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A Theoretical Study of the Uncatalyzed and BF_3-Assisted Baeyer−Villiger Reactions

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The mechanisms for the uncatalyzed and boron trifluoride (BF_3) assisted Baeyer−Villiger reactions between acetone and hydrogen peroxide have been investigated using high level ab initio [MP2 and CCSD(T)] and density functional theory (B3LYP) methods. Both steps in the uncatalyzed reaction are found to have very high transition state energies. It is clear that detectable amounts of the Crieege intermediate or the products cannot be formed without the aid of a catalyst. The main function of BF_3 in both the addition step and the rearrangement (migration) step is to facilitate proton transfer. In the addition step the complexation of hydrogen peroxide with BF_3 leads to an increased acidity of the attacking OH group, while in the rearrangement step BF_3 takes active part in the proton-transfer process. This latter step is found to be rate determining with an activation free energy of 17.7 kcal/mol in organic solution. The products of the reaction are BF_2OH, hydrogen fluoride, and methyl acetate. Thus, BF_3 is not directly regenerated from the reaction.

Introduction

Baeyer−Villiger oxidation, which involves the transformation of ketones to esters and lactones, is one of the more important reactions in synthetic organic chemistry. The reaction is readily conducted using peracids as the oxygen-donating reactant.[1,2] Especially peracids with electron-withdrawing groups, such as trifluoroperacetic acid, are powerful reagents for this reaction.[1−3] In contrast, the use of simple peroxides requires addition of strong catalysts, such as boron trifluoride (BF_3), to produce reasonable yields.[4] A number of enzymes have also been found to catalyze the Baeyer−Villiger reaction.[5,6] For example, monooxygenases and dioxygenases incorporate one and two oxygen atoms from molecular oxygen (O_2), respectively, into the substrate. Most of these enzymes are dependent on NADPH or other cofactors for the catalytic process. Recent studies have shown that some lipases can catalyze Baeyer−Villiger oxidation from hydrogen peroxide without the need of any explicit cofactors.[7,8] The mechanism for this process is not fully understood, and it has been argued that the enzymes only catalyze the formation of peracids and that the actual reaction takes place outside the enzyme.[8]

It is well established that the Baeyer−Villiger reaction proceeds via a tetrahedral intermediate, the so-called Criegee intermediate.[1,2] In the case of the reaction with peracids, the second step, the migration of the alkyl or aryl group, is generally considered to be rate-determining.[1,2] However, there are several examples in the literature of reactions where the first step, the addition, has been found to be rate-determining.[1,2] The migratory aptitude of various groups in unsymmetrical ketones has been shown decrease in the following order: *tert*-alkyl > cyclohexyl > *sec*-alkyl > benzyl > phenyl > *p*-alkyl > cyclopentyl > methyl.[1,2] In addition electron-donating susbtituents have been shown to facilitate the migration of the phenyl group.[1,2] Steric and electronic factors are both considered to be of importance for determining the migratory preferences.[1,9]

The mechanism for the Baeyer−Villiger reaction with peracids has been the focus of a number of theoretical studies, and the details of the reaction are now fairly well understood.[10−13] It has been shown that the carboxyl moiety of the peracid plays an active role in the proton transfer in the migration step.[11,12] A similar proton-transfer mechanism cannot be obtained with simple peroxides, and this may be one reason for the lower reactivities of the latter in Baeyer−Villiger oxidation.

In this work we have studied the Baeyer−Villiger reaction between acetone and hydrogen peroxide. Both the uncatalyzed reaction and the BF_3-assisted reaction have been analyzed. We believe that the very different reaction conditions in the BF_3-assisted reaction compared to the peracid reaction makes it very interesting for a theoretical study. The results may increase our general understanding of the Baeyer−Villiger reaction and help

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us understand the particular mechanisms that are present in enzymes.

To give a proper background to the theoretical work the experimental procedure for performing the BF_3-assisted reaction will be presented in some detail.[4] However, it should be pointed out that this presentation is just for background purposes, and anyone interested in performing the reaction should consult the original paper. In the first step of the procedure 90% hydrogen peroxide solution is mixed with boron trifluoride etherate ($BF_3 \cdot Et_2O$) in an approximately 1:2 ratio (0.21 mol and 0.4 mol). The mixture is allowed to age before the experiment is continued. This is presumably to allow the hydrogen peroxide molecules time to form complexes with BF_3. After the aging, the solution is added dropwise during 2 h to a mixture of the ketone (0.2 mol) and ether (20 mL). In the original work,[4] two different ketones were used, 2-octanone in the first experiment and thereafter 2-heptanone. The reaction is highly exothermic and requires cooling. In the original experiment, 95% of the peroxide was consumed within 1 h after the end of the addition. *n*-Hexyl acetate was formed in a yield of 60% percent from 2-octanone. The remaining 40% was in form of 2-octanone, 32%, and hexanol, 8%. The latter was presumably formed by hydrolysis of *n*-hexyl acetate. It should be noted that there was no trace of methyl heptanoate found.

