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# Acid-Catalyzed Nucleophilic Additions to Carbonyl Groups: Is the Accepted Mechanism the Rule or an Exception?

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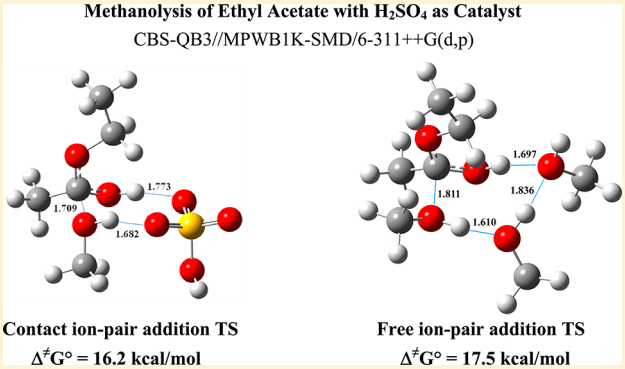
Supporting Information

**ABSTRACT:** The transesterification reaction, and in particular the methanolysis of ethyl acetate with sulfuric acid as catalyst, is used as a model reaction to study the acid-catalyzed nucleophilic addition to a carbonyl group. Continuum solvation methods (SMD and IEF-PCM) and the MPWB1K functional are used. The reaction mechanism is studied in methanol and in acetonitrile as solvents. Our results indicate that the acid-catalyzed addition mechanism is stepwise, and the transition state (TS) is a contact ion-pair. The counteranion of the acid catalyst remains in the reaction site playing an important role in the TS of this reaction. Changes in the reaction kinetics and the ionic/nonionic nature of the TS with the ionizing ability of the solvent and the strength of the acid catalyst are explored. Additional calculations at the CBS-Q3 level of theory reinforce the conclusions of this paper. The results obtained allow the generalization of important ideas regarding the mechanism of the nucleophilic addition to carbonyl groups.




## 1. INTRODUCTION

The strong-acid catalyzed nucleophilic addition to a carbonyl group is generally accepted to occur via a stepwise ionic mechanism including the formation of a protonated adduct (see Figure 1 for an example that focuses on the transesterification reaction).[1−6] It is assumed that, independent of the solvent, the acid catalyst and the nucleophile, the counteranion (conjugate base) of the acid used as catalyst remains solvated without interacting with the substrate (i.e., it does not participate in the transition state (TS) of the reaction) once the substrate becomes protonated.[2,4] Hence, these reactions are supposed to undertake a specific acid catalysis. In such a system, the reaction rate in a given solvent is proportional to the concentration of protonated solvent molecules, which form after the dissociation of the acid catalyst take place.

Strong mineral acids are completely dissociated in water; therefore, the role of the undissociated acid as catalyst can be ruled out, leaving in place the accepted mechanism which makes sense.[2] The addition mechanism is stepwise (the protonation of the carbonyl group, the nucleophilic attack, and the deprotonation of the nucleophile take place as three consecutive elementary kinetic events) and the TS is ionic (i.e., it is a free ion-pair; complete charge separation between the counteranion of the acid catalyst and the protonated carbonyl compound can be assumed). However, the use of the same assumptions for reactions using different substrates, or carboxylic acids as catalysts in relatively nonpolar solvents seems to be an overgeneralization.[7] In 1972, Jencks made use of 3D reaction-coordinate contour diagrams (without quantum-mechanical calculations) to attempt to answer very interesting questions regarding the mechanism for the general acid−base catalysis of complex reactions in water.[7] For example, discussing the stability of intermediates, Jencks explored the possibility of concerted versus stepwise mechanisms. He predicted the possibility of a change in mechanism depending on the acid or basic strength of the catalyst and the reactant. Furthermore, some experimental studies have shown the possible role of the counteranion in the acid hydrolysis of glycoside,[8,9] and polysaccharide.[10,11] In the first reaction, Yokohama et al. observed that as the 1,4-dioxane composition of a water−dioxane solvent mixture increased, the counteranion of the acid catalyst became less solvated and its role in the hydrolysis was further pronounced.[9]

After having performed an extensive study on the Baeyer−Villiger (BV) oxidation,[12−15] we have found that the

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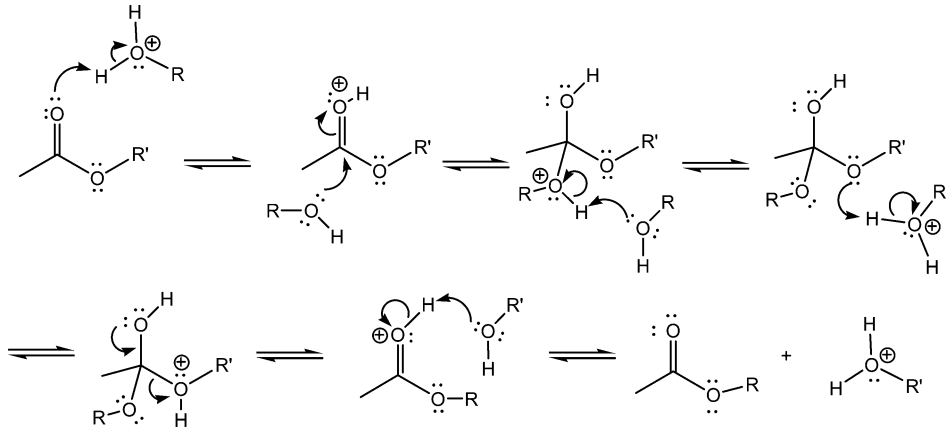

