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Substituent effects in the Baeyer–Villiger reaction of acetophenones: a theoretical study

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This paper reports the first complete theoretical study of substituent effects on the mechanism of the Baeyer–Villiger (BV) reaction in non-polar solvents taking into account the lowest-energy mechanism that has been proposed for this rearrangement which is non-ionic and fully concerted. The BV reaction of *p*-substituted acetophenones, *p*-$XC_6H_4COCH_3$ (X = NO_2, CN, H, CH_3, OCH_3), with performic (PFA) and trifluoroperacetic (TFPAA) acids, catalyzed by formic (FA) and trifluoroacetic (TFAA) acids, respectively, using the MPWB1K functional and the 6-311G(d,p) and 6-311++G(d,p) basis sets, are studied. Solvent effects are taken into account by means of the PCM continuum model using dichloromethane as solvent. Electron-donating substituents on the aryl group have a relatively small activation effect on the first step, but a pronounced activation effect on the second to the point of being able to change the rate-determining step (RDS) of the reaction, as observed in the case of *p*-methoxyacetophenone with TFPAA acids. After analyzing the changes in Gibbs free energy of activation, geometrical parameters, and charge distributions of the transition states (TSs), explanations are provided for the two distinct effects that substituents on the ketone have on the kinetics of the addition and migration steps of the BV oxidation. The effect of the acid/peracid pair used is also discussed. Copyright © 2008 John Wiley & Sons, Ltd.

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Keywords: DFT calculations; Baeyer–Villiger; oxidation; mechanism; acetophenone; substituent effect; PFA; TFPAA

INTRODUCTION

The Baeyer–Villiger (BV) rearrangement[1] is the oxidation of a ketone to an ester or lactone by treatment with a peracid; aldehydes can also be oxidized to carboxylic acids. This reaction is an important synthetic procedure because of its exceptional regioselectivity and stereoselectivity.[2–4] It is well accepted that the mechanism for the BV oxidation in non-polar solvents is a two-step reaction that involves the carbonyl addition of a peracid to form the so-called Criegee intermediate.[5] This adduct undergoes an intramolecular migration of an alkyl or aryl group from the ketone moiety to one of the two peroxide oxygens with concurrent cleavage of the O—O bond (Fig. 1).[6]

Although the migration is accepted to be the rate-determining step (RDS), some kinetic results for the reaction have been controversial regarding this issue.[3,7–10] It has been noted that when the ketone is unsymmetrical, groups with better capacity to stabilize the incipient positive charge will migrate more readily, though other factors may also be involved.[3,11,12] Despite extensive studies of the effects of substituents on the rates of the BV rearrangement, not much detailed information is known regarding the correlation between the substitution pattern of the ketone and its reactivity. This has been rationalized on the basis that any step in the BV reaction can be rate-determining depending on the substrate, catalyst, and so forth.[3,13–17] In the case of acetophenones the migration has been proposed as the RDS on the basis of the negative ρ-value obtained for the Hammett plot of the BV reaction of these ketones with trifluoroperacetic (TFPAA) acid. This statement was further confirmed by the kinetic isotope effect (^{14}C) observed on the reaction of *meta*-chloroperbenzoic acid (*m*-CPBA) with these ketones.[10] However, the *p*-methoxy derivative showed lack of isotope effect, which has been explained on the basis of the strong electron-donating capacity of the *p*-methoxy substituent. In contrast, others have considered that the isotopic labeling results are consistent with a switch in the RDS from the aryl migration to the carbonyl addition when going from electron-withdrawing to electron-donating substituents.[3,11,18]

Due to the importance of the BV reaction as an extensively applied method in organic synthesis, a number of theoretical studies have been made to elucidate its mechanism.[18–35] To the best of our knowledge, the complete reaction mechanism,

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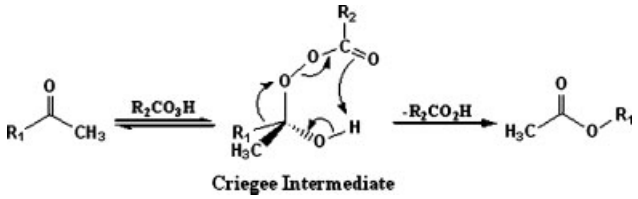


