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The Baeyer–Villiger reaction: solvent effects on reaction mechanisms†

Nelaine Mora-Diez,*[a] Samantha Keller[a] and J. Raúl Alvarez-Idaboy*[b]

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This study focuses on the Baeyer–Villiger reaction of propanone and performic acid, with formic acid as catalyst. Continuum solvation methods (EIF-PCM and CPCM) and two density functionals (B3LYP and MPWB1K) are used to study solvent effects on two types of reaction mechanisms: concerted non-ionic and stepwise ionic. The ionic mechanism is the one found in most organic chemistry textbooks; it begins with the protonation of the ketone by the acid catalyst, even though this reaction normally takes place in non-polar solvents such as dichloromethane. Our calculations show that the concerted non-ionic pathway, which is the least energetic in non-polar solvents such as dichloromethane, becomes more energetic the more polar the solvent. After investigating a variety of non-ionic and ionic pathways in water, it is found that the addition step seems to be ionic but the migration step, which is rate-determining, is uncatalyzed, non-ionic and fully concerted. These results confirm the experimental findings in solvents of low to medium polarity that the rate constant of the reaction decreases as the solvent polarity increases. Moreover, we find that contrary to what is commonly accepted, in the addition and migration ionic steps the deprotonation of the ionic species occurs in a concerted manner with the other chemical events taking place.

1. Introduction

In the Baeyer–Villiger (BV) reaction,[1] ketones are oxidized to esters or lactones by interaction with peracids. This reaction is used extensively in organic synthesis due to its excellent regioselective and stereoselective control, and has been extensively studied and well reviewed over the last 100 years.[2–4] The mechanism of the reaction is known to involve two main steps. The first is the carbonyl addition of a peroxyacid to a ketone, producing a tetrahedral adduct known as the Criegee intermediate.[5] The second step is the migration of the alkyl or aryl group from the ketone moiety to the nearest peracid oxygen atom, with the simultaneous dissociation of the O–O bond.[6] The second step is usually rate determining, but it has also been shown that a rate-determining addition can take place depending on the reactants and conditions used.[2,7–17] In unsymmetrical ketones, the substituent with the best ability to stabilize a positive charge is the one that preferentially migrates,[4] although there are factors other than electronic ones that determine migratory ability.[11,12]

It is also well known that the BV reaction is clearly acid catalyzed, either by Brønsted acids or by Lewis acid catalysts with a hydrogen peroxide oxidant. Though the generally accepted mechanism for the BV rearrangement in organic chemistry textbooks is an ionic one (see Fig. 1 for an example),[18] there is no experimental evidence in favour of an ionic mechanism in the non-polar solvents in which this reaction commonly takes place. Several variations of ionic mechanisms, shown in ESI Appendix 1,† have been proposed for this reaction in a variety of organic chemistry textbooks. Assumption of an ionic mechanism would mean that the reaction involves a protonated ketone prior to the addition step, and possibly structures such as a positively charged Criegee intermediate or ester. In non-polar environments such as dichloromethane, it is unjustified to assume that these ions can be stabilized sufficiently to facilitate an ionic mechanism. In a recent review,[4] a possible general mechanism is proposed for the BV reaction that depends on the solvent acidity. This review proposes that ionic reactants and Criegee intermediates are formed in highly acid media, but it does not provide details on how the actual transformation from one species to another takes place. A stereoselectivity study considered different possibilities of migration steps from charged (cationic and anionic) Criegee intermediates, ruling out the possible migration from neutral Criegees.[19]

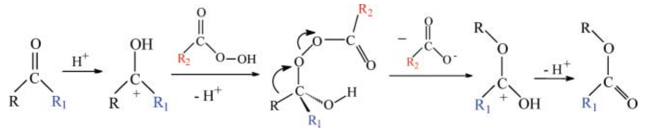

Fig. 1 A currently accepted mechanism for the BV reaction.[18a]

An alternative to an ionic mechanism for the BV reaction is a neutral and concerted one in which no ions are formed. Several computational studies of the BV mechanism have been published in which concerted transition states (TS) have been modelled assuming a neutral mechanism in non-polar solvents.[15,16,20–32] The complete mechanism, including the Brønsted acid catalysis on the addition and migration steps, has been modelled only by Okuno,[15] Grein *et al.*,[20] and our group.[32] Strong evidence for a neutral and concerted mechanism was recently shown for the BV reactions of propanone and cyclohexanone with trifluoroperacetic acid, catalyzed by trifluoroacetic acid

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[a]*Department of Chemistry, Thompson Rivers University, Kamloops, BC, V2C 5N3, Canada. E-mail: nmora@tru.ca*
[b]*Facultad de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, 04510, México D.F., México. E-mail: jidaboy@unam.mx*

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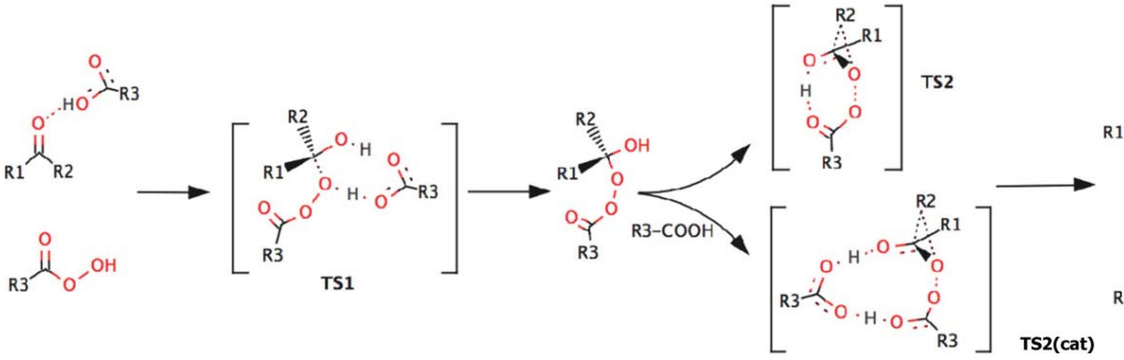

