The mechanism of the Baeyer–Villiger rearrangement: quantum chemistry and TST study supported by experimental kinetic data†

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The mechanism of the Baeyer–Villiger rearrangement is modelled for the reaction of propanone with trifluoroperacetic acid, catalyzed by trifluoroacetic acid in dichloromethane, using three DFT methods (B3LYP, BH&HLYP and MPWB1K) and MP2. These results are refined and used to calculate the overall reaction rate coefficient using conventional Transition State Theory. The excellent agreement between the calculated (1.00×10^{-3} L mol^{-1} s^{-1}) and the experimental (1.8×10^{-3} L mol^{-1} s^{-1}) rate coefficients at the MPWB1K level strongly supports the mechanism recently proposed by our group. This DFT method is then used to study the mechanism of a larger system: cyclohexanone + trifluoroperacetic acid, for which a very good agreement between the calculated and the experimental rate coefficients is also found (1.37 and 0.32 L mol^{-1} s^{-1}, respectively). The modelled mechanism is not ionic but neutral, and consists of two concerted steps. The first one is strongly catalyzed while the second one, the migration step, seems not to be catalyzed for the systems under study. The results of this work could be of interest for understanding other reactions in non-polar solvents for which ionic mechanisms have been assumed.

1. Introduction

The Baeyer–Villiger (BV) rearrangement[1] which involves the oxidation of a ketone to an ester or lactone, is a powerful synthetic tool frequently employed due to its excellent regioselective and stereoselective control. Therefore the reaction has been the subject of a large number of investigations for more than a century (for reviews on this topic see references 2, 3 and 4). It is well known that the BV oxidation initially involves the carbonyl addition of a peroxyacid to a ketone (or an aldehyde) to produce the tetrahedral Criegee intermediate.[5] However, there is still no agreement on the mechanism of the acid catalysis for this step. The most controversial part is whether the protonation of the carbonyl oxygen and the carbonyl addition occur in a stepwise or concerted manner. This distinction implies that in the former case the reaction would occur through an ionic mechanism while in the latter it would be neutral. A new concerted transition state (TS) for the addition step was recently reported by our group.[6] This TS leads to a Gibbs free-energy of activation that is 12.7 kcal mol^{-1} lower than the previously reported concerted TS.[7] This result confirmed the idea that the first step of the BV reaction in non-polar solvents is termolecular (although effectively bimolecular) and acid-catalyzed.

In the second part of this reaction, the adduct undergoes the intramolecular migration of an alkyl or aryl group from the ketone moiety to the nearest peroxide oxygen with the simultaneous dissociation of the O–O bond.[8] Nevertheless, it is not totally clear if this reaction is acid-catalyzed, or if it occurs in a concerted (neutral) or stepwise (ionic) manner. A recent publication from our group showed that the second part of the BV reaction of propanone and cyclohexanone with performic acid, in a non-polar solvent and in the presence of formic acid, occurs in a concerted manner and appears not to be acid catalyzed.[9] The lack of experimental data on this reaction limited us from going any further.

Even though the migration process has been postulated to be the rate-determining step (RDS), it has also been shown that a rate-determining addition can be feasible depending on the reaction conditions and the reactants.[2,10–19] A recent experimental study of the reaction of cyclohexanone with *m*-chloroperbenzoic acid showed that the first (addition) step is the RDS.[16] Our calculations are in agreement with this finding.[9]

The currently accepted mechanism for the BV rearrangement in organic chemistry books is an ionic mechanism (see Fig. 1).[20] The generalization of the idea that in solution reactions should be ionic in spite of the solvent polarity[21] is in clear contradiction with the work of Benson,[22] who proposed that the change in reaction rates when performing a reaction in the gas phase and in non-polar solvents is usually due to liquid-phase effects since the mechanism is most likely unchanged. This difference in reaction rates is due to

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† Electronic supplementary information (ESI) available: Preliminary calculations of the BV reaction of propanone at four levels of theory (Table S1); calculated $K_{eq(1)}$, $\kappa_{(2)}$, $k_{(2)}$ and k (for the catalyzed and uncatalyzed second step) values at different temperatures in the range of 280 to 320 K for the reactions of propanone and cyclohexanone with the corresponding Arrhenius plots (Tables S2 and S3); comparison of the effect of diffuse functions on the thermodynamic calculations of the reaction of propanone (Table S4); Mulliken charge distribution of the stationary points of the reaction of propanone (Fig. S1); plot of the energy change along the relaxed scan of the forced protonation of propanone by TFAA (Fig. S2); MPWB1K/6-311G(d,p)–Onsager Cartesian coordinates of the important stationary points of the calculated kinetic mechanisms. See DOI: 10.1039/b712608e

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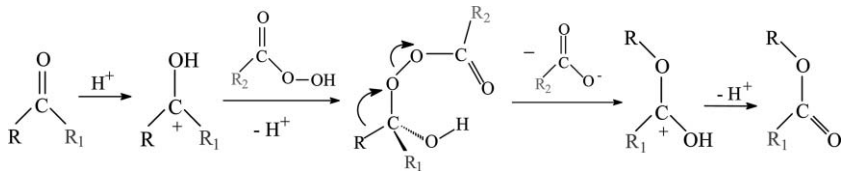

Fig. 1 Currently accepted mechanism for the BV rearrangement.[20]

the lost of translational degrees of freedom in Gibbs free-energy barriers when going from the gas to the solvent phase. Since ions are not stabilized in the gas phase and in non-polar solvents as much as they are in polar environments, the assumption of their existence when proposing a mechanism for a reaction that takes place in non-polar solvents seems unjustified.

