

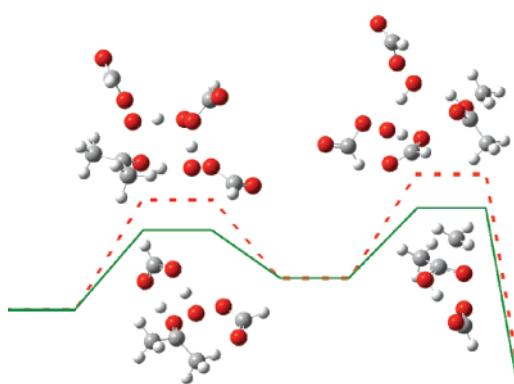
Reinvestigating the Role of Multiple Hydrogen Transfers in Baeyer–Villiger Reactions

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A comparison between a tetramolecular mechanism (*J. Org. Chem.* **2007**, *72*, 3031) and our previously proposed mechanism has been performed. The results show that the tetramolecular mechanism is less favored in terms of Gibbs free energy, and therefore, the reaction in acidic media is acid catalyzed. The role of the catalyst in the migration step has been corrected and discussed. A new transition state is proposed for this step. The change in the rate-determining step for the cyclohexanone + performic acid reaction supports our results.

There is general agreement that the Baeyer–Villiger¹ reaction occurs by a two-step mechanism in which the carbonyl addition of a peracid to ketones, or aldehydes, is followed by a migration within the tetrahedral adduct, known as the Criegee intermediate.² Although the latter is accepted to be the rate-determining step (RDS), some kinetic data for the reaction indicate that the RDS could depend on the reaction system.^{3–8} A recent study⁹ has shown that in the reaction of cyclohexanone with *m*-chloroperbenzoic acid (MCPBA) the first addition step is the RDS; a proper mechanism should therefore agree with that

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experimental fact. In this work, we will show that the mechanism we propose properly describes the change in RDS. Several theoretical studies have already been performed to explain this mechanism in more detail.^{10–17}

A new mechanism for the Baeyer–Villiger rearrangement of ketones by performic acid (PFA) has recently been proposed.¹⁸ This mechanism challenges experimental evidence since the acid or basic catalyst is missing in both reaction steps. Instead of acid, two additional molecules of PFA play the role of catalyst. This idea contradicts the kinetic data of this reaction which show that it is first order with respect to peracid concentration.^{4,19} Although in ref 18 it was accepted that the first step of the mechanism previously proposed by us¹⁷ has a lower Gibbs reaction barrier, it was concluded that “the uncatalyzed B–V reactions occur readily in the combination of a ketone and a trimer of peracids”. If we take into account that under normal experimental conditions a partner acid always accompanies the peracid,^{4,19} the previous conclusion contradicts the fundamentals of transition state theory. According to this theory, a chemical system moves from one state of equilibrium to another by all possible intermediate paths, but the most economical energy path will be that which is most often traveled. Obviously, the way the system discriminates between two paths exponentially depends on their difference in energy. Utilizing the difference in activation free energies between our mechanism and that proposed in ref 18 (16.67 vs 20.36 kcal/mol), which seems not to be the case as will be shown later, our path for the first step will be 94 times faster than the new one at room temperature, that is, almost 2 orders of magnitude.

Even though quantum chemical calculations are a powerful tool in the study of chemical reaction mechanisms, sometimes they lead to inaccurate results because the chosen model for the reaction is not appropriate for describing the real system. In this work, it will be shown that the discrepancy between the theoretical results and experimental evidence in ref 18 is because the chosen model does not properly describe the real system, and that the previously proposed mechanism is the most appropriate so far.