Fig. 2 The calculated mechanism for the BV reaction in non-polar solvents.[32] TS1 is the concerted non-ionic addition TS; TS2 and TS2(cat) are the uncatalyzed and catalyzed concerted non-ionic migration TSs, respectively; R1, R2 and R3 are aliphatic or aromatic groups.

in dichloromethane.[32] Fig. 2 shows the general (non-ionic and concerted) reaction mechanism proposed for BV reactions in non-polar solvents; a reaction profile is shown in ESI Figure S1.† The calculated rate coefficients applying transition state theory agree exceptionally well with the experimental values. These calculations, performed at the MPWB1K/6–311++G(d,p)-IEF-PCM//MPWB1K/6–311G(d,p)-Onsager level of theory, show that the addition step is acid catalyzed but that apparently the migration step is not. An experimental study of the temperature dependence of the rate constant would help elucidate the exact nature of the second step.[32]

Hawthorne and Emmons reported the rate constants for several BV reactions of a variety of aliphatic and aromatic ketones (22 ketones were studied) with trifluoroperacetic acid, in the presence of trifluoroacetic acid, in two solvent mixtures: ethylene chloride ($\varepsilon = 10.5$) and the more polar mixture acetonitrile ($\varepsilon = 37.5$)-ethylene chloride (10 : 1 volume).[8] As in most cases, these are BV reactions for which the migration step is the rate-determining one. Their results consistently show that the rate constants of these reactions are higher in the least polar solvent. These results in solvents of medium to low polarity are in clear contradiction with the idea of a completely ionic mechanism for the BV reaction. A possible conclusion to be derived from their work is that the rate-determining step (RDS) of these reactions is non-ionic—the other reaction step might be ionic or not depending on solvent polarity. Their work does not report changes in the reaction mechanism of the BV reaction due to changes in solvent polarity, which is a question that has not yet been investigated. The concerted non-ionic mechanism is favoured over an ionic one when the BV reaction is modelled including solvent effects in relatively non-polar dichloromethane,[32] but this result has not been extended to studies of the reaction in more polar solvents. Several computational studies of solvent effects on the energetics and regioselectivity of reactions have been previously performed making use of continuum solvation models (see, for example, ref. 33–35).

In this paper, the mechanism of the BV reaction of propanone with performic acid (PFA), catalyzed by formic acid (FA), is modelled at reliable levels of theory. Using a polarizable continuum solvent model, we explore the effect of the solvent polarity on the concerted mechanism that has been previously proposed for BV reactions.[32] We also model possible pathways by which an ionic mechanism may occur in more polar solvents and, by doing so, predict the likelihood of a concerted or ionic mechanism for the BV reaction depending on solvent polarity.

2. Computational methodology

All calculations were performed with the Gaussian 03 program package.[36] Two density functional methods were used: B3LYP[37] and MPWB1K.[38] The latter functional was recently developed for kinetic calculations and was chosen for this study because of the way it reproduced the experimental rate coefficient of a similar BV reaction.[32]

Initially, gas-phase optimizations and frequency calculations were performed with each DFT method using the 6–311G(d,p) basis set. By means of the IEF-PCM[39] continuum solvation model, solvent effects were considered through single-point energy calculations with the same method and the 6–311++G(d,p) basis set. The Gibbs free energies in solvent (G_{solvent}) were calculated by adding the total energy in the solvent (E_{solvent}) and the gas-phase thermal correction to the Gibbs free energy (TCG_{gas}) at 298.15 K. Seven solvents, as implemented in this PCM model, were used to study the effects of solvent polarity on the reaction mechanism: dichloromethane ($\varepsilon = 8.93$), acetone ($\varepsilon = 20.70$), ethanol ($\varepsilon = 24.55$), methanol ($\varepsilon = 32.63$), nitromethane ($\varepsilon = 38.20$), dimethylsulfoxide (DMSO) ($\varepsilon = 46.70$), and water ($\varepsilon = 78.39$).[40] Later, full optimizations and frequency calculations of the stationary points in the reaction were performed, including solvent effects as described above, using the 6–311++G(d,p) basis set. Intrinsic reaction coordinate (IRC) calculations were also performed at this level for any new TS calculated. All the calculations reported in this paper were performed at the MPWB1K/6–311++G(d,p)-IEF-PCM level of theory (including solvent effects in both the geometry optimizations and the frequency calculations), unless otherwise indicated. The CPCM[41] continuum solvation method was also applied for calculations in water.

Calculations in solvents employ the UAHF atomic radii when constructing the solvent cavity. In this united atom topological model, a sphere is placed around each solute heavy atom so that hydrogen atoms are enclosed in the sphere of the atom to which they are bonded. The solvent effects on the energies, geometries, and charge distributions of the concerted reaction show two distinct trends depending on the character of the solvent. Therefore, the solvents considered are divided into two groups: dichloromethane, acetone, nitromethane and DMSO making up

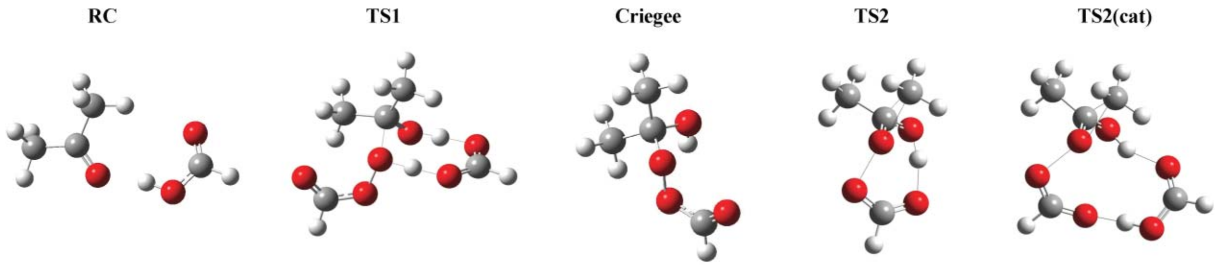

Fig. 3 Structures of the reactant complex (RC), the Criegee intermediate and the TS of the concerted catalyzed addition (TS1), and uncatalyzed (TS2) and catalyzed (TS2(cat)) migration steps of the BV reaction of propanone, performic acid and formic acid.

