 6-311+G(d,p) basis set has also been applied to the study of ONO−O−, (H2O)n (n = 1 or 2) complexes31. Koppenol and Klasinc studied the cis and trans conformers as well as the transition state for torsional motion of ONO−O− at the HF/6-31(d) level32. In their calculations, the trans conformer is slightly more stable than the cis form, and the rotational barrier was thought to be quite high. However, correlated methods (MP2) were also used to study this molecule, and they predict that the cis conformer is more stable than the trans conformer33,34.

The metal salts of peroxynitrite have also been studied using ab initio methods. We use the same nomenclature as McGrath and Powland’s early paper on ONO−OH35b, which distinguishes different conformers by their dihedral angles. For example, the structure with a cis ONO−O arrangement and the alkali atom bonded to the terminal oxygen with a perpendicular orientation is called ‘cis,perp’. Figure 1 describes the conformational aspects of the conformers studied.

Comparisons of ONO−OLi, ONO−ONA and ONO−OK establish several conformational trends35. When the alkali atom size increases from Li to K, the relative stability between cis,cis and trans,cis decreases for the five-membered ring. The rotation of the OM bond away from the planar cis,cis conformation (i.e. NO−OM torsion) also becomes easier as the alkali atom changes from Li to Na to K. For the latter, the cis,perp minimum disappears, and cis,trans ONO−OK is a transition state that gives an activation barrier of 9−10 kcal mol−1 for NO−OK torsion. The B3LYP method predicts that trans,perp (or trans,trans in the case of ONO−ONA) will be 2−4 kcal mol−1 higher in energy than trans,cis ONO−OM. The transition state energies for converting cis,cis ONO−OM to trans,cis or trans,perp ONO−OM do not show a systematic trend with respect to the alkali atom, although the barriers (relative to the cis,cis structure) are in the 20−30 kcal mol−1 range.

A comparison of HF, MP2 and density functional methods in a system with Hartree–Fock wave function instabilities, ONO−OM (for M = Li, Na and K), shows that DFT methods are able to avoid the problems that ab initio methods have for this difficult class of molecules. The computed MP2 frequencies and IR intensities were more affected by instabilities than HF. The hybrid B3LYP functional reproduced the experimental frequencies most reliably. The cis,cis conformation of ONO−OM was highly preferred because of electrostatic attraction and was strongest in the case where M = Li. The small Li cation can fit in best in the planar five-membered ring. This is completely different from the nonionic
ONO−OH, which has only a slight preference for the cis,cis conformation and low barriers for NO−OH torsion\textsuperscript{28b}. The rotational barrier for ONO−O torsion was significant [20, 27 and 22 kcal mol\(^{-1}\)] for M = Li, Na and K, respectively, at the B3LYP/6-311+G(d) level of theory, as is the case for anionic ONO−O\(^{−}\) (27 kcal mol\(^{-1}\))\textsuperscript{33,36}.

C. Higher-lying Metastable States of Peroxynitrous Acid

As noted above, the peroxynitrite anion (NOO−O\(^{−}\)), formed by the direct combination of nitric oxide (NO) and superoxide anion (O\(_{2}\)\(^{−}\)), is stable in alkaline solution. At physiological pH the anion is partially protonated, and its fate in aqueous media has been a primary point of contention. It was suggested that this strong oxidant might be a source of very potent biologically relevant hydroxyl radicals\textsuperscript{22b,23,25,26}. One of the more intriguing aspects of HO\(^{−}\)ONO chemistry is the earlier suggestion that O−O bond homolysis was slow, and the reactive species is a vibrationally excited form of HO−ONO\textsuperscript{22b}. However, its very short lifetime of ca \(10^{−11}\) s would preclude its involvement in bimolecular reactions, and Pryor and coworkers\textsuperscript{26a} advocated the existence of a higher-energy metastable form of peroxy nitrous acid (HO−ONO\(^{*}\)) that is in steady-state equilibrium with ground-state HO−ONO. Conventional wisdom has proposed homolysis to produce either *OH and *NO\(_{2}\) or a caged radical (*OH···*NO\(_{2}\)). Careful experimentation has suggested that the yield of hydroxyl radicals at room temperature in deoxygenated and bicarbonate free water at pH 6.8 is about 10\%\textsuperscript{24}.

However, reports of the yields of hydroxy radicals from the decomposition of HO−ONO have ranged from 0 to 40\%\textsuperscript{24a}. To date, no experimental evidence has been presented for the presence of such a metastable species. There have been numerous theoretical studies that have described the geometry\textsuperscript{37a}, decomposition pathways\textsuperscript{37b} and reactivity\textsuperscript{37c–e,38} of peroxy nitrous acid. There is no low-energy channel in the dissociation of peroxy nitrous acid that leads to the often anticipated products HNO and singlet oxygen (\(\text{^1}O_{2}\))\textsuperscript{37b}. The lowest-energy pathway remains the formation of a radical pair (*OH + *NO\(_{2}\)) that may recombine to form nitric acid among other products. High-level \textit{ab initio} calculations of the ground state (GS) and the low-lying excited states of peroxy nitrous acid predict that the O−O bond dissociation is 18.8 \(±\) 1 kcal mol\(^{-1}\). Vertical excitation energies suggest two low-lying excited state bands at 296 and 240 nm with the \(\text{^1}A''\) state being bound\textsuperscript{39}. A thermally excited form (HO−ONO\(^{*}\)) of peroxy nitrous acid has until recently eluded description.

Bach and his coworkers have only recently reported\textsuperscript{27} cis and trans higher-lying singlet minima of peroxy nitrous acid (HO···ONO) at several levels of theory, including CASSCF. The ground state (GS) structures of HO−ONO have been studied theoretically by a number of groups\textsuperscript{16a,27,37,38}. While the cis form is the ground state at B3LYP, the perpendicular conformer is slightly more stable at the QCISD and CASSCF levels (Figure 2).

A search for the so-called ‘excited state’, that would presumably have a highly elongated O−O bond, required a relatively high level of theory. A potential problem associated with the location of such a biradicaloid species on the unrestricted potential energy surface (PES) is that despite attempting to optimize the geometry with an unrestricted (UB3LYP) description, the wave function can converge to the restricted PES ((S2) = 0). However, you can be assured of at least starting the geometry search with an unrestricted initial guess by mixing HOMO and LUMO (guess = mix\textsuperscript{7a}, (S2) = 1.0). Following this protocol, using a fairly flexible basis set [6-31+G(d,p) or larger] with a relatively small step size, a singlet species (A’ symmetry) was located having an elongated O−O distance...
of 2.17 Å that was only 14.4 kcal mol⁻¹ [UB3LYP/6-311+G(3df,2p)] higher in energy than its cis-peroxynitrous acid GS precursor (Figure 2, cis-2). A second higher-lying minimum (trans-2) derived from the trans conformer of HO–ONO was observed and was 12.8 kcal mol⁻¹ higher in energy than ground-state HO–ONO. At the UQCISD(T) level, trans-2 was 12.7 kcal mol⁻¹ higher in energy than GS cis-HO–ONO, in excellent agreement with the DFT calculations. The ONO fragment of the metastable states appeared to correlate with the \(^2A_1\) state of the NO₂ radical with an ONO bond angle of 134°. The transition state for O–O bond stretching (TS\(_{cis-1}\), \(R_{O-O} = 1.947\) Å, \(\nu = 314.5i\) cm⁻¹) was found to be only 0.2 kcal mol⁻¹ higher in energy than cis-2. The TS associated with formation of a slightly more stable singlet, trans-2, was 13.2 kcal mol⁻¹ above the GS cis minimum for HO–ONO (TS\(_{trans-1}\), \(R_{O-O} = 1.889\) Å, \(\nu = 333.9i\) cm⁻¹). The TS for interchanging cis-2 and trans-2 (TS-3) involves a simple in-plane migration of the OH group between the two terminal oxygens of the ONO radical fragment (\(\nu = 112.0i\) cm⁻¹). The expectation values of the \(S^2\) operator (\(\langle S^2 \rangle = 0.76\) and 0.73) for cis-2 and trans-2 suggested a significant contamination of the singlet wave function with triplet character.
A complete active space (CASSCF) calculation\textsuperscript{7b}, to assess the multireference character of the wave function, used an active space comprising 12 electrons and 10 active orbitals [CAS(12,10)]. With a 6-311+G(d,p) basis set, the optimized geometries of cis-2 and trans-2 were quite close to those obtained with the DFT method (Figure 2). Another indication of the closeness of the DFT and CASSCF geometries was gleaned from single-point Brueckner Doubles calculations\textsuperscript{5a} on the energy differences between the GSs and cis-2 and trans-2. At the BD(TQ)/6-311+G(d,p) level, the energy difference between GS cis-HO—ONO and cis-2 was 15.5 kcal mol\textsuperscript{-1} with the DFT geometry and 15.2 kcal mol\textsuperscript{-1} with the CASSCF geometries. These energy differences were also in good accord with the DFT energies provided in Figure 2. Similarly, the energy differences between minimum GS perp-HO—ONO and trans-2 were 14.0 and 13.0 kcal mol\textsuperscript{-1} at the DFT and CASSCF geometries, respectively. A CIPT\textsuperscript{7d} correlation correction to the CASSCF wave function suggested an energy difference between the GS perp- and trans-2 of 4.9 kcal mol\textsuperscript{-1}. A multireference configuration interaction (MRCI)\textsuperscript{7d} calculation with the above active space (6.8 million contracted configurations) gave energy differences between GS and metastable conformers of 11.7 and 9.0 kcal mol\textsuperscript{-1} for cis-2 and trans-2, respectively. The O—O bond dissociation enthalpy for GS cis-HO—ONO was calculated to be 22.0 kcal mol\textsuperscript{-1} at the G2 level of theory\textsuperscript{10a}. The calculated dissociation limits for the GS cis-, GS perp- and GS trans-HO—ONO were 17.3, 15.9 and 14.6 kcal mol\textsuperscript{-1}. With zero-point energy corrections [ZPE at B3LYP/6-311+G(3df,2p)] these dissociation limits were 15.3, 14.3 and 13.4 kcal mol\textsuperscript{-1}, values well above the energies of the higher-lying minima located.

The O—O dissociation energy of 15.3 kcal mol\textsuperscript{-1} for GS cis-HO—ONO was in good accord with the Gibbs experimental enthalpy and free energy of activation (18 ± 1 kcal mol\textsuperscript{-1}, ΔS⁰ = 3 eu and 17 ± 1 kcal mol\textsuperscript{-1}, ΔS‡ = 12 eu, respectively) for the isomerization of peroxynitrite to its nitrate form (presumably by a dissociative mechanism). However, the calculated Gibbs free energy (5.9 kcal mol\textsuperscript{-1}) for dissociation of cis-HO—ONO (ΔS = 36 eu) was significantly less than the experimental value for O—O dissociation in solution. While gas-phase and solution entropies are not directly comparable, the existence of cis-2 and trans-2 in the gas phase remains an open question. Similar questions concerning the weakly bound HO and *NO₂ radicals reported by Houk and coworkers\textsuperscript{37e} (structure 4, Figure 2) were also raised by Musaev and Hirao\textsuperscript{40a}. The relationship of the above gas-phase calculations to HO—ONO under physiological conditions now becomes the more relevant question. This question cannot be addressed directly, but can be estimated with full geometry optimizations of cis- and trans-2 using the COSMO solvent model\textsuperscript{41}. In THF solvent, the energy difference between GS cis-HO—ONO and cis-2 and trans-2 was 12.3 and 10.2 kcal mol\textsuperscript{-1} [B3LYP/6-311+G(d,p)]. In methanol solvent, these energy differences increased to 13.9 and 12.4 kcal mol\textsuperscript{-1}, and in water media, the energy increases were 14.3 and 12.7 kcal mol\textsuperscript{-1} [15.4 and 14.2 kcal mol\textsuperscript{-1} with the larger 6-311+G(3df,2p) basis set]. Significantly, cis-2 and trans-2 both existed as energy minima in polar media with elongated O—O distances (2.140 Å and 2.089 Å) for cis-2 and trans-2 in water.

Since hydrogen bonding is not explicitly treated in the COSMO solvent model, the stability of trans-2 H-bonded to water molecules can be examined. Minima were located for trans-2 H-bonded to one, two, three and four H₂O molecules with O—O distances of 2.13, 2.12, 2.15 and 2.11 Å, respectively [BLYP/6-311+G(d,p)]. As anticipated, the overall complexation energy increased almost linearly with increasing numbers of H₂O molecules (−5.6, −15.9, −28.2 and −34.7 kcal mol\textsuperscript{-1}, respectively). Attempts to optimize cis-2 H-bonded to three waters resulted in a perp-2·3H₂O complex (<HOON = 68°). The energy difference between this complex and trans-2 H-bonded to 3H₂O was only 0.3 kcal mol\textsuperscript{-1} (see below). By contrast, the interaction between the radical pairs in 4\textsuperscript{37e} (Figure 2) was sufficiently weak that the complex completely dissociated upon inclusion of just two H₂O molecules\textsuperscript{40a}.\n
1. General and theoretical aspects of the peroxide group

1.786 Å

1.793 Å

1.777 Å

2.145 Å

1.827 Å

2.949 Å

<HOON = −166.8

E_{rel} = 0.0 kcal mol⁻¹

Both cis- and trans-2 when H-bonded to 3H₂O resulted in perpendicular complexes (<HO—ON = 91.4° and 116.2°, ΔE = 0.3 kcal mol⁻¹). The energy differences between trans-2•3H₂O and the corresponding GS perp-HO—ONO•3H₂O were 12.1 and 12.2 kcal mol⁻¹ for the perp-2•3H₂O complex, thereby supporting the existence of these higher-lying singlets in aqueous media. It was suggested that solvated forms of cis-2•3H₂O and trans-2•3H₂O are representative of the elusive higher-lying biradicaloid minima that have been advocated by Pryor²⁶ as the metastable forms of peroxynitrous acid (HO−ONO*) largely responsible for the rich chemistry associated with this highly reactive oxidant.

D. Dissociative Pathways for Peroxynitrous Acid

Density functional theory has also been recently applied to several dissociative pathways of HO—ONO and its anion (ONO−O⁻) in aqueous solution. For example, the Gibbs free energy for the homolysis of peroxynitrous acid (HO−ONO → HO⁺ +ONO⁻) is calculated to be ΔG (aq.) = 11.1 kcal mol⁻¹, a value in good agreement with experiment (13.6 kcal mol⁻¹). For peroxynitrite homolysis (ONO−O− → NO₂ + O²⁻) the calculated ΔG (aq.) = 13.0 kcal mol⁻¹ was obtained for ion–molecule complexes with water⁴².

The mechanism of the forward and reverse reaction of HOO• radical with NO has also been examined at the B3LYP/6-311+G(3df,2p) level⁴³. The dominant pathway for the formation of HO−NO₂ from the reaction of these two radicals involves the direct fragmentation of intermediate HO−ONO. The alternate pathway, isomerization of HO−ONO to nitric acid, is 5.2 kcal mol⁻¹ higher in energy.

The reaction between hydroxyl radical and NO₂ has also been characterized by Dolco and Röthlisberger⁴⁴ using the B3LYP method. These two radicals combine spontaneously to form HNO₃ and cis, cis peroxynitrous acid. Formation of the trans, perp rotamer had a small activation barrier of 4.5 kcal mol⁻¹. When this work was extended to the aqueous solution phase, HO−ONO was found to have a hydrophilic end (OH) and a hydrophobic portion (the ONO fragment) that induces a solvent cage. This group was the first to show that an explicit solvation model was required in order to get an adequate description of the conformational aspects of HO−ONO. The relative energy difference between the cis and trans conformers was enhanced in aqueous solution and the rotational barrier is increased to 21 kcal mol⁻¹ due to solvent reorganization, a value much higher than that predicted in the gas phase⁴⁴b.

A high-level ab initio study of related reactions of alkyl nitrates (RO−NO₂) at the G3 and B3LYP/6-311+G(d,p) levels has revisited the reactions of alkyl peroxy radicals (ROO•) with nitric oxide. Activation barriers for the isomerization of RO−ONO to RO−NO₂ were found to be too high to account for the formation of alkyl nitrates
in tropospheric reactions. Since such isomerization reactions result in the loss of the high-energy O−O bond, they are typically highly exothermic based upon the analogous HO−ONO → HO−NO₂ isomerization that has a calculated energy difference of 29.1 kcal mol⁻¹ at the G3 level⁴⁵.

E. HO−ONO Reactivity

1. Two-electron oxygen atom transfer to N, S, P and Se nucleophiles

The similarity of the structure of peroxynitrous acid to the simplest peroxy acid, peroxyformic acid, immediately raised the question as to its relative reactivity as an oxygen atom donor. This became particularly relevant when it was recognized that the O−O bond dissociation energy (∆G° = 21 kcal mol⁻¹)¹⁶,²⁵ of HO−ONO was much lower than that of more typical peroxides. Consequently, peroxynitrous acid (HO−ONO) can be both a one- and two-electron oxidant. Since the O−O bond in HO−ONO is so labile, its chemistry is also consistent in many cases with that of the free hydroxyl radical.

Although one-electron oxidations may occur with the intermediacy of the hydroxyl radical, viscosity tests that serve to inhibit the diffusion of HO⁺ have provided evidence against the formation of free hydroxyl radicals²⁶a. This prompted the suggestion by Houk and coworkers³⁷e that the hydroxyl radical is formed in a tight cage in aqueous solution, still capable of performing one-electron oxidations.

Two-electron oxidations (oxygen atom transfer) of amines, sulfides²⁶b and selenides⁴⁶ by HO−ONO have been observed experimentally. Earlier theoretical studies by Houk and coworkers³⁷e suggest that HO−ONO should provide oxidative reactivity comparable to that of organic peroxyacids. Transition structures were located for the concerted peroxyacid oxidations of H₂S, NH₃ and ethylene. The activation energies of these reactions were calculated to be 13–18 kcal mol⁻¹ [B3LYP/6-31G(d)], confirming that these two-electron oxidations by HO−ONO are energetically feasible. For comparison, transition structures were also calculated for the peroxyformic acid oxidation of H₂S, NH₃ and ethylene at the B3LYP/6-31G* level; these are very similar in both energetics and geometries to those calculated earlier by Bach and coworkers at the MP2/6-31G* level¹⁷. Each transition structure involves substantial stretching of the O−O bond and only slight hydrogen transfer to the departing ONO⁻ anion fragment in much the same manner as peracid oxidation. This should not be too surprising since these two peroxides are formally isoelectronic.

The relatively short half-life of peroxynitrous acid hampers experimental studies of its reactions as an oxidizing agent. Therefore, theoretical methods can play a particularly useful role in describing the chemistry of peroxyacid. For comparison of the HO−ONO fragment geometries found in transition structures, the geometric parameters of HO−ONO at various levels of theory are presented in Figure 3.

For practical reasons the two-electron oxidations of such prototypical substrates as alkenes, sulfides, amines and phosphines with peroxynitrous acid have been studied since this type of oxygen atom transfer reaction is similar to the corresponding oxidations with peroxyformic acid, where both experimental⁴⁷ and computational data are available¹²b,¹⁷,¹⁹a,³⁵,⁴⁸ The oxidative reactions (equations 3–6) of these key substrates can serve as models for the oxidizing activity of HO−ONO in biochemical transformations involving substrates with the same functional groups or fragments⁴⁹. In this manner it can be ascertained whether biochemical reactions can share their basic mechanistic features with oxidations of the prototype molecules.
FIGURE 3. The geometry of the lowest-energy (cis,cis) conformation of peroxynitrous acid calculated at B3LYP/6-311+G(3df,2p), QCISD/6-31G* (bold numbers), CISD/6-31G* (in parentheses), B3LYP/6-311G** (in square brackets) and MP2(full)/6-31G* (in curly brackets) computational levels.

Bach and coworkers reported two-electron oxidations by HO−ONO of methyl substituted nucleophiles Me3N, Me2S and Me3P. It is generally believed that methyl substitution provides more realistic substrates for such model studies. The TSs are given in Figure 4. Relatively low activation barriers of 7.4, 7.5 and 0.6 kcal mol−1 respectively at the B3LYP/6-311G(d,p) level of theory attest to the reactivity of HO−ONO as an oxygen atom donor. A comparison of the activation barriers of peroxynitrous acid, peroxyformic acid and dimethyldioxirane at higher levels of theory are given in Table 2.

A comparison of the mechanisms of reaction of dimethyl sulfide and dimethyl selenide with peroxynitrite anion (ONO−O−) and peroxynitric acid (ONO−OH) has also been reported by Musaev and Hirao at the B3LYP/6-311+G(d,p) level of theory. The gas phase reactions with peroxynitrite were found to proceed by an oxygen atom transfer (two-electron oxidation) to produce the corresponding oxides, DMSO and DMSeO, and the NO2− anion. As anticipated, the activation barrier was found to be 6–7 kcal mol−1 lower for the third row Se nucleophile. The reaction of the neutral peroxide, HO−ONO, was suggested to be far more complex with the potential for both a concerted and stepwise mechanism for the oxidation of DMS in the gas phase. The stepwise process first involves homolysis to the radical pair, HO+ + NO2−, which can then coordinate with DMS to afford the intermediate adduct, (CH3)2S(OH)(NO2), as exemplified below for a model compound of ebselen (Figure 5). There is a small barrier for the transfer of a hydrogen atom to form the thermodynamic products DMSO and HNO2. In solution, it was suggested that the two pathways would be in competition.

\[
\begin{align*}
\text{Me}_2\text{S} + \text{HO}−\text{ONO} & \longrightarrow \text{Me}_2\text{S}−\text{O} + \text{HONO} \quad (4) \\
\text{Me}_3\text{N} + \text{HO}−\text{ONO} & \longrightarrow \text{Me}_3\text{N}−\text{O} + \text{HONO} \quad (5) \\
\text{Me}_3\text{P} + \text{HO}−\text{ONO} & \longrightarrow \text{Me}_3\text{P}−\text{O} + \text{HONO} \quad (6)
\end{align*}
\]
FIGURE 4. Transition structures for the oxidation of trimethylamine (a), trimethylphosphine (b) and dimethyl sulfide (c,d) with peroxynitrous acid optimized at the B3LYP/6-311G**, MP2(full)/6-31G* (in parentheses) and QCISD/6-31G* (in brackets) levels.
A similar mechanistic dichotomy was suggested for the reactions of these two oxidants with a model compound of ebselen (1,2 benzisoselenazol-3(2H)-one)\(^{40b}\). The concerted two-electron pathway was found to be more favorable at the enthalpy level. However, inclusion of entropy effects favors a stepwise mechanism (Figure 5). Musaev and coworkers also reexamined the possible involvement of the weakly bound hydrogen bonded structure, \(\text{OH} \cdots \text{ONO}^*\), (Figure 6), arising from homolysis of HO–ONO that was first described by Houk and coworkers\(^{37e}\). However, it was soon discovered that at the Gibbs free-energy level, with entropy corrections, this weakly bound structure is not stable relative to the \(\text{OH} + \text{ONO}^*\) dissociation limit in the gas phase. It was also shown that the weak interaction between these radicals vanishes when increasing numbers of water molecules are explicitly included in the optimization. This point was also addressed above in the section on metastable HO–ONO.

2. Epoxidation of ethylene and propylene

High-level calculations of alkene epoxidation reactions with peroxyformic acid, HO–O (C=O)H, which is isoelectronic with peroxynitrous acid [HO–O(N=O)], have indicated
a symmetrical transition structure with C—O bond lengths that are either equal (ethylene) or close to each other (propylene). B3LYP computational results for alkene epoxidation reactions with peroxymonosulfuric acid are in good agreement with the data of higher-level calculations (QCISD(T)/QCISD, CASSCF, BD)\textsuperscript{12b}. It has been suggested that B3LYP calculations perform quite well for the transition structure geometries of epoxidation reactions. Both experimental and B3LYP data have recently appeared that also suggest that peracid epoxidations of alkenes proceed by a symmetrical transition structure\textsuperscript{51}. Recent extended high-level CASSCF studies aimed specifically at this question have confirmed the original suggestion that if the wave function of the alkene is electronically symmetrical then one should anticipate a highly symmetrical TS\textsuperscript{52}. These studies have also confirmed the spiro nature of most such symmetrical TSs and have basically disproved the existence of planar TSs\textsuperscript{53} under typical conditions.

The oxidation of the simplest symmetrically substituted alkene, ethylene, is noteworthy in that an asymmetric ‘spiro’ transition state is observed. When constrained to $C_s$ symmetry with equal forming carbon–oxygen bond lengths, the energy increases by only 0.1 kcal mol\textsuperscript{−1}. The spiro TS has the plane of the HO—ONO (or peracid) at right angles to the axis of the C═C bond. In an idealized spiro TS this angle is exactly 90°. While the formation of sulfoxides from sulfides by peroxynitrous acid is well-established\textsuperscript{26b}, epoxidations have not yet been observed in solution.

Both MP2 and B3LYP calculations resulted in unsymmetrical transition structures for ethylene and propylene epoxidations with peroxynitrous acid (Figure 7). The difference in the C—O bond distances between the ethylene carbons and the spiro-oxygen in b of Figure 7 is 0.393 Å at the B3LYP/6-311G** level and even larger (0.575 Å) at the MP2 level. Geometry optimization at the B3LYP/6-311+G(3df,2p) level also gave unsymmetrical transition structures with geometrical parameters close to those calculated with the smaller 6-311G** basis. The geometry optimizations carried out at the CISD and QCISD levels, however, led to an almost symmetrical transition structure for ethylene [a, the differences in the C—O bond distances are 0.001 Å at both the QCISD/6-31G* and CISD/6-31G* levels, Figure 7] and propylene [(a), Figure 8]. The harmonic frequencies
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FIGURE 7. Geometrical parameters of symmetrical transition structure a for ethylene epoxidation with peroxynitrous acid optimized at the QCISD/6-31G* and CISD/6-31G* (values are in parentheses) levels and unsymmetrical transition structure b resulting from the geometry optimizations at the B3LYP/6-311+G(3df,2p), B3LYP/6-311G** (values in parentheses), B3LYP/6-31G* (values in square brackets) and MP2(full)/6-31G* (in curly brackets) levels. The full set of QCISD/6-31G* geometrical parameters for A is given as the most reliable data.