In a recent review,[4] a possible general mechanism for the BV reaction is proposed that depends on the acidity of the reaction medium but the polarity of the solvent in which this reaction takes place is not taken into account. This review focuses on the reactants, the Criegee intermediate and the ester product, but it does not provide details on how the actual transformation from one species to another takes place. The ketone protonation is assumed to occur in high-acidity media. In addition, ionic Criegee intermediates are proposed in both high- and low-acidity (basic) media. The general mechanism proposed resembles more a reaction scheme than a mechanism itself, probably because the details of the reaction mechanism are still unclear.

Since the BV reaction is one of the most well known and widely applied methods in synthetic organic chemistry, several computational studies of its mechanism have been published.[6,7,9,19,21,23–31] Although most of these studies have modelled concerted TSs and have assumed a neutral mechanism in non-polar solvents, these findings have not yet been compiled in organic chemistry textbooks or review papers.[4,20] To the best of our knowledge there is no experimental evidence in favour of an ionic mechanism for the BV reaction in non-polar solvents such as dichloromethane—one of the most frequently used solvents for this reaction. The complete reaction mechanism of the BV reaction, including the addition and migration steps, and the Brønsted acid catalysis, has only been studied by Okuno,[18] Grein *et al.*,[7] and our group.[9]

In this paper we aim at modelling the complete BV reaction mechanism of propanone and cyclohexanone with trifluoroperacetic acid, catalyzed by trifluoroacetic acid in dichloromethane, at reliable levels of theory. Using different ketones (as well as a new peroxyacid and acid catalyst) we hope to explore their effect on the BV mechanism we have previously proposed.[6,9] Since experimental rate coefficients are available for both reactions, calculations of these quantities will be performed to test our hypothesis from a quantitative point of view by applying conventional Transition State Theory (TST). To the best of our knowledge, no theoretical calculations of rate coefficients of BV reactions have yet been performed. Furthermore, the mechanisms of these BV reactions have not been previously studied computationally even though they are the ones for which more reliable experimental kinetic data exist.[4] We also hope to continue the theoretical verification of our hypothesis that the mechanism of reactions that take place in non-polar solvents, such as the case of most BV reactions, is most likely not ionic.

2. Computational methodology

The calculations were performed with the Gaussian 03[32] program package. For electronic energies, solvent effects and thermodynamic corrections, we have tested four methods: MP2, B3LYP, BH&HLYP, and MPWB1K, a functional that was recently especially developed for kinetic calculations.[33] We have performed gas-phase geometry optimizations with each method employing the 6-311G(d,p) basis set, which were confirmed by frequency calculations at the same level of theory. In all cases IRC calculations were performed to test that the calculated TSs connect with the proper reactants and products. The energy results were improved by single-point energy calculations with the same method and the 6-311++G(d,p) basis set including solvent effects (the IEF-PCM continuum solvation model using dichloromethane as solvent and the UFF radii). Using this procedure the method that best reproduced the experimental rate coefficient of the reaction of propanone was chosen to further refine the calculations. Geometries and frequencies were then calculated with the Onsager solvent model and the 6-311G(d,p) basis set, followed again by single-point energy calculation with the IEF-PCM method and the 6-311++G(d,p) basis set. This methodology was also used for the study of the reaction of cyclohexanone. For modelling the ionic system the relaxed scan was performed at the MPWB1K/6-311G(d,p) level of theory including the IEF-PCM solvation model.

In order to make appropriate comparisons between the calculated and experimental data, several thermodynamic corrections were applied on the calculated ΔG values. The standard state for the ΔG values was changed from 1 atm to 1 M, in order to relate the calculated Gibbs free energies of activation ($\Delta G^{\neq}$) with experimental rate coefficients that are reported in concentration units. As a consequence of the change in standard state, the ΔG values decrease by 1.89 kcal mol^{-1} for bimolecular reactions at 298.15 K. In addition, we have used the approach proposed by Benson[22] according to which the $\Delta G^{\neq}$ of reactions in non-polar solutions at 298.15 K decreases by 2.56 kcal mol^{-1} for bimolecular reactions with respect to the $\Delta G^{\neq}$ in the gas phase. For a more detailed description of these corrections please see references 6 and 34. To the best of our knowledge, these corrections have not been simultaneously considered in previous theoretical calculations on these reactions, except in our latest publications on this topic using model reactions for which no experimental data are available.[6,9]

In a simplified approach, the complex mechanism of the BV reaction could be rationalized as having an initial reversible step in which the Criegee intermediate (a short-lived species) is formed, followed by a second step that leads to the formation of the corresponding ester. The last step is exergonic ($\Delta G < 0$) enough to be irreversible. In the first step the ketone and the acid form a

$$\text{ketone-acid complex + peroxyacid} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{Criegee + acid} \xrightarrow{k_2} \text{ester + acid + acid'}$$