one group, and ethanol, methanol, and water making up the other. This distinction between non-protic and protic solvents is due to the difference in the ALPHA scaling parameter by which the (UAHF) sphere radii are multiplied in the PCM model, which is 1.4 for the non-protic solvents and 1.2 for the protic ones.[40] Different groups of calculated values have also been found in other studies depending on the nature of the solvent (protic or non-protic) when applying the PCM solvation model with the UAHF radii.[42]

In the calculation of the change in Gibbs free energy along the reaction pathway, several thermodynamic corrections were applied to obtain results that can be compared with other theoretical works on this topic. The first correction was a change in standard state from 1 atm to 1M, which results in a decrease in ΔG of 1.89 kcal mol^{-1} for bimolecular reactions. Additionally, the approach proposed by Benson was used, according to which the ΔG in solution at 298.15 K decreases by 2.56 kcal mol^{-1} (for bimolecular reactions) with respect to the ΔG in the gas phase.[43,44] For a detailed description of these corrections see ref. 30 and 45.

Benson's correction is a way to take into account the limitation to the free movement of species in the liquid phase (cage effect) in comparison to what happens in the gas phase (ideal gas model). This movement limitation in the liquid phase does not directly depend on solvent polarity; in any case it should depend on the viscosity of the solvent, which is not considered in this correction. In non-polar solvents in which the solvation energy of a solute is almost negligible, Benson's correction reflects the most important aspect affecting a solute relative to its existence in the gas phase (ideal model). In polar solvents other factors also contribute to the solute–solvent interaction energy; these are accounted for through the application of continuum solvation models. However, these models do not account for the effect of the explicit presence of solvent molecules interacting with a solute. The use of Benson's correction could be considered a way to account for the entropic effect of the presence of solvent molecules around a solute. A more detailed discussion of this effect can be found in ref. 44. Benson's correction has been applied in several computational kinetic studies.[15,30–32,45]

3. Results and discussion

The concerted non-ionic pathway has already been shown to be the only energetically feasible mechanism for the BV reaction in non-polar solvents (see Figs. 2 and S1†).[32] In the first part of this work the concerted non-ionic addition and migration steps are modelled for the BV reaction of propanone with performic acid using formic acid as catalyst in several solvents with relative static permittivities (dielectric constants) from 8.93 (dichloromethane, DCM) to 78.39 (water). The second part of this work discusses several possible reaction mechanisms in water where the stepwise-ionic and concerted non-ionic mechanisms are compared.

3.1. Solvent effects on concerted non-ionic reaction pathway

3.1.1. Mechanism description. The first chemical process to be considered in the BV reaction is the formation of the reactant complex (RC) between the ketone and the acid. Such a complex is sometimes more stable in Gibbs free energy than the isolated reactants and there is experimental evidence of this, *e.g.*, between acetophenone and trifluoroacetic acid.[8] The concerted addition process could be conceived in two consecutive bimolecular steps, as previously shown.[8] First the RC is formed and later it interacts with the peracid to form the Criegee in what could be considered a reversible step. The migration step is exergonic ($\Delta G < 0$) enough to be irreversible and leads to the formation of the ester and acid. The structures of the RC and the Criegee intermediate are shown in Fig. 3.‡

For the concerted neutral mechanism, the TSs of the addition and migration steps of the BV reaction in the seven solvents considered are calculated. The first TS (TS1) is the formic acid catalyzed addition of performic acid to the carbonyl of propanone. The most relevant features of the addition TS have been previously described for the BV reactions of several ketones, acids and peracids.[30–32] In TS1, formic acid facilitates the protonation of propanone as it simultaneously deprotonates performic acid, allowing the C–OO bond of the Criegee intermediate to be formed. Previous studies of this TS confirm that it is fully concerted and that it is the lowest energy possible TS for the first step of the BV reaction.[30–32]

The second TS is the migration of the methyl group of propanone from the carbonyl to the nearest peracid oxygen atom. This migration can be catalyzed or uncatalyzed, and TSs for both cases have been characterized in previous work by our group.[31,32] In the uncatalyzed case (TS2), the main movements in the TS are the cleavage of the O–O bond and the migration of the methyl group. In a concerted manner, the hydrogen attached to the oxygen

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‡ The Gibbs free energy of the RC between propanone and the acid in DCM is −1.67 kcal mol^{-1} relative to the isolated reactants. Other possible RCs were considered and their *G* values in kcal mol^{-1} relative to the isolated reactants are indicated in parentheses: acid–peracid (−0.57), propanone–peracid (−0.53) and propanone–acid–peracid (1.55). In agreement with the experimental results,[8] our calculations for the BV reaction under study indicate that the complex between propanone and the acid is the lowest-energy RC for this reaction.