In ref 18, a complex between three performic molecules and ketone has been chosen as reactant. In thermochemistry and thermochemical kinetics, the reactants are, by default, the isolated reactants and not a complex between some of them. These complexes could be introduced in the reaction profile as intermediates, not as the starting point of the reaction. For a simplification of the kinetic mechanism, it is possible to change the reference starting point from isolated reactants to some reactant complex, but to do so, it is necessary to show that the

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complex is more stable than the isolated reactants in terms of Gibbs free energy. However, in ref 18, the complex is significantly less stable than the isolated reactants. The total ΔG involved in the process of trimer formation is 7.36 kcal/mol.¹⁸ This intermediate was taken as the zero energy. Therefore, all subsequent points along the reaction path are underestimated by 7.36 kcal/mol. This intermediate, as well as the tetramolecular complex in ref 18, appears to be unimportant in the calculation of the ΔG^\ddagger , as it will be shown later.

In ref 18, it was concluded that “reaction readily occurs” with a ΔG^\ddagger of 24.75 kcal/mol which seems to be incorrect. A barrier of such magnitude corresponds to a rate constant of 5.8×10^{-6} L³ mol⁻³ s⁻¹, that is, a very slow reaction. Moreover, using the proper zero energy, the calculated barrier rises to 32.35 kcal/mol and the corresponding rate constant decreases to 1.93×10^{-11} L³ mol⁻³ s⁻¹, that is, the reaction will not occur in a significant extension under normal conditions. It should be noted that the units correspond to a fourth-order reaction, usually only found in enzymatic reactions. In practice, all of the previously reported rate constants are second order (and first order with respect to peracid concentration), assuming bimolecular mechanisms. There is no kinetic evidence that the reaction is second order with respect to the peracid concentration, whereas the proposed mechanism¹⁸ implies third order.

In published work,¹⁸ the obtained data for the reaction of propanone (Prop) with performic acid were compared with our previous results.¹⁷ The transition state we proposed for the addition step was modeled, and it was concluded that it is lower in energy than the newly modeled one. However, the zero energy was chosen again as the complex between performic acid, formic acid (FA), and ketone. Therefore, the results comparison is not valid. Additionally, a second (migration) transition state was also modeled. However, it is not in line with those previously modeled by other authors^{16,22} or with that proposed for the first step.¹⁷ In the present work, we have calculated the transition state that actually corresponds to the mechanism in ref 17. The role of this transition state is discussed below.

In ref 18, the barrier for the first step, proposed by Grein et al.,¹⁶ was criticized. However, the results for the second step were not compared with those from this scientifically sound work. Such a comparison would show that the noncatalyzed transition state modeled by Grein et al., and previously proposed by Cardenas et al. in 1997,¹¹ is an appropriate transition state for the migration step as discussed below.

For the above-mentioned reasons, we decided to model the mechanism proposed in ref 18, as well as ours, only this time for both steps. In order to perform these calculations in a fast and qualitatively reliable way, which would allow comparisons with previous results, the B3LYP functional was chosen. Full geometry optimizations have been performed with the 6-311++G-(d,p) basis set using Onsager continuum model followed by frequency calculations at the same level of theory. Local minima and transition states were properly identified by the number of imaginary frequencies, 0 or 1, respectively. Intrinsic reaction coordinate calculations (IRC) were performed on both sides of the transition states to ensure that the reactants and products connect as expected. The energy results were improved by

TABLE 1. Enthalpies and Gibbs Free Energies (in kcal/mol) Relative to the Isolated Reactants for Both Mechanisms: Formic Acid Catalyzed and Catalyzed by Two Performic Acid Molecules (in parenthesis are the values corresponding to the uncatalyzed reaction for the second step)

	ΔH peracid catalyzed propanone	ΔG peracid catalyzed propanone	ΔG acid catalyzed propanone	ΔG acid catalyzed cyclohexanone
complex ^a	3.43	9.34	-0.59	-0.11
TS1	12.91	29.76 [34.29] ^b	20.34 [20.16] ^b	21.02
Criegee	0.68	8.13 [2.26] ^b	8.13 [2.26] ^b	12.4
TS2	20.09	36.15	26.06 (26.04)	21.35 (20.32)
ester	-66.56	-73.31	-73.31	-69.93