**Figure 1.** Currently accepted mechanism for the acid-catalyzed transesterification reaction.

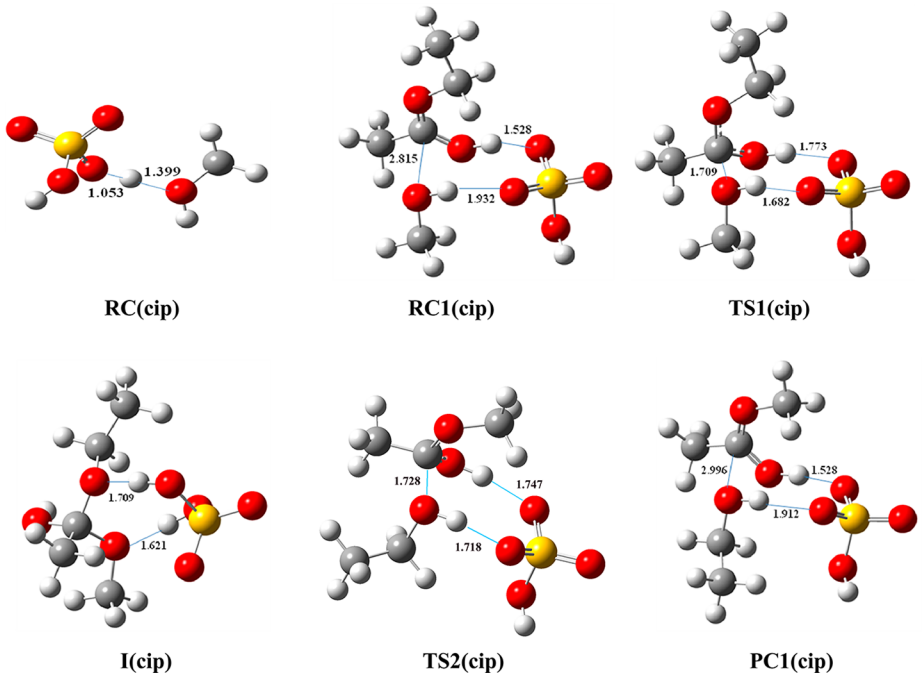


**Figure 2.** Contact ion-pair (cip) mechanism: structures and relevant bond distances (in Å) of important intermediates (RC, RC1, I, PC1) and the TSs of the methanol addition (TS1) and the tetrahedral-intermediate decomposition (TS2) catalyzed by $H_2SO_4$ in methanol at the MPWB1K-SMD/6-311++G(d,p) level of theory.

nucleophilic addition of the peracid to the ketone in dichloromethane (DCM), catalyzed by the corresponding carboxylic acid, is concerted and nonionic. The theoretical kinetic results obtained are in agreement with experimental data.[16] The protonation of the ketone, the nucleophilic attack of the peracid, and its deprotonation take place simultaneously (without significant charge separation) in a basically nonionic TS in which the acid catalyst participates, facilitating the hydrogen transfers.[12−14,15a] However, the theoretical study of the same process in water concluded that it is a typical specific acid-catalyzed reaction.[15b] These results[12−15] have already been recognized and/or used by related studies on this topic.[17] Is the nucleophilic addition step of the BV oxidation in DCM a special case or is it a limiting case for relatively weak acid catalysts and nucleophiles in nonpolar solvents?

Methanol and alcohols in general are polar and protic; therefore, they are among the most ionizing organic solvents whose properties are relatively similar to those of water. Even though the p$K_a$ of HCl in methanol is positive (1.2),[1,18] HCl is a strong acid in this solvent. To the best of our knowledge, the first p$K_a$ of sulfuric acid in methanol has not been measured. However, it is expected to be very close to that of HCl (to verify this we calculated this value applying the CBS-QB3-SMD method and obtained a p$K_a$ of 1.5). The degree of dissociation of an acid depends on its concentration and p$K_a$ value. If the concentration of $H_2SO_4$ is analogous to that of experiments where it is used as catalyst,[19,20] we should expect that the concentration of its dissociated and undissociated forms will be very similar (e.g., for a 0.1 M acid with p$K_a$ = 1.0, the degree of dissociation is ca. 0.62).[18] This makes the sulfuric acid−methanol pair an ideal system for the mechanistic study of the nucleophilic addition to a C═O group. The transesterification is indeed a typical reaction in this environment which would be the closest to the reaction conditions for the hydration of a ketone, a nucleophilic addition which takes place via a specific acid catalysis through a free ion-pair TS; the counteranion of


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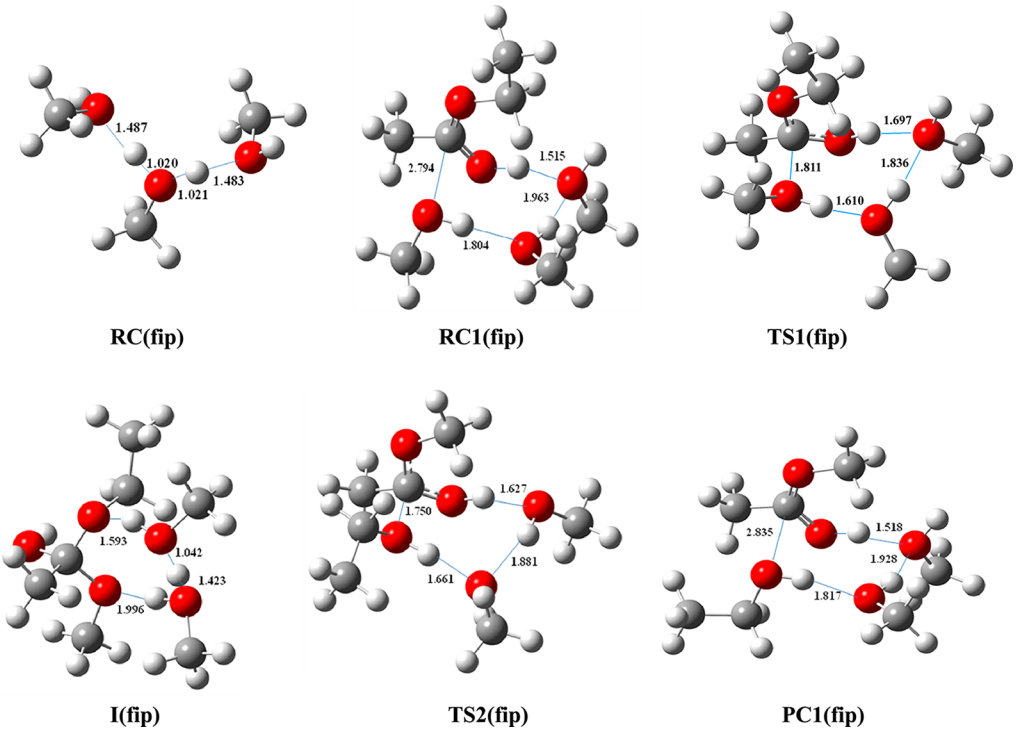


**Figure 3.** Free ion-pair (fip) mechanism: structures and relevant bond distances (in Å) of important intermediates (RC, RC1, I, PC1) and the TSs of the methanol addition (TS1) and the tetrahedral-intermediate decomposition (TS2) catalyzed by $H_2SO_4$ in methanol at the MPWB1K-SMD/6-311++G(d,p) level of theory.