Table 1 Enthalpies and Gibbs free energies (in kcal mol^{-1} at 298.15 K) of the optimized stationary points relative to the isolated reactants for the reaction of propanone with performic acid (PFA) using formic acid (FA) as catalyst[a]

		RC + PFA		TS1		Criegee + FA		TS2[c] + FA		TS2(cat)		Ester + 2 FA	
Solvent	ε[b]	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG
Dichloromethane	8.93	−5.65	−1.67	0.82	18.45	−8.44	0.77	19.57	29.45	12.32	28.26	−74.17	−73.37
Acetone	20.70	−5.31	−1.45	1.64	19.14	−8.07	1.35	19.95	29.77	13.07	29.05	−73.90	−73.16
DMSO	46.70	−5.15	−1.41	2.01	19.44	−7.92	1.55	20.10	29.89	13.40	29.38	−73.77	−73.07
Methanol	32.63	−1.14	1.48	9.94	27.16	−5.36	4.08	23.99	33.81	21.43	37.72	−72.70	−71.98
Water	78.39	−1.03	2.57	10.52	28.61	−5.19	4.96	24.19	34.85	21.90	39.06	−72.57	−70.88

[a] Level of theory: MPWB1K/6–311++G(d,p)-IEF-PCM; [b] Relative static permittivities taken from Ref. 39; [c] Uncatalyzed TS.

atom of the Criegee intermediate migrates to the leaving acid. In the concerted catalyzed migration TS (TS2(cat)), a formic acid molecule deprotonates the Criegee and protonates the leaving acid as the migration of the methyl group and the breaking of the O–O bond take place. Fig. 3 shows the structures of the three concerted non-ionic TSs.

3.1.2. Analysis of the results§.

The standard Gibbs free energy and enthalpy changes relative to the isolated reactants for the stationary points optimized along the BV reaction pathway at the MPWB1K/6–311++G(d,p)-IEF-PCM level of theory are reported in Table 1. For simplicity, the results in five of the seven solvents considered are reported. Very similar qualitative results are obtained when using the B3LYP functional (see ESI Table S8).† Two separate trends of data are obtained because of the use of the UAHF radii, one for non-protic solvents and another for the protic ones, with higher *H* and *G* values relative to the isolated reactants in the latter group. The ΔG and ΔH of activation of the two steps of the BV reaction increase as solvent polarity increases within the two groups of solvents.¶‖

Though the Gibbs free energies of all species along the reaction pathway are reduced by the increasing polarity of the solvent, the stabilization effect is stronger on the isolated reactants (see ESI Table S12†), resulting in an increase in the three ΔG of activation ($\Delta G^{\ddagger}$) values as polarity increases. Since for a given solvent the product charge separation in the three TSs discussed decreases in the order TS2, TS1 and TS2(cat) (see ESI Appendix 3),† one would expect the decrease in $\Delta G^{\ddagger}$ as solvent polarity increases to follow the same order, as shown in ESI Table S12.† The relative *G* values of the reactant complex and the Criegee intermediate also increase with solvent polarity for the same reason.

The study of the solvent effects on the concerted non-ionic BV reaction mechanism indicates that regardless of which functional is used (B3LYP or MPWB1K) or which approach is followed to account for solvent effects (in geometries and frequencies, or only in energies), the Gibbs free energy barriers in all the processes considered increase with solvent polarity. Even though the product charge separation in the different TSs increases, leading to a greater stabilization due to solvation, the reactants are considerably more stabilized. These results are in agreement with the experimental data reported by Hawthorne and Emmons and confirm the idea that at least in non-protic solvents of low to medium polarity, the BV reaction has a non-ionic RDS. Our results show that the most favourable reaction mechanism in non-polar solvents, which is non-ionic and fully concerted, becomes more energetic the more polar the solvent.

3.2. Mechanistic discussion of the BV reaction in water

Since water is the most polar solvent used in this study, it is the most likely candidate to stabilize the ions that would be involved in ionic BV reaction mechanisms such as those indicated in the standard organic chemistry texts that deal with this well-known reaction.[18] What follows is a mechanistic discussion of additional BV reaction pathways (non-ionic and ionic) that could take place in water, even though this reaction normally takes place in non-polar solvents such as dichloromethane. The results of the calculations in water discussed in this section, using the B3LYP and MPWB1K functionals and two continuum solvation methods (EIF-PCM and CPCM), are reported in Table 2. In all cases, continuum solvent effects are applied to the geometry optimizations and frequency calculations.

3.2.1. Water as catalyst: concerted non-ionic mechanism.

Since water is a proton donor and acceptor, it is possible that in an aqueous environment a water molecule could act as a catalyst in an analogous way to the formic acid catalyst in the previously proposed concerted transition states (TS1 and TS2(cat)). This concerted and non-ionic pathway was also modelled in water. Fig. 4 displays the structures of the two concerted water-catalyzed transition states, TS1(H_2O) and TS2(cat)(H_2O).

The $\Delta G^{\ddagger}$ of the concerted water-catalyzed addition is 8.4 (6.4) kcal mol^{-1} higher than the formic-acid-catalyzed addition when using the MPWB1K (B3LYP) functional. The transition vector in TS1(H_2O) mostly involves the two proton transfers facilitated by the water molecule, and to a much smaller degree, the addition of the peracid to the carbonyl carbon of the ketone. The $\Delta G^{\ddagger}$ of the concerted water-catalyzed migration is found to be 1.1–1.4 kcal mol^{-1} higher than the uncatalyzed migration, but it is lower by 2.1–3.1 kcal mol^{-1} than the formic-acid-catalyzed migration. The transition vector in TS2(cat)(H_2O) shows mostly the motion

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§ For a discussion of solvent effects on the charge distributions in the concerted TSs, refer to ESI Appendix 2 and Tables S1 to S6. A brief discussion of solvent effects on the geometry of the concerted TSs (see ESI Table S7) appears in ESI Appendix 3.†

¶ The same trends in enthalpy and Gibbs free energy changes are observed when solvent effects are estimated by single-point PCM calculations on the gas-phase optimized geometries. The values of ΔG and ΔH for all steps in the reaction relative to isolated reactants (shown in ESI Tables S9 and S10)† are generally in agreement with the values in Tables S8 and Table 1 within ±2 kcal mol^{-1}.