^a Refers to complex between ketone and formic acid or three performic acid molecules, depending on the mechanism. ^b Refers to corresponding values calculated with the same methodology but using the MPWB1K DFT method.

single-point calculations with the same functional and the 6-311++G(3df,3pd) basis set, including the solvent effects (on electronic energies) using IEF-PCM continuum model and dichloromethane as solvent. The quantum mechanical results are expected to be more reliable than those from ref 18 since the same functional is being used but with larger basis sets but especially because the single-point calculation energies using the IEF-PCM continuum model are more accurate than those using the Onsager model. The calculations were all performed with the Gaussian 03²⁰ program package.

To obtain more reliable ΔG^\ddagger , we have used 1 M as the reference state and added thermodynamic corrections to the gas-phase ΔG values to simulate the effect of the liquid phase in the same way as proposed by Benson,²¹ first used for this reaction by Okuno,²² and later by other authors for different systems.^{17,23,24} For more details, see ref 17. In Table 1, we have tabulated all ΔG values relative to the isolated reactants. It should be noted that the relative energies of the Criegee intermediate and the ester product do not depend on the mechanism since they would be more stable than any complex relevant to the studied reaction which could involve them. To study the influence of the possible change in RDS, two ketones were modeled: propanone and cyclohexanone (Chex) with very different migrating abilities.

Figure 1 shows the transition state for the acid-catalyzed second (migration) step. This transition state is very different than the one modeled in ref 18 (recalculated in this work), which was attributed to the acid-catalyzed mechanisms. In the present transition state, the acid catalyst protonates the carbonyl oxygen of the Criegee intermediate instead of the departing oxygen atom as proposed in ref 18. This transition state and the uncatalyzed one are more stable than that of ref 18 by approximately 2.7 kcal/mol.

The small stabilization of the reactant complexes between ketones and formic acid, only modeled in the acid-catalyzed mechanism, has two consequences: (i) the ΔG^\ddagger increases in the same proportion; and (ii) the reaction can be considered bimolecular, being the reactants the complex and performic acid. This was first proposed by Hawthorne and Emmonds⁴ for trifluoroperacetic acid + propanone in 1958 and has been systematically ignored. Since the acid is usually in excess, it is reasonable to expect that the concentration of the complex is

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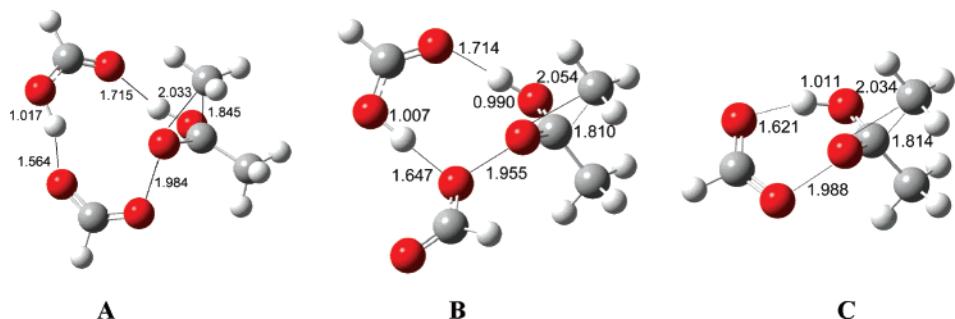


FIGURE 1. Transition states of the acid-catalyzed migration step showing the main bond distances in angstroms (A catalyzed, B ref 18, C noncatalyzed).