The triplet instability of both RB3LYP and RHF solutions is responsible for the difference in the symmetry of the ethylene–peroxynitrous acid transition structure. In general, an unsymmetrical transition structure with alkene epoxidation when an alternative symmetrical structure is possible, appears to be associated with an unstable wave function. For the epoxidation of propylene with HO−ONO, both the QCISD and CISD calculations result in a Markovnikov-type transition structure, where the electrophile is slightly skewed toward the least substituted carbon, with a small difference in the bond lengths between the spiro-oxygen and the double-bond carbons (0.106 and 0.043 Å, respectively; Figure 8). The B3LYP calculations also lead to an unsymmetrical Markovnikov-type transition structure (b). However, the MP2/6-31G* geometry optimization results in an anti-Markovnikov-type structure (c) (Figure 8). The CCSD(T)/6-31G* and BD(T)/6-31G* barriers for ethylene epoxidation with HO−ONO calculated with the QCISD/6-31G*...
FIGURE 8. Geometrical parameters of the nearly symmetrical transition structure (a) for propylene epoxidation with peroxynitrous acid optimized at the QCISD/6-31G* and CISD/6-31G* (values are in parentheses) levels and unsymmetrical transition structures (b) and (c) resulting from the geometry optimizations at the B3LYP/6-311G** and MP2(full)/6-31G* levels, respectively.

Optimized geometries are 18.4 and 19.9 kcal mol$^{-1}$, respectively$^{12b}$. The BD(T) barrier coincidently is the same as the BD(T)/6-31G*/QCISD/6-31G* barrier for the epoxidation of ethylene with peroxyformic acid. The CCSD(T)/6-31G*/CCSD/6-31G* (19.4 kcal mol$^{-1}$)$^4$ and CCSD(T)/6-31G*/QCISD/6-31G* barriers for both reactions are also close to each other. A basis set extension to the 6-311G** basis set does not result in a significant change of the CCSD(T) barrier for the C$_2$H$_4$ + HO$^-$ONO reaction (19.1 kcal mol$^{-1}$). The B3LYP calculations with the 6-311G** and 6-31G* basis sets lead to transition structure geometries and activation barrier values (12.8 and 13.4 kcal mol$^{-1}$, respectively) for the epoxidation of ethylene (Figure 7) that are quite similar. The basis set extension to the 6-311+G(3df,2p) basis set results in a modest increase in the barrier to 14.8 kcal mol$^{-1}$. These B3LYP barrier heights are, however, underestimated when compared with the QCISD(T)/QCISD and QCISD(T)/CISD barriers (18.4 and 19.3 kcal mol$^{-1}$, respectively). The B3LYP barrier is also underestimated for the epoxidation of propylene with HO$^-$ONO (a barrier of 10.2 kcal mol$^{-1}$) when compared to the QCISD(T)/6-31G*/QCISD/6-31G* barrier (15.5 kcal mol$^{-1}$)$^{12b}$. A similar trend of the B3LYP functional in underestimate the activation barrier has been found for the alkene epoxidation reactions with peroxyformic acid$^{38}$. As noted for the epoxidation of alkenes with HO$^-$O(C=O)H, the activation barriers calculated at the QCISD(T)/6-31G* level with the B3LYP optimized geometries are close to those computed at the more computer-time-demanding QCISD(T)/6-31G*/QCISD/6-31G* and QCISD(T)/6-31G*/CISD/6-31G* levels of theory. It was gratifying to observe the same trend with HO$^-$ONO, notwithstanding the fact that the B3LYP and QCISD (or CISD) transition state geometries differ from each other to a much greater extent than those for epoxidations with peroxyformic acid$^{38}$. 
3. Peroxynitrite anion oxidations

The peroxynitrite anion appears to be a relatively poor one-electron oxidant, although DFT calculations indicate that it is capable of alkene epoxidation. The fact that it has a substantially longer lifetime than peroxynitrous acid in solution makes this a much more viable oxidant. The transition structure for the oxidation of ethylene by peroxynitrite is shown in Figure 9. This reaction is exothermic ($\Delta E = -21.0$ kcal mol$^{-1}$) with an activation barrier of 11.6 kcal mol$^{-1}$ based upon isolated reactants. However, the lower barrier is most likely just a consequence of the fact that the system is negatively charged. As expected, for the gas phase, there is an ion–molecule complex that is 4.8 kcal mol$^{-1}$ more stable than the reactants. This transition structure differs markedly from that found for neutral HO−ONO; the transition structure is highly asymmetrical. This is a nucleophilic addition transition state, and the second phase of the reaction would involve cyclization of the oxirane ring and expulsion of NO$_2$$^-$. This reaction would be especially facile for electron-deficient alkenes, analogous to the Michael-type epoxidation of enones by basic hydrogen peroxide. The oxidation of the more nucleophilic amines and sulfides, on the other hand, will be highly disfavored. Reactions of peroxynitrite are further complicated by its rapid reaction with spurious carbon dioxide. In fact, some earlier studies that did not take this into account gave questionable results. There is effectively no barrier to the exothermic ($\Delta E = -25.7$ kcal mol$^{-1}$) formation of the peroxynitrite adduct with CO$_2$ (ONO$_2$CO$_2$$^-$, Figure 10). Homolysis of the O−O bond to form $^+$NO$_2$ and the carbonate radical ($^+$CO$_3$$^-$) requires only 8.7 kcal mol$^{-1}$. The optimized structure exhibits a nearly 90° dihedral angle about the O−O bond.

Musaev and Hirao have also reported theoretical studies on the reaction mechanisms of dimethyl sulfide and dimethyl selenide with peroxynitrite (ONO−O$^-$).

4. A comparison of peroxynitric acid and peroxynitrous acid

Peroxynitric acid (O$_2$NO−OH) is another important reactive two-electron oxidative species in this series of nitrogen-containing peroxides. The activation barriers reported by Houk and coworkers for two-electron oxidation of NH$_3$, H$_2$S and H$_2$C=CH$_2$ are similar to those found for HO−ONO. It differs from peroxynitrous acid mainly in its...
stability as a function of pH. The O−O bond strength in O\textsubscript{2}NO−OH is calculated\textsuperscript{37d} to be ca 20 kcal mol\(^{-1}\) greater than that of HO−ONO. The central N−O bond of O\textsubscript{2}NO−OH is weaker than its O−O bond in agreement with experimental observation that dissociation produces NO\textsubscript{2} and OOH. The O−O BDE of O\textsubscript{2}NO−OCO\textsubscript{2}− is 26 kcal mol\(^{-1}\) greater than that of ONO−OCO\textsubscript{2}− which accounts for its insensitivity to the presence of CO\textsubscript{2}.

A theoretical study reported earlier by McKee\textsuperscript{54} of the N\textsubscript{2}O\textsubscript{4} potential energy surface produced a new and interesting N\textsubscript{2}O\textsubscript{4} isomer that ostensibly couples two NO\textsubscript{2} radicals through oxygen−oxygen bonds (ONO−ONO). This intermediate arises by the oxidation of nitric oxide (NO) by dioxygen. This interesting intermediate actually has a calculated negative O−O BDE due to the electronic reorganization energy acquired through the formation of GS NO\textsubscript{2} radicals. Subsequently, Houk and his coworkers\textsuperscript{55} extended this study to include the rearrangement of this unusual peroxide. The well-known [3,3]-sigmatropic shift of 1,5-hexadiene (the Cope rearrangement)\textsuperscript{56} provides an excellent template for the corresponding O−O bond cleavage and ‘inorganic Cope rearrangement’ of ONO−ONO as shown in Scheme 1. These data are consistent with the \(^{18}\text{O}_{2}\) labeling distribution derived from trapping of intermediate ONO−NO\textsubscript{2}.

5. One-electron oxidation. The oxidation of methane with metastable peroxynitrous acid

Two fundamental questions of pertinence to the relevance of higher-lying metastable states of peroxynitrous acid are their relative stability in aqueous media and possible
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Involvement in biological reactions. In principle, hydrocarbon oxidation can take place by at least three pathways (Scheme 2). The concerted or two-electron pathway has been described by Rauk and coworkers\(^{37c}\). The free radical pathway, advocated by many, has also been part of the controversy. The recent description of a metastable form of peroxynitrous acid (HO−ONO\(^*\)) further complicates this mechanistic picture\(^{27}\).

While it is well established that HO−ONO can be involved in such two-electron processes as alkene epoxidation and the oxidation of amines, sulfides and phosphines\(^{38}\), the controversy remains concerning the mechanism of HO−ONO oxidation of saturated hydrocarbons. Rauk and coworkers advanced the hypothesis that the reactive species in hydrocarbon oxidations by peroxynitrous acid, and in lipid peroxidation in the presence of air, is the discrete hydroxyl radical formed in the homolysis of HO−ONO\(^{37c}\). The HO−ONO oxidation of methane (equation 7) on the restricted (\(\langle S^2 \rangle = 0.0\)) two-electron surface, of \(\Delta E^\text{‡} = 31.1\ \text{kcal mol}^{-1}\) (TS-\(6_R\), Figure 11). However, the more important question is whether hydrocarbon oxidation proceeds by a one-electron process involving the metastable form of peroxynitrous acid.

The initial prereaction complex (MIN-\(5\)) between GS HO−ONO (cis-conformer) and CH\(_4\) is stabilized by only 0.4 kcal mol\(^{-1}\) (Figure 11). As in the case of the HO−ONO molecule itself, a transition state (TS-\(6\)) for the O−O bond elongation process was observed, where HO−ONO is complexed with a molecule of methane (C−O distance 3.54 Å). This metastable O−O bond elongation TS-\(6\) is only 10.2 kcal mol\(^{-1}\) higher in energy than isolated reactants and had \(\langle S^2 \rangle = 0.34\). The structure of the HO−ONO fragment is almost identical with the TS for formation of cis-metastable HO−ONO from GS HO−ONO with an O−O bond distance of 1.871 Å and a \(\langle S^2 \rangle = 0.4\). The difference in energy between this minimum and TS-\(6\) is only 0.6 kcal mol\(^{-1}\) and an \(\langle S^2 \rangle = 0.76\) is consistent with its biradicaloid nature. The TS for hydrogen abstraction from methane occurs on the one-electron surface and confirms the involvement of the ‘excited’ form of peroxynitrous acid. MIN-\(10\) is a structure that can be described as NO\(_2\) and CH\(_3\) radicals interacting with a water molecule. As a consequence of
FIGURE 11. B3LYP/6-311+G(d,p) energy diagram for the reaction of HO−ONO and CH₄. Relative energies in kcal mol⁻¹ are with respect to isolated reactants (values in parentheses are with ZPE correction).
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The biradical nature of the peroxide group, with the calculated $\langle S^2 \rangle = 1.0$, suggests that the transition structure for concerted transfer of a hydroxyl radical to produce methanol, with hydrogen transfer to the NO$_2$ radical fragment forming H−ONO (TS-10), is just 5.2 kcal mol$^{-1}$ higher in energy than MIN-9. This transition structure ($\langle S^2 \rangle = 0.74$) is almost symmetrical with the O···H distances between the NO$_2$ and the H$_2$O fragment of 2.092 and 2.095 Å and an O···C distance of 2.44 Å. An IRC calculation reveals that this TS connects the H$_3$C···H$_2$O···HONO complex to the CH$_3$OH···HONO complex (MIN-11), and that during the reaction pathway the first process is the C−O bond formation and after the barrier is crossed a H transfer from the developing CH$_3$−OH$_2^+$ takes places leading to products, MIN-11. This final H-bonded product complex is 55.6 kcal mol$^{-1}$ more stable than isolated HO−ONO and methane. The very large difference in activation energies between closed-shell TS-6$_R$ and TS-8 ($\Delta \Delta E^\ddagger = 15.7$ kcal mol$^{-1}$) strongly supports the direct involvement of the metastable form of peroxynitrous acid (HO−ONO*) advocated with tremendous insight by Pryor and coworkers$^{26}$ at the very outset of this rich new area of chemistry.

6. The 1,2-rearrangement of peroxynitrous acid to nitric acid

Another relevant pathway for peroxynitrous acid decomposition in aqueous solution is O−O bond dissociation and rearrangement of HO−ONO to nitric acid, HO−NO$_2$, since it could potentially involve the ‘excited’ form of peroxynitrous acid (HO−ONO*). Location of the TS for this formal 1,2-OH shift has proven to be difficult but both Sumathi and Peyerimhoff$^{37a}$ and Dixon and collaborators$^{37b}$ have reported activation barriers for this reaction (39.0 kcal mol$^{-1}$, B3LYP and 21.4 kcal mol$^{-1}$, MP2). Presumably the latter second-order perturbation method does not treat the diradical nature of the TS adequately$^{37a}$. More recently Bach and coworkers$^{27b}$ reported an activation barrier of 40.8 kcal mol$^{-1}$ with an O−O distance of 2.53 Å and an O−N distance of 2.382 Å in the transition state for OH to migrate from O in the NO$_2$ fragment to N in the NO$_2$ fragment of HO−NO$_2$ (Figure 12). In the TS the OH is essentially stationary between the two NO oxygens and animation of the single imaginary frequency ($\nu_i = 690.0i$ cm$^{-1}$) showed largely a rocking motion of the ONO nitrogen toward the OH group. This concerted rearrangement takes place on the restricted PES ($\langle S^2 \rangle = 0.0$). While the magnitude of the barrier may seem surprisingly high for such a loosely bound TS, it should be remembered that all 1,2-rearrangements to a lone pair of electrons are 4-electron processes that are formally forbidden and hence have a very high barrier. Thus, all three studies$^{37a,b}$ conclude that the facile rearrangement of HO−ONO to HO−NO$_2$ involves dissociation to its free radical components and simple recombination.

FIGURE 12. Transition structure for the isomerization of peroxynitrous acid to nitric acid optimized at the B3LYP/6-311+G(d,p) level of theory. Classical reaction barrier, TS total energy and imaginary frequency (vectors represented by the arrows) are 40.8 kcal mol$^{-1}$ (with respect to cis-GS HO−ONO), −280.86143 au and 690i cm$^{-1}$, respectively
V. THE CHEMISTRY OF DIOXIRANES

A. Background

For most of the past century rather simple oxidizing agents such as hydrogen peroxide, alkyl and aryl hydroperoxides and peracids have been used as the preferred oxidizing agents in a variety of synthetic applications. However, over the past two decades a second major area of peroxo chemistry has evolved that has found specific uses for dioxiranes in complex organic syntheses. In the earlier stages of development rather primitive dioxiranes were prepared or generated in situ by oxygen transfer from water-soluble peroxo compounds such as OXONE to simple ketones. The characterization of dioxiranes has been seriously hampered by the fact that the parent dioxirane has only been observed as a labile species in the gas phase and its geometry determined by microwave spectroscopy. The most commonly used dioxirane, dimethyldioxirane (DMDO), was isolated from an acetone solution by Jeyaraman and Murray and can be kept at room temperature for several days. Methyl(trifluoromethyl)dioxirane (TFDO) was first isolated by Curci and coworkers and has served well as a highly reactive oxygen atom donor. Since these are very labile oxidants, we must rely heavily upon calculations at a high level of theory for structural information (Figure 13).

Dimesityldioxirane, a crystalline derivative, has been isolated by Sander and colleagues and subjected to X-ray analysis. The microwave and X-ray data both suggest that dioxiranes have an atypically long O–O bond in excess of 1.5 Å. Those factors that determine the stability of dioxiranes are not yet completely understood but what is known today will be addressed in this review. A series of achiral, and more recently chiral oxygen atom transfer reagents, have been adapted to very selective applications in the preparation of complex epoxides and related products of oxidation. A detailed history and survey of the rather remarkable evolution of dioxirane chemistry and their numerous synthetic applications is presented in Chapter 14 of this volume by Adam and Cong-Gui Zhao. Our objective in this part of the review is to first provide a detailed theoretical description of the electronic nature of dioxiranes and then to describe the nuances of the mechanism of oxygen atom transfer to a variety of nucleophilic substrates.

FIGURE 13. B3LYP/6-311+G(3df,2p)-optimized structures of dioxirane (DO), dimethyldioxirane (DMDO) and methyl(trifluoromethyl)dioxirane (TFDO). Bold numbers for DO are experimental microwave-structural data.
B. Molecular Orbital Treatments of Dioxirane

The dioxirane ring presents a unique type of O–O bond in that this three-member ring peroxide is marginally stable at best and its atypical reactivity as an oxidizing agent was initially attributed to its ring strain energy. This turns out not to be the case, since as explained below dioxiranes are not that highly strained. However, it was also discovered very early on that these cyclic peroxides have several higher-lying singlet excited states that may also contribute to their reactivity. In a seminal theoretical study Wadt and Goddard$^{61a}$ reported generalized valance bond (GVB) calculations that described the ground state of the parent dioxirane (DO) as a singlet that has its oxygen lone-pair electrons ($\pi$-type 2p orbitals) doubly occupied on both oxygen atoms. This ground state (GS) in the Goddard nomenclature$^{61}$ is thus referred to the $^1A(4\pi)$ state of DO (Scheme 3).

SCHEME 3
Since the O–O bond in DO is presumably quite weak, it has been suggested that the methylenebisoxo form of DO, dioxymethane, could potentially make a contribution to the overall chemistry of DO. The ground state of dioxymethane, a singlet diradical of $^1A$ symmetry, is derived simply by elongating the O–O bond until a singlet minimum is found where the $\pi$-type atomic 2p orbitals on both oxygens are singly occupied and the two oxygen lone-pairs reside in the O–C–O plane.

Goddard$^{61}$ predicted this diradical singlet $^1A(2\pi)$ state of dioxymethane to be 11.1 kcal mol$^{-1}$ higher in energy than GS DO. The corresponding 3$\pi$ state of dioxymethane, with one of the $\pi$-type atomic 2p orbitals singly occupied and the other doubly occupied, was only slightly higher in energy (2.8 kcal mol$^{-1}$) than the $^1A(2\pi)$ ground-state of dioxymethane. The $^1A(4\pi)$ state, a singlet minimum with an electron distribution similar to GS DO except for the elongated O–O bond, was 11.3 kcal mol$^{-1}$ higher in energy than GS dioxymethane and 22.4 kcal mol$^{-1}$ above ground-state dioxirane. In this earlier study the O–O bond distances were assumed to be the same as the equilibrium bond in GS-dioxymethane. The relative energies of DO and dioxymethane were later estimated to be almost identical by Karlström and coworkers$^{62}$ at the multiconfiguration self-consistent-field (MCSCF) level with DO being only 1.6 kcal mol$^{-1}$ lower in energy than dioxirane. The adiabatic energy barrier for the ring opening of DO to form dioxymethane was calculated to be 15.2 kcal mol$^{-1}$.

Subsequently, Bach and coworkers$^{48c,63}$ studied the structure and relative energy of dioxirane and dioxymethane at a variety of theoretical levels including complete active space self-consistent field (CASSCF). Their most reliable estimate of the energy at the QCISD(T)/6-31G(d) level with the geometry computed at the QCISD/6-31G(d) level (QCISD(T)/6-31G(d)/QCISD/6-31G(d)) suggested that DO was 12.4 kcal mol$^{-1}$ more stable than ground-state diradical dioxymethane. For the $2\pi$ state ($^1A_1$) of dioxymethane an O–O distance of 2.37 Å (MRDCI+Q/6-31G*) was found for this diradical GS of DO and its HOMO ($b_2$) is comprised of an antibonding combination of two oxygen lone-pairs oriented along the original O–O $\sigma$ bond axis. The higher-lying $3\pi$ and $4\pi$ excited states of dioxymethane (Scheme 3) were estimated to be 11.5 and 26.5 kcal mol$^{-1}$ higher in energy than the lowest-energy $^1A(2\pi)$ state of this diradical ground state$^{48c,63}$. At the MP2/6-31G(d) level the O–O bond lengths of GS DO and the singlet diradical 2$\pi$, 3$\pi$ and 4$\pi$ states of dioxymethane were found to be 1.53, 2.35, 2.14 and 2.20 Å, respectively. It is a very unique type of singlet minima containing an O–O bond that can exhibit four such different bond lengths. This type of excited state is reminiscent of the metastable form of peroxy nitrous acid described above.

It is also worthy of note that by symmetry considerations it is the higher energy 4$\pi$ state of dioxymethane that must be involved in oxygen transfer from dioxirane to a nucleophile. For example, oxygen transfer from DMDO to a typical nucleophilic two-electron $\sigma$- or $\pi$-donor (e.g. :Nuc = alkene, amine, phosphine, sulfide) proceeds via an $S_N$2-like displacement along the O–O bond axis with concomitant breaking of the O–O bond and formation of an O ← :Nuc bond. The ground state of dioxirane correlates with the 4$\pi$ configuration of methylenebisoxo affording the oxidized product and ground-state formaldehyde$^{20a}$. The primary electronic event for this $\sigma,\sigma$ approach ($\pi,\pi$ for Nuc = alkene) of a :Nuc involves transfer of electron density from the O–O bond and the :Nuc to the dioxirane O–O $\sigma^*$ orbital as the 4$\pi$ state intervenes. The orientation of the single electrons in both the 2$\pi$ and 3$\pi$ states would afford the excited state of the carbonyl group in acetone. The 4$\pi$ state is the only one of the three excited states that can produce acetone in its ground state. The above symmetry arguments presented for dioxirane also hold for DMDO. Consistent with this idea the 2$\pi$ diradical of dimethyldioxirane, with geometry optimization at the QCISD/6-31G* level, was calculated to be 19.1 kcal mol$^{-1}$.
[QCISD(T)] and 18.1 kcal mol$^{-1}$ at the MRCI+Q/6-31G* level (numerically optimized) higher in energy than ground-state DMDO$^{48c,63}$. A CASSCF study by Cantos and coworkers$^{64}$ also suggested that the ground-state of dioxymethane was located 11.1 kcal mol$^{-1}$ above DO and predicted a barrier for ground-state conversion of DO to dioxymethane of 25.8 kcal mol$^{-1}$. More recently, Anglada$^{65}$ has reported a high-level \textit{ab initio} MRD-CI (multireference single- and double-excitation configuration interaction) estimate suggesting that dioxymethane is only 5.8 kcal mol$^{-1}$ higher in energy than dioxirane. An activation barrier of 21.4 kcal mol$^{-1}$ was predicted for the ring opening of DO into dioxymethane. At this higher level the equilibrium geometries for DO, the TS for O–O bond elongation and dioxymethane were found to be 1.512, 2.108 and 2.359 Å. The calculated geometry for DO is in excellent agreement with the microwave data given in Figure 13.

Hoffmann and coworkers$^{66}$ have presented structural data on a series of dioxiranes substituted with electronegative substituents including difluorodioxirane. Difluorodioxirane is of particular interest because it has been described as potentially the most stable of the series of dioxiranes we have described. Cremer and coworkers$^{67}$ have predicted on the basis of \textit{ab initio} calculations that in contrast to the parent dioxirane (CO$_2$H$_2$), difluorodioxirane (CO$_2$F$_2$) should possess considerable thermodynamic stability. Difluorodioxirane is the only known dioxirane that is stable in the gas phase at room temperature.

C. The Electronic Structure of Dioxirane and Carbonyl Oxide

One of the most important features of the ozonolysis reaction of alkenes is one in which ozone adds to the C=C bond to form a primary ozonide (1,2,3-trioxolane). The Criegee mechanism$^{68}$ suggests that this unstable intermediate decomposes into a carbonyl compound and a carbonyl oxide that recombine to form a final isomeric ozonide (1,2,4-trioxolane). Direct spectroscopic evidence for a substituted carbonyl oxide has only recently been reported by Sander and coworkers$^{69}$ for the NMR characterization of dimesityl carbonyl oxide. Kraka and coworkers$^{70}$ have theoretically modeled dimesityl carbonyl oxide and confirmed the structural aspects reported by Sander and coworkers$^{69}$ on the basis of NMR data.

These highly reactive 1,3-dipolar species readily isomerize and undergo 1,3-cycloaddition reactions in addition to their cyclization to the corresponding dioxirane$^{71}$. It is within this latter context that we describe the more recent theoretical studies on carbonyl oxides and their relationship to dioxiranes. As a result of the lability of carbonyl oxides much of the research on this class of compound has been of a theoretical nature$^{62,67,72,73}$. There is a significant energy difference between a carbonyl oxide and its dioxirane that presents a driving force for cyclization. The activation barrier for the reverse reaction, ring opening to the higher-energy carbonyl oxide, has a prohibitive barrier. One of the earlier studies reported by Karlström and Roos$^{73}$ at the MCSCF level suggested a transition state for the rearrangement of the parent carbonyl oxide to dioxirane that was 23.9 kcal mol$^{-1}$ above ground-state carbonyl oxide. This barrier is reduced to 19.1 kcal mol$^{-1}$ at the QCISD(T) level$^{48c}$. At the MP4SDTQ//6-31G(d)/MP2/6-31G(d) level dioxirane is 29.2 kcal mol$^{-1}$ more stable than its isomeric carbonyl oxide. Calculations on carbonyl oxides have to be done with some caution because, as pointed out by Bach and his coworkers$^{48c}$, the calculated C–O and O–O bond lengths for these intermediates are highly sensitive to the level of theory used. The electronic character of carbonyl oxide changes from diradical (A) to zwitterionic (B and C) as the level of theory and basis set is augmented (Scheme 4). Increasing the number of methyl groups on the carbonyl oxide also increases its dipolar character$^{34}$. 
Bernhardsson and coworkers\textsuperscript{75a} have recently used CASPT2 calculations (electron-correlation correction to the CAS wave function) to model carbonyl oxides in solution. Solvation effects in acetonitrile solvent also suggest that the zwitterionic form would be favored with an elongation of the O–O bond length and a decrease in the C–O bond\textsuperscript{75b}. \textit{Ab initio} calculations have been recently reported for monofluorocarbonyl oxide\textsuperscript{67}, difluorocarbonyl oxide\textsuperscript{76}, methylcarbonyl oxide and cyclopropenone carbonyl oxide\textsuperscript{77}. In the recent literature the idea that carbonyl oxide can be an important source of OH radicals has also been presented\textsuperscript{78}.

The electronic structure and vibrational frequencies for dimethyl-substituted carbonyl oxide and its cyclic isomer dimethyldioxirane have also been reported by Kim and Schaefer\textsuperscript{79} (Figure 14) at the coupled cluster level with single and double excitation (CCSD), and the CCSD with connected triple excitations [CCSD(T)]. The relative energetics and isomerization barriers for dimethyldioxirane were also computed in that study with relatively large basis sets. At the highest level of theory employed, TZP [triple-$\zeta$ (TZ) quality basis set with one set of polarization functions] CCSD(T), dimethyldioxirane is predicted to be lower in energy than its carbonyl oxide by 23.2 kcal mol$^{-1}$ with the inclusion of zero-point vibrational energy (ZPVE) corrections. The energy barrier for the cyclization of dimethylcarbonyl oxide to DMDO (Figure 15)\textsuperscript{79} was reported to be 19.5 kcal mol$^{-1}$ at the same level of theory. The molecular structure of dimethyl-substituted carbonyl oxide has $C_s$ symmetry with a staggered conformation. The predicted C–O bond distance of 1.28 Å at the TZP CCSD(T) level of theory shows some double-bond character, which implies that the electronic structure of dimethylcarbonyl oxide prefers the zwitterionic form. The transition state for the cyclization of dimethyl carbonyl oxide to dimethyldioxirane has $C_1$ symmetry (Figure 15)\textsuperscript{79}.