‖ Additional calculations with the UFF force field radii were performed for comparison. See ESI Table S11.†

Table 2 Gibbs free energies of activation (relative to the isolated reactants, in kcal mol^{-1} at 298.15 K) of the optimized TS for the addition (TS1) and migration (TS2) steps of the BV reaction of propanone and performic acid in water[a]

	Addition				Migration				
	TS1[b]	TS1(H_2O)[c]	TS1(H_2O-i)[d]	TS1($2H_2O$-i)[d]	TS2	TS2(cat)[b]	TS2(cat)(H_2O)[c]	TS2(i)[e]	TS2(H_2O-i)[d]
MPWB1K/CPCM	28.0		**17.7**[f]	18.3[f]	**34.0**			36.0[f]	
MPWB1K/IEF-PCM	28.6	37.0	**22.7**	23.1	**34.9**	39.1	36.0	40.9	42.3
			19.2[f]	19.7[f]				37.5[f]	38.8[f]
B3LYP/IEF-PCM	28.8	35.2	**23.9**	29.9	**30.1**	33.6	31.5	38.5	40.1

[a] Level of theory: Method/6–311++G(d,p)-PCM. [b] Concerted formic acid-catalyzed TS. [c] Concerted water-catalyzed TS. [d] Ionic water-assisted TS. [e] Ionic TS. [d,e] Assuming a strongly acidic environment, the isolated reactants for the ionic TSs are propanone, performic acid and H_3O^+ (an additional H_2O molecule is required for TS1($2H_2O$-i)). If the acid environment is provided by formic acid, the ionic barriers increase by 5.1 kcal mol^{-1}. [f] The isolated reactants for the ionic TSs are propanone, performic acid and the solvated hydronium cluster ($H_3O^+(H_2O)_3$).

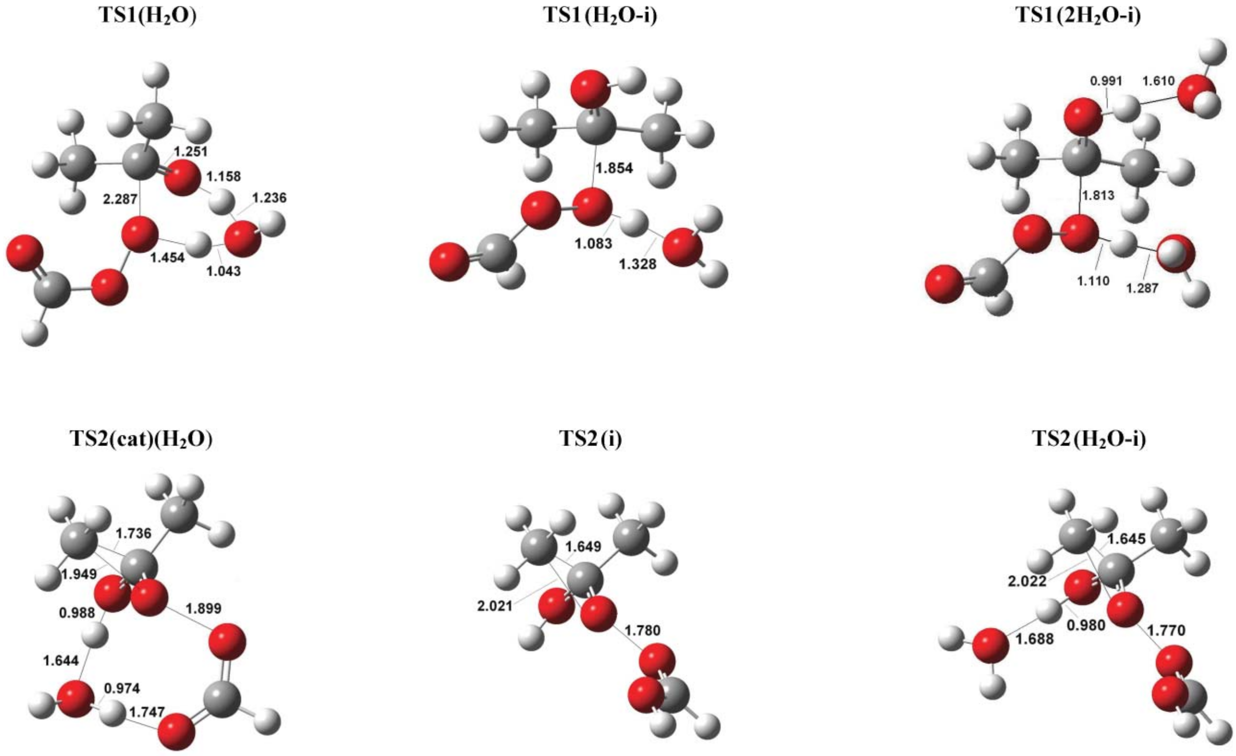

Fig. 4 Structures of the TS of the concerted (water-catalyzed) and ionic addition and migration steps and of the BV reaction of propanone and performic acid in water at the MPWB1K/6–311++G(d,p)-IEM-PCM level of theory.

of the methyl group migrating from the carbonyl carbon to the peracid oxygen and the cleavage of the O–O bond; the motion of the proton transfer is comparatively very small.**

3.2.2. Ionic mechanism. An ionic mechanism for the BV reaction would initially involve the protonation of the ketone, making the carbonyl carbon atom sufficiently electrophilic to accept the peracid. Though a protonated ketone would be unlikely in non-polar solvents, it is reasonable to think that this species could possibly be stabilized by solvation in water. In order to fairly compare the ionic and non-ionic pathways in water we should first assume a strongly acidic environment so that solvated hydronium ions are abundant and are able to protonate the ketone with the least amount of energy required. Using approximate experimental aqueous pK_a values for H_3O^+ (–1.74) and a protonated ketone (–7),[18a] we could estimate the change in Gibbs free energy required to protonate a ketone with H_3O^+ at 7.2 kcal mol^{-1}. Our calculation of 8.4 kcal mol^{-1} for propanone using the data reported in ESI Table S15† is in good agreement with this value. The energy cost to protonate propanone would be higher if the acidity strength of the medium is decreased. For example, if the acid environment