**Table 1. Enthalpy and Gibbs Free Energy Changes (in kcal/mol) along the Reaction Profile of the Transesterification Reaction Catalyzed by $H_2SO_4$ via Contact and Free Ion-Pairs in Methanol at the MPWB1K-IEF-PCM/6-311++G(d,p), MPWB1K-SMD/6-311++G(d,p) and CBS-QB3//MPWB1K-SMD/6-311++G(d,p) (Shown in Parentheses) Levels of Theory (See Figures 2 and 3)**

| | contact ion-pair (cip) mechanism | | | | free ion-pair (fip) mechanism | | | |
|---|---|---|---|---|---|---|---|---|
| | $\Delta H$ | | $\Delta G$ | | $\Delta H$ | | $\Delta G$ | |
| | PCM | SMD | PCM | SMD | PCM | SMD | PCM | SMD |
| R[a] | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| RC1 | 1.1 | 1.5 | 10.0 | 8.3 | | 7.4 | | 15.0 |
| TS1 | 9.5 | 10.1 | 21.4 | 20.8 (16.2) | 13.4 | 13.7 | 25.4 | 22.5 (17.5) |
| I | 3.8 | 6.1 | 16.7 | 17.8 (12.4) | 7.4 | 8.3 | 21.5 | 19.8 (13.4) |
| TS2 | 9.5 | 11.1 | 22.2 | 21.8 (17.4) | 14.4 | 14.0 | 26.4 | 23.4 (18.0) |
| PC1 | | 2.8 | | 10.7 | | 9.3 | | 16.5 |
| P[b] | −0.5 | 0.0 | 0.6 | −0.3 | −0.2 | 0.7 | 0.9 | 0.3 |

[a]Reactants: ester **1** (ethyl acetate) + RC (complex: $H_2SO_4$−$CH_3OH$ (cip) or $CH_3OH$−$CH_3OH_2^+$−$CH_3OH$ (fip)); [b]Products: ester **2** (methyl acetate) + PC (complex: $H_2SO_4$−$CH_3CH_2OH$ (cip) or $CH_3CH_2OH$−$CH_3OH_2^+$−$CH_3OH$ (fip)).

the acid catalyst remains solvated and does not participate in the TS of this reaction.[3−5]

The aim of this work is to study the mechanism of the transesterification reaction (focusing on the methanolysis of ethyl acetate) as a particular case of an acid-catalyzed nucleophilic addition to a carbonyl group to assess the correctness of the accepted acid-catalysis mechanism in which the counteranion of the acid catalyst plays no significant role (see Figure 1). Two types of mechanisms (via contact and free ion-pairs) will be explored in methanol and acetonitrile. The last part of this study will compare the catalytic activity of two acids ($H_2SO_4$ and trifluoroacetic acid, TFAA) in methanol (a polar protic solvent) and in DCM (a nonpolar nonprotic solvent).

## 2. COMPUTATIONAL METHODOLOGY

Electronic structure calculations were performed with the Gaussian 09 program package,[21] using the SMD[22a] solvent model with the MPWB1K functional[22b] and the 6-311++G(d,p) basis set. Additional calculations were performed at the MPWB1K-IEF-PCM/6-311++G(d,p) (UAHF radii) and CBS-QB3//MPWB1K-SMD/6-311++G(d,p) (CBS-QB3 calculations using MPWB1K-SMD/6-311++G(d,p) geometries and frequencies) levels of theory. Frequency calculations were performed for all stationary points at the same level of theory as the geometry optimization. Local minima have only real frequencies, while transition states are identified by the presence of a single imaginary frequency that corresponds to the expected motion along the reaction coordinate. Interaction energies have not been corrected for BSSE because as it has been recently demonstrated it worsens the results.[23] The methodology used is justified by previous


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related studies, where any additional calculation details can also be found.[12−16]

## 3. RESULTS AND DISCUSSION

**3.1. Transesterification Reaction in Methanol: Contact vs Free Ion-Pairs.** The mechanism of the methanolysis of ethyl acetate in methanol using sulfuric acid as catalyst is calculated taking into account two possible pathways. In one case, the counteranion of the acid catalyst remains in the reaction site after protonating the substrate forming a contact ion-pair, and in the second one, it fully dissociates protonating a solvent molecule ($CH_3OH$) or the ester, and the counteranion fully detaches from the reaction site and remains solvated (hence, a free ion-pair is formed). Figures 2 and 3 display the structure and some bond distances of the main stationary points for the contact (cip) and free ion-pair (fip) mechanisms, respectively. The labels cip and fip are used to differentiate the stationary points of these two reaction pathways. The calculated standard Gibbs free energy and enthalpy changes relative to the isolated reactants at the three levels of theory considered are shown in Table 1. Figure 4 displays the reaction profile of the

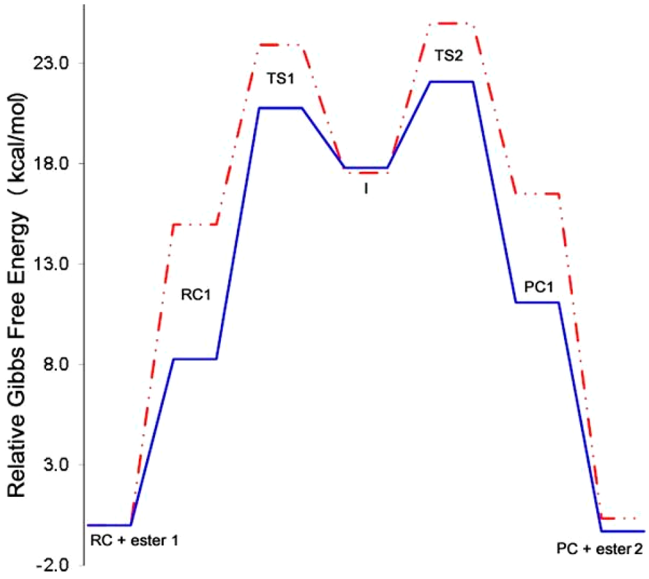


**Figure 4.** Reaction profile of the transesterification reaction in methanol catalyzed by $H_2SO_4$ via contact (solid line) and free (dash line) ion-pair mechanisms at the MPWB1K-SMD/6-311++G(d,p) level of theory (see Figures 2 and 3 for the structures along the reaction profile of the cip and fip mechanisms, respectively).

MPWB1K mechanisms. The natural population analysis (NPA) charge distribution of the stationary points of the reaction appear in Figures S1 and S2 of the Supporting Information (SI).