A few comments should be made regarding the experimental conditions and their implications for the reaction mechanism. First of all, we note that the reaction is performed under relatively apolar conditions. This is especially true in the beginning of the reaction when the reaction solution is essentially a mixture of ketone and ether. As the reaction proceeds, the polarity of the solution increases somewhat due to the formation of ester and water, but it still remains relatively low. This low polarity of the solution suggests that a mechanism that involves formation of ionic intermediates should be highly unlikely. It should also be noted that formation of peracids is not expected to play any important role in the reaction. In the later parts of the reaction we can indeed expect some formation of peracids, due to reaction between carboxylic acids formed by ester hydrolysis and hydrogen peroxide. However, since regular peracids react very slowly with simple ketones of the type RCH_2COCH_2R', peracid formation cannot explain the high reaction rates obtained in this experiment.[4] Another interesting issue is the role of BF_3. The general hypothesis seems to be that the BF_3 is complex bound to the peroxyl oxygens during the catalytic process. As mentioned, the reason for aging the peroxide/boron trifluoride etherate solution is probably to ensure complexation between hydrogen peroxide and BF_3. Still it cannot be assumed that the standard Gibbs free energy for complexation between hydrogen peroxide and BF_3 is so much lower than between ether and BF_3 that all peroxide molecules are complex bound to BF_3. Indeed, it has been found that when using mixtures of $BF_3 \cdot Et_2O$ and 90% H_2O_2 for catalysis of benzylic hydroperoxide rearrangement the yield can be substantially improved by using a 6:1 mixture rather than the regular 2:1 mixture.[14] It should also be noted that BF_3 is likely to bind stronger to the carbonyl oxygen of the ketone than to H_2O_2. As we will discuss later, this may not only be problem in that the ketone "steals" BF_3 molecules from the peroxide but also in that the ketone−BF_3 complex has a higher activation energy for the addition step than free ketone. Thus, the relatively low yield of the BF_3-assisted Baeyer−Villiger reaction may be a result of both the incomplete complexation between BF_3 and H_2O_2 and the formation of BF_3−ketone complexes.

Methods and Procedure

Geometries of the stationary points (minima and transition states) involved in the reactions have been optimized at the B3LYP/6-31+G* level. The stationary points have been further characterized by vibrational frequency analysis at the same level of theory. In some cases we also found it necessary to confirm that a transition state connected the correct minima by performing intrinsic reaction coordinate (IRC) calculations.

The combination of Becke's[15] three parameters mixing of exchange (B3) and the Lee−Yang−Parr[16] correlation (LYP) functional has been shown to provide accurate geometries and reaction energies.[17,18] The B3LYP functional has also been found to perform relatively well for prediction of activation energies.[19−21] However, there are indications that B3LYP consistently underestimates the barriers for certain types of reactions, such as open shell and proton-transfer reactions.[20−22] For comparison, we have therefore also computed MP2/6-31+G** energies at the B3LYP/6-31+G* optimized geometries. It is generally considered that MP2 produce relative energies for closed shell systems of similar accuracy as B3LYP. To estimate the accuracy of B3LYP and MP2 approaches for the systems studied here, the energies of the stationary points in the uncatalyzed Baeyer−Villiger reaction have also been calculated using a G2[23] type of extrapolation scheme:

$$\Delta E = \Delta E[\mathrm{MP2/6\text{-}311{+}G(2df,2p)}] - \Delta E[\mathrm{MP2\ /6\text{-}31G^*}] + \Delta E[\mathrm{CCSD(T)\ /6\text{-}31G^*}] \quad (1)$$

The B3LYP/6-31+G* optimized geometries were used for the MP2 and CCSD(T) calculations. This scheme provides an effective approach for estimating relative CCSD(T)/6-311+G(2df,2p) energies. It should be noted that the empirical correction used in regular G2 theory is not needed here,[23] since we only work with closed shell species and since the total number of electrons is not changed during the reaction. Zero point, enthalpy, and free energy corrections are computed using the unscaled B3LYP/6-31+G* frequencies. On the basis of earlier studies using similar schemes, we expect that this procedure can produce relative energies, including activation energies, with an accuracy of 2−3 kcal/mol.[23−26] With the exception that we have used B3LYP/6-31+G* rather than B3LYP/6-31G* geometries, this procedure is essentially identical to the G2MS approach of Froese et al., and we will call the procedure G2MS from now on.[26]

Solvation energies have been calculated using the recent implementation of the polarizable continuum model (PCM)[27]