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** Another water-catalyzed non-ionic migration TS was calculated with an additional water molecule which is hydrogen-bonded to the first one (TS2(cat)($2H_2O$)). The MPWB1K $\Delta G^{\ddagger}$ value for this TS relative to the isolated reactants is 38.7 kcal mol^{-1}. Hence, this TS is 2.7 kcal mol^{-1} more energetic than the version with only one water molecule acting as a catalyst, TS2(cat)(H_2O), and 3.8 kcal mol^{-1} more energetic than the uncatalyzed non-ionic migration TS, TS2. The structure, Cartesian coordinates and aqueous Gibbs free energy value of this TS appear in the ESI.

is provided by formic acid then the energy cost to protonate propanone would increase by 5.1 kcal mol^{-1} (pK_a(HCOOH) = 3.75),[46] but if a stronger acid such as trifluoroacetic acid is used instead, the additional energy cost would only be 0.3 kcal mol^{-1} pK_a(CF_3COOH) = 0.25).[46] This additional energy is that required to form H_3O^+ in the presence of a weak acid.

3.2.2.1. Ionic addition. Once the ketone is protonated in water, the next step is the addition of the peracid to the ketone's carbonyl carbon atom. Since it is unlikely that the peracid would be deprotonated in acidic media, the addition would take place with a neutral peracid adding to a positively charged protonated ketone, leading to a positively charged ionic TS and an ionic Criegee intermediate, with the positive charge situated at the peracid oxygen. The extra proton on the Criegee is to be transferred to a solvent molecule to allow the migration to follow.

We were able to locate an ionic water-assisted addition TS by adding an explicit water molecule into the system near the peracid's acidic hydrogen atom (TS1(H_2O-i)). It is a common practice to sometimes consider the presence of explicit solvent molecules together with continuum solvation models when calculating TSs in solution.[47] Fig. 4 displays the structures and main bond distances of several ionic transition states. As confirmed by an IRC calculation, in TS1(H_2O-i) the water molecule is already deprotonating the peracid, which indicates that the different chemical processes occur in a concerted manner and the final product of this addition is a neutral Criegee intermediate. This is a very important result since it is normally assumed in this and other addition reactions that the deprotonation of the species formed during the addition takes place afterward (see Appendix 1).†[48] The $\Delta G^{\ddagger}$ of this process is calculated to be 22.7 (23.9) kcal mol^{-1} with the MPWB1K (B3LYP) functional relative to the isolated reactants: propanone, PFA, H_3O^+.

The effect of additional water molecules was studied and a second water-assisted ionic addition TS (TS1($2H_2O$-i), see Fig. 4) was optimized with a $\Delta G^{\ddagger}$ of 23.1 kcal mol^{-1}, slightly higher than the previously calculated one. These results indicate that there is no reason to increase the number of explicit solvent molecules in the calculation of this species. The second water molecule is near the protonated-ketone part of the TS, and by inspecting the most important bond distances it can be seen that this TS is earlier than the previous one.

Looking for an alternative way to confirm the validity of our calculations in water for the addition step of the BV reaction, we attempted to calculate the ionic Gibbs free energies of activation from a different set of isolated reactants. A more realistic representation of the hydronium ion in water is obtained by assuming its solvation with three water molecules. Such a solvated hydronium cluster, $H_3O^+(H_2O)_3$, was optimized and used together with propanone and PFA as the initial state to calculate the ionic $\Delta G^{\ddagger}$ values to TS1(H_2O-i) and TS1($2H_2O$-i). It is important to note that when the final state is TS1($2H_2O$-i) and two water molecules, there are as many chemical species in the initial as in the final state and no corrections are required. This $\Delta G^{\ddagger}$ was calculated to be 19.7 kcal mol^{-1}. When the final state is TS1(H_2O-i) and three water molecules, the $\Delta G^{\ddagger}$ was calculated to be 19.2 kcal mol^{-1}. Notice that the ionic addition barriers with respect to the solvated hydronium cluster are smaller than before, which shows that this approach might be a better way of calculating the ionic barriers (see Table 2).††‡‡

3.2.2.2. Ionic migration. With a calculated energy cost of 24.5 (24.1) kcal mol^{-1} using the MPWB1K (B3LYP) functional, the neutral Criegee intermediate gets protonated at the carbonyl-oxygen position of the original peracid by interaction with a hydronium ion in a strongly acidic environment (see ESI Tables S14 and S15).† The energy cost of protonating the Criegee with respect to the solvated hydronium cluster is 21.0 kcal mol^{-1}. From this point the concerted ionic migration/elimination takes place.

Two different ionic transition states were located for the migration step of the BV reaction in water, TS2(i) and the water-assisted TS2(H_2O-i), both having a +1 charge (see Fig. 4). In both versions, the main transition vector shows the concerted migration of the methyl group and the breaking of the O–O bond. In the structure of TS2(i) the Criegee is protonated such that the leaving acid is neutral, and the positive charge ends up in the form of a protonated ester. After releasing 20.8 (21.3) kcal mol^{-1}, as calculated with the MPWB1K (B3LYP) functional, the protonated ester donates the proton to a nearby water molecule to form a neutral ester and a hydronium ion (see ESI Tables S14 and S15).† In TS2(H_2O-i), a water molecule is present to remove the proton from the carbonyl oxygen of the ketone part of the Criegee, but the motion of the proton is small compared to the other motions in the TS. IRC calculations on TS2(H_2O-i) show that the three events occur simultaneously, so the final products of the water-assisted ionic migration are two neutral molecules. The $\Delta G^{\ddagger}$ of the two ionic migration processes relative to the isolated reactants (propanone, PFA and H_3O^+) are within 1.4 (1.6) kcal mol^{-1} of each other, as calculated with the MPWB1K (B3LYP) functional. With the two functionals used, TS2(i) is favoured over TS2(H_2O-i). Once again, lower ionic barriers are obtained when using the solvated hydronium cluster as a reference point for the calculations.§§