The first chemical process of this reaction involves the formation of a reactant complex, RC, between the catalyst and one solvent molecule ($H_2SO_4\cdots CH_3OH$, RC(cip)) or between a protonated solvent molecule and two additional solvent molecules ($CH_3OH_2^+\cdots(CH_3OH)_2$, RC(fip)). The interaction between this complex and the ester (ethyl acetate) protonates the ester forming RC1. This intermediate has a geometry similar to that of the methanol addition TS (TS1(cip) and TS1(fip)). The NPA charge distribution analysis and the bond distances indicate that both RC1(cip) and TS1(cip) are contact ion-pairs (i.e., the charge separation is not complete, the $HSO_4^-$ moiety has a −0.90 charge).[24] Following the nucleophilic attack, a tetrahedral intermediate, I, which is doubly H-bonded to the catalyst, forms. In TS2, the tetrahedral intermediate decomposes, forming a new ester (methyl acetate) and releasing ethanol. Similarly, TS2(cip) and PC1(cip) are contact ion-pairs, while TS2(fip) and PC1(fip) are not. In TS1(fip), I(fip), TS2(fip) and PC1(fip) a helping solvent molecule is always present. The imaginary frequency of TS1 and TS2 does not involve much movement from the H atoms bonded to oxygen. Following the reaction path by integrating the intrinsic reaction coordinate (IRC) from each TS indicates that they are not concerted as in the case of the BV reaction. The Gibbs free energy of activation, $\Delta G^{\ddagger}$, of the second step of the transesterification, is larger (ca. 1 kcal/mol) than that of the addition step, as expected.

The results obtained (see Table 1 and Figure 4) indicate that the counteranion (the conjugate base, $HSO_4^-$) of the acid catalyst is not released from the reaction site as it participates in the TSs of the reaction. The three levels of theory considered (which includes the CBS-QB3 calculations) clearly show that the contact ion-pair mechanism is the most favorable route for this reaction. The calculated $\Delta G^{\ddagger}$ values of both steps are 1.7−1.6 kcal/mol (1.3−0.6 kcal/mol using the CBS-QB3 results) smaller when the reaction takes place via a contact ion-pair mechanism which makes the rate constant about 10 times larger than when the reaction takes place via a free ion-pair mechanism. Our calculations show that since methanol is a less ionizing solvent than water, the interaction between the protonated substrate and $HSO_4^-$ is stronger than with the solvent.

The transesterification reaction in methanol with $H_2SO_4$ is indeed an acid-catalyzed nucleophilic addition reaction that could be placed in between the two extremes we have initially described: an ionic stepwise strong-acid catalysis (e.g., the hydration of a ketone) and a nonionic concerted acid catalysis (e.g., the addition step of the BV reaction in DCM). Compared with the conditions of the BV reaction, the transesterification takes place in a more ionizing solvent, with a stronger acid catalyst ($H_2SO_4$) and a better nucleophile (methanol). The nucleophilic addition takes place without the deprotonation of the nucleophile following the protonation of the ester. The addition TS is not concerted, and it is much more ionic in character than in BV, but not totally ionic, which is why it is classified as a contact ion-pair. Contrary to what is assumed, the counteranion of the acid catalyst does not become solvated upon dissociation but participates in the TS of this reaction, thus forming a contact ion-pair with the substrate.

**3.2. Transesterification Reaction in Acetonitrile: Contact vs Free Ion-Pairs.** To show the role of the ionizing ability of the solvent on the energetic differences between the two mechanisms, the same calculations are performed using acetonitrile as solvent. Even though acetonitrile has a very similar dielectric constant to that of methanol, it has a lower ionizing ability. Evidence of this is the fact that, though the p$K_a$ of sulphuric acid in methanol is not known with certainty, it is assumed to be close to 1; however, in acetonitrile this p$K_a$ is 7.2.[24] Acetonitrile is nonprotic and basic; hence, it can solvate cations well. However, since it lacks very electropositive or acid atoms, it cannot solvate anions as well.

For simplicity, the reactant complexes have been ignored when calculating the reaction profile. The structures and Cartesian coordinates of the calculated TSs in acetonitrile are reported in the Supporting Information. As can be seen from


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Table 2 and Figure 5, the MPWB1K-SMD Gibbs free energies of activation are significantly smaller (by 6−8 kcal/mol) when

**Table 2. Enthalpy and Gibbs Free Energy Changes (in kcal/mol) along the Simplified Reaction Profile of the Transesterification Reaction Catalyzed by $H_2SO_4$ via Contact and Free Ion-Pairs in Acetonitrile at the MPWB1K-SMD/6-311++G(d,p) and CBS-QB3//MPWB1K-SMD/6-311++G(d,p) (Shown in Parentheses) Levels of Theory**

| | contact ion-pair (cip) mechanism | | free ion-pair (fip) mechanism | |
|---|---|---|---|---|
| | $\Delta H$ | $\Delta G$ | $\Delta H$ | $\Delta G$ |
| R[a] | 0.0 | 0.0 | 0.0 | 0.0 |
| TS1 | 9.5 | 21.5 (14.1) | 17.7 | 27.6 (25.7) |
| I | 3.9 | 16.5 (9.0) | 16.9 | 27.1 (24.8) |
| TS2 | 9.9 | 21.9 (14.7) | 18.3 | 29.7 (27.8) |
| P[b] | −0.5 | −0.5 | −0.3 | −0.5 |

[a]Reactants: complexes ($H_2SO_4$−ethyl acetate) and ($CH_3OH$−$CH_3CN$); [b]Products: complexes ($H_2SO_4$−methyl acetate) and ($CH_3CH_2OH$−$CH_3CN$)

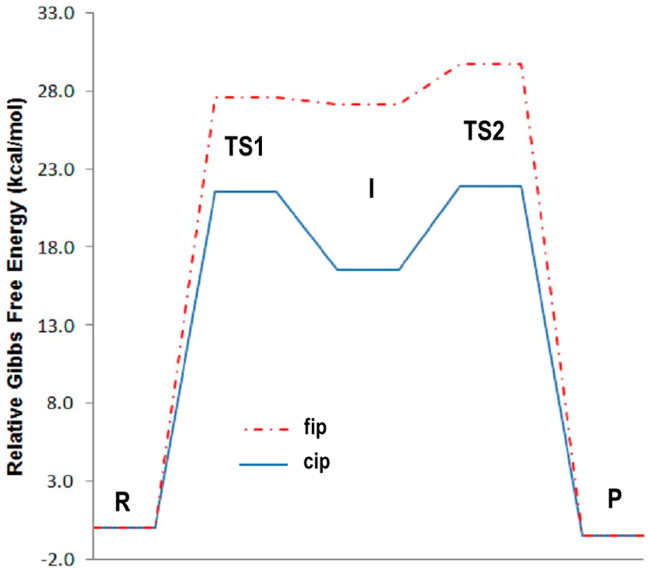


**Figure 5.** Simplified reaction profile of the transesterification reaction in acetonitrile catalyzed by $H_2SO_4$ via contact (solid line) and free (dashed line) ion-pair mechanisms at the MPWB1K-SMD/6-311++G(d,p) level of theory.

the reaction takes place via a contact ion-pair mechanism. The CBS-QB3 results establish a much greater difference between these two mechanisms favoring the contact ion-pair mechanism by 11−13 kcal/mol. These results support and reinforce our conclusions in the previous section about the mechanism of this reaction.