Scheme 1

stable (reactant) complex (Scheme 1), whose formation between propanone and trifluoroacetic acid has been empirically proven.[11]

Assuming the steady-state approximation the overall rate coefficient could be expressed as:

$$k = \frac{k_1 k_2}{k_{-1} + k_2} \tag{1}$$

This equation has two limiting cases. The first one is for $k_{-1} \gg k_2$, *i.e.*, the barrier of the second step is considerably larger (by 2 kcal mol^{-1} or more) than that of the reverse first-step. In this case, eqn (1) becomes eqn (2) and the second step is the RDS.

$$k = \frac{k_1 k_2}{k_{-1} + k_2} = \frac{k_1 k_2}{k_{-1}} = K_{\mathrm{eq(1)}} k_2 \tag{2}$$

The second case is for $k_{-1} \ll k_2$, *i.e.*, the barrier of the reverse first-step is considerably larger than that of the second step. In this case, eqn (1) becomes eqn (3) and the first-step is the RDS.

$$k = \frac{k_1 k_2}{k_{-1} + k_2} = \frac{k_1 k_2}{k_2} = k_1 \tag{3}$$

These rate coefficients can be calculated using the thermodynamic formulation of TST shown in eqn (4), where κ is the tunneling correction, σ is the reaction path degeneracy, $\Delta G^{\neq}$ is the Gibbs free energy of activation at temperature T, and k_B and h are the Boltzmann and Plank constants, respectively.

$$k = \sigma\kappa \frac{k_B T}{h} \exp\left(\frac{-\Delta G^{\neq}}{RT}\right) \tag{4}$$

Tunnelling corrections were calculated using an asymmetrical Eckart barrier. The reaction path degeneracy is equal to 2 for both steps in propanone, but for the reaction of cyclohexanone, σ equals 1 and 2 for the first and second steps, respectively. In both reactions $\sigma = 1$ for the reverse first step. The tunnelling corrections and rate coefficients in the temperature range of 280 to 320 K, used to determine the Arrhenius factors and activation energies, were calculated using the on-line facilities of the Virtual Kinetic Laboratory.[35]

New research has made it possible to reproduce rate coefficients with an error in $\Delta G^{\neq}$ of less than 1 kcal mol^{-1} [36–39] for relatively small systems in the gas phase using high-level *ab initio* calculations. This is an outstanding level of accuracy but it strongly depends on the methodology employed. Obtaining the same level of accuracy for a relatively large system in solution is a remarkably difficult task. Accordingly, for such systems a difference with the experimental data of ±2 kcal mol^{-1}, *i.e.*, 1–2 orders in rate coefficients, can be considered a very good agreement at the present time.

3. Results and discussion

In the first part of this work we have modelled the addition and migration steps of the reaction of propanone with trifluoroperacetic acid (TFPAA) using trifluoroacetic acid (TFAA) as catalyst. The choice of this system was based on the availability of confident kinetic results[4] and on the relatively small size of the ketone. Two extreme cases will be considered: a non-ionic fully concerted reaction pathway (exploring the catalyzed and non-catalyzed options) and the ionic case. Afterwards the reaction with cyclohexanone will be studied.

3.1. The neutral mechanism with two concerted steps

The modelled mechanism consists of two steps. The most relevant features of the first one were previously described for another BV reaction.[6] In this step, propanone, TFAA and TFPAA are transformed into the corresponding Criegee intermediate through a concerted TS in which simultaneously propanone is protonated, the C–OO bond is formed and TFPAA is deprotonated. The transition vector is therefore complex because it involves a series of atomic displacements in which the largest motions correspond to the two proton migrations and the formation of the C–OO bond. TFAA acts as catalyst by being the proton donor (to the ketone) and acceptor (from TFPAA) entity. All these processes are synergetic, that is to say, each one facilitates and makes possible the other two. The protonation of propanone enhances the electrophilicity of its carbonyl carbon atom, which in turns facilitates the addition of TFPAA and increases the nucleophilicity of TFAA. The addition of TFPAA increases the acidity of its proton which facilitates its removal by TFAA.

The structure of the TS of the first step (Fig. 2) and its Mulliken charge distribution (ESI† Fig. S1) illustrate the previous findings and support a concerted and neutral (non-ionic) mechanism. The sum of the atomic charges of the reactants in the TS (TS1) are 0.249 for TFPAA, 0.097 for propanone and −0.347 for TFAA. The corresponding Mulliken charge distribution of the products in the TS is more balanced: 0.074 and −0.074 for the Criegee intermediate and the leaving TFAA, respectively, which is in agreement with a neutral mechanism. In the reactant complex the carbonyl carbon of the ketone is positively charged (0.66), while in the TS it is negatively charged (−0.22) because it has already accepted the negative charge of the peroxide oxygen which has been increased due to the concerted deprotonation. The charge of the leaving proton of TFPAA increases from 0.31 to 0.75 when in the TS because it is migrating as a "proton" but it is close to covalent bond distances from both oxygen atoms, therefore, ionicity can be disregarded. These bond distances (1.144 and 1.246 Å) are typical of radical hydrogen abstractions where there

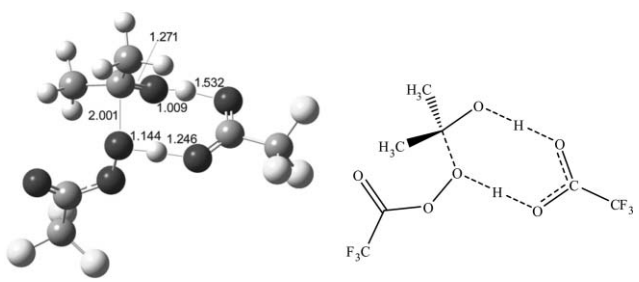

Fig. 2 Structure of the concerted TS of the addition step of the BV reaction of propanone at the MPWB1K/6-311G(d,p)–Onsager level of theory.

