The design of organic catalysis for epoxidation by hydrogen peroxide

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Abstract The potential of various organic species to catalyze epoxidation of ethene by hydrogen peroxide is explored with B3LYP/6-31G* DFT calculations.

Keywords Catalysis · Epoxidation · Oxidation · Peroxides

Introduction

Hydrogen peroxide, 1, is a cheap and environmentally-friendly oxidant, since the only by-product is water, but it is not reactive enough for many applications. Catalysts to promote the epoxidation of alkenes, oxidation of sulfides, etc., by hydrogen peroxide are potentially of great value. While there are many examples of promotion of H₂O₂ reactions by transition metal ions, in this paper we discuss a different approach, based on the following simple idea. Water oxide [1], 2, is unknown, but would be expected to be an extremely powerful oxidant. Although water oxide is never likely to be involved as a reaction intermediate, a compound that could remove a proton from one oxygen of hydrogen peroxide as it attacked a substrate, while more or less simultaneously donating a proton to the other oxygen, thus creating a water molecule, could be a powerful catalyst for reactions of H₂O₂, as shown for a hypothetical RC(X)YH catalyst in 3 below.

Traditionally, alkene epoxidation has been carried out with peroxycarboxylic acids, although many other methods have been developed in recent years, especially for enantioselective epoxidation. Epoxidation with peroxycarboxylic acids is not very sensitive to solvent polarity and the accepted “butterfly” mechanism [2, 3] is concerted and involves a complex series of electron shifts [4, 5], as shown in 4 above. In this paper the process shown in 5 above for epoxidation of ethene is modeled, and the energetics are compared with those calculated for 4. The main objective is to define the best choice of proton transfer catalyst, but we also explore the potential for further hydrogen-bonding assistance, with a view to the eventual design of hosts that might catalyze hydrogen peroxide reactions with control of stereochemistry. Since the dielectric properties inside the host cannot be predicted, we have restricted our study to the gas phase, and have not attempted to model environmental effects.

Computational methods

All DFT calculations were performed with the Jaguar program package [6], using Becke’s three-parameter exchange functional [7] with the correlation functional of Lee, Yang and Parr (B3LYP) [8]. All species were characterized by full...
geometry optimization with the standard 6-31G* basis set, and minima and transition states were characterized by analytical frequency calculations. The single imaginary frequency of the transition states was animated in the Spartan '04 program [9], and it was confirmed that this vibration involved the stretching of the O–O bond with one oxygen moving more or less symmetrically towards the alkene-carbon atoms, and with one hydrogen moving towards the putative water molecule. IRC calculations were carried out in Spartan '04 for the reactions catalyzed by one and two formic acid molecules, and these confirmed that the transition states reported below do evolve to the starting complexes and epoxide products.

Protein Database (PDB) files for the species illustrated in the Figures are available as Electronic Supplementary Material.

Results and discussion

What form should the proton acceptor/proton donor catalyst take? Optimization of a complex of formic acid with hydrogen peroxide leads to the structure shown in Fig. 1a. The two hydrogen bonds are close to linear and of comparable length. Thus, the RC(X)YH species shown in 3 and 5 above appears to be a good starting point for catalysis design. Some alternative geometries for the catalyst are explored later.

Transition states have been located at the B3LYP/6-31G* level for the epoxidation of ethene by hydrogen peroxide catalyzed by various HC(X)YH species. Activation parameters calculated relative to ethene and an optimized complex of hydrogen peroxide with the catalyst are given in Table 1 and the transition state for the case of formic acid is shown in Fig. 1b. As can be seen, the latent epoxide ring is more or less perpendicular to the general plane containing the hydrogen peroxide and formic acid molecules; this type of transition-state geometry has been described as “spiro”, as opposed to “planar”. 

A priori, it is not obvious whether it is desirable to have a strongly basic X-group to promote deprotonation of the epoxidizing oxygen atom or to go for a strongly acidic Y–H group to protonate the developing hydroxide ion. However, it can be seen from Table 1 that more acidic species are better catalysts, although methanesulfonic acid is not a significant improvement on trifluoroacetic acid. Proton donation to hydrogen peroxide is clearly more important than proton removal in the transition state. This is reasonable on the grounds that normal alkenes like ethene are attacked by electrophilic reagents. Full proton transfer would create H$_3$O$_2^+$ [10–12], a powerfully electrophilic species formed in solutions of hydrogen peroxide in very strong acids that is known to be an extremely powerful (but very indiscriminate) oxidant [10–14].