Since acetonitrile is a relatively polar solvent, it seems reasonable to assume that sulfuric acid does protonate it. However, this is unlikely to happen in a solvent of much lower polarity such as DCM. As the calculations show, the free ion-pair mechanism is much less favored in acetonitrile than in methanol. The lower the ionizing ability of the solvent, the more unlikely the free ion-pair mechanism, which is the one widely accepted and taught. The progression from free ion-pair (e.g., hydration of a ketone), to contact ion pair (e.g., our current study of the transesterification reaction in methanol and acetonitrile), to nonionic TS (e.g., the BV reaction in DCM) can be appreciated as the ionizing ability of the solvent is reduced (together with a reduction of the strength of the nucleophile and the acid catalyst used).

Sometimes the calculated Gibbs free-energy difference between two mechanisms that differ in the total charge of the supermolecule can be an artifact due to the error introduced by the solvation model. This situation would be highly improbable in this case since a mixed model with explicit solvent molecules and the SMD continuum model is applied. To increase our confidence in these results and the methods used, the acid dissociation constant ($pK_a = -\log K_a = \Delta G/RT \ln 10$) of sulfuric acid in acetonitrile is calculated using one explicit molecule of acetonitrile as solvent and another one as proton acceptor (see Scheme 1). The calculated $pK_a$ of 7.8, which

**Scheme 1. Equilibrium Used To Calculate the $pK_a$ of $H_2SO_4$ in Acetonitrile**

$$H_2SO_4\cdots CH_3CN + CH_3CN \leftrightarrows HSO_4^- + CH_3CNH^+\cdots CH_3CN$$

corresponds to a $\Delta G$ of 8.9 kcal/mol, is in excellent agreement with the experimental value of 7.2.[25] This result is within chemical accuracy (the error of 0.6 $pK_a$ units corresponds to a 0.8 kcal/mol error in the calculated $\Delta G$). The differences found between the two types of mechanisms considered in this study are not an artifact of the calculations. There are no experimental $pK_a$ values for $H_2SO_4$ in methanol or DCM; therefore, we did not do these calculations.

**3.3. Transesterification Reaction: Two Catalysts in Two Solvents.** In this section, we explore energetic (see Table 3), geometric (see Figures 6 and 7), and NPA charge distribution changes (see Figures S3 and S4, Supporting Information) in the addition TS of the methanolysis of ethyl acetate when changing the nature of the acid catalyst (from $H_2SO_4$ to trifluoroacetic acid, TFAA) and the ionizing ability of the solvent (from methanol to DCM). The TS is a bidentate contact ion-pair between the counteranion of the acid catalyst and the protonated ester and the nucleophile. Furthermore, the addition mechanism is stepwise because, as confirmed by IRC calculations, the addition TS is not concerted.

The calculated standard Gibbs free energy and enthalpy changes relative to the isolated reactants at the MPWB1K-SMD/6-311++G(d,p) level of theory are shown in Table 3. The average $\Delta G^{\ddagger}$ increase for both steps when changing catalyst from $H_2SO_4$ to TFAA is 4.5 kcal/mol. The $\Delta G^{\ddagger}$ values increase with both catalysts when using DCM instead of methanol as solvent. The hydrogen transfer between the catalyst and the ester occurs to a lesser extent when changing from $H_2SO_4$ to TFAA (a much weaker acid) and when reducing the polarity of the solvent in each case. This O−H bond distance goes from 1.773 ($H_2SO_4$, methanol) to 1.578 Å (TFAA, DCM). If the ester is less protonated, it is less electrophilic to the nucleophilic attack of methanol. The opposite occurs when considering the hydrogen exchange between methanol and the protonating acid. Trifluoroacetate is a much stronger base than the hydrogensulfate ion and it is better at helping to remove the hydrogen atom of methanol, which helps in making it more nucleophilic. This O--H bond distance goes from 1.682 to 1.618 Å and from 1.573 to 1.551 Å when changing from $H_2SO_4$ to TFAA in methanol and DCM, respectively. Two opposite forces operate at the same time, reducing the overall effect on the $\Delta G^{\ddagger}$ values due to the change


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**Table 3. Enthalpy and Gibbs Free Energy Changes (in kcal/mol) along the Simplified Reaction Profile of the Transesterification Reaction (cip Mechanism) Catalyzed by $H_2SO_4$ and TFAA at the MPWB1K-SMD/6-311++G(d,p) Level of Theory in Different Solvents**

| | $H_2SO_4$ | | | | TFAA | | | |
|---|---|---|---|---|---|---|---|---|
| | methanol | | DCM | | methanol | | DCM | |
| | $\Delta H$ | $\Delta G$ | $\Delta H$ | $\Delta G$ | $\Delta H$ | $\Delta G$ | $\Delta H$ | $\Delta G$ |
| R[a] | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| TS1 | 10.1 | 20.8 | 9.2 | 22.1 | 14.2 | 25.1 | 14.1 | 25.7 |
| I | 6.1 | 17.8 | 3.6 | 16.7 | 5.7 | 16.6 | 5.9 | 17.1 |
| TS2 | 11.1 | 21.8 | 9.6 | 22.9 | 15.1 | 26.5 | 15.2 | 27.6 |
| P[b] | 0.0 | −0.3 | −0.6 | 0.2 | −0.2 | −0.4 | −0.3 | −1.0 |

[a]Reactants: ester **1** (ethyl acetate) + RC (complex: $H_2SO_4$−$CH_3OH$); [b]Products: ester **2** (methyl acetate) + PC (complex: $H_2SO_4$−$CH_3CH_2OH$).