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is no possible ionicity. Our calculations show that this catalyzed TS is the lowest-energy possible concerted TS for the first step of this reaction.[6]

The second step of this reaction could be catalyzed or not. These alternatives were previously considered in a model BV reaction.[9] Since we are considering a non-ionic pathway at this point, both TSs would be concerted. The catalyzed step would be bimolecular (involving the Criegee and TFAA) while the uncatalyzed case would be unimolecular.

For the non-catalyzed migration the proton attached to the oxygen atom of the Criegee intermediate migrates to the leaving acid, as previously proposed in references 7 and 19. This TS is also neutral and concerted. The departure of TFAA facilitates the migration of the methyl group, which favours the formation of the carbonyl double bond, and makes easier the migration of the proton to the oxygen atom of the leaving TFAA, and *vice versa*. The structure of the corresponding TS is shown in Fig. 3. The largest atomic displacements in the transition vector correspond to the cleavage of the O–O bond concerted with the migration of the methyl group. The protonation of the leaving acid is of minor importance but noticeable. The analysis of the Mulliken charge distribution of ESI† Fig. S1 (TS2) shows that the total charge of the leaving TFAA is −0.197 which confirms a (non-ionic) neutral mechanism. It is also important to notice the increase in charge of the migrating methyl group from 0.228 in the Criegee intermediate to 0.375 in the TS, which is in agreement with the assumption that the migrating ability is related to the capability of this group to delocalize this positive charge.[19] It should also be noticed that the positive charge on the peroxide oxygen that is accepting the methyl group increases from 0.049 in the Criegee intermediate to 0.202 in the TS because of the rupture of the O–O bond, which is one of the most important features of this TS.

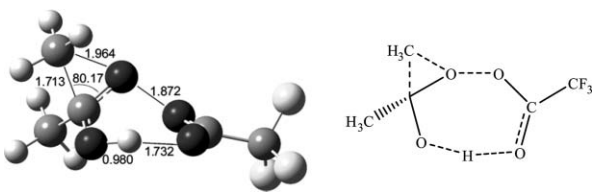

Fig. 3 Structure of the concerted non-catalyzed TS of the migration step of the BV reaction of propanone at the MPWB1K/6-311G(d,p)–Onsager level of theory.

The catalyzed TS of the second step is also concerted (see Fig. 4). Simultaneously the methyl group migrates and the Criegee is deprotonated, and two TFAA molecules leave (one of them is the catalyst and the other one is the leaving fragment from the Criegee that captured a proton from the catalyst). The largest atomic displacements in the transition vector correspond once again to the cleavage of the O–O bond concerted with the migration of the methyl group; the two proton migrations are of minor importance but noticeable. Once again TFAA acts as catalyst by being the proton donor (to the leaving group) and acceptor (from the Criegee) entity. Again, these processes are synergetic: the protonation of the leaving TFAA facilitates the rupture of the O–O bond which makes possible the migration. The migration itself favours the formation of the C=O double bond which makes

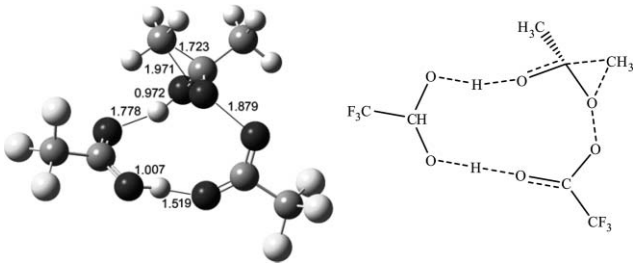

Fig. 4 Structure of the concerted TS, catalyzed by TFAA, of the migration step of the BV reaction of propanone at the MPWB1K/6-311G(d,p)–Onsager level of theory.

possible the deprotonation of the Criegee by the weak nucleophile TFAA, activated by the protonation of the leaving TFAA.

Which of the above TSs is the one with lower energy is expected to depend on the migration ability of the alkyl group, the strength of the acid catalyst, and the leaving ability of the generated acid. The Gibbs free energies, relative to the reactant complex between propanone and TFAA, corresponding to all the stationary points along the reaction coordinate of the reactions studied at four levels of theory, are reported in Table S1 of the ESI.† The geometries of all the stationary points are very similar regardless of the method used in the optimization calculations.