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Scheme 1

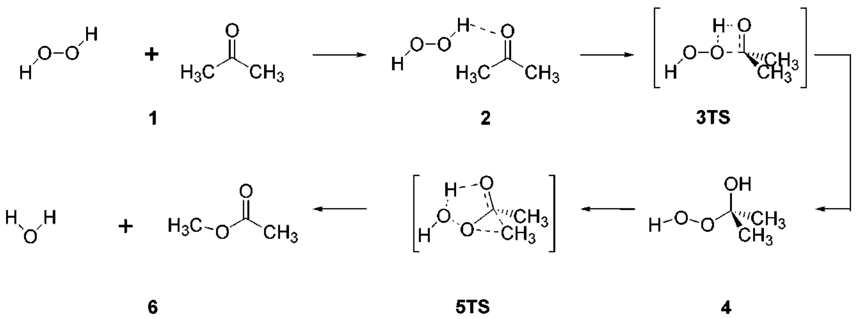

Table 1. Relative Energies (kcal/mol) of the Stationary Points in the Uncatalyzed Baeyer−Villiger Reaction[a]

	B3LYP/6-31+G*	MP2/6-31+G**	G2MS[b]	ΔZPE	$\Delta\Delta H_g$	$\Delta\Delta G_g$	$\Delta\Delta G_{PCM}$	ΔG°_g	ΔG°_{sol}
1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	−8.2	−9.0	−8.5	1.8	2.2	9.9	4.3	−1.4	1.0
3TS	32.2	32.8	32.7	−1.0	−1.5	9.6	5.2	42.3	45.6
4	−9.2	−15.5	−15.2	3.6	2.7	14.8	4.6	−0.4	2.3
5TS	38.0	42.1	38.0	−0.6	−1.6	10.9	4.3	48.9	51.3
6	−68.5	−73.8	−72.2	0.5	0.9	1.3	0.8	−70.9	−71.7

[a] The definitions for the energetics (with respect to the reactants **1**) are: ΔE: classical energy, ΔZPVE: zero-point vibrational energy, $\Delta\Delta H$: enthalpy correction, $\Delta\Delta G_g$: free energy correction, $\Delta\Delta G_{PCM}$: PCM solvation free energy correction, $\Delta G^\circ_g = \Delta E(\mathrm{G2MS}) + \Delta\Delta G_g$, $\Delta G^\circ_{sol} = \Delta G^\circ_g + \Delta\Delta G(1\mathrm{atm} \rightarrow 1\ \mathrm{M}) + \Delta\Delta G_{PCM}$. $\Delta\Delta H_g$ and $\Delta\Delta G_g$ are calculated at 298 K and 1atm, with the vibrational frequencies obtained at the B3LYP/6-31+G* level. $\Delta\Delta G(1\mathrm{atm} \rightarrow 1\ \mathrm{M})$ is the correction factor (1.89 kcal/mol per molecule) for changing the standard state from 1 atm (0.041 M) to 1 M. The ΔG°_{sol} values correspond to a standard state of 1 M solution in a solvent which has the same properties as pure acetone. [b] See the Methods and Procedure section for the definition of the G2MS energy.

in Gaussian 98.[28] The solute cavities in these calculations were made up of overlapping spheres centered at the atomic nuclei. The radii of these spheres were taken as the van der Waals radii of Bondi as implemented in Gaussian 98 and scaled by a constant of 1.0 for acidic hydrogens and 1.2 for all other atoms.[27] The solvent parameters, including the dielectric constant, were the same as those implemented for acetone in the program. The final free energies in solution were calculated by adding the solvation energies to the computed gas-phase free energies. Thus, using this approach, the loss in translational and rotational entropy upon forming a covalent bond will be the same in the gas phase and in solution. This is in agreement with the findings of Jencks.[29] He has argued that the loss in translational rotational entropy upon forming covalent bonds in solution is not that different from the gas phase. Others have calculated the entropy losses in aqueous solution upon forming molecular complexes and covalent bonds to be around 50−70% of those in the gas phase.[30−32] Since we are studying reactions between neutral molecules in organic solvents, it should be a relatively good approximation to estimate the entropy changes from their gas-phase counterparts. However, the calculated rotational and translational entropy effects should be considered as upper bounds to their true values.

The Gaussian 98 suite of programs were used for all quantum chemical calculations reported in this article.[28]

Results and Discussion

Uncatalyzed Reaction. The uncatalyzed reaction starts from the reactants acetone and hydrogen peroxide, and in the first step an initial complex (**2**) is formed (see Scheme 1). The reaction then proceeds via a four-membered transition state (**3TS**) to the Criegee intermediate (**4**). This step involves the simultaneous proton transfer from the peroxyl oxygen and nucleophilic attack of the peroxyl oxygen on the carbonyl carbon. The following step proceeds via a transition state (**5TS**) that features both a five-membered and a three-membered ring. During this step, one of the carbon−carbon bonds is broken, and the methyl group is transferred to form a carbon oxygen bond. Simultaneously, the oxygen−oxygen bond is broken and the proton is transferred over to the outer oxygen, which leads to the expulsion of water. It may seem surprising that this whole process proceeds in a concerted fashion without the formation of any intermediates. However, we have confirmed by IRC calculations that the process indeed is concerted. The products of the reaction are water and methyl acetate.