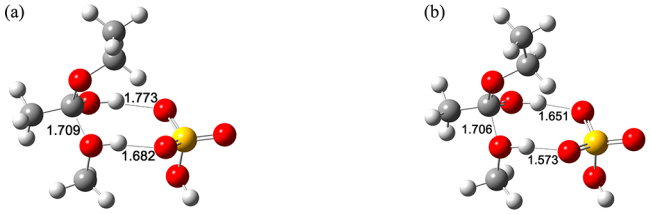


**Figure 6.** Structure and relevant bond distances (in Å) of the methanol addition TS (TS1) catalyzed by $H_2SO_4$ in (a) methanol and (b) DCM.

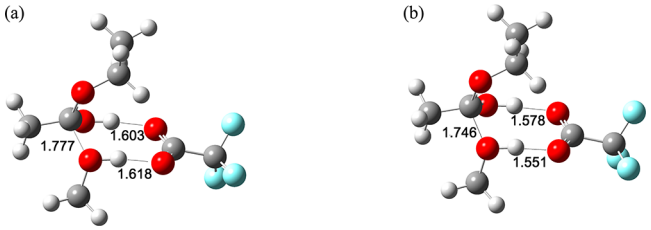


**Figure 7.** Structure and relevant bond distances (in Å) of the methanol addition TS (TS1) catalyzed by TFAA in (a) methanol and (b) DCM.

in catalyst. The variation in $\Delta G^{\ddagger}$ would be much greater if the protonating ability of the acid were the only factor to influence this reaction. The overall effect is that the nucleophilic attack is less effective with TFAA, as expected.

It is of interest to consider the NPA charge distribution in these TSs. The charge on the conjugate base of the catalyst in TS1 changes as follows: −0.91 ($HSO_4^-$, methanol), −0.86 ($HSO_4^-$, DCM), −0.84 ($CF_3COO^-$, methanol), and −0.81 ($CF_3COO^-$, DCM). The reduction in solvent polarity, in addition to reducing the extent of both hydrogen transfers, reduces the charge separation in the contact ion-pair TS increasing its covalent (nonionic) character. When a weaker acid is used as catalyst, this charge separation is also reduced. In this theoretical exercise we are getting closer to the situation found in the BV reaction; if the nucleophile were to be changed from methanol to an organic peracid, the TS would be clearly nonionic and concerted.[12−14]

It is clear from this part of our study that the ionizing ability of the solvent and the strength of the acid catalyst determine important aspects of the mechanism of the nucleophilic addition. The strength of the nucleophile is of course also to be considered. These three aspects determine the degree of the proton transfer (dissociation) from the acid catalyst to the carbonyl compound, which in turn determines if the addition TS is a free ion-pair (with the counteranion of the acid solvated and not involved in the TS), a contact ion-pair, or nonionic. They also determine if the mechanism is stepwise or concerted.

**3.4. Activation−strain Model and the Catalytic Effect of the Acid.** In order to evaluate the magnitude of the catalytic effect of the acid in the addition TS of the methanolysis of ethyl acetate, the activation−strain model is considered.[26] In this fragment-based approach that can be used to understand chemical reactivity, the activation energy ($\Delta E^{\ddagger}$) is decomposed into the activation strain, $\Delta E^{\ddagger}_{strain}$, and the TS interaction, $\Delta E^{\ddagger}_{interaction}$, i.e., $\Delta E^{\ddagger} = \Delta E^{\ddagger}_{strain} + \Delta E^{\ddagger}_{interaction}$. $\Delta E^{\ddagger}_{strain}$ is the energy related with deforming the reactants from their equilibrium geometry to the geometry they acquire in the TS. It can be calculated from the difference between the sum of the energies of the reactant fragments within the TS and the sum of the energies of the isolated reactants. While $\Delta E^{\ddagger}_{strain}$ is a destabilizing factor, $\Delta E^{\ddagger}_{interaction}$ is related to the stabilizing

**Table 4. Activation-Strain Model Calculations (in kcal/mol) Using MPWB1K-SMD/6-311++G(d,p) Geometries of Reactants and the Acid-Catalyzed Addition TSs of Several Transesterification (fip and cip Cases) and BV Reactions**

| | transesterification (TS1)[a] | | | | | BV (TS1)[b] | |
|---|---|---|---|---|---|---|---|
| | fip | cip | | | | TFPAA | PFA |
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| catalyst: | $CH_3OH_2^+$ | $H_2SO_4$ | TFAA | $H_2SO_4$ | TFAA | TFAA | FA |
| solvent: | $CH_3OH$ | $CH_3OH$ | $CH_3OH$ | DCM | DCM | DCM | DCM |
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| $\Delta E^{\ddagger}_{strain}$ | 116.2 | 122.8 | 100.5 | 117.2 | 102.2 | 115.2 | 91.6 |
| $\Delta E^{\ddagger}_{interaction}$ | −114.0 | −125.3 | −94.4 | −120.5 | −98.3 | −119.8 | −90.2 |
| $\Delta E^{\ddagger}$ | 2.2 | −2.4 | 6.2 | −3.3 | 4.0 | −4.6 | 1.4 |

[a]Acid-catalyzed addition step of the methanolysis of ethyl acetate with the catalyst shown in the specified solvent. [b]Acid-catalyzed addition step for the BV reaction of propanone with TFPAA/TFAA and with PFA/FA in DCM.


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effect between the reactant fragments when forming the TS. It can be calculated as the difference between the energy of the TS and the sum of the energies of the reactant fragments within the TS. The aim of the activation-strain model is to make qualitative predictions based on the calculated trends in activation barriers with the rigidity of the reactants ($\Delta E^{\ddagger}_{strain}$) or the ability of the reactants to engage in stabilizing electrostatic or donor−acceptor orbital interactions along a particular pathway or TS ($\Delta E^{\ddagger}_{interaction}$).

The activation−strain model was applied to the transesterification reaction under study, i.e., the methanolysis of ethyl acetate, in five different situations: the fip (reaction 1) and cip (reaction 2) mechanisms in methanol catalyzed by sulfuric acid, and the cip mechanisms catalyzed by sulfuric acid in DCM (reaction 4) and by TFAA in methanol (reaction 3) and in DCM (reaction 5). MPWB1K-SMD/6-311++G(d,p) geometries of reactants and the acid-catalyzed addition TSs were used. The energies of the reactant fragments in each TS were obtained from single-point calculations at the same level of theory. Energies without thermal and entropic corrections are used to calculate $\Delta E^{\ddagger}_{strain}$ and $\Delta E^{\ddagger}_{interaction}$. The values used are reported in the Supporting Information. Table 4 shows the main results obtained, which are also graphically represented in Figure 8.