Figure 1. The Baeyer–Villiger reaction

including the addition and migration steps and the Brønsted acid catalysis, has only been investigated by Okuno,[21] Grein *et al*.,[31] and our group.[34] A new acid-catalyzed concerted transition state (TS) for the addition step that leads to a Gibbs free energy of activation lower by 12.7 kcal/mol than the previously proposed one, was recently reported by our group.[32] This result confirms the idea that in the first step of the BV reaction the peracid addition is concerted with the protonation of the ketone and the deprotonation of the peracid. In addition, we have provided theoretical evidence in favour of the uncatalyzed TS previously proposed in 1997 by Cardenas *et al*.[26] for the migration step of this reaction.[33,34] Taking into account the lowest-energy mechanism proposed, rate coefficients for the BV reactions of propanone and cyclohexanone with TFPAA acid, catalyzed by trifluoroacetic (TFAA) acid in dichloromethane, were calculated applying TS theory. These calculations, performed at the MPWB1K/6-311++G(d,p)-IEF-PCM//MPWB1K/6-311G(d,p)-Onsager level of theory, agree exceptionally well with the experimental values providing stronger evidence for the new mechanism proposed.[34]

This study attempts to explain in detail the substituent effects on the BV reaction of several *p*-substituted acetophenones with performic (PFA) and TFPAA acids, taking into account our previous findings on the BV reaction.[33,34] The aim of this paper is to shed light on several questions regarding this system by studying the effects of the substituent in the ketone and the acid/peracid pair on the kinetics of the BV reaction and the geometries and charge distributions of the addition and migration TSs. The results of this work complement our previous investigations and are fully coherent with the experimental data.

COMPUTATIONAL METHODOLOGY

The electronic structure calculations were performed with the Gaussian 03 program package[36] using the recently developed MPWB1K functional[37] and the 6-311G(d,p) basis set in the gas phase. The energy results were improved by single-point calculations with the same functional and the 6-311++G(d,p) basis set, including solvent effects by means of the IEF-PCM continuum model using dichloromethane as solvent and the UFF radii.

The Gibbs free energy values in solvent were calculated by adding the total energy in solvent and the gas-phase thermal correction to the Gibbs free energy at 298.15 K. The standard state of the calculated ΔG values was changed from 1 atm to 1 M. The thermodynamic correction to the gas-phase ΔG values to simulate the effect of the liquid phase, as proposed by Benson,[38] was also applied. This correction was first used in the BV reaction by Okuno[21] and later on by others.[32–34,39,40] For details, refer to References [32] and [39].

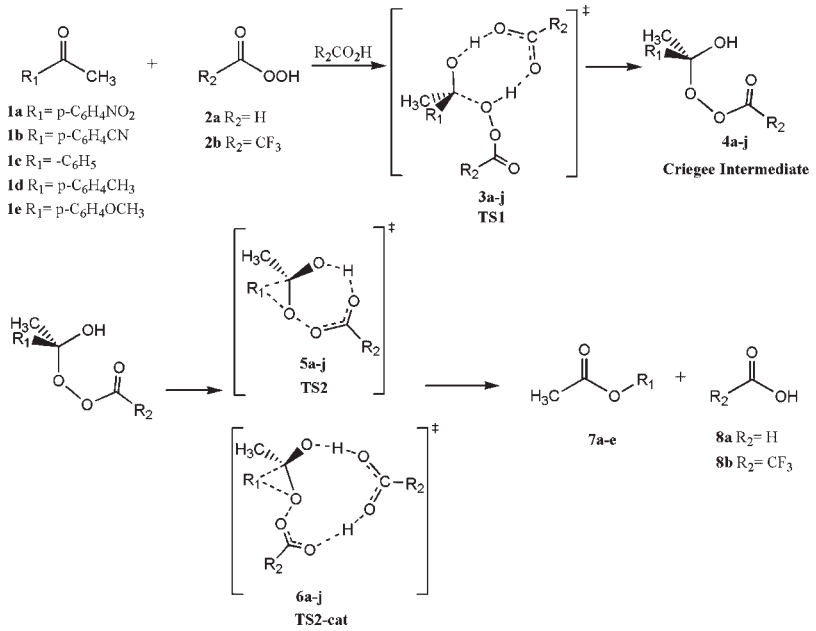
In a simplified approach, the complex mechanism of the BV reaction could be rationalized as having an initial reversible step in which the Criegee intermediate (a short-lived species) is formed, followed by a second step that leads to the formation of the corresponding ester. The last step is exoergic ($\Delta G < 0$) enough to be irreversible. Initially, the ketone and the acid catalyst can form a (reactant) complex. When the complex is more stable in Gibbs free energy than the isolated reactants (which has been empirically proven in the case of acetophenone and TFAA)[8] the standard Gibbs free energy change of activation of the first step is calculated relative to the complex; otherwise the calculation is relative to the isolated reactants (as in the reaction with PFA).