Regarding the energetics for the reaction, we will first consider the energies of the stationary points without any corrections for zero point or thermal effects. The G2MS energies, which are considered to be the most accurate of those presented in Table 1, show that there is high activation barrier of nearly 32 kcal/mol for the formation of the Criegee intermediate. The Crieege intermediate is stabilized relative to the reactants by more than 15 kcal/mol. It is also more stable than the initial complex by 6.5 kcal/mol. The relative energy of the second transition state is even higher than that of the first. This leads to an overall activation energy of 38 kcal/mol. The overall reaction energy is highly exothermic, −72.2 kcal/mol. Comparing the G2MS and B3LYP/6-31+G* relative energies, we note that the DFT approach is surprisingly accurate for predicting the transition state energies. The differences between the methods are less than 0.5 kcal/

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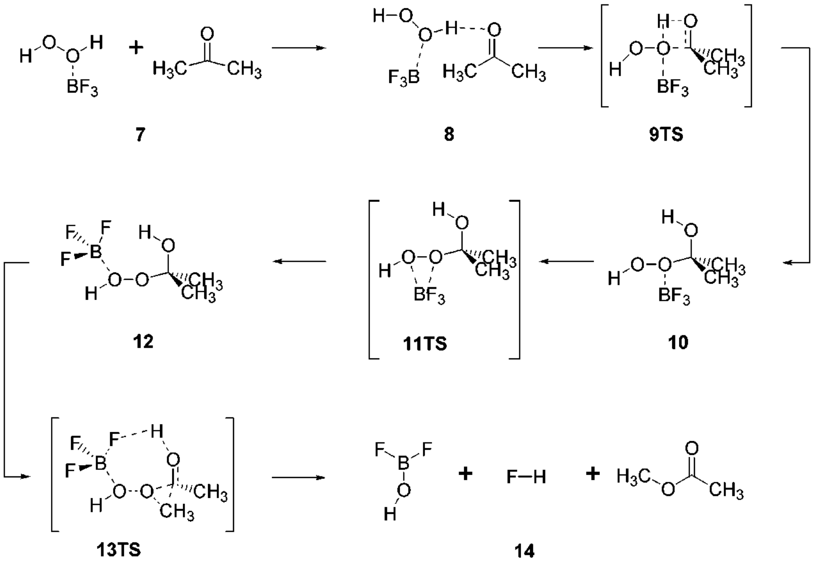
Scheme 2



mol. This is in contrast to other proton-transfer reactions where we and others have found this method to underestimate transition state barriers.[22,33] Instead here the major fault of the B3LYP/6-31+G* approach is that it underestimates the stability of the Criegee intermediate by 6 kcal/mol. In addition, the total reaction energy is underestimated by nearly 4 kcal/mol in comparison to the G2MS result. The MP2/6−31+G** level of theory is found to produce slightly better energetics than B3LYP/6-31+G*. For this method the major discrepancy when compared to G2MS is a 4.1 kcal/mol overestimation of the second transition state energy.

Zero point corrections have rather minor effects on the energetics for the reaction. The most prominent effect is a 3.6 kcal/mol destabilization of the Criegee intermediate. The $\Delta\Delta H_g$ correction essentially follows the zero point correction with only minor deviations. Considerably larger corrections are seen when the entropy effects are considered. In particular, the formation of the initial complex is accompanied by a considerable increase in the free energy correction due to loss of translational and rotational entropy. After application of the free energy corrections, we note that the energies of the two transition states are extremly high, 42.3 and 48.9 kcal mol for **3TS** and **5TS**, respectively. The Criegee intermediate is also destabilized, and the gas phase free energy is only 0.4 kcal/mol lower in energy than the reactants.

The major effect of the solvation correction is a stabilization of the reactants and products relative to the other stationary points on the potential energy surface. Some favorable solvation is lost upon the formation of the initial complex and this is not recovered until the dissociation of the products. We had expected some solvent stabilization of the first transition state, since the first reaction step involves proton transfer which is usually more favored in solution. To check that the unfavorable solvent effect upon the first transition state is not an artifact from the use of gas phase geometries, we reoptimized the transition state with the PCM method. However, this only led to a minor correction of the geometry and solvation energy. Thus our results indicate that solvent effects raise rather than lower the transition state energies. The calculated overall free energy of activation in solution is as high as 51.3 kcal/mol. In conclusion, it is clear that the uncatalyzed reaction both in the gas phase and in solution is so slow that essentially no observable product can be expected. Some experimental studies have indicated that the reaction of peroxides with ketones under certain conditions leads to the formation of tetrahedral compounds corresponding to the Criegee intermediate as products, but that the reaction cannot proceed further.[5] Our results clearly suggest that this scenario requires the presence of some kind of catalyst that can facilitate the formation of the Criegee intermediate.