Further evidence supporting the importance of proton transfer to the non-epoxidizing oxygen atom may be gleaned from examination of the geometry of the transition states. Thus, in the transition state for epoxidation catalyzed by formic acid, the OH bond in formic acid has lengthened to 1.13 Å, compared with 1.00 Å in the initial complex, and the distance from this proton to the oxygen atom in H$_2$O$_2$ has shortened from 1.77 to 1.32 Å. Furthermore, animation of the single imaginary frequency shows that motion of this proton is strongly coupled to the O–O stretching process. On the other hand, proton loss from the epoxidizing oxygen

| Table 1 Activation parameters for epoxidation of ethene from B3LYP/6-31G* calculations |
|-----------------------------------------------|----------------|----------------|----------------|
| Peroxy acid or catalyst+H$_2$O$_2$ | $\Delta$H$^\ddagger$ (kJ mol$^{-1}$) | $\Delta$G$^\ddagger$ (kJ mol$^{-1}$) | PA of conjugate anion (kJ mol$^{-1}$) |
| CF$_3$CO$_2$H | 44.6 | 84.4 |
| HCO$_3$H | 59.4 | 101.8 |
| CF$_3$CO$_2$H+H$_2$O$_2$ | 60.7 | 109.5 | 1,481 |
| HCO$_2$H+H$_2$O$_2$ | 73.9 | 120.7 | 1,393 |
| HCONH$_2$+H$_2$O$_2$ | 103.3 | 151.9 |
| Formamidine+H$_2$O$_2$ | 109.9 | 157.6 |
| CH$_3$SO$_3$H+H$_2$O$_2$ | 56.9 | 111.8 |
| 7 $R^1$=H $R^2$=CN+H$_2$O$_2$ | 98.7 | 1,424 |
| 7 $R^1$=CN $R^2$=H+H$_2$O$_2$ | 83.8 | 1,343 |
| 8 $R^1$=H $R^2$=CN+H$_2$O$_2$ | 48.4 | 1,245 |
| 8 $R^1$=CN $R^2$=H+H$_2$O$_2$ | 83.3 | 1,472 |

Fig. 1  a Hydrogen peroxide complex with formic acid; b Transition state for epoxidation of ethene with H$_2$O$_2$ catalyzed by HCO$_2$H
atom of the hydrogen peroxide has hardly begun at the transition state, since the OH bond has only stretched by 0.02 Å, although the distance from the proton to the carbonyl group of formic acid has shortened from 1.81 to 1.63 Å.

In order to provide some calibration of the activation parameters in Table 1, the transition state for epoxidation of ethene by peroxyformic acid was optimized using Jaguar. The accepted \( \Delta H^\ddagger \) value was reproduced and \( \Delta G^\ddagger \) was found to be 101.8 kJ mol\(^{-1} \) (see Table 1). This transition state has been the focus of much work [16, 17], with lively debate concerning spiro vs planar transition state geometries. As a result of high level ab initio and CASSCF calculations [15], it now appears that the spiro geometry is preferred, and that the economical B3LYP DFT method is a useful and reasonably accurate method that can be applied to studies of larger systems. The corresponding epoxidation of ethene with peroxytrifluoroacetic acid (see Table 1) resulted in lowered activation parameters, in qualitative agreement with the known high reactivity of CF\(_3\)CO\(_2\)H.

Comparison of the activation parameters for the mechanism shown in 5 (Table 1) with those for epoxidation via 4 with the corresponding peroxyacids, shows that the catalyzed process to be poorer by about 15 kJ mol\(^{-1} \) in \( \Delta H^\ddagger \). The catalyzed process 5 with carboxylic acids as catalysts is clearly a reasonable possibility, worthy of further optimization. When carboxylic acids are mixed with hydrogen peroxide, an equilibrium is set up involving formation of the peroxycarboxylic acid. Equilibration is quite slow, however, taking about 1 h at ambient temperature when 30% H\(_2\)O\(_2\) is added to a large excess of 88% HCO\(_2\)H [18, 19]. Since this reaction almost certainly involves nucleophilic attack at the carbonyl group of the carboxylic acid, equilibration is much slower for acetic and other simple carboxylic acids [20], although it could be faster for strong acids like CF\(_3\)CO\(_2\)H. The slow rates for this equilibration rule out its incorporation into a viable catalytic cycle. Most discussions of the promotion of hydrogen peroxide reactions by acids concentrate on the formation of new peroxodic species [21], rather than the proton transfer process proposed here, although there have been several recent reports of electrophilic activation of hydrogen peroxide by perfluorinated alcohols [22–24] and phenol [25]. In the absence of strong acids, it is likely that this activation involves clusters of strongly hydrogen-bonded solvent molecules, as suggested by Berkessel for catalysis by HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) [24].