Another route to the formation of carbonyl oxides is the reaction of methylene (CH$_2$) with dioxygen. This oxidative process involving methylene with O$_2$ is one of the most important reactions in the combustion of unsaturated hydrocarbons. The reaction between CH$_2$ ($X^3B_1$) + O$_2$ has been studied by Anglada and Bofill\textsuperscript{77a} in the gas phase by carrying out CASSCF and CASPT2 calculations with the 6-31G(d,p) and 6-311+G(3df,2p) basis
sets. The reaction proceeds by the addition of O$_2$ to methylene and may proceed on either a singlet or a triplet potential energy surface. In both cases, the initial product is the carbonyl oxide (H$_2$COO) that may isomerize to dioxirane and beyond as shown in Scheme 580.

The reaction in its singlet multiplicity is computed to be exothermic by 50.9 kcal mol$^{-1}$ with an activation enthalpy of 1.9 kcal mol$^{-1}$ at 298 K. The triplet reaction is computed to be exothermic by 26.9 kcal mol$^{-1}$ with an activation enthalpy of 5.4 kcal mol$^{-1}$ at 298 K. According to classical transition state theory, the branching ratio for the reaction in its triplet state multiplicity changes from negligible at 298 K to about 26% at 1800 K, and this ratio equals the formation of atomic oxygen, O($^3$P). The carbonyl oxide can isomerize to dioxirane with an activation enthalpy of 18.7 kcal mol$^{-1}$ or to formic acid which dissociates into HCO and OH with an activation enthalpy of 32.5 kcal mol$^{-1}$77b. The triplet H$_2$COO ($A^3A''$) decomposes into H$_2$CO ($X^1A_1$) + O ($^3P_g$). The process is computed to be exoergic by about 27 kcal mol$^{-1}$ and has an activation enthalpy of 2.9 kcal mol$^{-1}$.

At the same time Fang and Fu reported on the identical reaction also using CASSCF methods with a relatively large active space81. CAS(14,12)/cc-pVDZ calculations are reported for the reaction of 3CH$_2$ + 3O$_2$ → products. On the singlet potential energy surface, a transition state has been located with an energy barrier of 1.65 kcal mol$^{-1}$, which is in good agreement with the experimental estimation of 1.0–1.5 kcal mol$^{-1}$. For the triplet case, the formation of CH$_2$OO has an energy barrier of 5.79 kcal mol$^{-1}$, and the triplet CH$_2$OO produced could be further decomposed into CH$_2$O + O($^3$P) with an energy barrier of 2.92 kcal mol$^{-1}$. The geometries of some key points were also located at the CAS(8,6)+1+2/cc-pVDZ level of theory for comparison.
It has been argued by Cremer and coworkers\textsuperscript{82a} that the parent carbonyl oxide, CH\textsubscript{2}COO, does not readily decompose into HCO\textsuperscript{+} + OH radical because of a relatively high activation enthalpy of 31 kcal mol\textsuperscript{−1}. However, a relatively low activation pathway (Δ\text{H}^0_\text{f} = 14.4 kcal mol\textsuperscript{−1}) was found for methyl-substituted carbonyl oxides that were capable of undergoing a 1,5-hydrogen migration to produce a vinyl hydroperoxide. This methyl-substituted vinyl hydroperoxide readily undergoes O–O bond cleavage to produce the OH radical. This led to the important conclusion that gas-phase ozonolysis of substituted alkenes leads to the formation of hydroxyl radicals—a reaction of serious consequences for the chemistry of the atmosphere. The origin of the weakness of the O–O bond in vinyl hydroperoxides has been noted previously\textsuperscript{16a}. The two competing potential pathways for the decomposition of dimethyl carbonyl oxide are shown in Scheme 6. A theoretical investigation of a series of reactions that project mechanisms for the formation of formic acid in the atmosphere from the simplest Criegee intermediate, CH\textsubscript{2}COO, has also been reported\textsuperscript{82b}.

Schindler and coworkers verified the formation of hydroxyl radicals kinetically\textsuperscript{83} and further RRKM calculations by Cremer and coworkers placed the overall concept on a more quantitative basis by verifying the measured amount of OH radical\textsuperscript{84}. An extensive series of calculations on substituted alkenes placed this overall decomposition mechanism and the involvement of carbonyl oxides in the ozonolysis of alkenes on a firm theoretical basis\textsuperscript{78}. The production of OH radicals in solution phase was also suggested on the basis of a series of DFT calculations\textsuperscript{85a}. Interestingly, both experiment and theory support a concerted [4+2] cycloaddition for the ozone–acetylene reaction rather than a nonconcerted reaction involving biradical intermediates\textsuperscript{85b}.

Using statistical-dynamical methods and transition state theory, Zhang and coworkers demonstrated that excited carbonyls dissociate promptly to produce OH radicals (11%) or isomerize to form dioxirane (32%) or are collisionally stabilized (57%)\textsuperscript{86}.

In a recent paper Anglada, Cremer and coworkers have discovered several new facets of the alkene ozonolysis mechanism that impacts the area of alkene epoxidation as well\textsuperscript{87}. A comparison of the reactivity of the three isomeric oxidizing carbonyl oxides, dioxirane and methylenebisoxy with ethylene was achieved using CASPT2, CCSD(T) and B3LYP with a relatively large 6-311+G(2d,2p) basis set. Contrary to expectation, carbonyl oxide prefers to react with ethylene via a [4+2] cycloaddition reaction (activation enthalpy, Δ\text{H}^\neq = 1.0 kcal mol\textsuperscript{−1}) to produce 1,2-dioxolane with a reaction enthalpy of −65 kcal mol\textsuperscript{−1} rather than the epoxidation reaction (Δ\text{H}^\neq = 11.3 kcal mol\textsuperscript{−1}) forming oxirane and formaldehyde. Epoxidation of ethylene by dioxirane is also slower, having a calculated activation enthalpy of 13.7 kcal mol\textsuperscript{−1}. The biradical methylenebisoxy was observed to undergo a pseudo-[4+2] cycloaddition (Δ\text{H}^\neq = 1.8 kcal mol\textsuperscript{−1}) leading to 1,3-dioxolane in a highly exothermic reaction (Δ\text{H} = −84.5 kcal mol\textsuperscript{−1}). These combined data will require a reevaluation of many aspects of the ozonolysis reaction.

D. Oxygen Atom Transfer from Dioxiranes and Carbonyl Oxides

Dioxiranes are three-membered ring peroxides that serve as paradigm examples of electrophilic species. Dimethyldioxirane (DMDO), in particular, is a powerful oxidant with unusual synthetic utility that can be produced \textit{in situ} by the reaction of acetone with Caroate (2KHSO\textsubscript{5}·KHSO\textsubscript{4}·K\textsubscript{2}SO\textsubscript{4}). Consequently, a great many such synthetic procedures are carried out in acetone solvent. Methyl(trifluoromethyl)dioxirane (TFDO) was synthesized a few years later by Curci and coworkers\textsuperscript{59}, demonstrating that electron-withdrawing groups can markedly increase the reactivity of dioxiranes. Most of the theoretical calculations on the mechanism of dioxirane epoxidation have been accomplished at the DFT level since this topic came under general scrutiny when this method came into vogue.
1. General and theoretical aspects of the peroxide group

**Scheme 6**

Path I:

- Initial compound
- Transition state (TS)
- Compound after initial reaction
- Ester formation

Path II:

- Initial compound
- Transition state (TS)
- Compound after initial reaction
- Compound after second reaction
- Final compound with solvent cage

**TS**
1. A comparison of DFT theory with higher-level methods

In the past several years the B3LYP variant of density functional theory (DFT) has been used extensively for calculations involving oxygen atom transfer. A comparison of the performance of DFT calculations with other high-level \textit{ab initio} methods has presented credible evidence that this relatively efficient DFT functional is quite adequate for answering mechanistic questions about the epoxidation of alkenes. A systematic study by Bach and coworkers\textsuperscript{12b} on the epoxidation reactions of ethylene, propylene, and \textit{cis}- and \textit{trans}-2-butene with peroxyformic acid and of ethylene with dioxirane and dimethyldioxirane has provided an internally consistent series of activation energies and geometries for comparison. The transition structures for the epoxidation of ethylene and propylene with peroxyformic acid and of ethylene with dioxirane and dimethyldioxirane were calculated at the B3LYP level, as well as at the QCISD and CCSD levels. The B3LYP method provided symmetrical transition structures with nearly identical C–O bond distances, whereas the MP2 calculations favor unsymmetrical transition structures as noted for TS-a (Figure 16).

An interesting comparison of the electronic character of peroxyformic acid and dioxirane has been provided by Deubel\textsuperscript{88} through an analysis of the donor–acceptor interactions in a series of transition states (TS) for the epoxidation of alkenes. It was suggested that alkenes are attacked by peroxyformic acid (PFA) in an electrophilic way. A relationship between the electronic character of the reagent and its reactivity has been suggested: the more electrophilic the attack on the C=C bond, the faster the reaction. In contrast, dioxirane (DO) has been identified as both an electrophilic and nucleophilic oxidant, depending upon the substituents on the C=C double bond. The substrates with electron-withdrawing groups are attacked by DO in a nucleophilic way. These reactions have comparably low activation barriers. For instance, acrylonitrile epoxidation with dioxirane is significantly faster than the corresponding reaction with PFA and proceeds via a transition state earlier on the reaction coordinate and with a larger extent of asymmetry.

The geometrical parameters of the transition structures calculated using the B3LYP functional are close to those found at the QCISD and CCSD levels. While the activation

![Figure 16](image-url)
barriers for the epoxidation reactions calculated at the B3LYP/6-31G* and B3LYP/6-
31+G* levels are very close to the MP4SDTQ/6-31G*/MP2/6-31G* and MP2/6-31G*/
MP2/6-31G* values, these activation energies are systematically lower for peracid epoxi-
dation (up to 5–6 kcal mol$^{-1}$) than the barrier heights calculated at such higher correlated
levels as the QCISD(T)/6-31G*/QCISD/6-31G*, CCSD(T)/6-31G*/CCSD/6-31G* and
BD(T)/6-31G*/QCISD/6-31G* levels. The opposite trend is true for dioxirane epoxi-
dation, where the activation barriers are slightly overestimated. DFT calculations on
the epoxidation reactions of ethylene and propylene with peroxyformic acid using the
BH&HLYP functional also lead to symmetrical transition structures, but the calculated
barriers are overestimated when compared with the QCISD(T) results. The activation bar-
riers calculated for these epoxidation reactions at the QCISD(T)/6-31G*/B3LYP/6-31G*
level are very close to those computed at the QCISD(T)/6-31G*/QCISD/6-31G* level.

One of the objectives of the present review is to provide some guidance that suggests
the most reasonable or affordable method of calculation balanced against the accuracy of
the method. Some generalized conclusions derived from the above systematic compari-
son include:

(1) In contrast to the results of the MP2 calculations, the nature of the transition
structures in the alkene epoxidation reactions calculated at the B3LYP level agree well
with those computed using higher correlated methods such as QC1 and CC. Therefore,
while the MP2 calculations are biased in favor of unsymmetrical transition structures,
the B3LYP method is capable of providing the correct transition structure geometry for
simple unconjugated alkenes if the B3LYP solution for the wave function is stable.

(2) The transition structures for the epoxidation of ethylene and propylene with per-
oxoformic acid and of ethylene with dioxirane and dimethyldioxirane calculated at the
B3LYP, QCISD and CCSD levels are symmetrical with a spiro orientation of the elec-
trophilic oxygen, whereas the MP2 calculations favor unsymmetrical transition structures.
The geometries of the transition structures calculated using the B3LYP functional are
close to those found at QCISD, CCSD, CCSD(T) levels as well as those found at the
CASSCF(10,9) and CASSCF(10,10) levels for the transition structure of the epoxidation
of ethylene.

(3) The activation barriers for the epoxidation reactions calculated at the B3LYP/6-31G*
and B3LYP/6-31+G* levels are systematically lower (up to 5–6 kcal mol$^{-1}$) than the bar-
rier heights calculated at such higher correlated levels as the QCISD(T)/6-31G*/QCISD/6-
31G*, CCSD(T)/6-31G*/CCSD/6-31G* and BD(T)/6-31G*/QCISD/6-31G*, although
the transition structure geometries calculated at these levels of theory are in good agree-
ment. In contrast, the BH&HLYP6-31G* barrier for the epoxidation of ethylene and
propylene with peroxyformic acid is overestimated by up to 8 kcal mol$^{-1}$ when compared
with the barriers calculated at the QCISD(T), BD(T) and CCSD(T) levels of theory. The
activation barriers calculated at the QCISD(T)/6-31G*/B3LYP/6-31G* level appear to be
close enough to those computed at the QCISD(T)/6-31G*/QCISD/6-31G* level to adopt
this protocol for relatively large systems.

2. Epoxidation of alkenes with carbonyl oxides and dioxiranes

Since Kim and Schaefer have shown that dimethylcarbonyl oxide is 23 kcal mol$^{-1}$
higher in energy than its corresponding cyclic dioxirane (DMDO)\textsuperscript{79}, one might assume
that the barrier for oxygen atom transfer from the higher-energy carbonyl oxide should
be lower. However, alkene epoxidation by carbonyl oxide is 20–30 kcal mol$^{-1}$ more
exothermic than oxidation by dioxirane\textsuperscript{48d}. As a result of the greater exothermicity of the
reactions with carbonyl oxide, the barriers are as much as 10 kcal mol$^{-1}$ lower than for
oxidation by dioxirane\textsuperscript{48d}. This concept was examined more closely for the oxidation of
ethylene since the carbon–carbon double bond is weakly nucleophilic and considerable experimental data on the formation of epoxides from alkenes are available. However, since carbonyl oxides are not sufficiently stable to be employed as a laboratory reagent, their inclusion here is more of a theoretical nature. It should also be recalled as noted above that carbonyl oxides, at least in the gas phase, prefer a [4+2] cycloaddition pathway in reactions with alkenes instead of the anticipated epoxidation TS.87

The transition states for the epoxidation of ethylene by carbonyl oxide and dimethylcarbonyl oxide are shown in Figure 17. The orientation of approach of the electrophilic oxygen is approximately symmetrical in nature but the TS is essentially planar with the O–O–C fragment lying along the C=C bond axis. This is distinctly different from the transition structures for dioxirane and peracid epoxidation where a spiro, but typically symmetrical, TS is observed. Additionally, the developing C–O bonds are considerably longer, indicating a more reactant-like structure in agreement with Hammond’s postulate.

FIGURE 17. Transition structures for the epoxidation of ethylene by carbonyl oxide [Δ(E+ZPVE) = 10.2 kcal mol⁻¹] and dimethylcarbonyl oxide [Δ(E+ZPVE) = 10.3 kcal mol⁻¹] optimized at the B3LYP/6-311+G(d,p) level of theory. Bond lengths given in brackets are at the MP2/6-31G(d) level, and the corresponding barriers are 14.8 and 12.9 kcal mol⁻¹.87
Ethylene epoxidation with unsubstituted carbonyl oxide is ca 5 kcal mol\(^{-1}\) more exothermic than with dimethylcarbonyl oxide, yielding an even earlier transition state.

In contrast to dioxirane oxidation, the transition states for carbonyl oxide oxidation are not affected as much by RHF-UHF wave function instability problems, and there is good agreement between the MP2, MP4 and QCISD(T) barrier heights. Methyl substitution on the carbonyl oxide has very little effect on the barrier heights, but it can be anticipated that methyl substitution of the alkene would lower the barriers significantly\(^{19d}\). The calculated changes in the barriers due to solvation are much smaller than for dioxirane oxidation, primarily because the differences between the reactant and transition state dipoles are smaller.

In summary, transition structures with dioxirane and dimethyldioxirane are unsymmetrical at the MP2/6-31G* level, but are symmetrical at the QCISD/6-31G* and B3LYP/6-31G* levels. The transition states for oxidation of ethylene by carbonyl oxides do not suffer from the same difficulties as those for dioxirane and peroxyformic acid. Even at the MP2/6-31G* level, they are symmetrical (Figure 17). The barriers at the MP2 and MP4 levels are similar and solvent has relatively little effect. The calculated barriers agree well with experiment\(^{71}\). In a similar fashion, the oxidation of ethylene by peroxyformic acid has been studied at the MP2/6-31G*, MP4/6-31G*, QCISD/6-31G* and CCSD(T)/6-31G* and B3LYP levels of theory\(^{48d}\). The MP2/6-31G* level of theory calculations lead to an unsymmetrical transition structure for peracid epoxidation that, as noted above, is an artifact of the method. However, QCISD/6-31G* and B3LYP/6-31G* calculations both result in symmetrical transition structures with essentially equal C–O bonds.

In the past several years dioxiranes have rapidly grown into one of the more useful oxidative reagents in the arsenal of the synthetic chemist. Its unique ability ranges from the transfer of an oxygen atom to the C–H bond of a saturated hydrocarbon to that of oxidation of atoms containing a lone pair of electrons such as amines and sulfides. Their use now rivals that of peracids in the epoxidation reaction due in part to their application under neutral conditions and to comparable or even enhanced rates of reaction\(^{89}\). However, by far the most common application for dioxiranes remains the oxidation of a carbon–carbon double bond. A concerted oxygen atom transfer for the dioxirane epoxidation reaction has been advocated by both Bach\(^{12b}\) and Houk\(^{90}\) and their coworkers. It is generally accepted that an S\(_N\)2-like attack of the alkene \(\pi\)-bond on the dioxirane peroxide \(\sigma\) O–O bond is responsible for the epoxidation step. The \(\text{spiro}\) orientation is a manifestation of a weak back-bonding interaction of the HOMO of the alkene with the \(\sigma^*\) O–O orbital of the dioxirane. Sarzi-Amade and coworkers reported a comparison of the transition structures for the epoxidation of ethylene and \(Z\)-2-butene with the parent dioxirane (DO) and DMDO that also suggested a symmetrical \(\text{spiro}\) approach to the C=C\(^{91}\).

In marked contrast to the generally accepted mechanism, the involvement of a radical pair produced by an alkene-induced O–O bond homolysis was suggested by Minisci and coworkers\(^{92}\). In a combined experimental and theoretical study Curci, Houk and coworkers\(^{93}\) sought to differentiate between a radical pathway and the commonly accepted concerted mechanism. Both product and kinetic studies tended to exclude a radical pathway. Computational studies at the B3LYP/6-31G* level on the epoxidation of isobutylene with DMDO predicted an activation energy (\(\Delta E^\# = 15.3\) kcal mol\(^{-1}\)) significantly lower than the O–O bond dissociation energy of DMDO of 23.1 kcal mol\(^{-1}\) estimated by Cramer and coworkers\(^{94a}\). Thus, both theory and experiment support a concerted epoxidation mechanism. However, several authentic transition structures (first-order saddle points) have recently been located for the addition of the excited state of both DO and DMDO to ethylene and \(Z\)-2-butene involving a radicaloid pathway. These open-shell TSs are
connected to the corresponding epoxide products in a two-step mechanism and are lower in energy than the aforementioned closed-shell pathway.

This mechanistic dichotomy has many things in common with the recent developments in peroxynitrurous acid chemistry\textsuperscript{27} and deserves further study.

A typical closed-shell transition structure for DMDO epoxidation is exemplified by the epoxidation of \textit{E}- and \textit{Z}-2-butene. Baumstark and Vasquez have reported experimental studies that demonstrate the greater reactivity of \textit{Z}-alkenes in the DMDO epoxidation of \textit{E/Z}-pairs of alkenes\textsuperscript{94b}. As anticipated, approach of the dioxirane ring to the \textit{Z}-double bond in the less hindered manner, away from the methyl groups of DMDO,

TABLE 3. B3LYP/6-31G(d) activation barriers (\(\Delta E^\#\), kcal mol\(^{-1}\)) for the epoxidation of a series of alkenes with peroxyformic acid (PFA) and dimethyldioxirane (DMDO). The barriers in parentheses are at the B3LYP/6-31+G(d,p) level of theory. Other computational approaches are indicated by footnotes. The barriers have been computed with respect to isolated reactants

<table>
<thead>
<tr>
<th>Alkene</th>
<th>PFA</th>
<th>DMDO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene</td>
<td>14.1(14.9)</td>
<td>17.0\textsuperscript{a} [16.4]\textsuperscript{b}</td>
</tr>
<tr>
<td>Propene</td>
<td>12.0(12.6)</td>
<td>14.8\textsuperscript{a} [16.0]\textsuperscript{c}</td>
</tr>
<tr>
<td>\textit{t}-Butylethylene</td>
<td>11.2 (12.3)</td>
<td>14.0\textsuperscript{a}</td>
</tr>
<tr>
<td>1-Octene</td>
<td>11.2 (12.2)</td>
<td>14.1\textsuperscript{a}</td>
</tr>
<tr>
<td>Isobutene</td>
<td>10.8 (11.2)</td>
<td>13.0\textsuperscript{a} [13.7]\textsuperscript{c}</td>
</tr>
<tr>
<td>\textit{E}-2-Butene</td>
<td>10.5 (11.0)</td>
<td>12.8\textsuperscript{a} [13.4]\textsuperscript{c}</td>
</tr>
<tr>
<td>\textit{Z}-2-Butene</td>
<td>10.0</td>
<td>12.1\textsuperscript{a}</td>
</tr>
<tr>
<td>\textit{Z}-2-Pentene</td>
<td>9.3 (10.0)</td>
<td>11.6\textsuperscript{a}</td>
</tr>
<tr>
<td>Cyclopropene</td>
<td>12.0 (12.5)</td>
<td>14.5\textsuperscript{a}</td>
</tr>
<tr>
<td>Cyclobutene</td>
<td>11.0 (11.5)</td>
<td>13.7\textsuperscript{a}</td>
</tr>
<tr>
<td>Cyclopentene</td>
<td>9.3 (9.7)</td>
<td>12.1\textsuperscript{a}</td>
</tr>
<tr>
<td>Cyclohexene</td>
<td>9.7 (10.1)</td>
<td>12.1\textsuperscript{a}</td>
</tr>
<tr>
<td>Cycloheptene</td>
<td>9.8 (10.2)</td>
<td>12.2\textsuperscript{a}</td>
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<td>\textit{Z}-Cyclooctene</td>
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<td>\textit{E}-Cyclooctene</td>
<td>5.6 (6.1)</td>
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<td>4.0 (4.3)</td>
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<td>Norbornene (\textit{exo})</td>
<td>9.7 (10.3)</td>
<td>12.9\textsuperscript{a}</td>
</tr>
<tr>
<td>Norbornene (\textit{endo})</td>
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<td>15.4\textsuperscript{a}</td>
</tr>
<tr>
<td>Benzonorbornadiene (\textit{exo})</td>
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<td>12.2\textsuperscript{a}</td>
</tr>
<tr>
<td>Benzonorbornadiene (\textit{endo})</td>
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<td>17.0\textsuperscript{a}</td>
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<tr>
<td>Bicyclo[3.3.1]non-1-ene</td>
<td>5.2 (5.7)</td>
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<tr>
<td>Trimethylethylene</td>
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<td>Tetramethylethylene</td>
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<td>9.8\textsuperscript{a}</td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>11.7 (12.4)</td>
<td>14.3\textsuperscript{a} [15.9]\textsuperscript{c}</td>
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<tr>
<td>trans-2-cis-4-Hexadiene</td>
<td>9.4 (9.6)</td>
<td>11.5\textsuperscript{a}</td>
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<td>\textit{E}-Stilbene</td>
<td>13.2 (13.3)</td>
<td>15.1\textsuperscript{a}</td>
</tr>
<tr>
<td>\textit{Z}-Stilbene</td>
<td>11.8 (12.6)</td>
<td>14.6\textsuperscript{a}</td>
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<tr>
<td>Styrene</td>
<td>11.2 (11.7)</td>
<td>14.2\textsuperscript{a}</td>
</tr>
<tr>
<td>\textit{Z}-3-Methyl-3-penten-2-ol</td>
<td>9.2\textsuperscript{d}</td>
<td></td>
</tr>
<tr>
<td>Allyl alcohol</td>
<td>7.5\textsuperscript{e}</td>
<td>11.4\textsuperscript{f}</td>
</tr>
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</table>

\textsuperscript{a} Classical activation barriers computed at the B3LYP/6-311+G(3df,2p)//B3LYP/6-31+G(d,p) level of theory.
\textsuperscript{b} The numbers in brackets for ethylene are at the QCISD(T)/QCISD/6-31+G(d,p) level of theory.
\textsuperscript{c} The numbers in brackets for propylene, isobutylene, \textit{E}-2-butene and 1,3-butadiene entries are at the QCISD(T)/QCISD/6-31G(d) level of theory; QCISD(T)/6-31G(d)//B3LYP/6-31+G(3df,2p) gas-phase intrinsic barriers (\(\Delta E^\#\)) for the epoxidation of \textit{E}-2-butene with dimethyldioxirane (DMDO) and peroxyformic acid are 14.3 and 13.2 kcal mol\(^{-1}\), respectively.
\textsuperscript{d} Classical activation barrier computed at the B3LYP/cc-pVTZ level.
\textsuperscript{e} Classical activation barrier computed at the B3LYP/6-311G(d,p) level.
\textsuperscript{f} Classical activation barrier computed at the QCISD(T)/QCISD/6-31G(d) level.
is 3.4 kcal mol\(^{-1}\) lower in energy. DMDO epoxidation of \(E\)-2-butene has a calculated barrier (\(\Delta E^\neq = 15.5\) kcal mol\(^{-1}\), B3LYP/6-31G*)\(^{90b}\) that is 2.3 kcal mol\(^{-1}\) higher than that of the less encumbered \(Z\)-alkene. At the B3LYP/6-31+G(d,p) level the activation barriers for \(E\)- and \(Z\)-2-butene differ by only 1.4 kcal mol\(^{-1}\)\(^{19d}\). The calculated barrier at the QCISD(T)/QCISD/6-31G(d) level is 14.6 kcal mol\(^{-1}\). These data are summarized in Table 3.

The approach of DMDO to \(E\)-2-butene is spiro in nature with nearly equally developing C–O bond distances (Figure 18). The O–O bond in the TS is elongated to 1.879 Å. The calculated gas-phase enthalpy of activation (\(\Delta H^\neq = 13.5\) kcal mol\(^{-1}\)) is higher than the experimental \(\Delta H^\neq = 7.4\) kcal mol\(^{-1}\) for the DMDO epoxidation of cyclohexene\(^{95}\) in acetone solvent while the calculated entropy of activation (\(-39.7\) cal mol\(^{-1}\) K\(^{-1}\)) is in better agreement with experiment (\(-35.5\) cal mol\(^{-1}\) K\(^{-1}\)).