BF_3-Assisted Reaction. Considering the experimental setup, it must be assumed that the initial step of the reaction is the interaction between acetone and the $BF_3\cdot H_2O_2$ complex. This will lead to the formation of an initial complex **8** as shown in Scheme 2. This complex is considerably stronger bound than the initial complex in uncatalyzed reaction, since the coordination with BF_3 increases the positive charge on the OH hydrogen due to the electron-withdrawing capacity of BF_3. Due to the same effect, the acidity of this group will also be increased, which results in a lower activation energy for the second step. Looking at the transition state of this step, we also note that at the transition state the proton has already been transferred over to the carbonyl oxygen (see Figure 2). This is in contrast to the transition state for the uncatalyzed reaction where the proton is only partly transferred (see Figure 1). The energy of proton transfer is clearly reduced since BF_3 accepts and stabilizes the negative charge on the peroxyl oxygen. This leads to a more polar transition state and a much lower transition state energy than in the uncatalyzed reaction (see Table 2). The Criegee intermediate (**10**) that is formed in this step has BF_3 bound to the inner oxygen, i.e., the oxygen bound to carbon. We also considered the case in which the other end of hydrogen peroxide attacks the ketone. This reaction would lead to a Criegee intermediate in which BF_3 is bound to the outer oxygen. However, our calculations show that the transition state energy for this reaction is much higher than with BF_3

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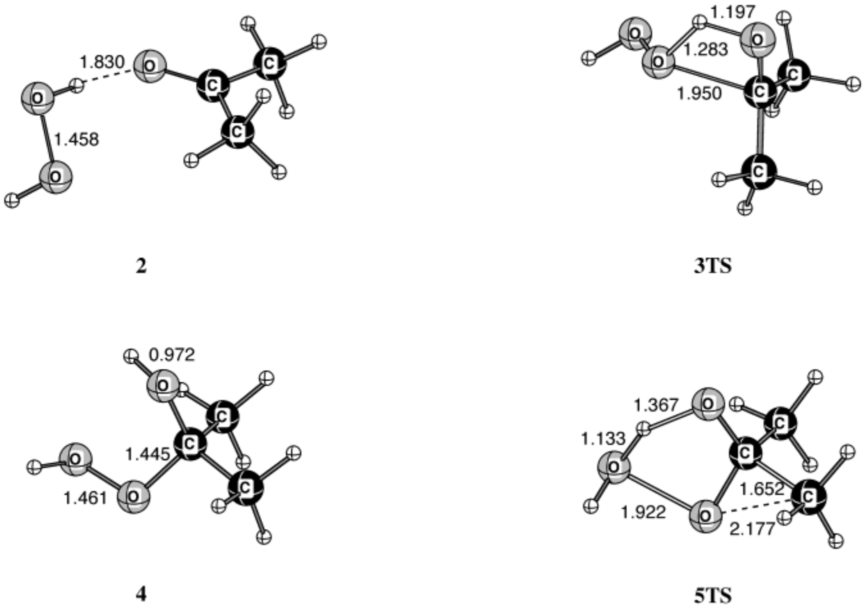
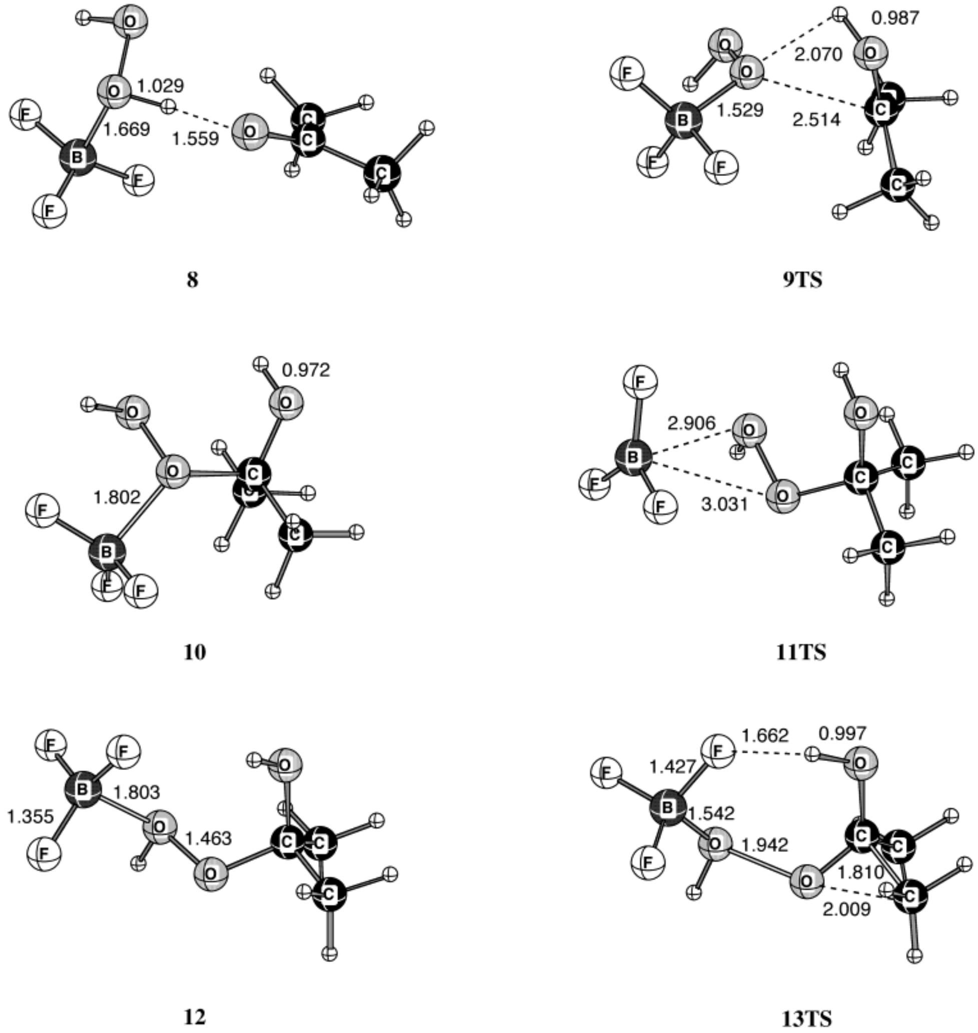