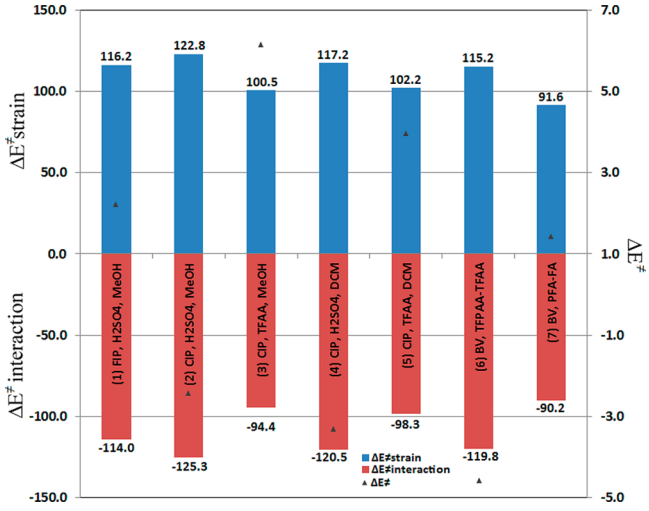


**Figure 8.** Graph showing the variations of $\Delta E^{\ddagger}_{strain}$, $\Delta E^{\ddagger}_{interaction}$, and $\Delta E^{\ddagger}$ (in kcal/mol) for the seven reactions considered.

Two of the BV reactions previously studied by our group were also included in this analysis.[14,15b] At this point, only the acid-catalyzed addition step is considered for the reactions of propanone with trifluoroperacetic acid (TFPAA) and with performic acid (PFA), catalyzed by TFAA (reaction 6) and formic acid (FA) (reaction 7), respectively, in DCM. The reactants and TSs of the BV reactions were recalculated at the MPWB1K-SMD/6-311++G(d,p) level of theory.

Using the calculated data for the seven reactions considered, comparisons can be made between several pairs of them: reactions 1 and 2 (transesterification reactions in methanol catalyzed by $H_2SO_4$, following two mechanisms (fip and cip)), reactions 2 and 3 (cip transesterification reactions in methanol catalyzed by $H_2SO_4$ and TFAA), reactions 4 and 5 (cip transesterification reactions in DCM catalyzed by $H_2SO_4$ and TFAA), and reactions 6 and 7 (two BV reactions in DCM involving propanone and two sets of nucleophile/catalyst: TFPAA/TFAA and PFA/FA). A general pattern can be observed.

Reactions 1 and 2: Following the activation-strain model, the cip addition step is once again predicted to be a less energetic pathway having a smaller $\Delta E^{\ddagger}$ (−2.4 kcal/mol versus 2.2 kcal/mol for the fip addition step). Furthermore, both $\Delta E^{\ddagger}_{strain}$ and $\Delta E^{\ddagger}_{interaction}$ (122.8 and −125.3 kcal/mol, respectively) are larger than the corresponding values for the fip addition step (116.2 and −114.0 kcal/mol, respectively). The higher $\Delta E^{\ddagger}_{strain}$ for the cip mechanism is in agreement with a more deformed and tighter TS, making this process unfavorable. However, the greater catalytic effect of sulfuric acid in this mechanism makes the cip TS have a larger $\Delta E^{\ddagger}_{interaction}$, and since for the most favorable pathway (the cip mechanism) $\Delta E^{\ddagger}_{interaction}$ is larger than $\Delta E^{\ddagger}_{strain}$, the electrostatic stabilizing interactions in the TS are the decisive factor controlling the kinetics of this reaction. In other words, the more stabilizing interaction between the components in the TS forces a greater deformation of the fragments, but in spite of this, the process is still more kinetically favorable.

The same trend is observed when comparing the other pairs of reactions indicated. For the most favorable pathway (the reaction with a predicted larger rate constant) the calculated $\Delta E^{\ddagger}$ is smaller, both $\Delta E^{\ddagger}_{strain}$ and $\Delta E^{\ddagger}_{interaction}$ are larger than for the other reaction, but $\Delta E^{\ddagger}_{interaction}$ is larger than $\Delta E^{\ddagger}_{strain}$, which indicates that the electrostatic interactions in the TS are more stabilizing than the destabilizing effect of reactants species having to form a much tighter and deformed TS.

This method is able to reproduce the much greater catalytic activity of sulfuric acid relative to TFAA for the transesterification reaction in a given solvent (see reactions 2 and 3 in $CH_3OH$ and reactions 4 and 5 in DCM). It also reproduces the fact that given the same ketone in DCM, the TFPAA/TFAA pair leads to a BV reaction with a greater rate constant than when the PFA/FA pair is used (reactions 6 and 7).

This model, applied as described in this section using energies without thermal and entropic corrections and using the isolated reactants as the reference state for structural changes when forming the corresponding TS (instead of using the lowest-G starting point for the reactions), is unable to properly reproduce the kinetic effect of the ionizing ability of the solvent when everything else is unchanged. However, the catalytic effect of the acid is properly described in different scenarios.

## 4. CONCLUSIONS

Three main things determine the mechanism of the nucleophilic addition to a carbonyl group: (a) the ionizing ability of the solvent, (b) the acid strength of the catalyst, and (c) the strength of the nucleophile. From this, two extreme types of mechanisms can be identified: (1) In a highly ionizing solvent with a strong acid catalyst and nucleophile, the mechanism is the traditionally accepted (see Figure 1). The acid catalyst is totally dissociated and its conjugate base (counteranion) is solvated and does not participate in the addition TS. The addition mechanism is stepwise and the TS is a free ion-pair. (2) In a nonpolar solvent with a weak acid catalyst and nucleophile, the undissociated acid catalyst participates in the TS, facilitating the hydrogen transfers that protonate the carbonyl oxygen atom and deprotonate the nucleophile. The addition mechanism is concerted and the TS is nonionic.


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Most nucleophilic additions will correspond to cases in between these two types of mechanisms. The transesterification reaction in methanol with $H_2SO_4$ as catalyst is one of them. The mechanism of this reaction is stepwise (nonconcerted). According to our calculations, even though the pathway with contact ion-pair TSs (something in between a free ion-pair and a nonionic TS) is slightly favored, it is very likely that both mechanisms take place as concurrent reactions. However, in a much less ionizing solvent such as acetonitrile, the contact ion-pair mechanism should be the most probable. Even though the nucleophile and the acid catalyst are very strong, the ionizing ability of the solvent does not allow a complete charge separation in the TSs and a contact ion-pair involving the counterion of the acid catalyst is formed. It has been shown how this charge separation is reduced when reducing the ionizing ability of the solvent and the strength of the acid catalyst. In solvents that are less basic than the reactants, the source of the proton is the molecular acid used as catalyst, not the dissociated one. In such cases, speaking of a specific acid catalysis would not be applicable.