Electron-withdrawing fluorine substitution on both peracids and dioxiranes has a rather large impact upon the reaction rate of oxygen atom transfer. Although the reactivity of dioxiranes has traditionally been ascribed to a driving force due to relief of ring strain and the favorable enthalpy attending the formation of a strong C=O \(\pi\)-bond, the recent reassessment of the strain energy of DMDO (SE = 11 kcal mol\(^{-1}\))\(^{20b}\) suggests that the enhanced reactivity just may be due to the relatively low-lying O–O \(\sigma^*\) orbital of the dioxirane. However, the involvement of the low-lying excited states of dioxiranes cannot be discounted at this time. The increased reactivity (\(\geq 1000\)-fold) of methyl (tri-fluoromethyl) dioxirane (TFDO) compared to DMDO has been accredited largely to the inductive effect of the CF\(_3\) group on the dioxirane ring. Since experimental rate data that

\[ E_{\text{tot.}} = -425.50986 \text{ au} \]
\[ \Delta H^\neq = 13.5 \text{ kcal mol}^{-1} \]
\[ \Delta S^\neq = -39.7 \text{ eu} \]

\[ E_{\text{tot.}} = -425.50967 \text{ au} \]
\[ \Delta H^\neq = 14.9 \text{ kcal mol}^{-1} \]
\[ \Delta S^\neq = -39.6 \text{ eu} \]

**FIGURE 18.** Transition structures for the epoxidation of \(Z\)-2-butene (a) and \(E\)-2-butene (b) with DMDO, optimized at the B3LYP/6-31+G(d,p) level of theory. Bond distances in parentheses for \(E\)-2-butene are at the QCISD/6-31G(d) level of theory. Thermal corrections to enthalpy (H) and entropy values have been calculated at the B3LYP/6-31G(d) level of theory.
TABLE 4. B3LYP/6-31G(d) activation barriers ($\Delta E^\#$, kcal mol$^{-1}$) for the epoxidation of a series of alkenes with dimethyldioxirane (DMDO) and methyl(trifluoromethyl)dioxirane (TFDO). The barriers in parentheses are at the B3LYP/6-31+G(d,p) level of theory. Other computational approaches are indicated by footnotes. The barriers have been computed with respect to isolated reactants.

<table>
<thead>
<tr>
<th>Alkene</th>
<th>DMDO</th>
<th>TFDO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene</td>
<td>18.2 (17.7) [15.2]$^a$</td>
<td>11.3 (11.1)</td>
</tr>
<tr>
<td>Propylene</td>
<td>16.6 (16.0)</td>
<td>9.6 (9.1)</td>
</tr>
<tr>
<td>1-Octene</td>
<td>15.8 (15.2)</td>
<td>8.2 (8.0)</td>
</tr>
<tr>
<td>Isobutylene</td>
<td>15.3 (14.0) 16.0 $^b$</td>
<td>7.3 (6.8)</td>
</tr>
<tr>
<td>$E$-2-Butene</td>
<td>15.5 (14.8) [14.6]$^c$</td>
<td>6.9 (6.9)</td>
</tr>
<tr>
<td>$Z$-2-Butene</td>
<td>14.1 (13.4)</td>
<td>5.6 (5.6)</td>
</tr>
<tr>
<td>Cyclohexene</td>
<td>13.5 (12.6) 14.7 $^b$</td>
<td>5.3 (5.2)</td>
</tr>
<tr>
<td>Norbornene (exo)</td>
<td>13.3 (13.0)</td>
<td>5.5 (5.5)</td>
</tr>
<tr>
<td>Norbornene (endo)</td>
<td>15.9 (15.8)</td>
<td></td>
</tr>
<tr>
<td>Trimethylethylene</td>
<td>13.7 (12.8)</td>
<td>4.8 (4.9)</td>
</tr>
<tr>
<td>Tetramethylethylene</td>
<td>14.0 (12.8)</td>
<td>4.8 (4.7)</td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>14.9 (14.6)</td>
<td>7.6 (7.3)</td>
</tr>
<tr>
<td>Styrene</td>
<td>14.3 (13.8)</td>
<td>6.7 (6.3)</td>
</tr>
</tbody>
</table>

$^a$ The barrier in brackets for ethylene is at the QCISD(T)//QCISD/6-31+G(d,p) level.
$^b$ Classical activation barriers computed at the B3LYP/6-311+G(3df,2p)//B3LYP/6-31+G(d,p) level.
$^c$ The barrier in brackets for $E$-2-butene is at the QCISD(T)//QCISD/6-31G(d) level of theory; QCISD(T)/6-31G(d)//B3LYP/6-311+G(3df,2p) gas-phase intrinsic barrier ($\Delta E^\#$) for the epoxidation of $E$-2-butene with dimethyldioxirane (DMDO) is 14.3 kcal mol$^{-1}$.

make this comparison in reactivity are relatively sparse, a theoretical gas-phase study on a series of alkenes has provided the best source of comparison to date. These data$^{19d}$ are summarized in Table 4.

From this series of calculations it is noted that the gas-phase reactivity of TFDO is substantially greater than that of DMDO. This rate difference has been ascribed largely to the inductive effect of the CF$_3$ group. Fluoro-substituted dioxiranes have also played a unique role in the chiral epoxidation of alkenes. Houk and coworkers$^{96}$ have identified a novel stereoelectronic effect that increases the rate of epoxidation when the fluorine substituent is anti to the oxygen of the developing C=O group in the TS for epoxidation.

3. Relative rates of dioxirane epoxidation in solution

Theoretical data reported by Bach and coworkers$^{19d}$ strongly support the surprising contention that the inherent gas-phase reactivity of DMDO is comparable to that of a typical peracid like peroxyformic acid. How can this assertion be resolved based upon the observed greater reactivity of DMDO in relatively polar or protic solvents? It is well-established experimentally that protic solvents disrupt the internal H-bond in a peracid and markedly slow the rate of epoxidation. Moreover, the rate of oxygen transfer from a peracid responds only modestly to acid catalysis$^{97}$. In contrast, Baumstark and Vasquez$^{94b}$ showed that the protic solvents enhance the rate of DMDO epoxidation of $p$-methoxystyrene. Murray and Gu$^{95}$ showed that the protic solvents methanol and acetic acid increase the rate of epoxidation of cyclohexene by DMDO at 25 °C by factors of 5 and 7.5 compared with acetone. In moist acetone, the rate is enhanced both by the polarity of the medium and the effects of hydrogen bonding on the distal oxygen of DMDO in the TS for epoxidation. Indeed, Curci and coworkers$^{98}$ have reported a rate ratio of 74 for the epoxidation of cyclohexene with DMDO in acetone versus perbenzoic acid (PBA) in CH$_2$Cl$_2$. The classical activation barrier ($\Delta E^\#$) of 12.6 kcal mol$^{-1}$ for the gas-phase
TABLE 5. Calculated [B3LYP/6-311+G(d,p)] activation parameters (kcal mol$^{-1}$ and eu) for the epoxidation of cyclohexene and isobutene with dimethyldioxirane (DMDO), peroxybenzoic acid (PBA), m-chloroperoxybenzoic acid (m-CPBA) and peroxyformic acid (PFA). Solvent corrections were performed with the COSMO model. The numbers in bold are experimental values$^{95,136}$. Numbers in parentheses are at the B3LYP/6-311+G(3df,2p)//B3LYP/6-311+G(d,p) level of theory.

<table>
<thead>
<tr>
<th></th>
<th>DMDO/ cyclohexene</th>
<th>PBA/ cyclohexene</th>
<th>m-CPBA/ cyclohexene</th>
<th>PFA/ isobutene</th>
<th>DMDO/ isobutene</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta E^#$ (gas phase)</td>
<td>12.6 (14.7)</td>
<td>12.0 (14.3)</td>
<td>10.9 (13.4)</td>
<td>11.2 (13.0)</td>
<td>14.0 (16.0)</td>
</tr>
<tr>
<td>$\Delta H^{298}_\text{gas}$</td>
<td>12.6</td>
<td>11.9</td>
<td>10.9</td>
<td>24.0</td>
<td>25.0</td>
</tr>
<tr>
<td>$\Delta S^{298}_\text{gas}$</td>
<td>-38.1</td>
<td>-37.6, -32.9</td>
<td>-38.1, -27.8</td>
<td>-36.3</td>
<td></td>
</tr>
<tr>
<td>$\Delta E^#$ (CHCl$_3$)</td>
<td>11.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta H^{298}_\text{CHCl}_3$</td>
<td>11.4, 5.0</td>
<td>12.2</td>
<td>11.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta G^{298}_\text{CHCl}_3$</td>
<td>16.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta E^#$ (CH$_2$Cl$_2$)</td>
<td></td>
<td>12.2</td>
<td>11.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta H^{298}_\text{CH}_2\text{Cl}_2$</td>
<td></td>
<td>12.1</td>
<td>11.3, 10.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta G^{298}_\text{CH}_2\text{Cl}_2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta E^#$ (acetone)</td>
<td>10.7</td>
<td>10.6</td>
<td>10.9</td>
<td>10.6</td>
<td>11.1, 9.3</td>
</tr>
<tr>
<td>$\Delta H^{298}_\text{acetone}$</td>
<td>10.7, 7.4</td>
<td>10.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta G^{298}_\text{acetone}$</td>
<td>16.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta E^#$ (benzene)</td>
<td>12.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta H^{298}_\text{benzene}$</td>
<td>12.1, 10.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DMDO epoxidation of cyclohexene (Table 5) is reduced by 4.1 kcal mol$^{-1}$ when a single water molecule is hydrogen-bonded to the distal oxygen of DMDO (a bimolecular process relative to a prereaction cluster of DMDO, H$_2$O) and by 6.3 kcal mol$^{-1}$ with two complexed water molecules [B3LYP/6-311+G(d,p)]. The H-bonded DMDO-CH$_3$OH prereaction cluster has a stabilization energy of $-6.9$ kcal mol$^{-1}$. The calculated barriers for the DMDO epoxidation of $E$-2-butene with and without water catalysis are 11.0 and 14.4 kcal mol$^{-1}$ at the same level of theory (Figure 19)$^{19d}$. These composite data strongly suggest that the presence of adventitious water or other hydrogen donors can markedly affect the observed rate of epoxidation. For example, Murray and Gu have reported $\Delta H^\# = 5.0$ kcal mol$^{-1}$ for the DMDO epoxidation of cyclohexene in CDCl$_3$ and 7.4 kcal mol$^{-1}$ in acetone as solvent$^{95}$. Curci and coworkers also reported an $E_a$ value of 9.3 kcal mol$^{-1}$ for the DMDO epoxidation of isobutylene in acetone$^{83}$. These barriers are significantly lower than the 13–18 kcal mol$^{-1}$ gas-phase barriers reported$^{19d}$ at the B3LYP level of theory (Tables 3 and 4). Activation barriers of 12.6, 11.4 and 10.7 kcal mol$^{-1}$ for the DMDO epoxidation of cyclohexene in the gas phase, CHCl$_3$ and acetone, respectively, were estimated by using the COSMO solvent model [B3LYP/6-311+G(d,p), Table 5]. However, the current solvent correction models do not explicitly treat hydrogen-bonding interactions. Importantly, the calculated activation barriers for peracid cyclohexene epoxidation, 12.0 (PBA, gas phase) and 10.9 kcal mol$^{-1}$ (MCPBA, gas phase), are not as sensitive to the solvent as is DMDO. For example, estimated barriers for the PBA/cyclohexene in CH$_2$Cl$_2$ and in benzene both had the same calculated $\Delta E^\#$ values of 12.2 kcal mol$^{-1}$. These results and the comparison with experimental data are given in Table 5. As is evident, the activation enthalpies for the peracid epoxidation of cyclohexene in CH$_2$Cl$_2$ and benzene are in very good agreement with experiment. A summary of the relative calculated activation barriers for the epoxidation of ethylene with PFA and DMDO at various levels of theory is given in Table 6. The effect of the flexibility of the basis set upon the activation barrier for epoxidation of a series of selected alkenes at the QCISD level is presented in Table 7.
FIGURE 19. B3LYP/6-311+G(d,p)-optimized transition structures for the epoxidation of cyclohexene with DMDO in the presence of one (a) and two (b) water molecules. The transition structure for the epoxidation of $E$-2-butene (c) is optimized at the same level of theory in the presence of one water molecule. The classical barriers are estimated using total electronic energies of the transition structures, cyclohexene ($-234.71316$ au), $E$-2-butene ($-157.27453$ au), DMDO with one water molecule ($-344.81523$ au) and DMDO with two water molecules ($-421.28672$ au).
### Table 6. Classical reaction barriers ($\Delta E^\#, \text{kcal mol}^{-1}$) for ethylene epoxidation with peroxyformic acid (PFA) and dimethyldioxirane (DMDO) at various levels of theory

<table>
<thead>
<tr>
<th>Method</th>
<th>Ethylene + PFA</th>
<th>Ethylene + DMDO</th>
</tr>
</thead>
<tbody>
<tr>
<td>B3LYP/6-31G(d)</td>
<td>14.1</td>
<td>18.2</td>
</tr>
<tr>
<td>B3LYP/6-31+G(d,p)</td>
<td>14.9</td>
<td>17.7</td>
</tr>
<tr>
<td>B3LYP/6-311+G(3df,2p)/B3LYP/6-31+G(d,p)</td>
<td>17.0</td>
<td>19.6</td>
</tr>
<tr>
<td>B3LYP/6-311+G(3df,2p)</td>
<td>16.9</td>
<td>19.1</td>
</tr>
<tr>
<td>QCISD(T)/QCISD/6-31G(d)</td>
<td>18.8</td>
<td>19.4</td>
</tr>
<tr>
<td>QCISD/6-31+G(d,p)</td>
<td>23.4</td>
<td>22.3</td>
</tr>
<tr>
<td>QCISD(T)/QCISD/6-31+G(d,p)</td>
<td>16.4</td>
<td>15.2</td>
</tr>
<tr>
<td>B3LYP/6-311+G(3df,2p)/QCISD/6-31G+(d,p)</td>
<td>17.0</td>
<td>18.9</td>
</tr>
<tr>
<td>QCISD(T)/6-31G+(d,p)/B3LYP/6-311+G(3df,2p)</td>
<td>16.2</td>
<td>14.9</td>
</tr>
<tr>
<td>CCSD(T)//CCSD(T)/6-31G*</td>
<td>19.4</td>
<td>18.4</td>
</tr>
<tr>
<td>CCSD(T)/6-31G+(d,p)//B3LYP/6-311+G(3df,2p)</td>
<td>16.2</td>
<td>14.9</td>
</tr>
<tr>
<td>CCSD(T)//CCSD(T)/6-31G*</td>
<td>17.1</td>
<td>15.5</td>
</tr>
</tbody>
</table>

* The TS geometry was optimized at B3LYP/6-31+G(d,p) with a single-point energy correction at B3LYP/6-311+G(3df,2p).

** References 122 and 124.

### Table 7. Summary of the reaction barriers (kcal mol$^{-1}$) for the epoxidation of simple alkenes with peroxyformic acid (PFA) and dimethyldioxirane (DMDO)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>$\Delta E^#$</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene + PFA</td>
<td>16.4</td>
<td>QCISD(T)/QCISD/6-31+G(d,p)</td>
</tr>
<tr>
<td></td>
<td>18.7</td>
<td>QCISD(T)/B3LYP/6-31G(d)</td>
</tr>
<tr>
<td></td>
<td>18.8</td>
<td>QCISD(T)/QCISD/6-31G(d)</td>
</tr>
<tr>
<td></td>
<td>17.4</td>
<td>QCISD(T)/B3LYP/6-31G+(d,p)</td>
</tr>
<tr>
<td></td>
<td>18.6</td>
<td>QCISD(T)/6-311+G(3df,2p)/QCISD/6-31+G(d,p)</td>
</tr>
<tr>
<td>Propylene + PFA</td>
<td>15.9</td>
<td>QCISD(T)/B3LYP/6-31G(d)</td>
</tr>
<tr>
<td></td>
<td>16.0</td>
<td>QCISD(T)/QCISD/6-31G(d)</td>
</tr>
<tr>
<td>Isobutylene + PFA</td>
<td>13.7</td>
<td>QCISD(T)/B3LYP/6-31G(d)</td>
</tr>
<tr>
<td></td>
<td>13.8</td>
<td>QCISD(T)/QCISD/6-31G(d)</td>
</tr>
<tr>
<td>E-2-Butene + PFA</td>
<td>13.3</td>
<td>QCISD(T)/B3LYP/6-31G(d)</td>
</tr>
<tr>
<td></td>
<td>13.4</td>
<td>QCISD(T)/QCISD/6-31G(d)</td>
</tr>
<tr>
<td></td>
<td>10.8</td>
<td>QCISD(T)/6-31+G(d,p)/QCISD/6-31G(d)</td>
</tr>
<tr>
<td></td>
<td>11.2</td>
<td>CBS-Q//QCISD/6-31G(d)</td>
</tr>
<tr>
<td></td>
<td>13.2</td>
<td>QCISD(T)/6-31G(d)//B3LYP/6-311+G(3df,2p)</td>
</tr>
<tr>
<td>1,3-Butadiene + PFA</td>
<td>15.9</td>
<td>QCISD(T)/QCISD/6-31G(d)</td>
</tr>
<tr>
<td>E-2-Butene + DMDO</td>
<td>14.6</td>
<td>QCISD(T)/B3LYP/6-31G(d)</td>
</tr>
<tr>
<td></td>
<td>14.6</td>
<td>QCISD(T)/QCISD/6-31G(d)</td>
</tr>
<tr>
<td></td>
<td>14.3</td>
<td>QCISD(T)/6-31G(D)//B3LYP/6-311+G(3df,2p)</td>
</tr>
<tr>
<td></td>
<td>9.7</td>
<td>CBS-Q//QCISD/6-31G(d)</td>
</tr>
<tr>
<td>Ethylene + DMDO</td>
<td>15.2</td>
<td>QCISD(T)/QCISD/6-31+G(d,p)</td>
</tr>
<tr>
<td></td>
<td>19.3</td>
<td>QCISD(T)/B3LYP/6-31G(d)</td>
</tr>
<tr>
<td></td>
<td>19.4</td>
<td>QCISD(T)/QCISD/6-31G(d)</td>
</tr>
</tbody>
</table>

* References 122.

** References 38 and 124.

* Based upon CBS-Q energy calculations on the QCISD/6-31G(d) optimized geometries of TS and corresponding isolated reactants.
Experimental rate data reported by Murray and Gu\textsuperscript{95} for the DMDO epoxidation of cyclohexene also suggest that an increase in solvent polarity results in an increase in the rate of epoxidation. The increased reactivity in polar solvents can be assigned to enhanced polarization of the TS relative to the reactants. Theoretical solvation studies by Houk, Jorgensen and coworkers are consistent with these observations\textsuperscript{90b} and suggest that in methanol solvent a strong H-bond forms between the two oxygens of DMDO with CH\textsubscript{3}OH and another H-bond to the distal oxygen in the TS. Miaskiewicz and Smith\textsuperscript{99} provided a comparison of activation barriers on intra- and intermolecular H-bonding interactions. Solvent polarity effects using the SCI-PCM solvent model\textsuperscript{100} show a decrease in the activation energy for DMDO epoxidation of 2-methyl-2-butene from 13.6 kcal mol\textsuperscript{-1} in the gas phase to 9.5 kcal mol\textsuperscript{-1} (B3LYP/6-31G*) when a dielectric constant of 20 is used (acetone solvent). The calculated activation enthalpy of 9.9 kcal mol\textsuperscript{-1} was in very good agreement with the aforementioned experimental $\Delta H^\neq = 7.4$ kcal mol\textsuperscript{-1} for epoxidation of the disubstituted alkene, cyclohexene, in acetone solvent.

A systematic study of the effects of hydrogen bonding and solvation has also been reported by Sarzi-Amade and coworkers\textsuperscript{101}. Using 2-propen-1-ol as a substrate at the B3LYP/6-31G* level, it was shown that the electron-withdrawing effect of the hydroxy substituent in allyl alcohol has a mild rate-retarding effect upon the rate of oxidation. However, theory predicts a slightly greater reactivity for allyl alcohol with respect to the epoxidation of propylene in the gas phase but inclusion of solvation effects (Tomasi solvent model\textsuperscript{102}, acetone) leads to a reversal in reactivity in agreement with experiment.

4. Oxidation of saturated hydrocarbons

Part of the mystique surrounding the often assumed high reactivity of dioxiranes stems from the observation that dioxiranes such as methyl(trifluoromethyl)dioxirane (TFDO) are capable of oxidizing saturated hydrocarbons to their alcohols at relatively low temperatures\textsuperscript{103} in high yields and with impressive stereoselectivities (equation 8).

\[
\begin{align*}
\text{R}_2\text{C}==\text{O} + \text{R}^1\text{R}^2\text{R}^3\text{H} & \rightarrow \text{R}^1\text{R}^2\text{R}^3\text{OH} + \text{R}_2\text{R}==\text{O} \\
\end{align*}
\]

The enhanced propensity of dioxiranes to insert oxygen into unactivated alkane C−H bonds was ascribed initially to the high ring strain energy (SE) of dioxiranes that has sometimes exceeded 30 kcal mol\textsuperscript{-1}. Since the SE of these three-membered peroxides has recently been substantially reduced (SE = ca 11–18 kcal mol\textsuperscript{-1}), a different explanation is required\textsuperscript{20b}.

The mechanism of this unique oxidation has been the subject of controversial debate focused on a concerted versus a stepwise dichotomy. Curci, Adam and coworkers\textsuperscript{103} advanced a one-step (concerted) electrophilic oxygen insertion (Scheme 7, path a) that is experimentally very difficult to distinguish from a stepwise process (path b) in which the TS proceeds to a caged radical pair that undergoes a very rapid ‘oxygen rebound mechanism’ by an $S_H^2$ reaction forming the observed products (ketone plus alcohol) with retention of configuration. What is considered by many to be compelling evidence for a concerted oxidation comes from complete retention of configuration for oxygen insertion into a chiral center\textsuperscript{103} and from the absence of radical rearrangements in radical clock studies\textsuperscript{104}. Radical clocks gave unrearranged products and are more consistent with concerted oxenoid insertion.

Despite the fact that a concerted oxygen insertion reaction appeared to be in complete agreement with existing experimental studies, Minisci and his group strongly advocated a
1. General and theoretical aspects of the peroxide group

SCHEME 7

Stepwise mechanism supported by the formation of radical intermediates. The ‘molecule induced mechanism’ shown in Scheme 8\textsuperscript{105} describes a radical pair that can either collapse to products or produce out-of-cage free radicals that lead to a variety of products\textsuperscript{92,106}.  

SCHEME 8

It was subsequently discovered that spurious dioxygen, present for most synthetic applications, could scavenge a small amount of the free radicals that escaped from the solvent cage, disrupting the free radical chain process, and give the typically observed alcohol insertion product. A much different product distribution was observed when dioxygen was rigorously excluded. This mechanistic anomaly was responsible for a lot of the confusion!

Theoretical studies with the DFT method provided strong support for the concerted pathway. The hydroxylation of hydrocarbons on the restricted energy surface (RB3LP) provided TSs with the requisite O–O bond elongation and substantial transfer of the C–H hydrogen to the attacking oxygen atom as shown below. Calculations at the G2 level by Bach and coworkers\textsuperscript{107} suggested that C–H bond homolysis is not thermodynamically favorable in hydrogen abstraction reactions of methane, propane and isobutane with either DMDO, the parent dioxirane DO, or DFDO.

Intrinsic reaction coordinate following (IRC) analysis by both Bach and coworkers\textsuperscript{107} and Du and Houk\textsuperscript{108} showed that these TSs were connected to both reactant and product without the formation of a radical intermediate consistent with an oxygen insertion into the C–H bond (see inset). Shustov and Rauk\textsuperscript{109} advocated a bifurcation on the descent
pathway on the product side at a point just below the TS that led to radical products. All three studies evidenced a UHF-RHF wave function stability. At that time such a problem was typically resolved by showing that the UHF solution is only marginally lower in energy and the restricted TS is assumed to be valid. However, in those cases where significant diradical character is involved such a transition structure may be flawed and a lower-energy TS on the unrestricted or open-shell potential energy surface may well be possible as noted below. This mechanistic controversy has been hampered due to experimental difficulties such as the aforementioned lack of stability of dioxiranes and by the fact that it is very difficult to obtain pure solutions of the more synthetically useful dioxiranes although solutions of TFDO are relatively stable, compared to the parent dioxirane (DO), and can be stored at $-20^\circ$C for 48 h with only minor losses. This presents an ideal case where theory can perhaps provide an answer more readily than experiment.

This mechanistic dichotomy is in one sense largely semantic in nature. The pertinent questions to answer are what is the lifetime of free radical species on the reaction coordinate and what is the rate of the subsequent $\text{SH}_2$ hydroxylation of the intermediate carbon radical (or radicaloid)? Although in many cases when an RHF-UHF wave function instability is noted, the resulting restricted TS may be adequately described and its geometry does not differ significantly from a TS located on the unrestricted surface. However, as noted above for the peroxynitrous acid oxidation of saturated hydrocarbons, where a unique type of singlet free radical intermediate is possible, the open-shell potential energy surface should also be examined. Dioxiranes are capable of experiencing O–O bond elongation to produce several singlet diradical intermediates that are energetically accessible on the PES for alkane oxidation. As noted above, Anglada$^{65}$ reported a high-level $\textit{ab initio}$ MRD-CI estimate suggesting that the diradical singlet form of DO is only 5.8 kcal mol$^{-1}$ higher in energy than its ground state. An activation barrier of 21.4 kcal mol$^{-1}$ was predicted for the ring opening of DO to this excited singlet.

Recent DFT calculations by Sarzi-Amade and his collaborators$^{110}$ may well have resolved this mechanistic difference between a biradicaloid TS (Scheme 7, path b) and a mechanism involving discrete long-lived free radicals (Scheme 8). Oxygen insertion into the C–H bond of isobutane by DMDO was studied computationally at the unrestricted B3LYP level. Transition structures that were diradicaloid in nature were found to lead to
insertion products via radical pair intermediates. These UB3LYP TSs were lower in energy than TSs located previously on the restricted PES (RB3LYP) supporting the possibility of radical pair formation in reactions of dioxiranes with saturated hydrocarbons.

In a subsequent exemplary theoretical study they were able to locate two transition structures on the UB3LYP/6-311+G(d,p) surface that not only differed geometrically from the previously reported concerted TSs (RB3LYP) but were lower in energy.