Since experimentally it has been found that the second step of this BV reaction is the RDS,[11] all methods, except MP2, provide a good qualitative description of the reaction mechanism since the $\Delta G^{\neq}$ of the second step is larger than that of the first one. It is in a case like this that eqn (2) applies for the calculation of the overall rate coefficient and the overall activation energy can be related to the activation energies of the elementary steps according to eqn (5). In the study that follows the MP2 calculations will not be considered.

$$E_{\mathrm{a}} = E_{\mathrm{a(1)}} + E_{\mathrm{a(2)}} - E_{\mathrm{a(-1)}} \tag{5}$$

The three DFT methods considered give very similar $\Delta G^{\neq}$ values for the first step but there are significant disagreements between the calculated $\Delta G^{\neq}$ values for the second step. The difference between the B3LYP and BH&HLYP $\Delta G^{\neq}$ values is larger than 9 kcal mol^{-1} and for a quantitative description of the reaction mechanism more accuracy is required. The apparently good qualitative description of the kinetic mechanism by these DFT methods is fortuitous. Another example of this is the difference between the $\Delta G^{\neq}$ values of the first and second steps, which are 1.12, 6.22, and 10.38 kcal mol^{-1}, for the B3LYP, MPWB1K, and BH&HLYP methods, respectively. The $\Delta G^{\neq}$ values of both steps are in the range of typical organic reactions except for the second step with the BH&HLYP method that is unreasonably high. Hence the BH&HLYP functional will not be considered any further. To discriminate between the other two functionals comparisons with experimental results are performed.

The reactant complex between propanone and TFAA is more stable in Gibbs free energy than the isolated reactants by 1.67 and 1.89 kcal mol^{-1} with the MPWB1K and B3LYP methods (see ESI† Table S1), respectively, in agreement with experiments.[11] Hence, the assumption of a bimolecular first step (see Scheme 1) is correct and the calculated overall second-order rate coefficient can be directly compared to the experimental value.[11] The kinetic calculations show that the MPWB1K potential energy surface

reproduces remarkably well the experimental value, while the B3LYP rate coefficient is overestimated. The experimental rate coefficient is only 1.7 times larger than the calculated one with the MPWB1K functional. This corresponds to an overestimation in $\Delta G^{\neq}$ of only 0.31 kcal mol^{-1}. Based on these results, MPWB1K was the functional chosen for further refining our kinetic calculations by considering solvent effects (Onsager method) in the geometry optimizations and frequency calculations, as explained in section 2. The Cartesian coordinates of the optimized stationary points of the reactions of propanone and cyclohexanone appear in the ESI.† Table 1 shows the relative enthalpies and Gibbs free energies of the stationary points relative to the reactant complex for the two reactions, while Table 2 displays the calculated kinetic magnitudes. The results obtained for cyclohexanone are discussed and compared to those of the propanone reaction in section 3.3.

The values of A and E_a reported in Table 2 were obtained from the Arrhenius plots of ln$k$ *vs.* $1/T$. These graphs and the tables with the calculated $K_{eq(1)}$, $\kappa_{(2)}$, $k_{(2)}$ and k values at different temperatures in the range of 280 to 320 K for the reactions considered, appear in Tables S2 and S3 of the ESI.†

The reactant complex of propanone with TFAA was found to be 1.75 kcal mol^{-1} more stable in Gibbs free energy than the isolated reactants, as expected. Although the catalyzed TS of the second step is more stable (in internal energy) and earlier than the uncatalyzed one, $\Delta G^{\neq}$ is lower for the uncatalyzed (intramolecular) migration than for the catalyzed one, in other words, the entropy loss is larger than the enthalpy gain in the latter case.

Since the Gibbs free energies of the reactants (reactant complex + TFPAA) and products (Criegee + TFAA) of the equilibrium of step 1 are very similar, an equilibrium constant value close to 1 is expected, and the activation energies of steps 1 and −1 should very similar to one another ($E_{a(1)} \approx E_{a(-1)}$). Hence, according to eqn (5), the overall activation energy could be determined by that of the second step which can be calculated from its enthalpy of activation by increasing its value by 1.19 or 0.59 kcal mol^{-1} according to eqn (6). The value of m is 2 and 1 for the catalyzed and uncatalyzed cases, respectively. This explains the close resemblance between the calculated E_a and $\Delta H^{\neq}_{(2)}$ values for both reactions.

$$E_a \approx E_{a(2)} = \Delta H^{\neq}_{(2)} + mRT \quad (6)$$

The effect of including diffuse functions in the single-point energy calculations of the stationary points was investigated for the reaction of propanone. These results are shown in Table S4 of the ESI.† There are not huge differences when the diffuse functions are eliminated. However, the calculated change in Gibbs free energy for the catalyzed reaction of the second step is lower than for the uncatalyzed one, which is one of the uncertainties of the present study that will be discussed later on. In addition, the stabilization of the reactant complex is almost twice as large as when diffuse functions are considered, which seems to be an overestimation.

An excellent agreement between the experimental (1.8×10^{-3} L mol^{-1} s^{-1}) and the calculated (1.00×10^{-3} L mol^{-1} s^{-1}) rate coefficients is obtained when only the first step is catalyzed by TFAA. These results strongly support, from qualitative and quantitative points of view, the previously proposed mechanism of two concerted (non-ionic) steps of which only the first one is acid catalyzed.[9] In the following section arguments against an ionic BV mechanism are provided.