RESULTS AND DISCUSSION

The effects of electron-donating (—OCH_3 and —CH_3) and electron-withdrawing (—NO_2 and —CN) groups at the *para* position of the migrating aryl group in acetophenones reacting with PFA and TFPAA acids in the presence of the corresponding acid catalysts, formic (FA) and TFAA acids, respectively, are studied. Substituent effects in the changes of TS geometries and charge distributions, as well as on enthalpy (ΔH) and Gibbs free energy (ΔG) differences in the two BV reactions, are discussed below.

The two steps of the BV reaction of the systems studied are shown in Scheme 1. Since it has been previously shown that an uncatalyzed addition is not energetically feasible,[21,31–33] we have only considered the calculation of the catalyzed addition TS (TS1).[32] For the migration step, both catalyzed and uncatalyzed options have been initially considered. In the first step the peracid (**2a-b**) is added to the carbonyl carbon of the acetophenone (**1a-e**) to form the corresponding Criegee intermediate (**4a-j**) through a concerted TS (TS1; **3a-j**), in which simultaneously the ketone is protonated, the C—OO bond is formed and the peracid is deprotonated; this process is acid-catalyzed (**8a-b**). In the second step the migration of the aryl group and the cleavage of the O—O bond occur simultaneously with the migration of the proton of the former carbonyl oxygen to the leaving acid.[21,33] The uncatalyzed (TS2; **5a-j**) and catalyzed (TS2-cat; **6a-j**) migration TSs are also neutral and concerted. For a more detailed description of these processes, refer to References [32–34] and Figure S7. In all the cases studied, the Gibbs free energy change of activation is lower for the uncatalyzed migration than for the catalyzed one; in other words, the entropy loss is larger than the enthalpy gain (Tables 1 and 2). Hence, our discussion only makes reference to the uncatalyzed migration.

The calculated Gibbs free energies and enthalpies at 298.15 K relative to the isolated reactants or the reactant complex of the different stationary points calculated along the reaction pathway of the BV oxidation of the acetophenones studied with PFA and TFPAA, obtained at the MPWB1K/6-311G++(d,p)-IEF-PCM//MPWB1K/6-311G(d,p) level of theory, are reported in Tables 1 and 2. The reactant complexes between the acetophenones and TFPAA are more stable in Gibbs free energy than the isolated reactants by 0.89–1.57 kcal/mol, whereas the corresponding complexes with PFA are less stable than the isolated reactants by 0.16–1.33 kcal/mol. Hence, the reported enthalpies and Gibbs free energies of the modeled stationary points for the PFA oxidations are relative to the isolated reactants, while in the case of the reaction with TFPAA these values have been reported relative to the reactant complex. The main geometrical parameters of TS1, the Criegee intermediate, and TS2, resulting



Scheme 1. Baeyer–Villiger reaction of acetophenones (**1a-e**) with a peracid (**2a-b**)

Table 1. Enthalpy and Gibbs free energy changes (in kcal/mol, at 298.15 K) of the modeled stationary points, relative to the isolated reactants for the BV reaction of *p*-substituted acetophenones with PFA using FA as catalyst[a]

	—NO_2		—CN		—H		—CH_3		—OCH_3	
System	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG
Reactants	0	0	0	0	0	0	0	0	0	0
Complex + PFA	−3.14	1.24	−3.51	0.99	−4.23	1.33	−4.01	0.31	−4.32	0.16
TS1	7.30	**23.21**	7.12	**22.97**	6.30	**22.00**	6.14	**21.78**	6.10	**21.80**
Criegee + FA	−4.87	3.84	−5.02	3.38	−4.07	4.60	−3.59	4.51	−2.94	5.65
TS2 + FA	20.27	**28.51**	19.50	**28.01**	16.68	**25.06**	15.56	**24.30**	13.80	**22.31**
TS2-cat	14.97	30.03	15.32	29.45	12.82	26.35	11.46	25.47	10.10	24.51
Products	−61.44	−68.16	−60.32	−66.13	−59.56	−66.90	−58.68	−66.04	−57.40	−64.68

[a] Level of theory: MPWB1K/6-311G++(d,p)-IEF-PCM// MPWB1K/6-311G(d,p).