UB3LYP/6-311+G(d,p)

\[
\begin{align*}
\text{concerted TS} & : \\
\text{co-linear TS} & : \\
\text{perpendicular TS} & : 
\end{align*}
\]

The classical activation barrier ($\Delta E^\neq$) for lower-energy diradical TS for isobutane oxidation was 12.2 kcal mol$^{-1}$ lower in energy than the closed-shell concerted TS ($\Delta E^\neq = 32.0$ kcal mol$^{-1}$) and involved approach of the alkane C–H perpendicular to the plane of the three-membered ring peroxide. A second TS ($\Delta E^\neq = 24.5$ kcal mol$^{-1}$) was somewhat higher in energy but the initial product of hydrogen abstraction had a much better orientation for the $\text{S}_2\text{H}_2$ hydroxylation step. Collapse of the intermediate 2-hydroxy isopropoxy radical–$t$-butyl radical pair to product acetone and $t$-butyl alcohol proceeded with a barrier of only 0.4 kcal mol$^{-1}$. They concluded that the PES on the open-shell pathway was indeed consistent with the ‘molecule induced homolysis’ and that genuine diradical TSs were involved. The question remains as to whether this is actually a ‘one-step nonconcerted’ process or a very rapid two-step process. Clearly, this theoretical analysis supports the contention that biradical TSs are involved in this oxidative process and conforms to the suggestions made by Curci and Adam based upon experimental studies with chiral substrates. This approximate reaction pathway was intuitively predicted by these experimentalists, suggesting that after a slow step the ‘alternative to direct collapse into products—some radical character develops’ or ‘cage radical pairs are formed after the slow step’.

Thus, it would appear that serious consideration must be given to at least partial involvement of open-shell species in the reactions of dioxiranes with both saturated and unsaturated hydrocarbons. Perhaps it should not be too surprising that those peroxides that have readily accessible low-lying singlet excited states like dioxiranes or metastable states like peroxyxynitrous acid can exhibit open-shell chemistry. For example, UB3LYP/6-31G(d) calculations on oxygen insertion by trifluoroperoxyacetic acid into the C–H bonds of methane and isobutane strongly support the viability of a one-step nonconcerted mechanism invoking a transition state with high diradical character and strong polarization. Such a process is ostensibly a two-step oxidation where the O–H bond forms first and
the C−O bond effecting oxygen insertion occurs subsequently but only a single transition state is observed and no minima corresponding to intermediates were located. Such diradicaloid transition states are difficult to treat theoretically and much additional work is needed before one can accurately assign such a mechanism.

VI. THE EPOXIDATION OF ALKENES WITH PERACIDS

A. Early Mechanistic Studies

Since the discovery of the peracid epoxidation reaction by Prilezajew in 1909\textsuperscript{112}, epoxides, as a class of compounds, have played a major role in organic chemistry both synthetically and in industry. Epoxides continue to provide synthetic intermediates as building blocks for the synthesis of more complex molecules. For most of the last century epoxides were prepared from alkenes primarily by their interaction with peracids. Certainly, the peracid functionality is among the more cleverly designed synthetic reagents since it can transfer an oxygen atom to a C=\text{C} bond by a 1,5-intramolecular hydrogen transfer to the carbonyl oxygen and still retain its highly stabilized carboxylic acid group. The use of chiral epoxides in synthetic chemistry gained particular favor in the 1970s with the discovery of the metal-catalyzed epoxidation that utilized the Sharpless epoxidation\textsuperscript{113}. During the last several decades a wide variety of oxygen atom transfer reagents have been disclosed and several of the most useful oxidizing agents are described elsewhere in this treatise. We will not include metal-catalyzed epoxidation reactions since they have recently been extensively reviewed\textsuperscript{114}. The mechanism of the peracid epoxidation of alkenes, a subset of this general class of reactions, has been the subject of experimental study for many years\textsuperscript{115,116}. More than fifty years ago Bartlett proposed\textsuperscript{117a} a mechanism where the terminal oxygen atom of the peroxy acid was transferred to the carbon–carbon double bond with simultaneous transfer of the proton of the peracid to the carbonyl oxygen. This was the accepted mechanism for many years and became known as the ‘butterfly mechanism’ because of the approximate shape of the proposed transition state (equation 9). The actual origin of this term is not known to us, but it was not in the original lecture delivered by Bartlett in a Frontiers in Chemistry lecture at Wayne State University in 1950\textsuperscript{117b}. In subsequent publications Bartlett and coworkers\textsuperscript{117c} reinforced the idea that the proposed transition state (TS) for oxygen atom transfer was planar in nature with the peracid group along the C=\text{C} bond axis.

\[
\begin{align*}
\text{C} \equiv \text{C} & \quad + \quad \text{O} \quad \text{H} & \quad \rightarrow & & \left[ \text{C} \quad \text{O} \quad \text{H} \quad \text{O} \right] & & \neq \\
\text{C} & \quad \text{O} & \quad \text{O} & \quad \text{C} & \quad \text{R} & \quad \rightarrow & & \text{C} \equiv \text{C} \quad \text{O} & \quad \text{O} & \quad \text{C} \quad \text{R} \quad + \\
& & & & & & & & \text{O} & \quad \text{C} \quad \text{R} & \quad \text{H}_2 \quad \text{O}
\end{align*}
\]

(9)

B. Hartree–Fock Level Theoretical Calculations

For more than forty years the Bartlett ‘butterfly’ TS was the generally accepted mechanism for peracid epoxidation and numerous experimental studies supported this transition structure\textsuperscript{115,116}. During these formative years theoretical calculations did not play a major role due to limitations of available methods that could adequately treat the peroxide functional group. Theoretical contributions in 1978 were at the Hartree–Fock (HF) level since
that was all that was available at that time. HF calculations by Plesnicar and coworkers\textsuperscript{118} with a very small basis set (STO-4G) suggested an unsymmetrical TS. However, early theoretical studies by Bach and coworkers\textsuperscript{48a} suggested a symmetrical approach of the peracids to the C=C and, more importantly, that the plane of the peroxyacid moiety preferred to be perpendicular to the C=C bond axis; the term ‘\textit{spiro} transition state’\textsuperscript{48} was coined to describe the local tetrahedral environment about the attacking electrophilic oxygen atom. The \textit{spiro} nature of the TS was based largely upon the supposition that the TS could be stabilized if the attacking oxygen lone pair could back bond to the $\pi^*$ orbital of the carbon–carbon double bond. In an idealized \textit{spiro} orientation the H–O–C–C dihedral angle is 90.0°. It was recognized early on that in the absence of electron-correlation corrections, HF calculations were not capable of adequately describing reactions that involved O–O bond cleavage\textsuperscript{119}. Thus, the possibility for serious contributions from theoretical studies did not present itself until 1991 when \textit{ab initio} calculations with electron correlation was feasible. The first report\textsuperscript{17b} of a transition structure for the peroxyformic acid epoxidation of ethylene at a correlated level of theory, second-order Møller–Plesset theory (MP2), was constrained to be symmetric and suggested an approximate \textit{spiro} orientation (TS-b, Figure 20). IRC calculations by Bach and coworkers\textsuperscript{17b} corroborated the basic tenets of the accepted mechanism where the 1,5-intramolecular hydrogen shift to the carbonyl oxygen took place after the barrier was crossed. These data were consistent with

![Figure 20. The transition states for peroxyformic acid zwitterion + ethylene (TS-a) and peroxyformic acid + ethylene (TS-b) at the HF/6-31G* and the MP2/6-31G* level (in parentheses). The energy is at the MP4SDTQ//HF/6-31G* level and MP4SDTQ//MP2/6-31G* (in parentheses)](image)
a relatively small kinetic isotope effect (KIE), $k_H/k_D = 1.17$, for the O–H group on the peracid\textsuperscript{120}. The peroxyformic acid O–H distance in the TS for ethylene epoxidation was only slightly elongated at 1.006 Å in support of the IRC data. It is particularly noteworthy that Hartree–Fock calculations gave a completely erroneous TS where the 1.5-hydrogen shift occurred prior to the oxygen atom transfer (TS-a, Figure 20). Since the O–O bond dissociation energy (BDE) for a peracid is essentially zero at the HF level\textsuperscript{16a}, stretching the O–O bond in the TS is without energetic consequences. Despite this obvious deficiency, a number of theoreticians continue to employ HF calculations for such reactions including QM/MM methods\textsuperscript{20c}.

At that period of time, this rather primitive transition structure for the peracid epoxidation of ethylene was sufficiently novel to warrant publication as a communication\textsuperscript{17b}! Today, calculating transition structures for epoxidation of a variety of complex alkenes with the actual peracid used experimentally, such as meta-chloroperoxybenzoic acid (m-CPBA), is commonplace\textsuperscript{19d}.

C. Synchronous versus Asynchronous Transition States

Calculations at the second-order Moller–Plesset (MP2) theory level were not without problems because the TSs for even simple alkenes, although spiro in nature, were highly unsymmetrical\textsuperscript{121}. Although the concerted nature of the mechanism has been generally accepted, the MP2 results initiated controversy over the synchronous versus asynchronous (equal or unequal developing C–O bonds) approach of the peracid to the C=C double bond. MP2 theory was used initially for most \textit{ab initio} calculations involving O–O bond cleavage and seemed to provide adequate energetics for such epoxidation reactions but very poor geometries\textsuperscript{17,122}. For example, the MP2 method gave an unsymmetrical transition structure\textsuperscript{121} for the peroxyformic acid epoxidation of ethylene, where the two developing C–O bonds were of unequal length (C–O = 1.805 and 2.263 Å) that was 0.2 kcal mol\textsuperscript{−1} lower in energy than a symmetrical spiro structure (a second-order saddle point)\textsuperscript{123}. However, the asymmetric nature of this TS was shown by Bach and coworkers\textsuperscript{17a} to be an artifact of the MP2 method since more highly correlated methods [QCISD, CCSD, CCSD(T)] gave very symmetrical spiro transition structures with synchronous formation of the developing C–O oxirane bonds for symmetrically substituted alkenes\textsuperscript{124}.

For example, a variety of computational methods suggested a spiro TS, with nearly identical developing C–O bonds, for the peroxyformic acid epoxidation of ethylene with the exception of the MP2 method (Figure 21). Similarly, a slightly asymmetric TS was noted for the epoxidation of isobutylene, with the exception of the MP2 method where the developing C–O bonds differed widely (1.899 and 2.192 Å, Figure 22). The calculated differences in the two developing C–O bonds for the epoxidation of a series of alkenes with the MP2, B3LYP and QCISD methods are given in Table 8.

The most convincing evidence for an essentially synchronous peracid epoxidation of simple alkenes came from a combined experimental and theoretical study by Singleton, Houk and coworkers\textsuperscript{125}. Experimental KIEs for the reaction of m-CPBA with 1-pentene, determined by the clever methodology developed by Singleton and Thomas\textsuperscript{126} utilizing the combinatorial high-precision determination of $^{13}$C and $^{2}$H KIEs at natural abundance, confirmed the symmetrical or nearly symmetrical nature of this epoxidation TS. These data were corroborated by B3LYP/6-31G* calculations on propylene that supported a synchronous transition state for peroxyformic acid epoxidation.

Conjugated and α,β-unsaturated C=C double bonds exhibit decidedly different behavior toward peracids. Bach and coworkers\textsuperscript{19b} have reported that both 1,3-butadiene and acrylonitrile afford asymmetric TSs consistent with their polarizable conjugated double bonds. The unsymmetrical character of the transition structures for both the epoxidation of
1. General and theoretical aspects of the peroxide group

![Diagram of selected geometrical parameters for transition structures](image)

**FIGURE 21.** Selected geometrical parameters of the transition structures for the epoxidation of ethylene with peroxyformic acid calculated at the QCISD/6-31G*, CCD/6-31G* (in parentheses), B3LYP/6-31G* (in square brackets) and MP2(FC)/6-31G* (in curly brackets) levels

**TABLE 8.** Differences (Å) in the O—C1 and O—C2 calculated distances of transition structures for the epoxidations of alkenes with peroxyformic acid using different methods

<table>
<thead>
<tr>
<th>Substrate</th>
<th>( \Delta R ) (MP2/6-31G*)</th>
<th>( \Delta R ) (B3LYP/6-31G*)</th>
<th>( \Delta R ) (QCISD/6-31G*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene</td>
<td>0.458</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Propylene</td>
<td>0.537&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.117</td>
<td>0.021</td>
</tr>
<tr>
<td>Isobutylene</td>
<td>(-0.293&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>0.190&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.044&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Z-2-Butene</td>
<td></td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>E-2-Butene</td>
<td></td>
<td>0.034</td>
<td></td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>0.519</td>
<td>0.417&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.305&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>0.465</td>
<td>0.460&lt;sup&gt;g&lt;/sup&gt;</td>
<td>0.358</td>
</tr>
</tbody>
</table>

<sup>a</sup> Two transition structures were found at the MP2/6-31G* level. The difference in the CO distances is given for a Markovnikov-type structure. While Markovnikov-type transition structures (albeit much more symmetrical) were found at the B3LYP and QCISD levels, this MP2 TS is 0.2 kcal mol<sup>−1</sup> higher than an anti-Markovnikov TS (for which the distance difference is \(-0.363\) Å).

<sup>b</sup> The MP2 transition structure exhibits a regiochemical preference for C1, in contrast to the B3LYP and QCISD results.

<sup>c</sup> 0.237 Å at the B3LYP/6-311+G(3df,2p) level.

<sup>d</sup> 0.069 Å at the CISD/6-31G* level.

<sup>e</sup> 0.424 Å at the B3LYP/6-311+G(3df,2p) level.

<sup>f</sup> 0.209 Å at the CISD/6-31G* level.

<sup>g</sup> 0.439 Å at the B3LYP/6-311+G(3df,2p) level.
FIGURE 22. Selected geometrical parameters of the transition structure for the epoxidation of isobutylene with peroxyformic acid calculated at the QCISD/6-31G*, CISD/6-31G* (in parentheses), B3LYP/6-31G* (in square brackets), B3LYP/6-311+G(3df,2p) (in italic in square brackets) and MP2/6-31G* (in curly brackets) levels.

1,3-butadiene and acrylonitrile (Figure 23) corresponds to a concerted reaction pathway although the C–O bond formation is asynchronous. Animation of the B3LYP/6-31G* vibrational mode corresponding to the negative eigenvalue of the Hessian for the transition structure of 1,3-butadiene and peroxyformic acid shows the transfer of the oxygen to C1 accompanied by O1–O2 bond elongation with sp² → sp³ rehybridization at the terminal carbon as it moves out of the plane toward the electrophilic oxygen. There is comparatively little motion of C2 in the TS [(a), Figure 23], and essentially no O–H bond motion is observed. By contrast, in the transition structure for the epoxidation of isobutylene with peroxyformic acid (Figure 22), the oxygen atom approaches the center of the C=C bond and both C1 and C2 carbons experience sp² → sp³ rehybridization with the lighter hydrogen atoms at C1, showing more motion than the two methyl groups. This type of S_N 2 attack by the π-bond along the O–O bond axis is consistent with the endocyclic restriction test developed by Woods and Beak to probe the geometry for alkene epoxidation. The dihedral angles between the peracid moiety and the C–C bond...
FIGURE 23. Selected geometrical parameters for the transition structures for the epoxidation of 1,3-butadiene (a) and acrylonitrile (b) with peroxyformic acid calculated at the QCISD/6-31G*, CISD/6-31G* (in parentheses), B3LYP/6-31G* (in square brackets) and MP2/6-31G* (in curly brackets) levels. The B3LYP/6-311+G(3df,2p) values are given in italic in square brackets. Bond lengths are given in Å.

axis (\(\angle_{OC3C2C1}\)) in TS (a) and TS (b) are skewed by 101.0° and 109.7°, to the CC axis of the double bond, indicating a deviation from an ideal (90°) spiro orientation as a consequence of the polarizability of the multiply bonded substituents on the \(\pi\) bond. The activation barrier for the epoxidation of acrylonitrile with peroxyformic acid is about 5–6 kcal mol\(^{-1}\) higher than that for the epoxidation of 1,3-butadiene (Table 9, Figure 23).

The unsymmetrical nature of peracid epoxidation TSs derived from MP2 calculations were at first considered to be corroborative evidence for the correct approach of the peracid since inverse KIE reported by Hanzlik and Shearer\(^{120}\) was suggestive of an unsymmetrical TS. Experimentally determined kinetic isotope effects (KIEs) are one of the few available experimental tools that can probe the geometry of a transition state. Significant secondary isotope effects should be anticipated in an electrophilic addition to an alkene when there is a discernible change in hybridization from sp\(^2\) to sp\(^3\) in the transition state at the isotopically substituted position. In a classic experiment, Hanzlik and Shearer\(^{120}\) used this concept to define the geometry of the transition state and the timing of the bonding changes in the epoxidation of a specifically deuteriated \(p\)-phenylstyrene (4-vinylbiphenyl) with \(m\)-chloroperoxybenzoic acid (Figure 24).

Since the sp\(^2\) carbon atoms become more sp\(^3\)-like in the resulting epoxide, the energy of activation for an sp\(^2\) \(\rightarrow\) sp\(^3\) change in hybridization is lower for a deuterium-substituted double bond and the KIE is inverse with \(k_H/k_D < 1\). The failure to observe an isotope effect for the arylethylene-\(\alpha\)-d\(_2\) (\(k_H/k_D = 0.99\)) and the observation of a significant KIE for the \(\beta,\beta\)-d\(_2\)-substituted styrene (\(k_H/k_D = 0.82\)) suggested that only the arylethylene-\(\beta\)-d\(_2\)-carbon had undergone a discernible change in its hybridization from sp\(^2\) to sp\(^3\). These data led Hanzlik and Shearer\(^{120}\) to the generalization that all transition structures...
TABLE 9. Activation barriers and reaction enthalpy changes (kcal mol\(^{-1}\)) for the epoxidation of alkenes with peroxyformic acid calculated at various computational levels

<table>
<thead>
<tr>
<th>Substrate</th>
<th>(\Delta E^\ddagger)</th>
<th>B3LYP (^a) 6-311+G (3df,2p)</th>
<th>QCISD(T)/(\text{B3LYP}^a)</th>
<th>MP4SDTQ/(\text{MP2}^a)</th>
<th>QCISD(T)/(\text{QCISD}^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene</td>
<td>14.1</td>
<td>18.7</td>
<td>16.3</td>
<td>18.8</td>
<td></td>
</tr>
<tr>
<td>Propylene</td>
<td>12.0</td>
<td>15.9</td>
<td>—</td>
<td>16.0</td>
<td></td>
</tr>
<tr>
<td>Allyl alcohol</td>
<td>7.5(^c)</td>
<td>11.4(^c)</td>
<td>7.7</td>
<td>(11.4)(^b)</td>
<td></td>
</tr>
<tr>
<td>1-Butene (syn)</td>
<td>12.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Z)-2-Butene</td>
<td>10.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(E)-2-Butene</td>
<td>10.4</td>
<td></td>
<td>10.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isobutene</td>
<td>10.8</td>
<td>13.8</td>
<td>10.6</td>
<td>13.7</td>
<td></td>
</tr>
<tr>
<td>1,3-Butadiene (syn)</td>
<td>11.7</td>
<td>14.3</td>
<td>15.7</td>
<td>12.4</td>
<td>15.7</td>
</tr>
<tr>
<td>1,3-Butadiene (anti)</td>
<td>11.8</td>
<td>15.9</td>
<td>12.5</td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>Styrene</td>
<td>11.2</td>
<td>13.9(^c)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Octene (syn)</td>
<td>11.2</td>
<td>14.2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Trimethylethylene</td>
<td>8.9</td>
<td></td>
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<td>Tetramethylethylene</td>
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</tr>
<tr>
<td>Allyl alcohol</td>
<td>4.0</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z-3-Methyl-3-penten-2-ol</td>
<td>(4.2)(^d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acrylonitrile (syn)</td>
<td>17.4</td>
<td>20.8</td>
<td>16.8</td>
<td>21.0</td>
<td></td>
</tr>
<tr>
<td>Acrylonitrile (anti)</td>
<td>17.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) The 6-31G(d) basis set was used for geometry optimizations.

\(^b\) QCISD(T)/6-31G(d)//MP2/6-31G(d) calculation; the same value was obtained for the QCISD(T)/6-311G(d,p)//B3LYP/6-311G(d,p) barrier.

\(^c\) The 6-311G(d,p) basis set was used for both single-point energy calculations and geometry optimizations.

\(^d\) Classical activation barrier with the 6-31G(d,p) basis set.

\(^e\) The basis set 6-311G(d,p) was used for geometry optimization of the anti-TS.

FIGURE 24. Proposed transition structure for epoxidation of an aryl-substituted styrene (4-vinylbiphenyl, left) and the transition structure for epoxidation of 1,3-butadiene (right, calculated at the QCISD/6-31G(*) level). The theoretical isotope effects were calculated at the MP2/6-31G* level using the Bell tunneling correction. For a discussion see Reference 19b. Bond lengths are given in Å
for epoxidation resemble the geometry of the transition structure for epoxidation of 1,3-butadiene given in Figure 24, where only one C−O bond of the oxirane product is formed, and that the unsymmetrical nature of the TS was not simply a consequence of a mono-substituted alkene.

As a theoretical model, diastereotopically distinct isotopic substitution in 1,3-butadiene was utilized by Bach and coworkers\textsuperscript{19b} to provide an independent test of the ability of high-level \textit{ab initio} calculations to accurately predict a transition structure for epoxidation. The calculated KIE for deuterium substitution at the \(\alpha\)-carbon in the TS for epoxidation of 1,3-butadiene (Figure 24) (H\textsubscript{a}) is 0.99, in excellent agreement with the experimental value for an aryl-substituted styrene. The KIE for diastereotopically distinct hydrogen (H\textsubscript{b}) on the \(\beta\)-carbon \textit{cis} to the vinyl substituent is 0.80, while that for H\textsubscript{c} is predicted to be 0.82. The calculated \(\beta,\beta\)-\textit{d\textsubscript{2}} KIE is 0.66 for this transition structure with H\textsubscript{c}, reflecting the extensive rehybridization at C\textsubscript{\(\beta\)}. The calculated primary KIE for the position of the transferring hydrogen of KIE\textsuperscript{=1.07} is lower than experiment (KIE\textsuperscript{=1.17})\textsuperscript{120} but consistent with an O\textsubscript{1}−H\textsubscript{1} bond distance of 0.995 Å (MP2/6-31G\* geometry) and a TS where the hydrogen is transferred after the barrier is crossed. Thus, both the MP2 and QCISD geometries suggest an unsymmetrical approach. For the sake of comparison, several computational methods were compared for the peroxyformic acid epoxidation of 1,3-butadiene (Figure 23) and all showed an unsymmetrical approach.

A systematic examination of the transition structures for the peroxyformic acid epoxidation at various levels of theory confirms the above suggestion that the MP2 method does provide adequate geometries for a conjugated carbon–carbon double bond in 1,3-butadiene (Figure 23). However, the inverse KIEs measured by Hanzlik and Shearer\textsuperscript{120} for 4-vinylbiphenyl are specific to conjugated alkenes and should not be used as evidence of an asynchronous epoxidation TS for simple nonconjugated alkenes\textsuperscript{53}.

In general, alkene epoxidations can be classified formally, as to the nature of the substrate and type of oxidant, into four main groups: (i) symmetrical alkene (e.g. ethylene) and symmetrical oxidizing agents [peroxyformic acid (PFA), dioxirane (DO) and peroxy nitrous acid, see Scheme 9], which can form a \textit{spiro}-type transition structure where the plane of the oxidant is at \textit{ca} 90° to the double bond; (ii) symmetrical alkene and unsymmetrical oxidant [e.g. oxaziridine]; (iii) unsymmetrical alkenes (propylene, isobutylene and 1,3-butadiene) and symmetrical oxidant; (iv) unsymmetrical alkene and unsymmetrical oxidant. With case (i), where the TS has an approximate \(C\text{\textsubscript{s}}\) plane of symmetry geometrically, in the absence of significant diradicaloid character in the wave function, a highly symmetrical TS should be anticipated on the basis of electronic considerations. In the other cases, an asymmetrical approach to the alkene double bond should occur since the electronic distribution of the wave function is asymmetric. However, for most closed-shell systems the electronic perturbation should be minimal and an approximate symmetrical \textit{spiro} TS typically results. Since the O−O bond in a peracid is a fairly typical O−O bond with a relatively high bond energy for a peroxy bond (\textit{ca} 45–50 kcal mol\textsuperscript{−1}), the extent of diradicaloid participation should be minimal. Obviously, with dioxiranes where the O−O bond can have several higher-lying biradicaloid singlet states, the opposite situation may well be observed. These generalizations do not preclude a variety of

\textbf{SCHEME 9}
other possible transition structures if a planar approach of the oxidizing reagent to the C−C bond axis is preferred on steric grounds. In this section we will discuss the transition structures for the first three of these oxidizing agents with symmetrical, unsymmetrical and conjugated alkenes that have been reported in the more recent literature.

Just such an example of a planar TS has been reported recently by Sarzi-Amade and his coworkers\textsuperscript{51b} who managed to locate only a planar-like TS and a planar TS (the peroxy acid plane contains the C=C bond axis), for \textit{anti}- and \textit{syn}-sesquinorbornenes. They are substrates that, because of steric constraints, cannot easily accommodate \textit{spiro}-like TSs. These planar TSs are ‘nonconcerted’ since they are strongly unsymmetrical and only one of the C−O bonds of the oxirane ring is significantly formed. IRC analysis, while confirming that formation of one C−O bond fully precedes that of the other, also suggests that all this can take place without formation of intermediates, that is, within a ‘nonconcerted one-step process’.

As noted elsewhere, one should only anticipate an asynchronous TS for alkene epoxidation when the possibility for significant diradical character is evident. In a systematic study of alkene epoxidation by the four classes of oxidant noted above (Scheme 9), Houk and coworkers described the varying asynchronous nature of the epoxidation TSs at the B3LYP/6-31G* level of theory\textsuperscript{90a}. These results were compared to the corresponding TSs derived from MP2 calculations. In general, it was noted that all of the epoxidations exhibit \textit{spiro} transition states; those with peroxyformic acid and dioxirane are early TSs and involve synchronous oxygen transfer. Ethylene epoxidation with peroxyxynitrous acid and oxaziridine are later TSs with an asynchronous oxygen atom transfer. However, as described above in Section IV.E (Figures 7 and 8) the HO−ONO epoxidation of ethylene at the more highly correlated QCISD level has an essentially symmetrical TS. When the C=C is substituted by methoxy, methyl, vinyl and cyano groups, the TS becomes more asynchronous as noted above. The activation barriers are lowered for all substituents but cyano with both peracid and dioxirane epoxidation.

This controversy\textsuperscript{12b,17a,90a,121,125} concerning the use of MP2 calculations for epoxidation reactions was rather short-lived since more efficient density functional calculations (DFT) came into general use and generally produced symmetrical \textit{spiro} transition structures. Consequently, the use of MP2 theory for O−O bond cleavage reactions has been largely discontinued. Most have assumed that the question of symmetrical versus asymmetrical approach of the peracid had been resolved. Recall that this same problem with MP2 calculations existed for the early calculations for dioxirane epoxidation (see Section V.D).