2 **3TS**

4 **5TS**

Figure 1. B3LYP/6-31+G* optimized structures of the stationary points involved in the uncatalyzed Baeyer−Villiger reaction. Selected bond lengths are given in angstroms.



8 **9TS**

10 **11TS**

12 **13TS**

Figure 2. B3LYP/6-31+G* optimized structures of the stationary points involved in the BF$_3$-assisted Baeyer−Villiger reaction. Selected bond lengths are given in angstroms.

bound to the inner oxygen. On the other hand we found that the rearrangement of Criegee intermediate to form an ester as product requires that BF$_3$ is bound to the outer oxygen. Thus, BF$_3$ needs to be transferred from the

Table 2. Relative Energies (kcal/mol) of the Stationary Points in the BF_3-Assisted Baeyer–Villiger Reaction[a]

	B3LYP/6-31+G*	MP2/6-31+G**	ΔZPE	$\Delta\Delta H_g$	$\Delta\Delta G_g$	$\Delta\Delta G_{PCM}$	$\Delta G^0{}_g$	$\Delta G^0{}_{sol}$
7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
8	−14.5	−17.6	1.1	1.6	11.2	5.7	−6.4	−2.6
9TS	10.8	9.8	1.2	0.8	13.4	−5.1	23.2	16.2
10	−7.0	−16.6	2.5	2.3	15.1	6.5	−1.5	3.1
11TS	−4.5	−11.4	1.8	1.8	12.2	7.8	0.8	6.7
12	−9.0	−16.3	2.8	2.4	15.4	3.5	−0.9	0.7
13TS	7.5	6.3	1.1	0.5	14.1	−0.8	20.4	17.7
14	−58.4	−63.7	−1.5	−0.8	−10.5	−1.5	−74.2	−70.8

[a] The definitions for the energetics (with respect to the reactants **1**) are: ΔE: classical energy, $\Delta ZPVE$: zero-point vibrational energy, $\Delta\Delta H$: enthalpy correction, $\Delta\Delta G_g$: free energy correction, $\Delta\Delta G_{PCM}$: PCM solvation free energy correction, $\Delta G^\circ{}_g = \Delta E(\mathrm{MP2}) + \Delta\Delta G_g$, $\Delta G^\circ{}_{sol} = \Delta G^\circ{}_g + \Delta\Delta G(1\ \mathrm{atm} \rightarrow 1\ \mathrm{M}) + \Delta\Delta G_{PCM}$. $\Delta\Delta H_g$ and $\Delta\Delta G_g$ are calculated at 298 K and 1atm, with the vibrational frequencies obtained at the B3LYP/6-31+G* level. $\Delta\Delta G(1\ \mathrm{atm} \rightarrow 1\ \mathrm{M})$ is the correction factor (1.89 kcal/mol per molecule) for changing the standard state from 1 atm (0.041 M) to 1 M. The $\Delta G^\circ{}_{sol}$ values correspond to a standard state of 1 M solution in a solvent which has the same properties as pure acetone.