3.2. Analysis of the ionic mechanism

We have calculated the hypothetical equilibrium for the protonation of propanone with TFAA in dichloromethane using the MPWB1K functional. This process is endergonic by 26.67 kcal

Table 1 Enthalpies and Gibbs free energies (in kcal mol^{-1} at 298.15 K) of the stationary points relative to the reactant complex (between the ketone and TFAA) for the reactions of propanone and cyclohexanone with TFPAA using TFAA as catalyst[a]

	Propanone reaction		Cyclohexanone reaction	
	ΔH	ΔG	ΔH	ΔG
Isolated reactants	6.49	1.75	6.20	2.59
Reactant complex + TFPAA	0	0	0	0
TS1	5.74	14.30	5.12	14.62
Criegee + TFAA	−2.08	0.54	−2.54	0.21
TS2 + TFAA	21.11[b]	22.94[b]	15.23[b]	18.11[b]
TS2	15.44	23.76	9.33	18.74
Ester or lactone + 2 TFAA	−69.96	−76.69	−67.42	−72.29

[a] Level of theory: MPWB1K/6-311++G(d,p)-IEF-PCM//MPWB1K/6-311G(d,p)–Onsager. [b] Uncatalyzed values of the second step.

Table 2 Rate coefficients ($k = K_{eq(1)}k_2$, in L mol^{-1} s^{-1}) and tunneling factors (both at 303 K), Arrhenius factors (in L mol^{-1} s^{-1}) and activation energies (in kcal mol^{-1}) (for the temperature range of 280 to 320 K) for the reactions of propanone and cyclohexanone with TFPAA using TFAA as catalyst (in both steps and only in the first step)

	Propanone reaction[a]		Cyclohexanone reaction[b]	
	Fully catalyzed	2nd step uncatalyzed	Fully catalyzed	2nd step uncatalyzed
k	1.66×10^{-4}	1.00×10^{-3}	0.315	1.37
κ	1.66	1.73	1.58	1.61
A	2.96×10^{7}	2.66×10^{12}	3.60×10^{6}	3.13×10^{11}
E_a	15.60	21.65	9.78	15.73

[a] Experimental value at 302.95 K: $k = 1.8 \times 10^{-3}$ L mol^{-1} s^{-1} (ref. 11). [b] Experimental value at 302.95 K: $k = 0.32$ L mol^{-1} s^{-1} (ref. 11).

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mol^{-1} and leads to an equilibrium constant of 2.79×10^{-20}. The usual errors attributed to continuum solvent models have to do with specific interactions such as hydrogen bonding with solvent molecules that tend to be poorly described, but in dichloromethane hydrogen bonding with the solvent is not possible. This Gibbs free energy difference is much greater than the $\Delta G^{\neq}$ of the first step and the effective $\Delta G^{\neq}$ of the reaction in the neutral mechanism which shows that it is unlikely that propanone gets protonated in a non-polar solvent.

The formation of an ion pair between the protonated ketone and the carboxylate anion might be possible. However, any attempt at such a calculation fails for obvious reasons: the proton migrates back to the carboxylate anion producing TFAA and propanone. In order to obtain an approximate idea of the energy involved in this process we have modelled it as a relaxed scan of the CO–H bond distance from that in the propanone–TFAA complex. The increment of this distance forces the protonation of propanone constraining the system to stay as an ion pair. It is not possible to obtain reliable thermodynamic corrections for this type of calculation but since in this supermolecular approach the process would be unimolecular these corrections should not be that important. For bond distances from 0.995 to 1.745 Å the energy increases continuously up to 13.2 kcal mol^{-1} (see ESI†Fig. S2). Therefore, this process is not possible without the assistance of a third molecule that would be the peroxyacid, *i.e.*, the concerted mechanism would take place. The assumption of the formation of a "partially protonated ketone" has no sense, and the formation of some kind of genuine ion pair has already been ruled out. Moreover, if the "TFAA anion" continues bonded to the "protonated ketone" this reaction would not be favoured since the TFAA anion should leave to produce the Criegee intermediate, and in this process it should acquire the proton so that the catalyst is regenerated.

Let us suppose that these calculations are not sufficiently accurate and that in fact propanone becomes protonated. This makes it highly electrophilic and the nucleophile is the peroxyacid with its weakly acidic proton. There are three hypothetical possibilities:

1—The peroxyacid is deprotonated in acid media by the ketone or the TFAA anion, but this process is unfeasible.

2—The neutral peroxyacid attacks the protonated ketone resulting in a positively charged oxygen atom, bonded to three atoms: C, H and O. This intermediate is hardly acceptable. We tried to model such a TS but it was impossible to locate it. Any attempt in this direction produces the reactants. If such a TS existed it would be easier to find computationally than those of the neutral mechanism.

3—The deprotonation is concerted with the peroxyacid attack. In such a case, it seems logical to assume that the reaction would start from the "ionic pair" in which the TFAA anion forms two hydrogen bonds: one with the peroxyacid H, and another one with the H in the protonated carbonyl group. Any attempt to find such a TS leads to the concerted neutral TS, *i.e.*, the charge separation is absolutely unnecessary and energetically disfavoured.