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†† The solvated hydronium cluster was used as the starting point to obtain a solvated reactant complex between propanone and the hydronium ion, H_3O^+(propanone)$(H_2O)_2$. This is an important intermediate of the ionic reaction in water. The Gibbs free energy cost for the formation of the propanone-hydronium cluster from the solvated hydronium cluster was calculated to be 1.66 kcal mol^{-1} taking the reaction path degeneracy into account. The Cartesian coordinates and G_{aq} values of the two clusters appear in the ESI.†

‡‡ Preliminary calculations of the addition of water to propanone at the same level of theory (MPWB1K/6–311++G(d,p)-IEF-PCM) give $\Delta G^{\ddagger}$ values of 18.8 kcal mol^{-1} (relative to propanone and the solvated hydronium cluster—no corrections are required because the hydration TS has two water molecules attached) and 22.3 kcal mol^{-1} (relative to propanone, $2H_2O$ and H_3O^+) for the addition. These values, following two different approaches, are 0.4–0.9 kcal mol^{-1} smaller than the corresponding values for the ionic BV addition. Nonetheless, the hydration is expected to have a much greater rate constant because in water the concentration of water molecules will always be much greater than practical concentrations of PFA.

§§ The MPWB1K ionic migration $\Delta G^{\ddagger}$ of TS2(i) relative to the protonated Criegee is 11.4 kcal mol^{-1}. This value is in reasonable agreement with the gas-phase energy barrier of 7.3 kcal mol^{-1} reported by Snowden *et al.*[19] calculated at the B3LYP/6–311G(d) level of theory for the cationic migration from the Criegee of acetaldehyde and PFA. Our value, for the Criegee of propanone and PFA, with a larger basis set and a different functional, includes solvent effects and additional entropic factors. Previous calculations have shown that the B3LYP functional underestimates the migration $\Delta G^{\ddagger}$.[32]

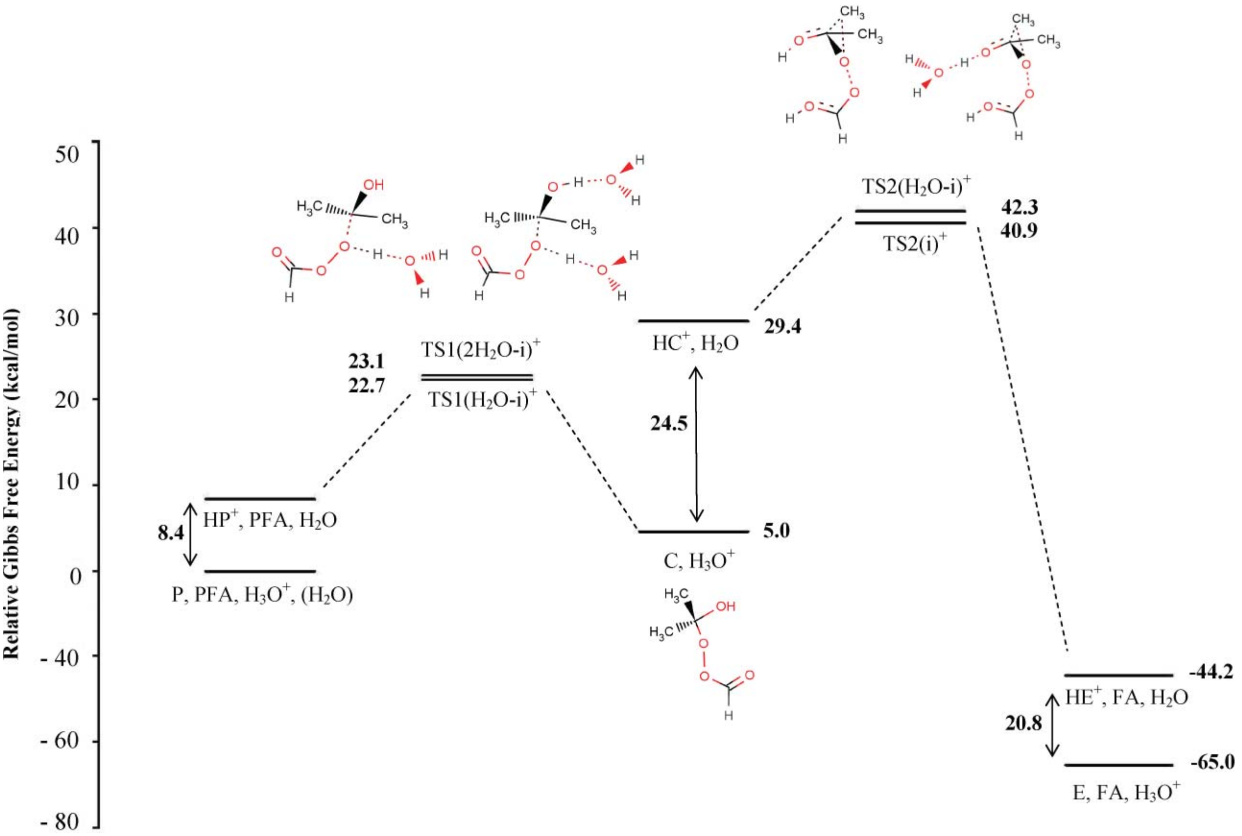

Fig. 5 Ionic BV reaction pathway in water calculated at the MPWB1K/6–311++G(d,p)-IEF-PCM level of theory, assuming a strongly acidic environment. The acid–base aqueous ΔG values were calculated using the data reported in the ESI, Table S15.† P: propanone, PFA: performic acid, C: Criegee intermediate, E: ester (methylacetate), FA: formic acid.