During the past decade DFT calculations have been utilized to show various aspects of the epoxidation reaction and the activation energies for numerous epoxidation reactions have been reported\textsuperscript{17b,19}; the \textit{spiro} orientation, with symmetrically substituted alkenes, has always been of lower energy than a planar approach where the peroxycacid is parallel to the C=C bond axis ($\langle$ H−O−C−C $=$ 0.0$^\circ$). The symmetrical nature of the transition structure for peracid epoxidation was also verified by Bach and coworkers\textsuperscript{124} at the complete active space [CASSCF (10,9)] level where it was demonstrated that the choice of active space is critical to determining the nature of the TS. A comparison of these CASSCF results with those of such highly correlated methods as MP2, QC1, CC and BD presented very strong evidence that a symmetrical \textit{spiro} TS is involved in peracid epoxidation of symmetrically substituted \textit{non}conjugated alkenes. The preferred \textit{spiro} approach is thought to be due to a small back-bonding interaction of the distal oxygen lone-pair of electrons with the C=C \pi orbital\textsuperscript{8a,128}. This favorable electronic interaction is maximized with a tetrahedral array around the developing oxirane oxygen and ‘turned off’ in the planar transition structure. These energy differences have been reported by several groups\textsuperscript{88,90a,129,130} to be relatively small and it has been almost universally assumed that the \textit{spiro} TS is operating. Recent
experimental\textsuperscript{51a} and theoretical\textsuperscript{51b} studies involving sterically encumbered alkenes also suggest that the \textit{spiro} TS is favored over a planar one. However, a recent report by Leszczynski and coworkers\textsuperscript{53} has called both the preferred transition structure for peracid epoxidation and the use of DFT calculations for such reactions into question. Based upon a series of CASSCF calculations, including the CASSCF(12,12)/6-311+ +G(d,p) level, they suggested a nearly planar orientation of the peroxyformic acid relative to the ethylene double bond (first-order saddle point). It was concluded that the electronic structure of this TS could only be described correctly by quantum-mechanical methods that are based upon multideterminantal approaches. This question was reexamined by Bach and Dmitrenko\textsuperscript{52} at several levels of theory including CASSCF, and convincing evidence was again presented that the \textit{spiro} orientation is in fact the preferred approach for alkene epoxidation with peracids and that the B3LYP variant of DFT calculations remain a useful and reasonably accurate method of choice for such studies. The problem with the planar TS suggested by the recent CASSCF results\textsuperscript{53} was most likely a consequence of choosing an unbalanced active space as noted much earlier\textsuperscript{124}. A similar exercise for dioxirane epoxidation by Dmitrenko and Bach\textsuperscript{131} also confirmed a \textit{spiro}, essentially symmetrical, approach of the dioxirane ring for the transition state. It should be emphasized that the PES for the approach of the electrophilic oxygen to the C\(=\)C\(\pi\)-bond is very shallow and minor changes in geometry may occur without a significant energy penalty.

Several general conclusions may be drawn concerning the mechanism of peracid epoxidation of alkenes:

(1) The epoxidations of propylene and isobutylene with peroxyformic acid proceed in a concerted way via slightly unsymmetrical Markovnikov-type transition structures where the differences in the bond distances between the double-bond carbons and the \textit{spiro} oxygen are only 0.021 and 0.044 Å at the QCISD/6-31G* level. In contrast, the more polarizable nature of the carbon–carbon double bond of \(\alpha,\beta\)-unsaturated systems results in a highly unsymmetrical transition structure for the epoxidation of 1,3-butadiene with an order-of-magnitude difference in the carbon–oxygen bond distances of 0.305 Å at the QCISD/6-31G* level. A highly unsymmetrical transition structure has been also found for the epoxidation of acrylonitrile.

(2) Epoxidations of methyl-substituted alkenes and \(\alpha,\beta\)-unsaturated systems as 1,3-butadiene and acrylonitrile with peroxyformic acid follow a concerted asynchronous pathway.

(3) Methyl substitution leads to a decrease in the epoxidation barriers from 18.8 kcal mol\(^{-1}\) for ethylene to 13.7 kcal mol\(^{-1}\) for isobutylene at the QCISD(T)/6-31G*//QCISD/6-31G* level.

(4) While the activation barrier for the epoxidation of 1,3-butadiene with peroxyformic acid (15.9 and 11.7 kcal mol\(^{-1}\) at the QCISD(T)//QCISD and B3LYP levels, respectively) is close to that for propylene epoxidation (16.0 and 12.0 kcal mol\(^{-1}\) at the QCISD(T)//QCISD/6-31G* and B3LYP/6-31G* levels, respectively), the barrier for acrylonitrile epoxidation is higher (21.0 and 17.3 kcal mol\(^{-1}\) at the QCISD(T)//QCISD/6-31G* and B3LYP/6-31G* levels, respectively). This increase in the barrier height reflects the decreased nucleophilicity of double bonds bearing electron-withdrawing substituents. The closeness of the barriers for propylene and 1,3-butadiene epoxidations supports the conclusion that both reactions have similar mechanisms albeit they differ in the asynchronous character of their transition structures.

(5) A comparison of the barriers for alkene epoxidations calculated at the QCISD(T)/6-31G*//B3LYP/6-31G* level with the QCISD(T)/6-31G*/QCISD/6-31G* and CCSD(T)/6-31G*/QCISD barriers leads to the conclusion that using the B3LYP geometries in the
D. Gas-phase Epoxidation of Selected Alkenes

Although experimental mechanistic studies of electrophilic addition to alkenes has been a major area of research for many years, more recent questions have been probed mainly by computational means. We are now in a position to visualize the transition structures for a great many such reactions with unique alkenes or those that are difficult to prepare with high strain energy (SE). For example, Bach, Adam and coworkers have reported that epoxidation barriers are only slightly greater for highly strained alkenes such as cyclopropene (SE = 55.2 kcal mol\(^{-1}\)) and cyclobutene (SE = 28.4 kcal mol\(^{-1}\)) than for cyclopentene (SE = 4.1 kcal mol\(^{-1}\)), which possibly reflects the fact that the resulting epoxide products are also strained. The SE for the simplest epoxide, oxirane or ethylene oxide is 26.3 kcal mol\(^{-1}\) with an accompanying reduction in SE with each alkyl substituent. The lack of correlation of rate with strain energy is quite evident in the relatively small \(\Delta E^\# = 0.8\) kcal mol\(^{-1}\) for cyclopropene versus cyclobutene (Table 10, Figure 25). All three TSs exhibit a highly symmetrical approach to the carbon–carbon double bond with a \(\text{spiro}\) orientation (90\(^\circ\)) of the plane of the peracid with respect to the C=C bond axis.

Alkenes strained by twist or \(\pi\)-bond torsion, such as E-cyclooctene, exhibit much lower barriers due to relief of strain in the TS for the oxygen transfer step. While the epoxidation of symmetrically substituted alkenes normally involve a symmetrical approach to the \(\pi\)-bond, the TSs for epoxidation of E-cyclooctene and E-1-methylcyclooctene exhibit highly asymmetric transition structures. The \(\Delta E^\# = 3.3\) kcal mol\(^{-1}\) for E versus Z-cyclooctene is clearly a reflection of the relative SE of these two medium ring alkenes (16.4 vs 4.2 kcal mol\(^{-1}\)). The classical activation barrier (\(\Delta E^\#\)) for the highly strained bicyclo[3.3.1]non-1-ene is also quite low (Table 10, Figure 26). In these twist-strain alkenes, the approach of the peracid deviates markedly from the idealized \(\text{spiro}\) approach suggesting that this part of the potential energy surface is quite soft.

Although it is generally accepted that the \(\text{exo}\) approach to norbornene is favored over the \(\text{endo}\), the magnitude of the \(\Delta E^\#\) is rarely measurable experimentally unless some fraction of the \(\text{endo}\) product can be detected. The \(\text{exo}\) approach to norbornene is favored over the \(\text{endo}\) orientation by nearly 3 kcal mol\(^{-1}\) for both PFA and DMDO, while the \(\text{exo}\) TS for benzonorbornadiene is favored by nearly 5 kcal mol\(^{-1}\) (Figure 27). The preferred \(\text{exo}\) approach does not appear to result from steric interactions. It is of particular interest that the \(\Delta E^\#\) for norbornene is only 0.9 kcal mol\(^{-1}\) greater than that for cyclohexene despite the SE = 19.2 kcal mol\(^{-1}\) for the strained bicyclic alkene. Thus, in the absence of twist-strain we observe little rate enhancement due to strain energy.

E. Factors Influencing the Rate of Epoxidation

We have discussed how the different methods of calculation can influence the nature of the transition states for peracid epoxidation. The method of calculation also has an impact on the calculated activation barriers (Table 9). A comparison of the barriers for alkene epoxidations calculated at the QCISD(T)/6-31G(d)/B3LYP/6-31G(d) level with the QCISD(T)/6-31G(d)/QCISD/6-31G(d) and CCSD(T)/6-31G(d)/QCISD barriers lead to the conclusion that using the B3LYP geometries in the QCISD(T) and CCSD(T) calculations can be both a cost-effective and reliable computational approach to study epoxidations of alkenes with peroxo acids. A comparison of the calculated barrier heights for a series of typical alkenes at different levels of theory is given in Table 9. In general,
1. General and theoretical aspects of the peroxide group

TABLE 10. B3LYP activation barriers (\(\Delta E^a\), kcal mol\(^{-1}\)) for the epoxidation of a series of alkenes with peroxyformic acid (PFA) showing the effect of the basis set (the first barriers are at the B3LYP/6-31G(d) level of theory, the barriers in parentheses are at the B3LYP/6-31+G(d,p) level)

<table>
<thead>
<tr>
<th>Alkene</th>
<th>PFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene</td>
<td>14.1 (14.9) 17.0(^a) [16.4](^b)</td>
</tr>
<tr>
<td>Propylene</td>
<td>12.0 (12.6) 14.8(^a) [16.0](^c)</td>
</tr>
<tr>
<td>(\tau)-Butylethylene</td>
<td>11.2 (12.3) 14.0(^a)</td>
</tr>
<tr>
<td>1-Octene</td>
<td>11.2 (12.2) 14.1(^a)</td>
</tr>
<tr>
<td>Isobutene</td>
<td>10.8 (11.2) 13.0(^a) [13.7](^c)</td>
</tr>
<tr>
<td>(E)-2-Butene</td>
<td>10.5 (11.0) 12.8(^a) [13.4](^c)</td>
</tr>
<tr>
<td>Z-2-Butene</td>
<td>10.0 12.1(^a)</td>
</tr>
<tr>
<td>Z-2-Pentene</td>
<td>9.3 (10.0) 11.6(^a)</td>
</tr>
<tr>
<td>Cyclopropene</td>
<td>12.0 (12.5) 14.5(^a)</td>
</tr>
<tr>
<td>Cyclobutene</td>
<td>11.0 (11.5) 13.7(^a)</td>
</tr>
<tr>
<td>Cyclopentene</td>
<td>9.3 (9.7) 12.1(^a)</td>
</tr>
<tr>
<td>Cyclohexene</td>
<td>9.7 (10.1) 12.1(^a)</td>
</tr>
<tr>
<td>Cycloheptene</td>
<td>9.8 (10.2) 12.2(^a)</td>
</tr>
<tr>
<td>(Z)-Cyclooctene</td>
<td>9.1 (9.6) 11.5(^a)</td>
</tr>
<tr>
<td>(E)-Cyclooctene</td>
<td>5.6 (6.1) 8.2(^a)</td>
</tr>
<tr>
<td>1-Methyl-(E)-cyclooctene</td>
<td>4.0 (4.3) 5.9(^a)</td>
</tr>
<tr>
<td>Norbornene ((exo))</td>
<td>9.7 (10.3) 12.9(^a)</td>
</tr>
<tr>
<td>Norbornene ((endo))</td>
<td>12.5 (13.2) 15.4(^a)</td>
</tr>
<tr>
<td>Benzonorbornadiene ((exo))</td>
<td>9.6 (10.2) 12.2(^a)</td>
</tr>
<tr>
<td>Benzonorbornadiene ((endo))</td>
<td>14.6 (15.1) 17.0(^a)</td>
</tr>
<tr>
<td>Bicyclo[3.3.1]non-1-ene</td>
<td>5.2 (5.7) 7.7(^a)</td>
</tr>
<tr>
<td>Trimethylcyclohexene</td>
<td>8.9 (9.1) 11.0(^a)</td>
</tr>
<tr>
<td>Tetrathienylenvalene</td>
<td>7.8 (7.9) 9.8(^a)</td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>11.7 (12.4) 14.3(^a) [15.9](^c)</td>
</tr>
<tr>
<td>(trans)-2-(cis)-4-Hexadiene</td>
<td>9.4 (9.6) 11.5(^a)</td>
</tr>
<tr>
<td>(E)-Stilbene</td>
<td>13.2 (13.3) 15.1(^a)</td>
</tr>
<tr>
<td>(Z)-Stilbene</td>
<td>11.8 (12.6) 14.6(^a)</td>
</tr>
<tr>
<td>Styrene</td>
<td>11.2 (11.7) 14.2(^a)</td>
</tr>
<tr>
<td>(Z)-3-Methyl-3-penten-2-ol</td>
<td>9.2(^d)</td>
</tr>
<tr>
<td>Allyl alcohol</td>
<td>7.5(^e) 11.4(^f)</td>
</tr>
</tbody>
</table>

\(^{a}\) Classical activation barriers computed at the B3LYP/6-311+G(3df,2p)//B3LYP/6-31+G(d,p) level.
\(^{b}\) The numbers in brackets for ethylene are at the QCISD(T)//QCISD/6-31+G(d,p) level.
\(^{c}\) The numbers in brackets for propylene, isobutylene, \(E\)-2-butene and \(1\)-butadiene entries are at the QCISD(T)//QCISD/6-31+G(d) level of theory; CBS-Q//QCISD/6-31G(d) gas-phase intrinsic barriers (\(\Delta E^*\)) for the epoxidation of \(E\)-2-butene with dimethyldioxirane (DMDO) and peroxyformic acid are 9.7 and 11.2 kcal mol\(^{-1}\), respectively.
\(^{d}\) Classical activation barrier computed at the B3LYP/cc-pVTZ level.
\(^{e}\) Classical activation barrier (\(\Delta E^*\)) computed at the B3LYP/6-31G(d,p) level.
\(^{f}\) Classical activation barrier computed at the QCISD(T)//QCISD/6-31G(d) level.

methyl substitution on the C=C leads to a decrease in the epoxidation barriers from 18.8 kcal mol\(^{-1}\) for ethylene to 13.7 kcal mol\(^{-1}\) for isobutylene at the QCISD(T)/6-31G(d)//QCISD/6-31G(d) level (Table 9).

One of the more intriguing features of peracid epoxidation is that the strength of the O—O bond has little impact on the rate of oxygen atom transfer. For example, peroxyacetic acid and peroxytrifluoroacetic acid have nearly identical O—O BDE (G2MP2, \(\Delta H^0 = \))
FIGURE 25. Transition structures for the epoxidation of cyclopropene, cyclobutene and cyclopentene with peroxyformic acid (PFA), optimized at the B3LYP/6-31+G(d,p) level of theory. The classical activation barriers are given at B3LYP/6-31+G(3df,2p)//B3LYP/6-31+G(d,p). Dihedral angles (\(\angle_{\text{spiro}}\) represents \(\angle_{\text{HOCC}}\)) indicate the deviation from an ideal \(\text{spiro}\) approach (\(\angle_{\text{spiro}} = 90^\circ\)) of the HO group in PFA onto the C=C bond of the alkene.

46.4 and 47.0 kcal mol\(^{-1}\))\(^{16a}\) but the latter peracid exhibits a \(\geq 10^5\) greater reactivity toward alkenes. The enhanced reactivity of CF\(_3\)CO\(_3\)H has been attributed to the effect of electron-withdrawing groups on the peroxy acid moiety on the charge distribution in the transition state for epoxidation. Conventional wisdom would suggest that the inductive effect of the electron-withdrawing CF\(_3\) group would increase the electron density at the
1. General and theoretical aspects of the peroxide group

**E-cyclooctene**

\[ \Delta E^\ne = 8.2 \text{ kcal mol}^{-1} \]

\[ \angle_{\text{spiro}} = 51.8^\circ \]

**Z-cyclooctene**

\[ \Delta E^\ne = 11.5 \text{ kcal mol}^{-1} \]

\[ \angle_{\text{spiro}} = 93.4^\circ \]

**E-1-methylcyclooctene**

\[ \Delta E^\ne = 5.9 \text{ kcal mol}^{-1} \]

\[ \angle_{\text{spiro}} = 49.3^\circ \]

**bicyclo[3.3.1]non-1-ene**

\[ \Delta E^\ne = 7.7 \text{ kcal mol}^{-1} \]

\[ \angle_{\text{spiro}} = 117.6^\circ \]

FIGURE 26. Transition structures for the epoxidation of selected cyclic alkenes with peroxyformic acid (PFA), optimized at the B3LYP/6-31+G(d,p) level of theory. The classical activation barriers are given at B3LYP/6-311+G(3df,2p)//B3LYP/6-31+G(d,p)
FIGURE 27. Transition structures for the epoxidation of norbornene and benzonorbornadiene, optimized at the B3LYP/6-31+G(d,p) level of theory. The classical activation barriers are given at B3LYP/6-31+G(d,p). The barriers in parentheses are at B3LYP/6-311+G(3df,2p)//B3LYP/6-31+G(d,p). Dihedral angles (∠spiro represents ∠HOCC) indicate the deviation from an ideal spiro approach (∠spiro is 90°).

developing carboxylate oxygen anion in the TS and by its stabilizing influence assist in heterolytic O–O bond scission. Using E-2-butene as a common substrate, Bach20a varied the substituent on the peroxo acid, R−CO₂H, where R = H, CH₃, CF₃, F and OCH₃. A summary of the calculated activation barriers is given in Table 11 (for more details see Reference 20a).
The activation barrier for epoxidation of \(E\)-2-butene with peroxyformic acid (\(\Delta E^\ddagger = 11.0\) kcal mol\(^{-1}\)) is 2.5 kcal mol\(^{-1}\) lower in energy than the activation energy for epoxidation with peroxyacetic acid. No inductive effect is observed for the methoxy group where the barrier for epoxidation with the percarbonate, CH\(_3\)O-CO\(_3\)H, is slightly increased (\(\Delta E^\ddagger = 12.8\) kcal mol\(^{-1}\)). However, the predicted effect of electron-withdrawing fluorine substituents is observed with the classical activation barriers for epoxidation with CH\(_3\)CO\(_3\)H versus CF\(_3\)CO\(_3\)H (\(\Delta E^\ddagger = 7.1\) kcal mol\(^{-1}\)). The activation barrier for the directly substituted fluoroperoxyformic acid, FCO\(_3\)H, is identical (\(\Delta E^\ddagger = 6.4\) kcal mol\(^{-1}\)) to that of CF\(_3\)CO\(_3\)H and ironically both have the same O−O distance (Figure 28) in the TS (1.769 Å).

Although no experimental rate comparisons are available with trifluoroperacetic acid since the reactions are too fast to measure\(^{135}\), the enhanced reactivity of CF\(_3\)CO\(_3\)H is usually ascribed to the fact that the developing trifluoroacetate anion leaving group is much more stable than the acetate anion. Intuitively, this should mean that additional negative charge should build up on the CF\(_3\)COO\(^-\) fragment in the TS. However, examination of the charges on the alkene fragment and the substituted carboxylate fragment are essentially identical and are quite comparable for all five TSs examined! In each case the charge on the OH fragment is essentially zero (Figure 28). Clearly, this suggests that conventional wisdom does not provide an explanation for this increased reactivity that has traditionally been ascribed to inductive stabilization of the developing anionic leaving group. The transition structures for both of the fluoro-substituted TSs come earlier along the reaction coordinate as evidenced by the shorter O−O bond (1.769 Å) relative to that of the peroxyformic and peroxyacetic acid TSs (1.83 Å). An earlier TS is also consistent with the longer C−O bonds in the developing epoxide ring.

From this theoretical analysis it may be concluded that the arguments pertaining to classical inductive effects cannot explain the increased rates of epoxidation due to either increased alkyl substitution on the double bond or the effect of electronegative substituents on the peracid. Our best rationale at this time is that the electron-withdrawing substituents lower the energy of the O−O \(\sigma^*\) orbital of the peracid, which has the effect of moving the TS closer to the reactants side of the reaction coordinate with a complementary lowering of the activation barrier. Consistent with this suggestion, and in consonance with the Hammond postulate, there is a linear relationship between the number of alkyl groups on the double bond and the overall heat of the reaction forming the epoxide product and the neutral carboxylic acid. The G2 energies of reaction (\(\Delta E\)) for epoxidation of ethylene, propylene, isobutylene and trimethylethylene are −47.7, −50.2, −52.0 and −55.1 kcal mol\(^{-1}\), respectively.
FIGURE 28. Effect of substitution in peracids on the activation barriers (kcal mol$^{-1}$) and charge distribution (electrons) for the epoxidation of $E$-2-butene. Charge distributions in B3LYP/6-31+G(d,p) optimized transition structures are calculated using NBO, B3LYP/6-31+G(d,p)
Another intriguing aspect of peracid epoxidation is the effect of pH upon the rate of epoxidation. Bach and coworkers\textsuperscript{97} have reported experimental studies showing that the rate of $m$-CPBA epoxidation of Z-cyclooctene was only increased 6.8-fold upon the addition of the catalyst trifluoroacetic acid. The predicted activation barrier for epoxidation of ethylene with fully protonated peroxyformic acid is indeed quite low ($\Delta E^\neq = 6.4$ kcal mol$^{-1}$). This relatively low activation barrier is largely a consequence of the fact that the system is positively charged. It was argued that under typical reaction conditions in nonpolar solvents, an effective concentration of protonated peroxy acid is not attainable, and the stability of the product epoxide is in question. At the same level of theory [QCISD(T)/6-31G(d)//QCISD/6-31G(d)] the gas-phase barrier of the uncatalyzed epoxidation reaction is 18.8 kcal mol$^{-1}$. The increase in rate of alkene epoxidations observed upon addition of carboxylic acids of moderate acidity was rationalized in terms of a pre-equilibrium forming a reactant cluster between the peroxy acid and the undissociated acid catalyst (HA). The hydrogen bond between HA and the peroxy acid, activating the latter, is capable of lowering the gas-phase barrier for epoxidation of ethylene by peroxyformic acid by about 3 kcal mol$^{-1}$ with respect to the uncatalyzed process.

F. Epoxidation of Allylic Alcohols

The pioneering studies by Henbest\textsuperscript{136a,b} mark the first demonstration that the stereochemical course of the peracid epoxidation reaction may be steered through synergistic interplay between conformational and hydrogen-bonding effects\textsuperscript{136c} in chiral allylic alcohols. This mechanistic concept has been designated by Adam and Wirth\textsuperscript{137a} as hydroxy-group directivity. For 3-hydroxycyclohexene it was shown\textsuperscript{136} that the cis epoxide was favored, which signifies that the perbenzoic acid attacks the $\pi$-bond from the same side that bears the allylic alcohol functionality. Acyclic allylic alcohols lack the inherent advantages of cyclic ones in regard to conformational preferences, unless imposed through appropriate substitution. The concept of allylic strain serves this purpose\textsuperscript{137b}, which allows differentiation of the two $\pi$-faces of the olefinic syn double bond by adequate alignment of the hydroxy group through steric effects. Bach and his coworkers\textsuperscript{138} provided the first computational verification of these concepts by demonstrating that the hydrogen-bonding interaction of peroxyformic acid with allyl alcohol (Figure 29) directed the electrophilic oxygen to the syn $\pi$-face of the C=C. This preliminary study was followed by a much more extensive study by Sarzi-Amade and coworkers\textsuperscript{130a}.

Calculations at the B3LYP/6-31G* and B3LYP/6-311+G**//B3LYP/6-31G* theory levels about the mechanism of epoxidation of chiral acyclic allylic alcohols (3-methyl-3-buten-2-ol and (Z)-3-penten-2-ol) lead to the following observations based upon the location of more than twenty TSs. Hydrogen bonding is operative in syn TSs with the OH group acting as hydrogen-bond donor while the carbonyl oxygen and the peroxy oxygen of the peracid compete with each other as hydrogen-bond acceptor. The geometry of all TSs should be classified as spiro butterfly, i.e. with the peroxy acid plane close to a perpendicular orientation to the C=C bond axis. No TSs were located that could be classified as planar or butterfly (i.e. with the peroxy acid plane oriented along the C=C bond axis). Hydrogen bonding stabilizes syn TSs and influences their geometry; however, it never succeeds in imposing a planar butterfly structure.

A complementary paper was reported soon after by Adam, Bach and coworkers\textsuperscript{139} where eight transition structures for the epoxidation of the chiral allylic alcohol (Z)-3-methyl-3-penten-2-ol with peroxyformic acid were computed by the B3LYP density functional method with 6-31G(d) and 6-31G(d,p) basis sets. The four lowest-energy transition structures and their respective prereaction clusters were fully re-optimized by employing 6-311+G(d,p) and correlation-consistent polarized valence triple-$\xi$ cc-pZTV basis sets.
FIGURE 29. Reactant cluster, transition state, TS, and the IRC path study (right drawing) of the epoxidation of allyl alcohol with peroxyformic acid showing the movement of atoms from the transition state (dark, P1) toward the products (light, P3) with an intermediate structure, P2. The reaction coordinate is in units of amu bohr, the relative energies are in kcal mol$^{-1}$ and the distances are in Å. Geometric parameters in parentheses are at the MP2/6-31G(d,p) (see text) level of theory.

The relative energies of the transition structures were found to be highly sensitive to the basis set applied. The transition state for *threo* product formation, *anti*-(*2S,3R,4S*)-TS, with the lowest total energy (at B3LYP/611+G(d,p) and B3LYP/AUG-cc-pZTV) of all the TSs examined, has a planar peracid moiety and is a precursor for the 1,4-migration of the peracid hydrogen atom to the peroxy carbonyl oxygen atom. The proton affinity, according to G2 calculations$^{138}$, is much larger for the carbonyl oxygen atom than for the distal peroxy oxygen. This suggests that gas-phase H-bonding to the carbonyl oxygen should be stronger.

The transition state for *erythro* epoxidation, *syn*-(*2R,3R,4S*)-TS, is only 0.9 kcal mol$^{-1}$ higher in energy and possesses a nonplanar peracid approaching the C=C bond in a manner intermediate between *spiro* and planar. The relative energy and nonplanarity of this *syn* transition structure is highly sensitive to the basis set applied. It was shown that
this approach agrees well with the experimental threo/erythro product ratio, in particular when the corrections for a solvent effect are made within the self-consistent isodensity polarized continuum model (SCI-PCM).