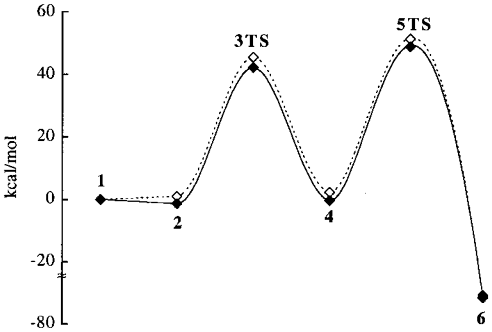


Figure 3. Computed free energy profiles for the uncatalyzed Baeyer–Villiger reaction. Filled diamonds refer to gas-phase free energies ($\Delta G^\circ{}_g$), and open diamonds refer to solution free energies ($\Delta G^\circ{}_{sol}$). See Table 1 for computational details.

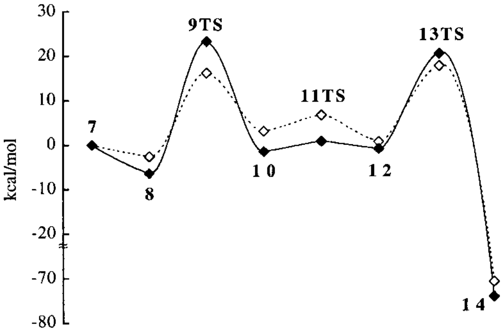


Figure 4. Computed free energy profiles for the BF_3-assisted Baeyer–Villiger reaction. Filled diamonds refer to gas-phase free energies ($\Delta G^\circ{}_g$), and open diamonds refer to solution free energies ($\Delta G^\circ{}_{sol}$). See Table 2 for computational details.

inner to the outer oxygen. This transfer proceeds via the transition state, **11TS** and results in the new Criegee intermediate (**12**). The transition state (**13TS**) for the rearrangement of **12** features both a three-membered and a seven-membered ring (see Figure 2). The three-membered ring concerns the migration of the methyl group to form a carbon–oxygen bond. The seven–membered ring facilitates the proton transfer to form the C–O double bond and the expulsion of OH^-. In contrast to the uncatalyzed reaction water is not directly formed as a product. Instead we find that the dissociation of **13TS** leads to the formation of BF_2OH and hydrogen fluoride in addition to the methyl acetate. In the original experimental article by McLure and Williams, it was suggested that HBF_3OH is formed as product.[4] However, this seems to be pure speculation and to our knowledge HBF_3OH has not been detected as a product or intermediate of the reaction. Rather, the fact that 8% of the ketone was transformed into the corresponding alcohol can be taken as support for the formation of hydrogen fluoride, since hydrolysis of esters is catalyzed by acids.

Looking at the relative energies without corrections for zero point or thermal effects, we first note that the transition state energies are considerably lower than for the uncatalyzed reaction. The energies of **9TS** are 10.8 and 9.8 kcal/mol at the B3LYP/6-31+G* and MP2/6-31+G** levels, respectively. The energies of **13TS** are even lower, 7.5 and 6.3 kcal/mol at the same levels of theory. Considering the good agreement between the two levels, and the good agreement between the B3LYP/6-31+G* and G2MS transition state energies for the uncatalyzed reaction, we believe the results to be highly reliable. There is a bigger disagrement in the energies of the Criegee intermediates. The MP2/6-31+G** energies shows the Criegee intermediates to be considerably more stable than the same energies obtained at the B3LYP/6-31+G* level. However, the trend is the same as for the uncatalyzed reaction, and since the MP2/6-31+G** results was shown to agree well with G2MS there, we beleive the MP2/6-31+G** energies to be more reliable also for the BF_3-assisted reaction.

The effects of introducing zero point and thermal effects are similar to those for the uncatalyzed reaction. Thus, the main effect comes from the loss of translational and rotational entropy when the reactants are brought together. Most of this entropy is lost already in the initial complex. However, despite this effect the gas-phase free energy for the intial complex is 6.4 kcal/mol lower than the free energy for the separated reactants. The relative energy of **9TS** is raised to 23.2 kcal/mol after the gas phase free energy correction. Thus, the activation free energy going from the initial complex to the first Criegee intermediate is as high as 29.6 kcal/mol, and as a consequence most molecules are likely to trapped in the intial complex. The energy of **13TS** is raised by a similar amount as **9TS**. The energies of Criegee intermediates are raised even more after the free energy correction, and they are only sightly lower than the corresponding energy for the separated reactants. In contrast, the relative energies of the products are lowered since the formation of three product molecules from two reactants leads to an increase in translational and rotational entropy.