While the RC(X)YH species shown in 3 and 5 above appears to be a good starting point for catalysis design, it seemed desirable to see whether separating the proton-donating and proton-accepting groups by more (or fewer) atoms would offer any significant advantages. For a reliable comparison with carboxylic acids, the catalyst must be symmetrical with respect to the proton exchange. Thus, squaric acid derivatives, 6, are unsatisfactory, although they might be attractive in other respects. Derivatives of pyrazole 7 and of 2-hydroxycyclopentadienone 8 were selected for comparison with carboxylic acids. Tropolone 9 is of course much more stable and readily available than 9 but it forms a

![Fig. 2](image-url)

**Table 2** Epoxidation of ethene by H\(_2\)O\(_2\) catalyzed by two acids; see Fig. 2 for the definition of primary and secondary

| Primary acid | Secondary acid | \( \Delta H^\ddagger \) (kJ mol\(^{-1} \)) | \( \Delta G^\ddagger \) (kJ mol\(^{-1} \)) |
|-------------|---------------|---------------------------------|---------------------------------|
| HCO\(_2\)H   | HCO\(_2\)H    | 67.67                           | 109.79                          |
| HCO\(_2\)H   | CF\(_3\)CO\(_2\)H | 56.96                           | 111.13                          |
| CF\(_3\)CO\(_2\)H | HCO\(_2\)H | 59.57                           | 113.41                          |
| CF\(_3\)CO\(_2\)H | CF\(_3\)CO\(_2\)H | 56.05                           | 101.79                          |
strong intramolecular H-bond, as do enolized β-diketones, and so these are unlikely to be good catalysts. In view of the clear importance of acidity for catalysis, we sought derivatives whose anions were of comparable proton affinity to formate and trifluoroacetate. The results are summarized in Table 1.

While 8, $R^1=H$, $R^2=CN$ yields the lowest value for $\Delta H^\ddagger$ so far, this is due to its extreme acidity, rather than any superiority derived from having two carbons separating the proton donating and proton accepting groups. This conclusion is backed up by examination of the transition state with 8, $R^1=H$, $R^2=CN$ as catalyst; the proton transfer from the catalyst is more or less complete, so this is almost a reaction of $\text{H}_2\text{O}_2$. Comparison based on relative PA-values shows that the carboxylic acids are somewhat superior to the 2-fluoroacetic acid, and so these are unlikely to be good catalysts. In view of the scope of reliable calculations and further exploration is underway. Clearly it would be desirable to design a host which was somewhat strained as the $\text{H}_2\text{O}_2$ complex, but where this strain would be relieved as the transition state was attained.

Conclusions and implications for host design

In the $\text{H}_2\text{O}_2$·2HCO$_2$H complex, the carbonyl carbons are separated by 6.30 Å, and the two H–C bonds subtend an angle of 160°. These parameters remain fairly constant as CF$_3$ groups are introduced. In the transition state for epoxidation of ethene in the presence of two formic acids, the separation of the carbonyl carbons is reduced to 5.97 Å, and two H–C bonds subtend a smaller angle of 115°. As CF$_3$ groups are introduced, this angle remains fairly constant, but the C…C distance decreases significantly, to 5.69 Å in the transition state involving two trifluoroacetic acids.

These geometrical parameters provide a useful guide to the design of potential hosts; the separation of around 6 Å requires quite a large host, but not so big as to be outside the scope of reliable calculations and further exploration is underway. Clearly it would be desirable to design a host which was somewhat strained as the $\text{H}_2\text{O}_2$ complex, but where this strain would be relieved as the transition state was attained.

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