Table 2. Enthalpy and Gibbs free energy changes (in kcal/mol, at 298.15 K) of the modeled stationary points, relative to the reactant complex for the BV reaction of *p*-substituted acetophenones with TFPAA using TFAA as catalyst[a]

	—NO_2		—CN		—H		—CH_3		—OCH_3	
System	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG
Reactants	5.12	0.89	5.38	0.94	6.16	1.03	6.32	1.57	6.49	1.42
Complex + TFPAA	0	0	0	0	0	0	0	0	0	0
TS1	8.79	**19.03**	8.19	**18.22**	7.64	**17.19**	7.41	**16.62**	7.18	**16.78**
Criegee + TFAA	−1.38	2.42	−0.29	2.37	0.93	2.80	1.61	3.79	2.31	4.14
TS2 + TFAA	18.92	**21.30**	18.27	**20.62**	16.19	**18.16**	15.00	**17.31**	14.23	**16.17**
TS2-cat	13.81	24.68	13.03	23.45	10.14	20.37	8.79	19.33	7.38	17.33
Products	−71.36	−82.84	−70.57	−80.77	−69.02	−81.44	−67.99	−80.05	−66.55	−78.84

[a] Level of theory: MPWB1K/6-311G++(d,p)-IEF-PCM// MPWB1K/6-311G(d,p).

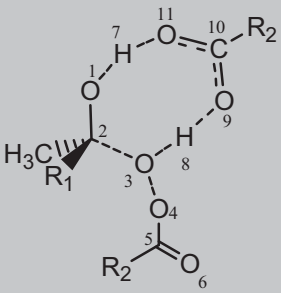
from the oxidation of the five acetophenones considered with PFA and TFPAA at the MPWB1K/6-311G(d,p) level of theory, are presented in Tables 3 and 4, respectively. The substituent effects on the TS structures of both steps of the BV reactions studied and their charge distribution (Figures S1–S6) agree with previous findings.[18,34]

In both BV reactions, the changes in the C_2—O_3 bond distance in TS1 show that it becomes more reactant-like (with respect to the addition process) the more electron-donating the substituent (going from 2.010 Å in *p*-NO_2 to 2.059 Å in *p*-OCH_3 for the reaction with PFA), and this effect is much more pronounced in the reaction with TFPAA (going from 2.064 Å in *p*-NO_2 to 2.086 Å in *p*-OCH_3). However, the proton-transfer processes, described by the changes in the O_1—H_7, O_{11}—H_7, O_3—H_8, and O_9—H_8 bond distances, show the opposite trend and to a much greater extent: TS1 becomes more product-like the more electron-donating the substituent and this is again more intensified in the reaction with TFPAA. The increase of the C_2—O_1 bond distance and the decrease of the O_1—H_7 bond distance as the electron-donating ability of the substituent increases should be related to the increased basicity of the ketone.[41] In a complex TS like this the concept of early or late TS is not a straightforward one, although the structural changes found in TS1 indicate that the proton-transfer processes, and in particular the protonation of the ketone, are the determining processes, as observed in the animation of the transition vector.

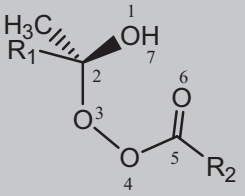
The natural population analysis (NPA) charge distribution (Figures S1–S6) for the addition reaction with both peracids shows that the protonation of the ketone increases the positive charge of the carbonyl carbon in TS1 (e.g., it goes from 0.60 to 0.69–0.70 in TS1 for the reaction with PFA), enhancing the electrophilicity of this atom and facilitating the addition process. When the protonation of the ketone is performed by TFAA, which is a stronger acid than FA, the charge on the carbonyl carbon and its electrophilicity increase even more (TS1 in Figures S3 and S6), facilitating the addition of the relatively less nucleophilic TFPAA to a greater extent than in the case of PFA. The addition of PFA has a higher Gibbs free energy of activation than with TFPAA in all cases.