The solvation correction shows a more irregular behavior for the BF_3-assisted reaction than for the uncatalyzed reaction (see Figures 3 and 4). In particular, we notice a considerable solvent-induced stabilization of **9TS**. However, considering that the transition structure has a zwitterionic character due to that the proton has already been transferred over to the carbonyl oxygen, this is not so surprising. Also **13TS** is stabilized due to solvent effects, but to a lesser degree than **9TS**. The remaining intermediate stationary points on the potential energy surface are destabilized relative to the product. For example, we note that most of the driving force for forming the initial complex has been lost, and also that the Criegee intermediates are higher in free energy than the reactants after the solvation correction. According to our calculations, the rearrangement step is rate determining in solution, and the activation energy is 17.7 kcal/mol. However, **9TS** is only 1.5 kcal/mol lower in the solution free energy than **13TS**. We have not found any experimental observation of the rate-determing step for this particular variant of the Baeyer−Villiger reaction. However, in general it is most common that the rearrangement is the rate-determining step.[1,2]

It should be noted that we have included the translational and rotational entropy effects on the solution reaction by their gas phase expressions. As we have discussed in the Methods and Procedure section, this may lead to some overestimation of these effects. Thus, the relative free energies in solution for the transition states and the intermediates are expected to be slightly overestimated. However, even if the entropy effects are overestimated by as much as 5 kcal/mol, which must be considered as an upper bound, this will not alter any of the main conclusions of this study. It may also be argued that we overestimate the solvent effects on the reaction since we have calculated the solvent effects for acetone while the reaction is performed in a less polar mixture of acetone and ether. However, this is not likely to have any major effect on the overall energetics for the reaction.

BF_3 plays a key role in the reaction mechanism; throughout the reaction it is bound to at least one of the peroxyl oxygens. Due to the way the experiment is conducted it can be assumed that at least initially a substantial amount of $BF_3 \cdot H_2O_2$ complexes are present. However, these complexes can dissociate and BF_3 can form complexes with other species. To estimate the importance of these we decided to calculate the free energies of complexation for the possible BF_3 complexes. At the B3LYP/6-31+G** level, the complex between BF_3 and acetone is more tightly bound than the $BF_3 \cdot H_2O_2$ complex by more than 3 kcal/mol. Thus, there is a considerable thermodynamic driving force for forming the BF_3·acetone complex. Our studies indicate that this complex is considerably deactivated for the Baeyer−Villiger reaction with $BF_3 \cdot H_2O_2$. Compared to the regular reaction between acetone and $BF_3 \cdot H_2O_2$, the relative energy of both the first and the last transition state is increased by more than 10 kcal/mol. This shows that in order to achieve a high reaction rate it is necessary to minimize the amount of BF_3·acetone complexes. Interestingly, our finding that the reaction results in the formation of BF_2OH and hydrogen fluoride (HF) rather than BF_3 and H_2O is actually an advantage. An accumulation of BF_3 would lead to the formation of BF_3·acetone complexes, which effectively would shut down the reaction. There is a thermodynamic driving force for forming BF_3 and H_2O from BF_2OH and HF. However, our studies show that this reaction has a relatively large free energy of activation in solution, 26 kcal/mol at the B3LYP/6-31+G** level.

Summary and Conclusions

The calculated gas phase free energies indicate that the Criegee intermediate in the uncatalyzed reaction is slightly stabilized relative to the reactants. However, after considering solvent effects we find that the Crieege intermediate has a slightly higher free energy than the reactants. In either case the activation free energy for forming the Crieege intermediate is more than 40 kcal/mol, which means that any detectable amount of the intermediate will not be formed without the presence of a catalyst. The activation energy for the rearrangement step of the reaction is even higher. This reaction clearly requires catalysis of both steps.

The first step of the BF_3-assisted reaction involves a nuchleophilic attack of the peroxyl oxygen that is attached to the BF_3. The electron-withdrawing ability of BF_3 facilitates the proton transfer from the peroxide to the ketone. The early proton-transfer activates the ketone for the nuchleophilic attack, and the activation energy is thereby lowered. After the formation of the first Criegee intermediate, BF_3 is transferred to the outer peroxyl oxygen to form the second Criegee intermediate. This intermediate is activated for the final rearrangement step. The transition state of this step features both a three-membered and a seven-membered ring. The seven-membered ring involves the proton transfer where BF_3 plays an integral part, while the three-membered ring concerns the CH_3 migration. Due to the special role of BF_3 in the proton-transfer process, BF_2OH and HF are the products of the reaction together with the ester. The relative energies of the Criegee intermediates are not considerably altered compared to the uncatalyzed reaction. However, the transition state energies of the first and final steps are substantially lowered. The rearrangement step is found to be rate determining with a activation free energy in solution of 17.7 kcal/mol. Complexation between acetone and BF_3 leads to a large reduction in the reaction rate.

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