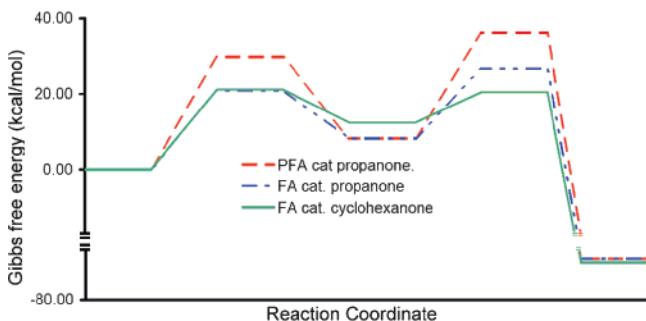


FIGURE 2. Reaction profile in terms of Gibbs free energy for both mechanisms and acid catalyzed for cyclohexanone + formic acid for the second step noncatalyzed ΔG^\ddagger was plotted.

close to the ketone concentration, and under these conditions, the reaction can be considered bimolecular using ketone and peracid concentrations.

The ΔG data in Table 1 are plotted in Figure 2. For easier visualization of the results, the complex for the performic acid-catalyzed reaction was omitted and the zero energy in the acid-catalyzed mechanism was taken as the energy of the stable complex between ketone and formic acid + performic acid. As can be seen in Table 1 and Figure 2, the mechanism proposed in ref 18 has a very large ΔH^\ddagger and ΔG^\ddagger . As proposed above, these ΔG^\ddagger are so large that the corresponding rate constants would be much smaller than that of the formic acid-catalyzed mechanism for both reaction steps.

Regarding the acid-catalyzed mechanism of propanone + PFA reaction, the results for the first step (this work) are consistent with our previous results using a peracetic acid + acetic acid system.¹⁷ The Gibbs free energy barriers are lower than those for peracetic acid + acetic acid, as expected from the higher reactivity of the performic + formic acid pair. For the second step, the results show that the enthalpy barrier is lowered by the catalyst by approximately 5 kcal/mol, but this is roughly canceled by the entropy loss. Both barriers are almost equal in terms of Gibbs free energy, but the noncatalyzed reaction is slightly favored.

Since the noncatalyzed reaction is unimolecular and the catalyzed reaction rate depends on the acid concentration, they should not be directly compared. The comparison would be fair in terms of rate coefficients: first order for noncatalyzed and pseudo first order for catalyzed reactions. This means that for acid concentrations up to 1 M the unimolecular reaction will be faster. Therefore, this reaction is expected to be the dominant one under most experimental conditions. The role of the acid in the second step could change depending on the reactants and

experimental conditions. The only clear conclusion is that the role of the catalyst, if any, is small in the migration step. The total rate coefficient calculated using conventional transition state theory is $5.01 \times 10^{-6} \text{ L mol}^{-1} \text{ s}^{-1}$ (for details, see Supporting Information). Accordingly, either the reaction is expected to be extremely slow under normal experimental conditions or the calculated ΔG^\ddagger values are overestimated: The second step is obviously the RDS.

The MPWB1K²⁵ functional was additionally used for modeling the first step of the propanone + PFA. The basis sets and solvent model were the same as those used for the B3LYP calculations. This DFT method was developed for, and assumed to give, more reliable geometries and energies of transition states. As shown in Table 1, the changes in ΔG^\ddagger for the acid-catalyzed mechanism between these two methods is -0.18 kcal/mol . For the PFA-catalyzed reaction, the corresponding change is 4.53 kcal. This result reinforces the validity of the acid-catalyzed mechanism and also supports the B3LYP results.

Regarding the acid-catalyzed mechanism of cyclohexanone + PFA, the main feature is the dramatic change in ΔG^\ddagger for the second step (compared to propanone + PFA), while for the first step, ΔG^\ddagger remains almost the same. This can be explained by assuming that the reactivity of both ketones is similar for the addition, but the migration ability of a cyclic secondary substituent in cyclohexanone is much higher than that of a methyl group in propanone. Consequently, the Gibbs free energy of the transition state of the migration step is lower than that of the first step becoming almost the RDS. Taking into account that the pK_a values of FA and MCBA are very close (3.77 and 3.83, respectively), the catalytic activity for the first step and the leaving ability for the second step are expected to be similar for both acids. Therefore, the change in the RDS agrees with experimental data for cyclohexanone + MCPB.⁹ The calculated overall rate coefficient for cyclohexanone + PFA is $1.84 \times 10^{-3} \text{ L mol}^{-1} \text{ s}^{-1}$, which seems to be slightly underestimated but within the range of Baeyer–Villiger reaction rate coefficients. The difference in rate coefficients between the reactions of both ketones is in line with their difference in reactivity.