The electron-donating ability of the substituent in the ketone has two opposite effects on the kinetics of the concerted acid-catalyzed addition step. It should in principle decrease the electrophilicity of the carbonyl carbon, but this translates to an increase of the basicity of the carbonyl oxygen (its negative charge in the ketone increases as the electron-donating ability of the substituent increases, as does the positive charge of the

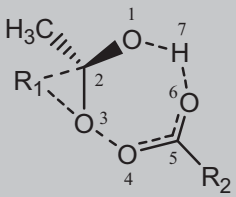
Table 3. Selected bond lengths (in Å) of the Criegee intermediate and the TS of the BV reaction of *p*-substituted acetophenones with PFA using FA as catalyst[a]



TS1 (3a-j)



Criegee (4a-j)



TS2 (3a-j)

Structure	X	C_2—R_1	R_1—O_3	C_2—O_1	C_2—O_3	O_1—H_7	O_6—H_7	O_3—O_4	O_{11}—H_7	O_3—H_8	O_9—H_8	C_{10}—O_9	C_{10}—O_{11}
TS1(**3a**)	NO_2	1.485	—	1.258	2.010	1.107	—	1.392	1.288	1.181	1.205	1.247	1.241
TS1(**3b**)	CN	1.483	—	1.259	2.018	1.100	—	1.392	1.298	1.183	1.204	1.247	1.241
TS1(**3c**)	H	1.476	—	1.263	2.036	1.075	—	1.393	1.342	1.179	1.208	1.249	1.238
TS1(**3d**)	CH_3	1.471	—	1.264	2.046	1.068	—	1.393	1.357	1.183	1.204	1.250	1.237
TS1(**3e**)	CH_3O	1.464	—	1.267	2.059	1.055	—	1.394	1.383	1.192	1.196	1.251	1.235
Criegee(**4a**)	NO_2	1.512	2.286	1.375	1.426	0.958	2.245	1.401					
Criegee(**4b**)	CN	1.512	2.287	1.375	1.426	0.958	2.249	1.400	—	—	—	—	—
Criegee(**4c**)	H	1.510	2.285	1.376	1.430	0.958	2.267	1.403	—	—	—	—	—
Criegee(**4d**)	CH_3	1.509	2.287	1.377	1.430	0.958	2.280	1.403	—	—	—	—	—
Criegee(**4e**)	CH_3O	1.507	2.283	1.377	1.431	0.958	2.301	1.404	—	—	—	—	—
TS2(**5a**)	NO_2	1.648	1.779	1.316	1.324	1.020	1.495	1.913					
TS2(**5b**)	CN	1.639	1.777	1.318	1.325	1.018	1.502	1.916	—	—	—	—	—
TS2(**5c**)	H	1.618	1.787	1.326	1.327	1.010	1.532	1.916	—	—	—	—	—
TS2(**5d**)	CH_3	1.602	1.788	1.330	1.330	1.006	1.546	1.917	—	—	—	—	—
TS2(**5e**)	CH_3O	1.572	1.787	1.337	1.339	1.002	1.563	1.917	—	—	—	—	—

[a] Level of theory: MPWB1K/6-311G(d,p).

Table 4. Selected bond lengths (in Å) of the Criegee intermediate and the TS of the BV reaction of *p*-substituted acetophenones with TFPAA using TFAA as catalyst[a]

Structure	X	C_2—R_1	R_1—O_3	C_2—O_1	C_2—O_3	O_1—H_7	O_6—H_7	O_3—O_4	O_{11}—H_7	O_3—H_8	O_9—H_8	C_{10}—O_9	C_{10}—O_{11}
TS1(**3f**)	NO_2	1.476	—	1.263	2.064	1.043	—	1.390	1.411	1.175	1.210	1.246	1.229
TS1(**3g**)	CN	1.475	—	1.263	2.070	1.040	—	1.390	1.419	1.176	1.208	1.246	1.228
TS1(**3h**)	H	1.468	—	1.268	2.076	1.025	—	1.391	1.461	1.192	1.193	1.249	1.225
TS1(**3i**)	CH_3	1.463	—	1.270	2.075	1.020	—	1.392	1.479	1.201	1.185	1.250	1.223
TS1(**3j**)	CH_3O	1.456	—	1.274	2.086	1.012	—	1.392	1.506	1.220	1.167	1.252	1.222
Criegee(**4f**)	NO_2	1.511	2.285	1.373	1.432	0.958	2.359	1.399					
Criegee(**4g**)	CN	1.511	2.285	1.374	1.432	0.957	2.360	1.400	—	—	—	—	—
Criegee(**4h**)	H	1.509	2.287	1.374	1.436	0.957	2.386	1.401	—	—	—	—	—
Criegee(**4i**)	CH_3	1.507	2.288	1.375	1.436	0.957	2.382	1.402	—	—	—	—	—
Criegee(**4j**)	CH_3O	1.506	2.285	1.375	1.437	0.957	2.376	1.402	—	—	—	—	—
TS2(**5f**)	NO_2	1.628	1.801	1.327	1.325	0.995	1.603	1.887					
TS2(**5g**)	CN	1.618	1.801	1.329	1.327	0.994	1.612	1.888	—	—	—	—	—
TS2(**5h**)	H	1.598	1.821	1.337	1.331	0.987	1.649	1.875	—	—	—	—	—
TS2(**5i**)	CH_3	1.580	1.825	1.341	1.336	0.985	1.658	1.872	—	—	—	—	—
TS2(**5j**)	CH_3O	1.557	1.839	1.349	1.345	0.981	1.687	1.855	—	—	—	—	—