Cyclic allylic alcohols have different steric requirements than the acyclic substrates discussed above. Sarzi-Amade and coworkers\textsuperscript{130b} addressed the mechanism of epoxidation of 2-cyclohexen-1-ol by locating all the transition structures (TSs) for the reaction of peroxyformic acid (PFA) with both pseudoequatorial and pseudooxial cyclohexenol conformers. Geometry optimizations were performed at the B3LYP/6-31G* level, and the total energies were refined with single-point B3LYP/6-311+G**//B3LYP/6-31G* calculations. Solvent effects were approximated with the CPCM method. It was reported that all TSs exhibit a spiro-like structure, that is, the dihedral angle between the peroxy acid plane and the forming oxirane plane is closer to 90° than to 0°. A stabilizing hydrogen-bonding interaction was found in the syn TSs. The syn,exo TSs with hydrogen bonding at the PFA peroxy oxygens were found to be more stable than syn,endo TSs hydrogen bonded at the PFA carbonyl oxygen. The calculations correctly predict the experimental dominance of attack leading to syn epoxide for both cyclohexenol conformers.

VII. OXYGEN ATOM TRANSFER FROM SELECTED HYDROPEROXIDES

A. The Oxidation of Amines

Hydrogen peroxide is the simplest hydroperoxide and for obvious reasons this is where the early theoretical attempts at computational descriptions of the OOH group were concentrated. A molecular orbital treatment of HO−OH was thoroughly reviewed in the last volume of this continuing series by Cremer\textsuperscript{1}. In this section we will examine principally the computational attempts to examine the mechanism of oxygen atom transfer from HO−OH and related hydroperoxides. As described above, the computational problems associated with reactions involving O−O bond cleavage have only recently been resolved to a satisfactory treatment. Early attempts to transfer an oxygen atom from HO−OH to the simplest nucleophile, ammonia, proved to be challenging because the TS for oxidation of ammonia first involved a 1,2-transfer of hydrogen to the distal oxygen of HO−OH. Therefore, the preliminary calculations by Bach and coworkers pertaining to reactions involving O−O bond cleavage in HO−OH were centered around the 1,2-hydrogen shift in HO−OH to form the zwitterionic structure, water oxide [H₂O−O+] (equation 10)\textsuperscript{119,140}. First, it should be recalled that, in general, a 1,2-hydrogen shift to an adjacent lone pair of electrons is formally a four-electron forbidden reaction and consequently will have a high activation barrier\textsuperscript{141}. The activation barrier for the 1,2-hydrogen shift in HO−OH to form water oxide (or oxywater) has a calculated ΔE\textsuperscript{1} ≠ = 55.4 kcal mol\textsuperscript{−1} (MP4SDTQ/6-31G*). The barrier for the reverse reaction reforming hydrogen peroxide is only 6.1 kcal mol\textsuperscript{−1} (ΔE\textsuperscript{2} ≠). The transition structure for the HO−OH oxidation of ammonia involved water oxide (equation 11) and the barrier was consequently quite high at 53.4 kcal mol\textsuperscript{−1}.

\[
\begin{align*}
\text{H}_1 \\
\text{O}_1 \text{O}_2 \\
\text{H}_2
\end{align*}
\quad \xrightleftharpoons{\Delta E\textsuperscript{1} ≠} \quad
\begin{align*}
\text{H}_1 \\
\text{O}_1 \text{O}_2 \\
\text{H}_2
\end{align*}
\quad \xrightleftharpoons{\Delta E\textsuperscript{2} ≠} \quad
\begin{align*}
\text{H}_1 \\
\text{H}_2
\end{align*}
\quad \text{TS}
\]

NH\textsubscript{3} + H\textsubscript{2}O−O \quad \xrightarrow{} \quad H\textsubscript{3}N−O + H\textsubscript{2}O

By contrast, the oxidation of ammonia with CH\textsubscript{3}O−OH proceeded more normally with the 1,2-hydrogen shift to the departing methoxide ion occurring after the barrier was crossed but a relatively high barrier was reported (ΔE\textsuperscript{=} = 46.5 kcal mol\textsuperscript{−1})\textsuperscript{19a}.
Since water oxide was a potentially new and unusually high-energy intermediate, its existence as an observable intermediate was questioned almost immediately. An \textit{ab initio} molecular electronic structure investigation of the oxywater–hydrogen peroxide isomerization by Schaefer and coworkers\textsuperscript{142} was initiated using self-consistent-field (SCF), configuration interaction including all single and double excitations (CISD), and coupled cluster with single and double excitations (CCSD) methods with a triple-zeta plus double-polarization (including \textit{f} functions on the oxygen atoms) quality (TZ2P+\textit{f}) basis set. The CCSD method with connected ‘triple excitations’ [CCSD(T)] was also used to obtain oxywater’s equilibrium geometry. A classical barrier to isomerization of water oxide of 5.7 kcal mol\textsuperscript{−1} (equation 10, $\Delta E_2^\ddagger$) was predicted at the highest level of theory. After correction for zero-point vibrational energies, the comparable ground-state activation energy is 3.2 kcal mol\textsuperscript{−1}. Although these \textit{ab initio} predictions could be decreased by 1 or 2 kcal mol\textsuperscript{−1} at yet higher levels of theory, there can be little doubt that oxywater is a genuine minimum on the H\textsubscript{2}O\textsubscript{2} potential energy hypersurface. It was concluded\textsuperscript{142} that oxywater is a high-energy minimum that awaits synthesis.

These high-level calculations encouraged Schwarz and his collaborators\textsuperscript{143} to initiate an experimental study to seek out this very elusive but interesting potential oxygen donor. Collisional activation, charge reversal and six different neutralization–reionization mass spectrometric experiments with H\textsubscript{2}O\textsuperscript{−}O\textsuperscript{+} radical cations and H\textsubscript{2}O\textsubscript{2}−radical anions were performed in order to probe the predicted existence of neutral water oxide, H\textsubscript{2}O–O, the long sought after tautomer of hydrogen peroxide, HO–OH. The experiments together with \textit{ab initio} calculations indicate that H\textsubscript{2}O–O is a local minimum on the [H\textsubscript{2}O\textsubscript{2}] potential energy surface, and the elusive molecule seems to be formed as a transient upon neutralization of the corresponding radical cation H\textsubscript{2}O\textsuperscript{−}O\textsuperscript{+} in the gas phase.

There have also been attempts to examine the relative stability of water oxide in a highly hydrogen-bonded aqueous environment\textsuperscript{141}. The reduction in the barrier to produce an effective water oxide reagent from HO–OH in protic media must reflect both the amelioration of the 1,2-hydrogen shift barrier and a decrease in electron density at the ‘electrophilic’ oxygen; however, the greatest effect comes from stabilization of water oxide itself by hydrogen bonding since this zwitterionic water oxide structure is more basic than HO–OH itself. This surface was examined initially (MP2/6-31G*) by including several water molecules in the TS for rearrangement\textsuperscript{141}. Although H\textsubscript{2}O\textsubscript{2} hydrogen bonded to two water molecules affording a cyclic structure is stabilized by 21.9 kcal mol\textsuperscript{−1}, the hydrogen-bonded cyclic array, involving water oxide, is 42.7 kcal mol\textsuperscript{−1} lower in energy than its separated entities, and only 7.0 kcal mol\textsuperscript{−1} above the energy of isolated H\textsubscript{2}O\textsubscript{2} plus two water molecules\textsuperscript{141}. A more recent DFT study [B3LYP/6-311++G(d,p)] of the solvent effect on the equilibrium between these two isomeric forms of hydrogen peroxide has arrived at basically the same conclusion\textsuperscript{144}. A proton relay can lower the barrier for the formation of hydrogen-bonded water oxide when the proton is passed successively between water molecules relative to a direct 1,2-hydrogen shift. However, even with three water molecules the barrier is 29.5 kcal mol\textsuperscript{−1}, which places this type of oxidant out of the practical range of most chemical reactions.

Although water oxide, once formed, proved to be a remarkably efficient oxygen atom donor, it is quite likely that it is simply too high in energy to be a viable oxidant. A second problem with the preliminary calculations by Bach and coworkers\textsuperscript{119} is that NH\textsubscript{3} is not a realistic nucleophile for such studies; it was what was feasible at that time\textsuperscript{145}. This inadequacy has only recently been ameliorated by Ottolina and Carrea\textsuperscript{146}, who used the more nucleophilic trimethylamine (TMA) as the attacking nucleophile and got an entirely different and much more chemically realistic hypersurface for the HO–OH oxidation of amines. The prior results at the MP2 level compared favorably with the results of the B3LYP/6-31+G* method, so the basic problem was in the nucleophile and not with the...
type of calculation. With both methods the transition structure for the HO—OH oxidation of TMA came much earlier on the reaction coordinate and resembled the anticipated $S_N2$-like displacement of the nitrogen nucleophile along the O–O σ* orbital with transfer of the hydrogen to the distal OH to form a neutral water leaving group after the barrier is crossed, as exemplified in Figure 30. These authors also reported the effect of one water molecule on the reduction of the activation barrier ($\Delta \Delta E_1 \neq 8.4 \text{ kcal mol}^{-1}$). An IRC analysis [B3LYP/6-31+G(d)] suggested that the single water molecule did not act

\[ \Delta(E+\text{ZPVE})^\neq = 24.7 \text{ kcal mol}^{-1} \]
\[ (25.8 \text{ kcal mol}^{-1}) \]

\[ \Delta(E+\text{ZPVE})^\neq = 17.4 \text{ kcal mol}^{-1} \]
\[ (18.3 \text{ kcal mol}^{-1}) \]

\[ \Delta(E+\text{ZPVE})^\neq = 12.2 \text{ kcal mol}^{-1} \]

FIGURE 30. B3LYP/6-31+G(d,p)-optimized transition structures for the oxidation of trimethylamine by hydrogen peroxide (a), with one water molecule (b), and two water molecules (c). The values of the imaginary frequency and the barriers [$\Delta(E+\text{ZPVE})^\neq$] are at the B3LYP/6-31+G(d,p) level. The barriers given in parentheses are at the B3LYP/6-31+G(d) level.
as a proton relay but produced a rather strong hydrogen bond to the departing OH group ($r_{O-H} = 1.57 \text{ Å}$).

The overall surface for the HO—OH oxidation of TMA was recently reexamined\textsuperscript{147} at the B3LYP/6-31+G(d,p) level using a slightly larger basis set that contained polarization functions on the hydrogens to treat more effectively hydrogen-bonding interactions. Although the TS with TMA\textsuperscript{146} came somewhat earlier than that with ammonia as the nucleophile, the major component of the reaction vector still corresponds to the 1,2-hydrogen shift to the distal oxygen as noted by the magnitude of the activation barrier ($\Delta E^\neq = 24.7 \text{ kcal mol}^{-1}$) and the relatively large imaginary frequency (782$i$ cm$^{-1}$) for the rate-limiting step\textsuperscript{21}. In this relatively simple case the hydrogen is transferred to the distal oxygen to produce a neutral water molecule in concert with the formal transfer of the proximal OH group to the nitrogen nucleophile of the tertiary amine (TS-a, Figure 30).

When one water molecule is included in the oxidation step (TS-b, Figure 30), a major contribution to the eigenvector in the TS is an interaction of a developing proton on the water molecule with the departing OH group. An IRC analysis [B3LYP/6-31+G(d,p)] clearly exhibits a proton relay from the water molecule (O$_3$) to the departing OH group (O$_1$) to form a neutral water leaving group after the barrier is crossed. This observation differs from the IRC reported earlier\textsuperscript{146} and may possibly be due to the fact that polarization functions were not included in the basis set (see above). The imaginary frequency associated with the TS for the oxidation step diminishes as the effect of water catalysis increases with one and two water molecules. The catalytic role of the hydrogen-bonded water molecules diminishes the necessity for the high-energy 1,2-hydrogen shift to stabilize the departing hydroxide ion as discussed in more detail below.

The activation barrier decreases with each additional water molecule but the overall catalytic role of the second water molecule (TS-c, Figure 30) on the position of the hydrogen shift is much in the same way as noted for a single water molecule. A proton relay from the closest H-bonded water molecule to the developing OH anion (O1) in the TS is in evidence late along the reaction coordinate as shown by an IRC calculation. The O—O distance is reduced to 1.91 Å in TS-c, reflecting the stabilizing influence of the two H-bonded waters to the developing hydroxide anion. The final product, trimethylamine oxide, is produced after a second sequential proton relay from the N—OH (from O2) to form the three neutral water molecules and the $(\text{CH}_3)_3\text{N}−\text{O}$ product. The overall reduction in the gas-phase activation energy [from isolated reactants TMA and HO—OH• (H$_2$O)$_n$] for one and two water molecules is 7.3 and 12.5 kcal mol$^{-1}$. Obviously, in bulk water solvent this reaction would proceed rapidly even with solvation of the nucleophile, that tends to lower the nucleophilicity of the amine (see below).

B. The Oxidation of N, S, P and Se Containing Nucleophiles

The early attempts to study sulfide oxidations computationally were plagued by many of the problems described above for amine oxidation. The use of HO—OH as the model oxidant was problematic because it was again difficult to pin down the position of the migrating proton in the transition state for the oxygen transfer step. Calculations at the MP2 level reported by Bach and coworkers\textsuperscript{19a} suggested that the 1,2-hydrogen shift could either precede the oxygen transfer step or occur after the barrier was crossed. Although the activation barriers for the HO—OH oxidation of dimethyl sulfide (DMS) were in general too high to be compatible with experimental data, it was shown that hydrogen bonding of the hydroperoxide itself or associated water molecules could effectively reduce the activation energy in agreement with experiment. Most of these problems have been recently resolved by a definitive DFT study by Chu and Trout\textsuperscript{148} that has served to exclude the involvement of water oxide in the oxidation of sulfides. Solvent effects were examined in this study by both including explicitly water molecules and with the polarizable
1. General and theoretical aspects of the peroxide group

FIGURE 31. Transition structure for the HO—OH oxidation of dimethyl sulfide with three water molecules fully optimized at the B3LYP/6-31++G(d,p) level. The reaction barrier ($\Delta E^\neq$) was calculated at the MP4//B3LYP/6-31++G(d,p) level with respect to the reactant cluster continuum model. When explicit water molecules were included, specific interactions including hydrogen bonding with 2–3 water molecules was shown to provide enough stabilization for the charge separation of the O–O bond cleavage in HO–OH. The energy barrier of the oxidation of DMS by hydrogen peroxide was estimated to be 12.7 kcal mol$^{-1}$ [MP4//B3LYP/6-31++G(d,p)] within the experimental range of the oxidation of analogous compounds (10–20 kcal mol$^{-1}$). This is a very satisfactory result when compared to the activation energy (13.5 kcal mol$^{-1}$) for thioxane oxidation by hydrogen peroxide in aqueous solution$^{149,150}$. The basic mechanism with the effective catalysis by three water molecules is represented by the transition structure shown in Figure 31.$^{148}$ Two of the water molecules serve to solvate the departing OH$^-$ as the O–O bond elongated to 1.8 Å in the TS for this nucleophilic S$_N$2-like displacement. A proton relay is very likely involved as seen above with the water-catalyzed tertiary amine oxidation since the final product, dimethyl sulfoxide [(CH$_3$)$_2$S-O], is produced after it transfers a proton.

The major reaction coordinates of the reaction are the breaking of the O–O bond of H$_2$O$_2$ and the formation of the S–O bond. The transfer of hydrogen to the distal oxygen of hydrogen peroxide occurs after the system has passed the transition state. Therefore, a two-step oxidation mechanism in which, first, the transfer of a hydrogen atom occurs to form water oxide and, second, the transfer of oxygen to the substrate occurs was deemed unlikely. Several important conclusions to be drawn from this study include:

1. For moderate pH values, perhaps between 2 and 12, the reaction coordinate leading to oxidation of dimethyl sulfide by H$_2$O$_2$ involves O–O bond cleavage with the formation of the S–O bond. Under these conditions, water molecules can stabilize the transition complex via specific interactions including formation of hydrogen bonds with H$_2$O$_2$.

2. Hydrogen transfer does occur during oxidation of DMS, but it is not the determining factor of the activation barrier. Hydrogen transfer can occur via multiple different pathways depending on the local solvent configuration.
(3) Water molecules can stabilize the charge separation in the TS by local polarization and via formation of hydrogen bonds with \( \text{H}_2\text{O}_2 \).

(4) For hydrogen transfer reactions involving \( \text{H}_2\text{O}_2 \) and DMS oxidation with a single water molecule, including solvent via a polarizable continuum model, has only a minor effect on the activation energies (<1 kcal mol\(^{-1}\) in most cases). This is consistent with the experimental observation that the rates of oxidation of organic sulfides are not a strong function of the solvent dielectric constant.

C. Electronic Factors Influencing Oxygen Atom versus Hydroxyl Transfer

The rate of heterolytic O—O bond cleavage in oxygen atom transfer reactions is largely a function of the stability of the oxyanion leaving group accompanying heterolytic O—O bond cleavage. For example, the O—O bond cleavage in a peracid \([\text{R(C=O)}\text{O}—\text{OH}]\) gives a fairly stable carboxylate anion (\( pK_a \) ca 5), while an alkyl hydroperoxide affords a relatively unstable alkoxide ion (\( pK_a \) ca 16–19). Oxygen atom transfer from the −OOH moiety can proceed by two basic pathways: (a) the formal transfer of the hydroxyl group closely followed by an intramolecular hydrogen transfer along the reaction coordinate or (b) a hydroxylation process where the intact OH group is transferred and the leaving alkoxide anion exists as a minimum connected to the TS. The former is best exemplified by the peracid epoxidation of an amine (Figure 32, a) that proceeds by the formal transfer of an essentially neutral OH\(^{20a}\) group to the nitrogen atom of the amine followed by an intramolecular 1,4-proton transfer to the carbonyl oxygen of the departing carboxylate leaving group. In a similar fashion, the epoxidation of a simple alkene is attended by the

![FIGURE 32. Mechanistic pathway for oxygen atom transfer from peroxyformic acid (a) and alkyl hydroperoxides (b) to trimethylamine](image-url)
cleavage of a relatively weak peracid O–O bond (ca 48 kcal mol\(^{-1}\)) and the formation of an epoxide and a neutral carboxylic acid. The energetics of the reaction are quite favorable with a typical \(\Delta H_{298}\) of epoxidation on the order of 48–59 kcal mol\(^{-1}\)\(^{19d}\).

Oxygen atom transfer from an alkyl hydroperoxide, however, has additional energy requirements. Since this is typically a heterolytic O–O bond cleavage, the instability of the developing anionic alkoxide can influence the reaction pathway. For example, the heterolytic cleavage of the O–O bond in \(t\)-BuO-OH affords the relatively poor \(t\)-butoxide leaving group (p\(K_a\) 19). Consequently, the \(S_N2\)-like attack on the distal oxygen by a nucleophile such as an amine is attended by a 1,2-proton transfer (Figure 32, b) to the departing alcoholate in order to produce neutral \(t\text{-}\)butyl alcohol and the N-oxide product. The activation barrier for oxygen atom transfer from a hydroperoxide, like HO–OH, is also controlled, to a very large extent, by the energetics of this 1,2-hydrogen transfer step. As noted above, concerted 1,2-hydrogen transfer reactions to an adjacent lone pair are four-electron processes and as such are formally forbidden\(^{17c}\). For example, the 1,2-hydrogen shift in \(t\)-BuO\(^-\)OH to form the high-energy tert-butyl alcohol oxide intermediate (equation 12) has an activation barrier of 49.5 kcal mol\(^{-1}\).

\[
\text{H}_3\text{C} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{H}_3\text{C} \quad \text{C} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{H}_3\text{C} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{H}_3\text{C} \\
\begin{array}{c}
\text{H}_3\text{C} \quad \text{O} \quad \text{O} \quad \text{H} \\
\text{H}_3\text{C} \quad \text{C} \quad \text{O} \quad \text{O} \\
\text{H}_3\text{C} \quad \text{O} \quad \text{O} \quad \text{H} \\
\end{array}
\]

This highly endothermic rearrangement (\(\Delta E = 40.1\) kcal mol\(^{-1}\)) has a very late TS as evidenced by the short O–H bond to the proximal oxygen. When the reaction vector is composed mostly of light-atom hydrogen migration, as in equation 12, the imaginary frequency is quite high at \(v_i = 1233\) i cm\(^{-1}\). Contrariwise, when the reaction vector consists mainly of heavy-atom OH motion as in peracid alkene epoxidation\(^{20a}\), the single imaginary frequency of the first-order saddle point is only about 300i to 450i cm\(^{-1}\) (see Table 12 for a summary)\(^{21}\).

Much of what is understood today about the influence of solvent on rates of oxidation reactions with hydrogen peroxide, alkyl hydroperoxides and peroxyacids can be attributed to the seminal studies by Edwards and his collaborators over thirty years ago\(^{149}\). They provided convincing experimental data that showed that a hydroxylic solvent (e.g. ROH) can participate in a cyclic transition state where a proton relay can in principle afford a neutral leaving group attending heterolytic O–O bond cleavage (equation 13).

\[
R_2'S + R''\text{OOH} \overset{\text{HA}}{\longrightarrow} \begin{bmatrix} R_2'S \text{O} \quad \text{O} ' \quad \text{H} \\ \text{H} \quad \text{H} \quad \text{H} \\ \end{bmatrix} \quad \rightarrow \quad R_2'SO + R''\text{OH} + \text{HA} \quad (13)
\]

On the basis of kinetic data, it was suggested that appreciable charge separation in the activated complex (equation 13) could be avoided by means of such proton transfers, where HA is a general acid (H\(_2\)O, ROH, RO\(^-\)OH). Upon change from a polar protic solvent to the nonpolar solvent dioxane, the reaction was observed to be second-order in hydrogen peroxide and the second molecule of H\(_2\)O\(_2\) obviously played the role of HA in the 1,4-proton shift. The rate of oxidation was shown to increase linearly with the p\(K_a\) of solvent HA. In general, it was concluded that solvent interactions provide a
TABLE 12. Reaction barriers (kcal mol\(^{-1}\)) calculated with respect to the isolated oxidizing agent and substrate. Numbers in parentheses are barriers calculated with respect to the prereaction complex. Classical activation energies (\(\Delta E^\ddagger\)) at the B3LYP/6-31G(d) level are given in plain numbers, Bold numbers correspond to B3LYP/6-31+G(d,p) calculations. The single imaginary frequencies (Imag. freq.) are at the B3LYP/6-31G(d) level. Fl = Flavin

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Oxidizing agent</th>
<th>(\Delta E^\ddagger) (kcal mol(^{-1}))</th>
<th>Imag. freq. (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene</td>
<td>H(C=O)O−OH</td>
<td>14.1; <strong>14.9</strong></td>
<td>448.0i</td>
</tr>
<tr>
<td>E-2-Butene</td>
<td>H(C=O)O−OH</td>
<td>10.5; <strong>11.0</strong></td>
<td>411.1i</td>
</tr>
<tr>
<td></td>
<td>r-BuOOH</td>
<td>32.2; <strong>32.2</strong></td>
<td>438.0i</td>
</tr>
<tr>
<td>(CH(_3))(_3)N</td>
<td>H(C=O)O−OH</td>
<td>3.3; <strong>3.0</strong></td>
<td>283.2i</td>
</tr>
<tr>
<td></td>
<td>r-BuO−OH</td>
<td>30.5; <strong>29.0</strong> (40.9)</td>
<td>800.4i</td>
</tr>
<tr>
<td>(CH(_3))(_2)S</td>
<td>tricyclic FIHO−OH</td>
<td><strong>12.2</strong>; <strong>12.3</strong></td>
<td>312.8i</td>
</tr>
<tr>
<td></td>
<td>MeO−OH</td>
<td><strong>27.1</strong> (32.4)</td>
<td><strong>697.9i</strong></td>
</tr>
<tr>
<td></td>
<td>MeO−OH···MeO−OH (dimer)</td>
<td>10.8; <strong>10.5</strong> (22.5; <strong>19.4</strong>)</td>
<td><strong>283.8i</strong></td>
</tr>
<tr>
<td></td>
<td>r-BuO−OH</td>
<td>30.0; <strong>27.2</strong> (36.5; <strong>32.2</strong>)</td>
<td>672.5i</td>
</tr>
<tr>
<td>(CH(_3))(_2)Se</td>
<td>tricyclic FIHO−OH</td>
<td><strong>14.1</strong>; <strong>12.7</strong></td>
<td>286.4i</td>
</tr>
<tr>
<td>(CH(_3))(_2)P</td>
<td>H(C=O)O−OH</td>
<td><strong>−3.7</strong>; <strong>−6.5</strong></td>
<td>248.1i</td>
</tr>
<tr>
<td></td>
<td>r-BuO−OH</td>
<td><strong>12.1</strong></td>
<td>535.9i</td>
</tr>
<tr>
<td>(CH(_3))(_2)S</td>
<td>tricyclic FIHO−OH</td>
<td><strong>2.6</strong>; <strong>−3.2</strong></td>
<td>206.4i</td>
</tr>
<tr>
<td>(CH(_3))(_2)P</td>
<td>H(C=O)O−OH</td>
<td><strong>−0.2</strong>; <strong>−0.3</strong></td>
<td>280.5i</td>
</tr>
<tr>
<td></td>
<td>r-BuO−OH</td>
<td>15.3; <strong>14.0</strong> (20.7)</td>
<td>358.4i</td>
</tr>
<tr>
<td>(CH(_3))(_2)Se</td>
<td>tricyclic FIHO−OH</td>
<td><strong>3.9</strong>; <strong>4.4</strong></td>
<td>327.0i</td>
</tr>
</tbody>
</table>

*The single imaginary frequency was calculated at the B3LYP/6-31+G(d,p) level.

mechanistic path which avoids significant charge separation in the activated complexes for displacements on peroxide molecules by neutral nucleophiles and that the effectiveness of the protic solvent is correlated with their relative acidities. An excellent example of the importance of the role of solvent participation is the oxidation of dimethyl sulfide by r-BuO−OH. Curci and coworkers\(^{150}\) showed that in aprotic solvents sulfide oxidation is second-order in hydroperoxide and that the second molecule of RO−OH plays the role of a protic solvent catalyst HA as exemplified in equation 13. The calculated activation barrier for the oxidation of DMS by monomeric CH\(_3\)O−OH is 32.4 kcal mol\(^{-1}\) relative to its prereaction complex (Table 12) as a consequence of the relatively poor methoxide leaving group\(^{21}\). A marked reduction in activation barrier for the oxidation of DMS was observed when the dimer of CH\(_3\)O−OH is employed (\(\Delta \Delta E^\ddagger = 13\) kcal mol\(^{-1}\)). More importantly, there is a change in mechanism that becomes immediately obvious upon examination of the imaginary frequencies of the two TSs (Figure 33). The TS for oxygen atom transfer from monomeric CH\(_3\)O−OH to DMS has a large degree of hydrogen atom motion involving a 1,2-hydrogen shift (\(v_i = 698i\)).