Thus, we conclude that the currently accepted ionic mechanism for the BV reaction[4,20] does not compete with the concerted (neutral) mechanism we are proposing and it is an incorrect extrapolation from known mechanisms in polar solvents since no experimental evidence or theoretical calculations have demonstrated such a case.

After verifying the concerted (neutral) mechanism by comparing the calculated and experimental rate coefficients for the BV reaction of propanone with TFPAA (catalyzed by TFAA in the first reaction step), and proving that the ionic mechanism is not possible, we proceed to study the effect of the ketone on the mechanism of the BV reaction. For this purpose we have chosen cyclohexanone because there are enough experimental data available for its BV reaction.[11] In addition to that, among the ketones studied, propanone reacts the slowest in the BV reaction while cyclohexanone reacts the fastest. Hence, if there is any change in the mechanism due to the migrating ability of the ketone, the study of the BV reaction of cyclohexanone should reveal it.

3.3. The neutral mechanism of the BV reaction of cyclohexanone

The calculation of the stationary points and the kinetic magnitudes of the reaction of cyclohexanone with TFPAA, in the presence of TFAA, was performed assuming the previously described concerted mechanism. These results are shown in Tables 1 and 2. Since it was previously shown that ketones form stable complexes with acids, the assumed reactants are once again the corresponding reactant complex and TFPAA. This was verified for the complex of cyclohexanone with TFAA which was found to be 2.59 kcal mol^{-1} more stable in Gibbs free energy than the isolated reactants. This reactant complex is 0.84 kcal mol^{-1} more stable than that of propanone. The similarity between the values of the overall activation energy and the enthalpy of activation of the second step is once again observed.

A larger rate coefficient is again obtained when the first step of the concerted mechanism is catalyzed while the second concerted step is not. This rate coefficient (1.37 L mol^{-1} s^{-1}) is only 4.27 times larger than the experimental one (0.32 L mol^{-1} s^{-1}) which corresponds to an underestimation in $\Delta G^{\neq}$ of only 0.85 kcal mol^{-1}. This is an excellent result within the so-called "chemical accuracy" of ± 1 kcal mol^{-1} usually only obtainable with the highest-level quantum mechanical calculations. This is another strong piece of evidence that the neutral concerted mechanism is correct since it would be almost impossible to reproduce two rate coefficients that differ in more than two orders of magnitude using an incorrect mechanism with the same methodology.

As can be concluded from our results,[6,9] the role of the catalyst is very important in the first step because the difference in $\Delta G^{\neq}$ between the uncatalyzed and TFAA-catalyzed step is larger than 20 kcal mol^{-1}. This means that (theoretically at least) the reaction is almost impossible without a catalyst. However, the role of the catalyst could be played by a solvent molecule or by a second peroxyacid molecule. The effectiveness of such catalysis would be proportional to the acid strength of the peroxyacid or the solvent. Given that together with any peroxyacid its corresponding acid is also present in considerable concentration, and that the same acid is a product of the reaction, the uncatalyzed reaction should not be observed experimentally. However, the second step which is the RDS of this reaction appears to be uncatalyzed. Apparently, the BV rearrangement is a complex consecutive reaction which does not occur without a catalyst, but it has a non-catalyzed (or perhaps weakly catalyzed) RDS. Although the acid molecule decreases the enthalpy of the TS of the second step, the entropy loss

overcomes it and the second step appears to be uncatalyzed, *i.e.*, the Criegee intermediate evolves through a unimolecular process to the ester (or lactone) and the corresponding acid. However, the $\Delta G^{\neq}$ difference between the catalyzed and the uncatalyzed TSs is relatively small (0.63 kcal mol^{-1}) and the catalyzed reaction includes the approximate correction for the liquid phase suggested by Benson,[22] therefore the results of this work are not conclusive with respect to the (catalyzed or uncatalyzed) nature of the second step. Nevertheless, since the Arrhenius equations of both mechanisms are very different in pre-exponential factor and activation energy (see Tables 2, S2 and S3 (ESI†)) the experimental determination of these parameters should elucidate this important feature of the mechanism. In our opinion, such an experiment should be performed in conditions similar to those of ref. 11, in a large excess of ketone and excess of acid.

It can be considered that the second step is the RDS for the studied ketones and for most of the others. However, for ketones with higher migrating ability than cyclohexanone, the addition step could be the RDS. The kinetic analysis made so far is valid for the reactions of ketones with TFPA, using TFAA as catalyst, and extrapolations to other systems should be carefully done.

Comparison of the addition step of both ketones shows that the $\Delta G^{\neq}$ is almost the same (around 14 kcal mol^{-1}) and that the difference in reactivity is a consequence of the difference in $\Delta G^{\neq}$ for the second step (of around 5 kcal mol^{-1}). Fig. 5 displays the most probable reaction profile of the two BV reactions studied calculated with the MPWB1K functional at 298.15 K. The equilibrium constant of the Criegee formation is between 0.60 and 0.68 for both reactions at this temperature.