[a] Level of theory: MPWB1K/6-311G(d,p).

proton being transferred from the acid in TS1), which, once protonated, increases the electrophilicity of the carbonyl carbon and facilitates the addition of the peracid. The overall substituent charge effect on the carbonyl carbon is almost nil. In going from *p*-NO_2 to the other substituents in TS1, the charge on the carbonyl carbon and oxygen atoms of the initial ketone increase. However, for the acetophenones with substituents that are more electron-donating than —CN, the charges on these atoms in TS1 are basically the same. These observations agree with the small decrease of the Gibbs free energy barrier for the addition step of the BV reaction with both peracids as the electron-donating ability of the substituent in the ketone increases. This decrease is more pronounced (1.21 kcal/mol) when going from *p*-nitroacetophenone to acetophenone. Once again, the charge distribution changes in TS1 indicate that the protonation of the ketone is the decisive chemical change in the concerted acid-catalyzed addition step, and electron-donating groups in the ketone facilitate its protonation, which produces an overall stabilization of TS1.[42] The comparison of the results using both peracids reinforces previous reasoning. TFAA is a stronger acid than FA, and TFPAA is a weaker nucleophile than PFA. Since the Gibbs free energy of activation of the addition step is larger for the BV reaction with PFA than for the reaction with TFPAA (Tables 1 and 2), this suggests that the strength of the acid is more important than the nucleophilicity of the peracid. The strength of the acid determines the strength of the acid-base interaction with the ketone and the increase of the electrophilicity of the carbonyl group of the reactant complex to be formed. This is the cause of the larger catalytic effect of TFAA over FA, which leads to lower activation barriers when TFPAA reacts.

In the uncatalyzed migration, the observed changes in the C_2—R_1, O_3—O_4, R_1—O_3, and C_2—O_1 bond distances when going from the Criegee intermediate to TS2 indicate that the aryl migration and the breaking of the O_3—O_4 bond are concerted (Tables 3 and 4), as previously shown.[18,26,34] In the case of the reaction with PFA when going from the Criegee intermediate to TS2, the C_2—R_1 and O_3—O_4 bond lengths are increased by average values of 0.106 and 0.514 Å, respectively. Meanwhile, the C_2—O_1 and R_1—O_3 bond lengths are shortened by average values of 0.051 and 0.502 Å, respectively. The biggest atomic displacements in the transition vector correspond to these processes, whereas the protonation of the leaving acid has a relatively small component. It is worth mentioning that the C_2—R_1 bond-breaking process is more susceptible to substituent effects than the R_1—O_3 bond-making process. As the electron-donating ability of the substituent increases, TS2 becomes more reactant-like (more resembling the Criegee intermediate) with respect to the three concerted processes: the migration of R_1, the cleavage of the O_3—O_4 bond, and the proton transfer. This effect is much more pronounced in the reaction with TFPAA. For the ketones studied, these findings are consistent with the observed ^{14}C kinetic isotope effect.[10]

The changes in the NPA charge distribution when going from the Criegee intermediate to TS2 (Figures S1–S5), provide important clues to understand substituent effects in the migration process. Considering the structures as divided into two fragments, the acid and the ester moieties, it is possible to observe that in all structures a partial negative charge is on the acid fragment and a partial positive charge is on the ester part. The charge separation between these two fragments in TS2 increases from 0.52 to 0.57 for the reaction with PFA as the electron-donating ability of the substituent in the ketone increases. As expected, electron-donating groups (—OCH_3 and —CH_3) help stabilize the positive charge on the ester fragment of TS2. The calculation of the Gibbs free energy barrier of the migration step of both BV reactions agrees with the experimental finding that it decreases the greater the electron-donating ability of the substituent in the acetophenone ($NO_2 > CN > H > CH_3 > OCH_3$), because the incipient positive charge of the migrating group gets better compensated and TS2 becomes more stable.[3] However, the substituent effects are more pronounced with PFA ($\Delta\Delta G = 6.20$) than with TFPAA

($\Delta\Delta G = 5.13$). This result can be explained by the higher acidity of TFAA relative to FA, which makes it a better leaving group when partially deprotonated, thus facilitating the migration.[8] Hence, the effect of increasing the electron-donating ability of the substituent is not as pronounced and the Gibbs free energies of activation for the migration step are much lower with TFPAA than with PFA (Tables 1 and 2).