As discussed above for amine oxidation, the activation barrier for sulfide oxidation can be reduced markedly by hydrogen-bonding interactions that stabilize the alkoxide anion leaving group resulting from O−O bond cleavage. This catalytic effect serves to reduce the energetic requirements for the obligatory 1,2-hydrogen shift in the TS for the oxygen transfer step. The marked reduction in the imaginary frequency from \(v_i = 698i\) to 284i cm\(^{-1}\) for the dimeric CH\(_3\)O−OH oxidation (Figure 33) is consistent with very little displacement of the hydrogen atom during vibration of the imaginary frequency as visualized graphically in Figure 34. In frame A, both hydrogens of the OOH groups are involved in hydrogen bonding to produce the prereaction dimer that is weakly H-bonded to the sulfur atom. In the dimeric TS (Figure 33) the second CH\(_3\)O−OH is strongly H-bonded to the separating peroxo bond. After the barrier is crossed in frame C (Figure 34)
the proton from the catalytic CH₃O−OH is transferred to the departing methoxide ion and the proton now residing on the ‘protonated sulfoxide’ is poised to neutralize the incipient CH₃O−O⁻ anion. This type of proton relay obviates the need for the 1,2-proton direct shift thereby reducing activation barrier.

It is not surprising that the proton relay for sulfide oxidation (Figure 34) can be extended to the involvement of both HO−OH and RO−OH dimers in the oxidation of amines¹⁴⁷. The dimeric forms of the hydroperoxides can reduce the activation barriers as evidenced by the HO−OH and CH₃O−OH dimeric oxidation of TMA (Figure 35). The activation barrier for TMA oxidation with dimeric HO−OH is effectively reduced by 12.1 kcal mol⁻¹ relative to the same oxidation of TMA with monomeric HO−OH (25.8 kcal mol⁻¹, Figure 30).

For the HO−OH dimeric TS with TMA, an IRC calculation clearly shows a proton relay in operation that serves to reduce the activation barrier by ameliorating the energetic requirements for a direct 1,2-hydrogen shift. The H-bonded hydrogen of the participating HO−OH group is transferred to the developing anionic OH group [H10 to O7, TS(a)] being displaced to produce a neutral water molecule leaving group after the barrier is crossed. This behavior is comparable to the above HO−OH oxidation of TMA catalyzed by a single water molecule (Figure 30)¹⁴⁶ where a proton relay from water was advocated in the TS. The involvement of a proton relay with dimeric HO−OH is potentially a reflection of the much greater acidity of HO−OH than H₂O as is also reflected in the lower classical barrier (ΔΔE¹ = 3.7 kcal mol⁻¹). The very short H-bond of the OOH group (rOH = 1.45 Å) in the CH₃O−OH dimer TS is also suggestive of a proton relay (Figure 35). The relatively low activation energy (19.5 kcal mol⁻¹) for the dimeric TMA oxidation is reduced by 8.2 kcal mol⁻¹ when compared to the monomeric CH₃O−OH oxidation of TMA¹⁴⁷. The barrier for the oxidation of TMA by dimeric CH₃O−OH is also 9.5 kcal mol⁻¹ lower than oxidation by monomeric t-butyl hydroperoxide (Table 12).
FIGURE 34. Graphical visualization of the imaginary vibration ($v_i = 284i$ cm$^{-1}$) characterizing the transition structure (B) for the oxidation of DMS with MeO$^-\cdot$OH dimer. Structures A and C correspond to the extreme points of the vibration. The TS optimization and frequency calculation are at the B3LYP/6-31+G(d,p) level.

FIGURE 35. Transition structures for the oxidation of trimethylamine (TMA) with the dimer of hydrogen peroxide (a) and the oxidation of TMA with dimeric CH$_3$O$^-\cdot$OH (b) optimized at the B3LYP/6-31+G(d,p) level of theory.
D. Model Studies on Enzymatic Oxidation of Heterocycles and Aromatic Rings

One of the most important oxygen atom transfer reactions in biochemistry involves catalysis by flavoenzymes\(^{151}\). These tricyclic isoalloxazine moieties are among the more versatile of the redox cofactors in biochemistry. C4a-hydroperoxyflavin (4a-FlHO-OH) has been implicated as the key hydroperoxide intermediate that serves as the oxygen atom donor. These enzymes are able to oxidize a number of substrates including the aromatic ring in hydroxy-substituted phenols\(^{152a}\). \(p\)-Hydroxybenzoate hydroxylase (PHBH) has become the paradigm aromatic hydroxylase because of extensive kinetic and X-ray structural studies\(^{152b}\). When the N5 nitrogen in C4a-hydroperoxyflavin is alkylated with an ethyl group, the N5-ethyl group prevents the elimination of H\(_2\)O\(_2\), and this model C4a-hydroperoxyflavin (4a-FlEtO-OH) can be prepared and isolated in the laboratory\(^{153}\).

The intrinsic reactivity of the N5-ethyl derivative \(12b\) has been extensively studied by Bruice in a series of papers where it has been reacted with amines, sulfides, alkenes and \(\Gamma^-\), and its reactivity has been compared to common oxidants such as hydroperoxides and peracids\(^{153}\).

\[
\begin{align*}
  &\text{(12)} & R' &= 2'-\text{OH ribityl side chain;} & R &= \text{H} \ (\text{FlHOOH}) \\
  &\text{(12a)} & R' &= \text{CH}_3, & R &= \text{H} \ (\text{Lumiflavin}) \\
  &\text{(12b)} & R' &= \text{CH}_3, & R &= \text{C}_2\text{H}_5 \ (\text{FlEtOOH}) \\
  &\text{(14)} & R' &= \text{C}_2\text{H}_4\text{OH}, & R &= \text{H} \ (\text{FlHOOH} \ 3)
\end{align*}
\]

It is particularly noteworthy that the state-of-the-art in theoretical chemistry has now reached the point where reasonably reliable \textit{ab initio} calculations can be carried out on model enzymatic reactions, albeit most of the important residues at the active site must be ignored at this level. Theoretical calculations at the B3LYP/6-31+G(d,p) level reported by Canepa, Bach and Dmitrenko\(^{20c}\) have been used to study the oxidation of dimethyl sulfide by a tricyclic model C4a-flavin hydroperoxide (R = H, R' = CH\(_2\)CH\(_2\)OH). The C-(4a)-flavin hydroperoxide (FlHO-OH \(14\)) contains the tricyclic isoalloxazine moiety, the C-4a-hydroperoxide functionality, and a hydroxyethyl group to model the effect of the 2'-OH group of the ribityl side chain of native FADHO-OH. The intrinsic gas-phase reactivity of this tricyclic hydroperoxyflavin is \(ca \ 10^9\) greater than of \(t\)-BuO–OH (Table 12). The \(S_N2\)-like attack of the nucleophile on the distal oxygen of the hydroperoxide and the relative reactivity of the peracid are in excellent agreement with the earlier experimental data of Bruice\(^{155}\). The oxidation of DMS by model 4a-FlHO-OH \(14\) had an activation barrier of only 11.4 kcal mol\(^{-1}\) (equation 14)\(^{20c}\).
It was shown that isolated N1- and N5-protonated cations of model 4α-FlHO-OH exhibit artificially low barriers as a consequence of their location in a high-energy region of the potential energy surface domain. In fact, charged structures, either cations or anions, will typically give an artificially low activation barrier.20c

A mechanistic study of the oxidation of a series of related heteroatoms containing nucleophiles by a model 4α-flavin hydroperoxide 14 has also been recently reported by Bach and Dmitrenko21 (Table 12). Using the paradigm model theoretical oxygen atom donor peroxyformic acid as a measure, the barriers for the epoxidation of ethylene, E-2-butene and DMS with bicyclic model 13 are an average of 9 kcal mol−1 greater than that for peroxyformic acid. Peroxyformic acid is also much more reactive toward DMS than methyl hydroperoxide (∆ΔE≠ = 23 kcal mol−1). It is also evident that DMS is a much better gas-phase nucleophile than ethylene, as evidenced by their difference in activation barriers (∆ΔE≠ = 11 kcal mol−1) for reaction with peroxyformic acid. While CH3O−OH and t-BuO−OH have comparable barriers for the oxidation of DMS (27.2 and 27.1 kcal mol−1), tricyclic model flavin FlHO-OH 14 exhibits a much lower activation barrier of only 14.3 kcal mol−1. Thus, one may consider this tricyclic model flavin hydroperoxide to be a ‘tertiary alkyl hydroperoxide’ with electronegative substituents that is a much better oxygen donor than t-BuO−OH. This increased reactivity is due at least in part to the pKa of the departing ‘alcohol’ due to the inductive stabilization of the alcololate leaving group by the electronegative elements surrounding C4. The experimentally estimated pKa of 4α-FlEtO-OH is 9.4, while the pKa of t-BuOH is approximately twice that. The role of Coulombic stabilization on the stability of the leaving group alcololate in the oxygen transfer step has been presented earlier by Bach and Su.17c

Bach and Dmitrenko21 have reported density functional calculations at the B3LYP/6-31+G(d,p) level that were used to study the mechanism of the oxidation of xenobiotics catalyzed by flavin-containing monoxygenases (FMOs).154 The xenobiotics were modeled by the oxidation of methyl-substituted N-, S-, P- and Se-containing nucleophiles. A mechanism for distinguishing oxygen atom versus hydroxyl transfer from RO−OH to (CH3)2N, (CH3)2S, (CH3)2P and (CH3)2Se was presented based upon the concept that the type or mechanism of oxidative process is related to the magnitude of the single imaginary frequency for the transition state for oxygen atom transfer (Table 12). Classical activation barriers for oxygen atom transfer from model triciclyc isaloxazine C-4a-hydroperoxide (FlHO-OH) to dimethyl sulfide, trimethylamine, trimethylphosphine and dimethyl selenide suggest that the reactivity of this biologically important oxidizing agent is intermediate between that of tert-butyl hydroperoxide and a peracid. The gas-phase reactivity of FlHO-OH 14 toward these four nucleophiles is estimated to be 107−1012 greater than that of t-BuO−OH but 102−106 less than that of peroxyformic
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TABLE 13. Reaction barriers (ΔE̸) and reaction energetics (ΔE_reac) calculated with respect to the isolated oxidizing agent, FlHO−OH 14, and substrate. Plain numbers correspond to B3LYP/6-31+G(d,p) calculations. Energy refinement at the B3LYP/6-31+G(3df,2p)//B3LYP/6-31+G(d,p) level of theory is given in bold.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>ΔE̸ (kcal mol⁻¹)</th>
<th>ΔE_reac (kcal mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH₃)₃N</td>
<td>12.3, 13.5</td>
<td>−5.3</td>
</tr>
<tr>
<td>(CH₃)₃P</td>
<td>5.0, 5.0</td>
<td>−90.7</td>
</tr>
<tr>
<td>(CH₃)₂S</td>
<td>12.7, 11.8</td>
<td>−43.7</td>
</tr>
<tr>
<td>(CH₃)₂Se</td>
<td>−3.2</td>
<td>−38.2</td>
</tr>
</tbody>
</table>

The oxidation of a heteroatom bearing a lone pair of electrons (e.g., amine, sulfide or phosphine) with increased nucleophilicity of the heteroatom typically results in an early TS, especially with phosphines. Since the N−O bond in an N-oxide is particularly weak, this can sometimes be an endothermic reaction, in contrast to the highly exothermic oxidation of a phosphine with its associated very strong P−O bond (Table 13).

The subject of the relative nucleophilicity and the role of solvent polarity in the hydroperoxide oxidation of heteroatoms has been a subject of controversy for a number of years. The predilection to assign phosphorus a much greater nucleophilic capacity than nitrogen or sulfur is based upon nucleophilic constants that were determined in methanol solvent. Second-row elements have always been considered to be more nucleophilic than those of the first row. Indeed, trimethylphosphine is far more reactive than Me₃N toward both t-BuO−OH (ΔΔE̸ = 15.0 kcal mol⁻¹) and C₄a-hydroperoxyflavin 14 (ΔΔE̸ = 7.9 kcal mol⁻¹). The oxygen atom transfer step for this highly exothermic reaction (−90.7 kcal mol⁻¹) comes much earlier along the reaction coordinate (Figure 36) with an O−P distance in the TS of 2.29 Å, a fairly short O−O distance (1.70 Å) and a correspondingly very low activation energy (ΔE̸ = 5.0 kcal mol⁻¹). In contrast, the overall reaction energy for the oxidation of Me₃N with tricyclic hydroperoxide is only −5.3 kcal mol⁻¹ and this later TS is reflected in a higher energy of activation (ΔE̸ = 13.5 kcal mol⁻¹). The relative reactivity of the N and P nucleophiles toward tricyclic FlHO−OH stands in marked contrast to the relative reactivities of these two nucleophiles toward the more reactive oxygen atom donor peroxyformic acid. The rate ratios for oxidation with tricyclic FlHO−OH 14 relative to t-BuO−OH for N, S, Se and P nucleophiles can be estimated from the calculated activation barriers to be 2 × 10¹², 4 × 10¹¹, 2 × 10¹¹ and 1⁷.

In an earlier report Bach and coworkers suggested that Me₃N and Me₃P had nearly the same gas-phase barriers with peroxyformic acid (ΔΔE̸ = 0.5 kcal mol⁻¹, MP4//MP2/6-31G*) and that their relative reactivity in protic solvent is better attributed to a much greater ground-state solvation of the more basic tertiary amine than the polarizability of the phosphorus. In a more recent study, a 3.3 kcal mol⁻¹ barrier difference was observed with HCO₃H in favor of the P nucleophile at B3LYP/6-31+G(d,p) (3.0 versus −0.3 kcal mol⁻¹, Table 12). Thus, the less reactive t-BuO−OH is a more discriminating oxidant with a later TS and the difference in barrier heights for N versus P oxidation widens. These data also point out that rate differences should be compared for a common set of nucleophiles and that when you use oxidants of different reactivity you should...
anticipate different rate ratios. The differences in activation barriers for N versus P as well as S versus Se oxidation decrease markedly as the oxygen donor propensity of the oxidizing agent increases (t-BuO−OH < flavinhydroperoxide < peracid).

As demonstrated above on relatively simple nucleophiles, native FADHO−OH\textsuperscript{151}, as modeled in this work by tricyclic FlHO−OH 14, is intermediate in reactivity between a peracid and RO−OH. Despite this it is still, surprisingly, capable of enzymatically oxidizing the aromatic ring in p-hydroxybenzoic acid (p-OHB). The two primary active site residues involved in the hydroxylation step in PHBH have been assigned to Tyr-201 and Arg-214. It is generally assumed that oxidation of the aromatic ring in p-OHB produces the hydroxylated cyclohexadienone tautomeric intermediate shown in Scheme 10. A recent model study by Bach and Dmitrenko\textsuperscript{156} on the enzymatic oxidation of p-hydroxybenzoic acid (PHBH) included two of the primary residues present at the active site at a level of theory where the reaction energy differences were reasonably accurate. This study provided a mechanistic rationale for the oxidation of this aromatic ring and also addresses the related question whether the H-bonding interactions of ionized p-OHB with Tyr-201 actually increase the rate of hydroxylation.

There have been relatively few theoretical studies aimed at the mechanism of PHBH processes. Vervoort and coworkers\textsuperscript{157} have suggested on the basis of AM1 calculations that a correlation exists between ln $k_{cat}$ for the conversion of a series of 4-hydroxylated substrates and the energy of their highest occupied molecular orbital (HOMO).

Peräkylä and Pakkanen\textsuperscript{158} studied the proton-transfer step in the ortho-hydroxylation of p-OHB. On the basis of HF/3-21G calculations, they arrived at the conclusion that the

FIGURE 36. Transition structure for the oxidation of (CH\textsubscript{3})\textsubscript{3}P with tricyclic FlHO−OH 14 optimized at the B3LYP/6-31+G(d,p) level of theory. Imaginary frequencies are at the B3LYP/6-31G(d) level
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SCHEME 10
intermediate in the hydroxylation step is the radical OH adduct of \( p \)-hydroxybenzoate. There have also been several attempts to define the hydroxylation step in PHBH using quantum mechanical/molecular mechanical (QM/MM) methods. Ridder and coworkers\(^{159} \) demonstrated a correlation of calculated activation energies with experimental rate constants for an enzyme-catalyzed aromatic hydroxylation. Billeter and coworkers\(^{160} \) studied the hydroxylation of \( p \)-hydroxybenzoate in its various anionic states and concluded that the dianion was the most probable form of \( p \)-OHB at the hydroxylation step. Both of these QM/MM studies used the closed-shell semiempirical AM1 method to study the hydroxylation step that involves \( O-O \) bond dissociation. As noted above, this level of theory is not capable of treating the \( O-O \) bond cleavage step in this enzymatic reaction\(^{21a} \). In this series of calculations, guanidine was included to model the role of Arg-214 and to maintain a net charge of ‘\(-1\)’ on the overall complex. Phenol was used to model Tyr-201, and it is H-bonded to \( p \)-OHB to examine its effect on the activation barrier for hydroxylation of \( p \)-OHB with FlHO–OH 14. One of the problems associated with this type of enzyme-modeling approach is that the model amino acid residues are not geometrically constrained by the interacting environment of the active site. A second difficulty is accurately measuring the influence of hydrogen bonding and Coulombic interactions in the ground state versus the transition state. Free energy relationships in a classical physical organic sense suggest that the mechanism of the hydroxylation step is best described as an electrophilic aromatic substitution\(^{161} \). On the basis of the spectra of substituted cyclohexadienones, Anderson and coworkers also suggest that a simple nucleophilic model may be correct\(^{162} \). Consistent with these fundamental concepts Bach and Dmitrenko\(^{156} \) suggested that electrophilic aromatic substitution proceeds by an \( S_N 2 \)-like attack of the aromatic sextet of \( p \)-OHB phenolate anion on the distal oxygen of FlHO–OH 14. The transition structure for oxygen atom transfer was fully optimized [B3LYP/6-31+G(d,p)] and had a classical activation barrier of 24.9 kcal mol\(^{-1} \) when measured from prereaction complex R-A (Figure 37). The \( O-O \) distance in TS-B was 1.84 Å and the distance to nucleophilic carbon of \( p \)-OHB, ortho to the phenolate oxygen, was 2.08 Å (Figure 37).

From these data the following conclusions were drawn:

(a) The B3LYP data suggest that C-(4a)-flavinhydroperoxide (FlHO–OH 14) is quite puckered with a N4-C4a-C10a-N10 dihedral angle of 41.8\(^{\circ} \). The ultimate alcohol product of the oxygen transfer reaction (FIHOH) and its precursor alcoholate leaving group (FlHO\(^{-} \)) are also both seriously puckered, and the latter has a strong H-bond between the 2′-OH group and N1 (1.89 Å).

(b) Prereaction complex R-a (Figure 37) has an overall stabilization energy of 53.4 kcal mol\(^{-1} \) relative to isolated reactants. The activation barrier for oxidation of R-A (TS-b) is 24.9 kcal mol\(^{-1} \). The single imaginary frequency of 401.5i cm\(^{-1} \) is consistent with oxygen atom transfer early on the reaction coordinate to a relatively stable alcoholate leaving group (FlO\(^{-} \)). The magnitude of the barrier for anionic TS-b suggests that the role of the Tyr-201 is to orient the \( p \)-OHB substrate and to properly align it for the oxygen-transfer step. Although the negatively charged phenolate oxygen does activate the C-3 carbon of \( p \)-OHB phenolate anion toward oxidation relative to ortho oxidation of the carboxylate anion, it appears that H-bonding the Tyr-201 residue to this phenolic oxygen stabilizes both the GS and the TS and therefore plays only a minor role, if any, in lowering the activation barrier.

**VIII. MISCELLANEOUS OXYGEN TRANSFER REACTIONS**

Since this is not an exhaustive search of the literature for all theoretical contributions from the past twenty years, we have elected to include selected interesting articles pertaining to unique calculations on the peroxo bond.
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Prereaction ground-state complex for 4α-flavinhydroperoxide with p-hydroxybenzoate complexed to guanidine (ARG214) and phenol (TYR201) optimized at B3LYP/6-31+G(d,p).

\[ \Delta E = 24.9 \text{ kcal mol}^{-1} \] (B3LYP/6-31+G(d,p))

Although hydrogen peroxide and alkyl hydroperoxides in general are not sufficiently reactive to epoxidize alkenes, there are some exceptions. Experimental observations show that direct olefin epoxidation by H₂O₂, which is extremely sluggish otherwise, occurs in fluorinated alcohol (R_fOH) solutions under mild conditions requiring no additional
catalysts. Theoretical calculations\textsuperscript{163} of ethylene and propylene epoxidation by H\textsubscript{2}O\textsubscript{2} in the gas phase and in the presence of methanol and of two fluorinated alcohols, presented in this paper, show that the fluoro alcohol itself acts as a catalyst for the reaction by providing a template that stabilizes specifically the transition state (TS) of the reaction. Thus, much like an enzyme, the fluoro alcohol provides a complementary charge template that leads to the reduction of the barrier by 5–8 kcal mol\textsuperscript{−1}. Additionally, the fluoro alcohol template keeps the departing OH and hydroxalkenyl moieties in close proximity and, by polarizing them, facilitates the hydrogen migration from the latter to form water and the epoxide product. The reduced activation energy and structural confinement of the TS over the fluoro alcohol template render the epoxidation reaction observable under mild synthetic conditions\textsuperscript{163}.

Examination of the hydroperoxy radical and its closed-shell ‘analogues’ including the analysis of the potential energy surfaces of the protonated forms of the HOO, HOF and the HO−OH was also recently reported by Bil and Latajka\textsuperscript{164}. The geometrical parameters of the protonated forms of the analyzed molecules were optimized at the level of B3LYP, MP2, MP3, MP4SDQ, CISD, CCD and the QCISD methods using 6-311+G(2d,2p) basis set. The unimolecular chemistry of the system [HO−OH]\textsuperscript{H+} has also been investigated by Uggerud and coworkers\textsuperscript{165a} using \textit{ab initio} quantum-chemical methods. In analogy with the isoelectronic systems [H\textsubscript{2}NNH\textsubscript{2}]\textsuperscript{H+} and [HONH\textsubscript{2}]\textsuperscript{H+}, the lowest-energy pathway for decomposition of protonated hydrogen peroxide is loss of an oxygen atom in its triplet electronic state, giving H\textsubscript{3}O\textsuperscript{+} as the ionic product. This process requires a crossover from the singlet to the triplet potential energy surface, and the minimum-energy crossing point was located. The proton affinity was also calculated and found to be in good accordance with experimental data. Uggerud and coworkers have also reported on the oxidative power of protonated hydrogen peroxide\textsuperscript{165b}. It was suggested that the oxidation of alkanes by protonated hydrogen peroxide does not occur by insertion of O into C−H, but by a multistep sequence in which a simple hydride transfer is the essential step. Earlier calculations by Bach and Su\textsuperscript{166} have provided a model for the approach of protonated hydrogen peroxide in the oxidation of saturated hydrocarbons.

\textit{Ab initio} molecular orbital theory at the correlated level of MP4SDTQ/6-31G**//MP2/6-31G** has been applied to investigate the reactions of NO\textsuperscript{+} and NOH\textsubscript{2}\textsuperscript{+} with methane. Reinvestmentigation of the theoretical reaction of CH\textsubscript{4} with NO\textsuperscript{+} by Olah and coworkers\textsuperscript{167} showed that the reaction path involves attack on carbon instead of C−H bond insertion. In contrast to NO\textsuperscript{+}, with superelectrophilic NOH\textsubscript{2}\textsuperscript{+} methane preferentially reacts via proton transfer to give CH\textsubscript{5}\textsuperscript{+} or by hydride abstraction. The results of the reaction of methane with NO\textsuperscript{+} were compared with such strong electrophiles as D\textsuperscript{+}, CH\textsubscript{3}\textsuperscript{+}, C\textsubscript{2}H\textsubscript{5}\textsuperscript{+}, OH\textsuperscript{+} and F\textsuperscript{+}, and the consequences on the reaction mechanism were discussed. The studies reaffirm the general pattern of electrophilic substitution of methane with strong electrophiles to proceed via five-coordinate carbocations involving 3c-2e C−H bond insertion.

Panin and Tulub\textsuperscript{168} have reported RHF(UHF)CMP2 and CASSCF calculations of potential energy surfaces’ sections of neutral particles and their corresponding protonated cations X−OH\textsuperscript{+} (X = C,N,O). It was shown that all cations should be relatively stable both with respect to X−O bond breaking and intramolecular rearrangements. Reactions of electron capture by these cations were also studied, providing evidence that under electric discharge in an atmosphere saturated with water vapor both neutral and charged molecules may serve as building units for more complicated systems.

\textbf{IX. ACKNOWLEDGMENTS}

The author is indebted to the efforts of his very talented senior associate, Dr. Olga Dmitrenko, for her assistance in the preparation of this review. He is especially thankful
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for her many intellectual contributions over the last six years to the papers of his cited in this summary of theoretical contributions to the chemistry of peroxides. The association with his former colleague, Professor Berny Schlegel, at Wayne State University in Detroit, is largely responsible for the transformation of this once hard-core experimentalist into the realm of theoretical chemistry. The author is also appreciative of the many collaborative efforts with his experimental colleagues during these many years. The financial support from the National Science Foundation and the National Computational Science Alliance under CHE990021N and use of the NCSA SGI Origin2000 and University of Kentucky HP Superdome have made it possible for the author to continue doing research since his retirement in 1996.

X. REFERENCES AND NOTES


21. (a) For a critique of problems related to the use of HF theory for the peroxy bond see Reference 21b.


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50. Recent experimental (a) and theoretical (b) studies involving sterically encumbered alkenes also suggest that the spiro TS is favored over a planar one:
1. General and theoretical aspects of the peroxide group

115. For summaries and incisive reviews, see: (a) B. Plesničar, in *The Chemistry of Peroxides* (Ed. S. Patai), Wiley, Chichester, 1983, p. 521.
   (b) The Frontiers in Chemistry lectures at Wayne State University, Detroit, were published as a series of lectures in the Record of Chemical Progress up until 1971 when this journal was discontinued.
123. The peroxyformic acid-ethylene TS calculated at the MP2 level and reported in Reference 17b (prior to the availability of MP2 frequencies in 1991) was constrained to be symmetrical with identical C−O bonds. This structure, however, was a first-order saddle point with an HF/6-31G* frequency calculation pointing to the dangers of using frequency calculations at a level lower than the geometry optimization.
1. General and theoretical aspects of the peroxide group


(c) D. M. Ziegler, *Drug Metab. Rev.*, 34, 503 (2002).