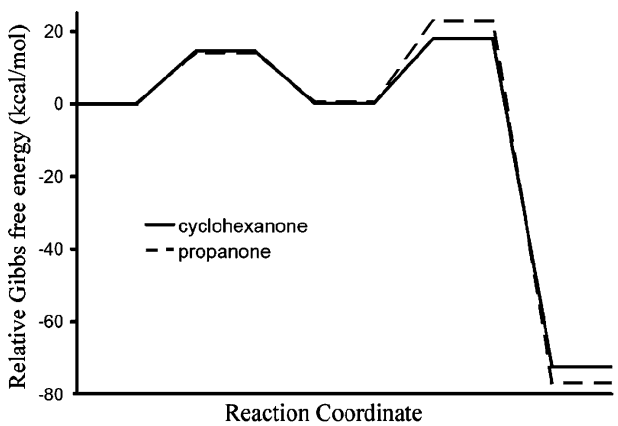

Fig. 5 Reaction profile of the BV reactions studied at 298.15 K calculated at the MPWB1K/6-311++G(d,p)-IEF-PCM//MPWB1K/6-311G(d,p)–Onsager level of theory, relative to the reactant complex: the first step is catalyzed while the second step shown is not.

Fig. 6 displays the addition TS of cyclohexanone which is very similar to that of propanone shown in Fig. 2 The second (uncatalyzed) TS is also similar to that previously calculated for propanone (see Fig. 7). In the present mechanism, the previous observation that the methyl group migrates in antiperiplanar conformation with respect to the O–O moiety[7,18,19,27,40] is confirmed. The TS for the migration of cyclohexanone is much earlier than that of propanone for all but the C–C bond distance. This is in agreement with the relative migration ability of these ketones. The novelty of the present work, regarding the uncatalyzed migration

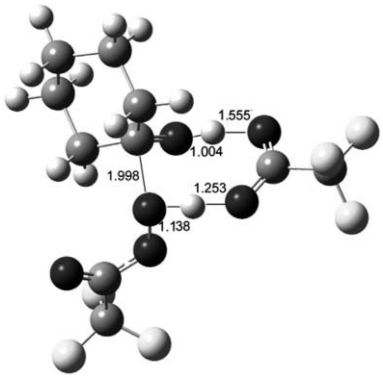

Fig. 6 Structure of the concerted TS of the addition step of the BV reaction of cyclohexanone at the MPWB1K/6-311G(d,p)–Onsager level of theory.

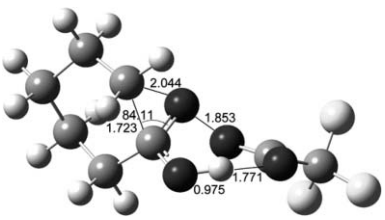

Fig. 7 Structure of the concerted uncatalyzed TS of the migration step of the BV reaction of cyclohexanone at the MPWB1K/6-311G(d,p)–Onsager level of theory.

TS of the two ketones, is that the agreement between calculated and experimental rate coefficients demonstrates that this is the lowest-energy TS.

In polar solvents the mechanism could be different. In such a case the reaction mechanism would not be unique and would depend on the solvent. This is just a possibility since the mechanism could also be that reported in this paper. To make this conclusion the reaction should be modelled assuming both ionic and neutral mechanisms in polar solvents, but that is the work of another study.

4. Conclusions

It has been shown that the mechanism of the BV rearrangement in non-polar solvents is not ionic but neutral and fully concerted in both steps. An exceptionally good agreement between the calculated and the experimental rate coefficients strongly supports the proposed mechanism for the BV reaction of propanone and cyclohexanone with TFPAA, assisted by TFAA. This is the first computational study of the kinetic mechanism of these reactions and it is also the first study in which rate coefficients of BV reactions have been theoretically determined and successfully compared with experiments.

In the first step, which is bimolecular, the protonation of the ketone and the addition/deprotonation of the peroxyacid are assisted by the acid catalyst. This mechanism is in agreement with previous evidence that the acid catalysis is general, not specific, which is due to the unfavoured acid dissociation in non-polar solvents. The second step, which seems to be unimolecular, was also shown to be concerted and apparently uncatalyzed. Due to the small difference in the $\Delta G^{\neq}$ between the catalyzed

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and the uncatalyzed second step, the experimental study of the temperature dependence of the rate constants is suggested to clarify the nature of this step. Calculated magnitudes for both cases are provided for future comparison with experimental data. Large pre-exponential factors and activation energies would correspond to the uncatalyzed case. The migration step was found to be the RDS for the studied systems, but this should not be extrapolated to different peroxyacid–acid pairs.

The recently developed MPWB1K functional produces excellent kinetic results for the modelling of these complex and computationally challenging reactions. The agreement between the calculated and experimental results is excellent, at relatively low computational cost, for the description of two consecutive reactions in which several kinds of bonds are simultaneously breaking and forming. The results using this functional for the present case are considerably more accurate than using the more popular B3LYP functional and the more computationally expensive MP2 method.

The use of Gibbs free energies, instead of thermally corrected electronic energies, converted to the proper reference state with liquid phase corrections, is of crucial importance for obtaining reliable kinetic results. Even though this might seem obvious, it is frequently overlooked in many theoretical studies.

The results of this work could have implications for other reactions in non-polar solvents considered stepwise and ionic, since, in all probability, some of them are both concerted and neutral. Researchers should be aware of this possibility.

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