The electronic effects of the substituents in the ketone (for the reactions with both peracids) are less pronounced in the addition step ($\Delta\Delta G = 1.41$ kcal/mol for PFA and $\Delta\Delta G = 2.25$ kcal/mol for TFPAA) than in the migration process, which remains rate-determining, with the exception of the TFPAA oxidation of *p*-methoxyacetophenone (Figs. 2 and 3). This fact provides an important clue in understanding the effect of the ketone, the peracid, and the catalyst in changing the RDS of the BV reaction.[3]

The substituent effects on the enthalpies ($\Delta H^{\neq}$) and Gibbs free energies ($\Delta G^{\neq}$) of activation of the two steps of the BV reactions under study agree with the changes in geometry previously discussed for both TSs. As expected, according to the Hammond postulate,[43] $\Delta H_1^{\neq}$ and $\Delta G_1^{\neq}$ show a slight decrease with the increased electron-donating ability of the substituent which is in agreement with an overall increase in product-like resemblance of TS1 (due to the proton-transfer processes) because step 1 is endothermic. $\Delta H_2^{\neq}$ and $\Delta G_2^{\neq}$ also decrease in the same order, but to a much greater extent, which is once again in agreement with the increased reactant-like resemblance of TS2, since step 2 is highly exothermic. Hence, both TS1 and TS2 tend to look more like the Criegee intermediate the more electron-donating the substituent in the aromatic ketone.

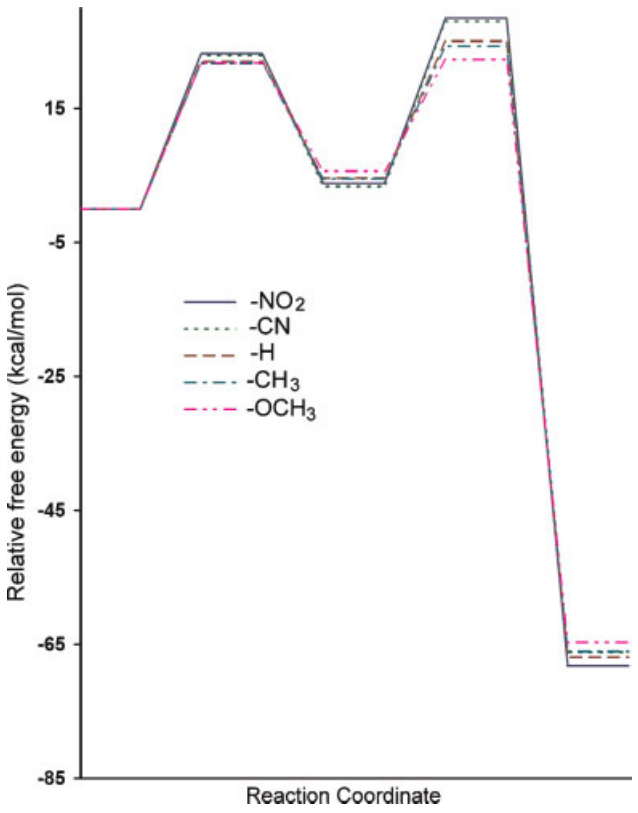


Figure 2. Reaction profile of the BV reaction of *p*-substituted acetophenones with PFA using FA as catalyst at 298.15 K, calculated at the MPWB1K/6-311++G(d,p)-IEF-PCM// MPWB1K/6-311G(d,p) level of theory, relative to the isolated reactants: the first step is catalyzed while the second step shown is not. This figure is available in color online at www.interscience.wiley.com/journal/poc