Fig. 5 shows the reaction scheme of the ionic BV reaction in water, including the ΔG_{aq} of the acid–base equilibria previously mentioned between the hydronium ion and propanone, the Criegee intermediate and the ester.

The consideration of additional explicit solvent molecules in the addition and migration ionic TSs led to an increase of 0.4 (6.0) and 1.4 (1.6) kcal mol⁻¹, respectively, with the MPWB1K (B3LYP) functional) in $\Delta G^{\ddagger}$. From these results it is concluded that there is no reason to increase the number of explicit solvent molecules in the calculation of these species.

3.2.3. Comparison of different pathways in water. Table 2 summarizes the results for the different pathways in water for the BV reaction studied, which are very similar regardless of the DFT functional and continuum solvation method used in the calculations.¶¶ In the following comparison of $\Delta G^{\ddagger}$ values in water, MPWB1K-IEF-PCM values will be used and the ionic barriers will be those calculated relative to the solvated hydronium cluster in a strongly acidic environment.

In the addition step, the ionic water-assisted TS1(H_2O-i) is the route with the lowest Gibbs free energy of activation. The next most stable addition TS (by 9.4 kcal mol⁻¹) is the concerted non-ionic formic acid-catalyzed addition TS1. The concerted non-ionic water-catalyzed addition is the least favourable addition pathway probably due to the entropy decrease involved in forming such a strained geometry with a water molecule. TS1(H_2O) is 17.8 kcal mol⁻¹ more energetic than the ionic water-assisted TS1(H_2O-i).

For the migration step, the lowest-energy pathway corresponds to the non-ionic concerted uncatalyzed migration (TS2). The water-catalyzed (TS2(cat)(H_2O)) and the ionic (TS2(i)) migrations are higher in energy than TS2 by 1.1 and 2.6 kcal mol⁻¹, respectively. The formic acid-catalyzed non-ionic (TS2(cat)) migration is the least favourable pathway, being 4.2 kcal mol⁻¹ higher in energy than TS2.

For a detailed discussion on the effects of acidity and solvent polarity on the mechanism of the BV reaction refer to ESI Appendix 4.† After investigating a variety of non-ionic and ionic pathways in water, the most polar solvent considered in this study, it was found that, independent of the acidity strength of the aqueous environment, the ionic addition pathway is the least energetic. However, the concerted uncatalyzed non-ionic migration is the least energetic pathway for the second step, which is rate-determining (see Fig. 6).

4. Conclusions

Solvent effects on different possible reaction pathways for the Baeyer–Villiger reaction of propanone with performic acid in the presence of formic acid as catalyst have been studied. The

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¶¶ Most of the calculations in water were also performed with the CPCM continuum solvation model. The MPWB1K-CPCM $\Delta G^{\ddagger}$ values are about 1.5 (0.6–0.9) kcal mol⁻¹ smaller than the ionic (concerted non-ionic) MPWB1K-IEF-PCM $\Delta G^{\ddagger}$ values. The results obtained, shown in Table 2, agree well with the IEF-PCM calculations previously discussed.

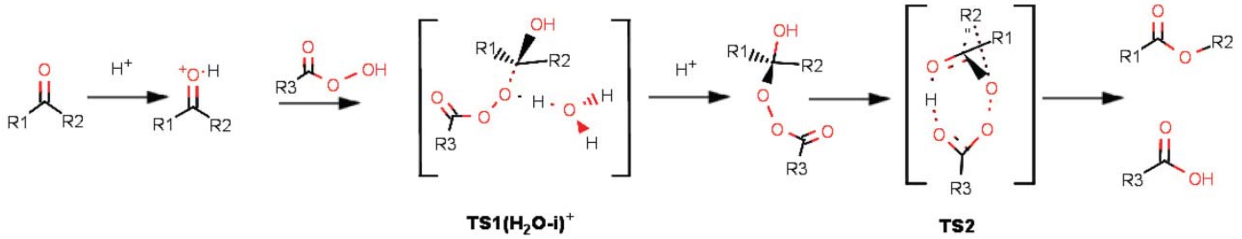

Fig. 6 The calculated mechanism for the BV reaction in water. TS1(H_2O-i) and TS2 are the water-assisted ionic addition TS and the uncatalyzed concerted non-ionic migration TS, respectively; R1, R2 and R3 are aliphatic or aromatic groups.

conclusions of this manuscript are independent of the method of calculation (MPWB1K or B3LYP) and the solvent model used (IEF-PCM or CPCM).

Our calculations show that, independent of solvent polarity, the migration step of the BV oxidation, which is usually the RDS, is non-ionic and concerted, while the addition step depends on solvent polarity. Two extreme types of mechanisms have been identified. The least energetic reaction pathway in non-polar solvents, which is non-ionic and fully concerted,[32] becomes more energetic as solvent polarity increases. Our calculations indicate that the experimental findings of Hawthorne and Emmons[8] should still apply in more polar solvent mixtures. As solvent polarity increases, the non-ionic rate-determining migration step becomes more energetic and the rate constant of the reaction decreases. For cases of BV reactions in which the addition step is rate determining,[11,13] an increase in solvent polarity may lead to an increase in the rate constant. This prediction could be tested experimentally taking into account that the change of solvent could change the RDS. It has also been found that, contrary to what is commonly accepted, the deprotonation of the ionic TSs occurs in a concerted manner with the other chemical events taking place.

While our study refers to the BV reaction, these results could be important for the study of other organic reactions that take place in non-polar solvents for which ionic mechanisms are assumed. This work questions the general assumption that organic reaction mechanisms in solution always involve ions.

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