By changing the nature of the solvent, the acid catalyst, and the nucleophile, an interesting spectrum of addition mechanisms could be found between the two extreme cases identified. The assumption of a unique type of mechanism for nucleophilic additions to carbonyl groups is an overgeneralization. In carrying out our research, it has been exciting to discover that several of this paper's conclusions are indeed consistent with those found by Jencks, who is considered one of the founders of mechanistic enzymology.[7] Acid-catalyzed nucleophilic additions to carbonyl groups that follow a mechanism such as the one depicted in Figure 1 (stepwise mechanism with free ion-pair TSs in which the counteranion of the acid catalyst plays no kinetic role, because it remains solvated after dissociating and protonating the substrate) are really an exception, not the rule.

## ■ ASSOCIATED CONTENT

### Supporting Information

NPA charge distributions (Figures S1–S4) and Cartesian coordinates of relevant stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

(1) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; Wiley: Hoboken, 2007; pp 1419–1421.
(2) Bender, M. L. *Chem. Rev.* **1960**, *60*, 53–113.
(3) Koekikallio, J. In *The Chemistry of Carboxylic Acids and Esters*; Patai, S., Ed.; Interscience: London, 1969; pp 103–136.
(4) Sridhnran, R.; Mathai, I. M. *J. Sci. Ind. Res.* **1974**, *33*, 178–187.
(5) Otera, J. *Chem. Rev.* **1993**, *93*, 1449–1470.
(6) Hori, K.; Ikenaga, Y.; Arata, K.; Takahashi, T.; Kasai, K.; Noguchi, Y.; Sumimoto, M.; Yamamoto, H. *Tetrahedron* **2007**, *63*, 1264–1269.
(7) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705–718.
(8) Painter, T. *Acta Chem. Scand.* **1973**, *27*, 2463–2484.
(9) Phan, D.; Yokoyama, T.; Matsumoto, Y. *Org. Biomol. Chem.* **2012**, *10*, 7382–7391.
(10) Zaranyika, M. F.; Moses, P.; Mavunganidge, T. *J. Polym. Sci., Part A* **1990**, *28*, 3565–3574.
(11) Charmot, A.; Katz, A. *J. Catal.* **2010**, *276*, 1–5.
(12) Alvarez-Idaboy, J. R.; Reyes, L.; Cruz, J. *Org. Lett.* **2006**, *8*, 1763–1765.
(13) Alvarez-Idaboy, J. R.; Reyes, L. *J. Org. Chem.* **2007**, *72*, 6580–6583.
(14) Alvarez-Idaboy, J. R.; Reyes, L.; Mora-Diez, N. *Org. Biomol. Chem.* **2007**, *5*, 3682–3689.
(15) (a) Reyes, L.; Alvarez-Idaboy, J. R.; Mora-Diez, N. *J. Phys. Org. Chem.* **2009**, *22*, 643–649. (b) Mora-Diez, N.; Keller, S.; Alvarez-Idaboy, J. R. *Org. Biomol. Chem.* **2009**, *7*, 3682–3690.
(16) Hawthorne, M. F.; Emmons, W. D. *J. Am. Chem. Soc.* **1958**, *80*, 6398–6404.
(17) See, for example: (a) Fu, H.; Xie, S.; Fu, A.; Lin, X.; Zhao, H.; Ye, T. *Org. Biomol. Chem.* **2012**, *10*, 6333–6340. (b) Bach, R. D. *J. Org. Chem.* **2012**, *77*, 6801–6815. (c) Qiao, Y.; Han, K.-L. *Org. Biomol. Chem.* **2012**, *10*, 7689–7706. (d) Itoh, Y.; Yamanaka, M.; Mikami, K. *J. Org. Chem.* **2013**, *78*, 146–153.
(18) Cox, B. G. *Annu. Rep. Prog. Chem., Sect. A. Inorg. Phys. Chem* **1973**, *70*, 249–274.
(19) Juvet, R. S.; Wachi, F. M. *J. Am. Chem. Soc.* **1959**, *81*, 6110–6115.
(20) Farkas, K.; Schächter, O.; Vromen, B. H. *J. Am. Chem. Soc.* **1949**, *71*, 1991–1994.
(21) Gaussian 09, Revision A.1: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M. R.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R. E.; Stratmann, O.; Yazyev, A. J.; Austin, R.; Cammi, C.; Pomelli, J. W.; Ochterski, R.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford, CT, 2009.
(22) (a) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *13*, 16378–6396. (b) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 6908–6918.
(23) (a) Alvarez-Idaboy, J. R.; Galano, A. *Theor. Chem. Acc.* **2010**, *126*, 75–85. (b) Wallnoefer, H. G.; Fox, T.; Liedl, K. R.; Tautermann, C. S. *Phys. Chem. Chem. Phys.* **2010**, *12*, 14941–14949.
(24) In RC1(cip) the protonated ester forms a contact ion pair with the counteranion of the catalyst, each with a charge of 0.90 and opposite sign, while solvated with the methanol molecule that will perform the subsequent nucleophilic attack. In TS1(cip) the positive charge is more distributed with only a +0.61 charge on the protonated ester moiety. This is a bidentate contact ion-pair with an important covalent bonding contribution. This situation does not take place in the other pathway considered. In RC1(fip) the protonated ester is solvated by several methanol molecules (the usual case when free ion-pairs are formed in this type of mechanism; the counteranion of the acid catalyst remains solvated in the reaction mixture without

interacting with the substrate). The species in RC(fip) and TS1(fip) are held together by several strong (covalent) hydrogen bonds.

(25) Kutt, A.; Leito, I.; Kaljurand, I.; Soovali, L.; Vlasov, V. M.; Yagupolskii, L. M.; Koppel, I. A. *J. Org. Chem.* **2006**, *71*, 2829−2838.

(26) See, for example: (a) van Zeist, W.-J.; Bickelhaupt, F. M. *Org. Biomol. Chem.* **2010**, *8*, 3118−3127. (b) de Jong, G. T.; Bickelhaupt, F. M. *ChemPhysChem* **2007**, *8*, 1170−1181. (c) Bickelhaupt, F. M. *J. Comput. Chem.* **1999**, *20*, 114−128.