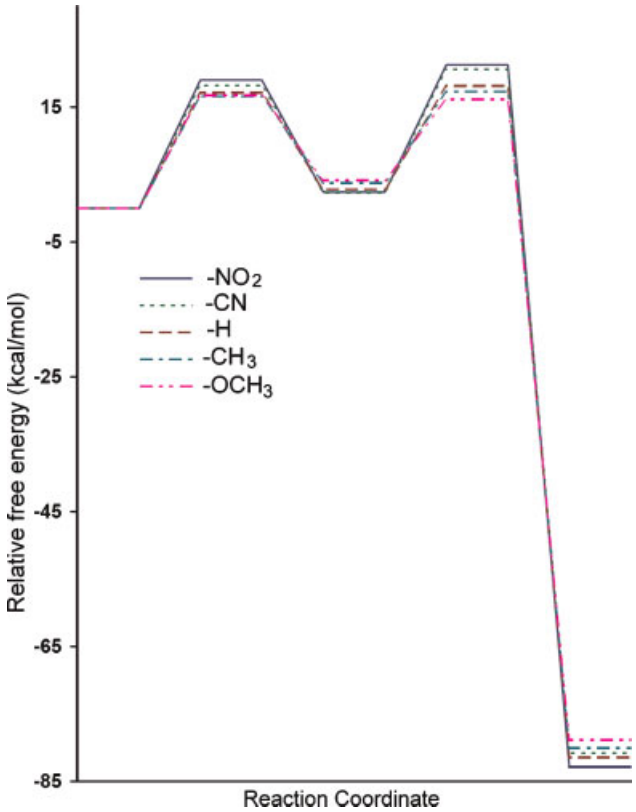


Figure 3. Reaction profile of the BV reaction of *p*-substituted acetophenones with TFPAA using TFAA as catalyst at 298.15 K, calculated at the MPWB1K/6-311++G(d,p)-IEF-PCM// MPWB1K/6-311G(d,p) level of theory, relative to the reactant complex: the first step is catalyzed while the second step shown is not. This figure is available in color online at www.interscience.wiley.com/journal/poc

CONCLUSIONS

The effects of electron-donating (—OCH_3 and —CH_3) and electron-withdrawing (—NO_2 and —CN) groups on the BV reaction of *p*-substituted acetophenones with PFA and TFPAA have been studied. The changes in enthalpy and Gibbs free energy barriers, TS geometric parameters and charge distributions in the addition and migration steps clarify the substituent effects on these reactions. The MPWB1K functional and the 6-311G(d,p) and 6-311++G(d,p) basis sets, including solvent effects by means of the IEF-PCM continuum model using dichloromethane as solvent, are applied.

It was found that the two steps of the BV reactions studied are concerted, and that the addition step is strongly catalyzed while the migration step is not. The electron-donating ability of the substituent has two opposite effects on the kinetics of the addition step. On one hand, it decreases the electrophilicity of the carbonyl carbon (slowing down the reaction) and on the other hand it increases the basicity of the carbonyl oxygen, which once protonated increases the electrophilicity of the carbonyl carbon and facilitates the addition of the peracid. The latter effect slightly prevails and this is the reason why there is a small

decrease in the Gibbs free energy of activation of the addition step as the electron-donating ability of the substituent in the ketone increases. Electron-donating substituents also facilitate the migration step due to stabilization of the partial positive charge on the migrating group. Substituent effects on the migration Gibbs free energy barrier are more pronounced making possible a change in the RDS, as observed in the TFPAA oxidation of *p*-methoxyacetophenone.

The comparison of BV reactions using different acid-peracid pairs shows that the addition step is less sensitive to their natures due to the opposite effects of acid strength and nucleophilicity of the peracid. The effect of the acid–peracid pair is much more pronounced in the migration step because it only depends on the leaving ability of the acid, which in turn depends on its strength.

These observations are important for understanding the effect of the substrate, the peracid and the catalyst in changing the RDS of the BV reaction. Taking into account the most favorable concerted non-ionic mechanism that has been proposed for this rearrangement in non-polar solvents,[33,34] this work reports the first complete theoretical study of substituent effects on the mechanism of the two steps of the BV reaction.

SUPPLEMENTARY INFORMATION

Electronic supplementary information (ESI) available: NPA charge distribution of the reactants, TS1, Criegee intermediate, TS2 and TS2cat (catalyzed by FA) for the BV oxidation of *p*-substituted acetophenones with PFA (Figures S1–S5); NPA charge distribution of the stationary points of the reaction of acetophenone with TFPAA (Figure S6); IRC from TS1 to the reactants for the BV oxidation of acetophenone with PFA (Figure S7); Figures and Cartesian coordinates of important stationary points in the reactions of acetophenone with PFA and TFPAA at the MPWB1K/6-311G(d,p) level of theory.

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