The transition state equation in its thermodynamic formulation can be found elsewhere and can be written as

$$k = \sigma \kappa \frac{k_B T}{h} \exp\left(\frac{-\Delta G^\ddagger}{RT}\right)$$

where κ is the transmission coefficient, also known as the tunneling correction, and σ is the reaction path degeneracy. The

tunneling correction can be ignored for this reaction since the hydrogen motions are concerted with those of the heavy atoms. The reaction path degeneracy is of minor importance. The equation used in ref 18 is

$$k = \frac{k_B T}{h} \left(\frac{RT}{P} \right) \exp \left(\frac{-\Delta G^\ddagger}{RT} \right)$$

It includes the RT/P factor that is a conversion from 1 atm standard state to 1 M standard state for a bimolecular reaction. From the similarity between our results and those in ref 18, it becomes evident that, in the latter, the Gibbs free energies were corrected to 1 M standard state and to liquid phase. Therefore, the RT/P factor is unnecessary. If this factor is excluded and the zero of energy is corrected, the ΔG^\ddagger would become 34.66 kcal/mol, which is 13.06 kcal/mol larger than the experimental value. This discrepancy with the experimental result is beyond any expected error in quantum chemical calculation and is an indication that the modeled mechanism is not the best choice.

Increasing the number of molecules in a transition state usually decreases the enthalpy barrier; however, the entropy loss is usually larger than the entropy gain, so the ΔG barrier increases. In the gas phase, this outcome is so large that the termolecular reactions are exceptionally rare. In solution, due to the solvent cage effect, this behavior is less significant yet still present. This is why third-order reactions usually involve a stable complex formation, which in turn would react with the third molecule in a bimolecular way. Following the same reasoning, fourth-order reactions are even less likely to occur and never in one step. It seems worthwhile to emphasize the importance of studying chemical reaction mechanisms in terms of ΔG instead of enthalpy or ZPE corrected energies.

According to our results, the catalytic role of two peracid molecules seems to be an artifact due to an inappropriate choice of zero energy in the reaction profile, at least under normal experimental conditions where a partner acid is always present.

A careful examination of relative energies (Table 1) shows that the complex between three performic molecules is not a minimum in terms of enthalpy or in terms of Gibbs free energy. Therefore, it would be just another point on the potential energy surface and not a proper intermediate, even if there is no partner acid present, which seems to be a hypothetical situation. In general, the acid is always present for two reasons: (i) it is a byproduct in variable amounts, usually in excess, in peracid synthesis; (ii) it is formed during the BV reaction. For these known reasons, there is usually an excess of acid in the reaction media.

The mechanism of the Baeyer–Villiger reaction, in acidic media, and in nonpolar solvents, appears to be generally acid catalyzed in the first step. Although the acid molecule decreases the enthalpy of the transition state of the second step, the entropy loss overcomes it and the second step appears to be uncatalyzed; that is, the Criegee intermediate evolves through a unimolecular process to the ester (or lactone) and the corresponding acid. The two-step mechanism modeled is neutral and concerted, and it does not include the generally accepted initial protonation of the ketone, but a hydrogen-bonded ketone and acid complex. The values of the calculated rate coefficients and the change in RDS for the two studied ketones support this mechanism.

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Supporting Information Available: Details on kinetic calculations, Cartesian coordinates of the key structures, B3LYP absolute energies and corrections, and full citation of Gaussian 03 program package. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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