A Theoretical Study of the Mechanism of Phosphine-Catalyzed Hydroalkoxylation of Methyl Vinyl Ketone

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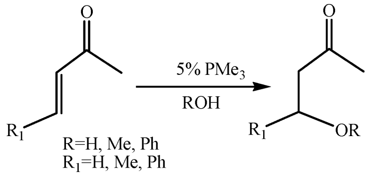
The mechanism of phosphine-catalyzed hydroalkoxylation of the methyl vinyl ketone has been investigated by the second-order Møller−Plesset perturbation theory and the conductor-like polarized continuum model. The free energy reaction profiles of the reaction in both gas phase and solution phase are explored and compared. Our results suggest that the first stage of the studied reaction is the generation of the base (the methoxide anion) with the help of trialkylphosphine, and the second stage is the hydroalkoxylation of the methyl vinyl ketone catalyzed by this base. In the first stage, trialkylphosphine first adds to the methyl vinyl ketone to form a phosphonium enolate intermediate and then this species deprotonates a methanol molecule to generate a methoxide anion. Both steps involve free energy barriers of about 20 kcal/mol. In the second stage, both the addition of the methoxide anion to the methyl vinyl ketone and the proton transfer process from methanol to the methoxyl enolate anion intermediate have activation free energies of about 16 kcal/mol. The reaction in the second stage is exothermic by 10.2 kcal/mol at room temperature. A comparison of the free energy reaction profiles in the gas phase and the solution phase demonstrated that the generation of the methoxide anion could only occur in the presence of the polar solvents. The mechanism proposed in the present work is in reasonable agreement with the known experimental facts.

1. Introduction

The preparation of β-hydroxy ketones and β-alkoxy ketones, the important intermediates and targets in organic chemistry,[1] is a challenge in organic synthesis. Usually, β-hydroxy ketones could be prepared via the Aldol reaction or sequential epoxidation and reduction of enones.[2] There also existed several methods for the synthesis of β-alkoxy ketones.[1,3] Compared with these typical methods, the direct Michael addition of water or alcohol to enones provides an attractive and practical synthetic method. However, such a direct addition has not been generally realized under mild reaction conditions with simple catalysts.[4] Very recently, Stewart, Bergman, and Toste[5] reported a general method for the hydration and hydroalkoxylation of enones and other α,β-unsaturated substrates[6] (Scheme 1). Interestingly, in the presence of trialkylphosphine, the direct catalytic addition of water and alcohols to α,β-unsaturated compounds was observed with 56−85% conversion at ambient temperature. Little retro-aldol or ketalization products were produced in this reaction, although in analogous base-catalyzed systems the rates of the retro-aldol reaction are competitive with hydration.[7] Thus, this approach provided an excellent method for direct preparation of β-alkoxy ketones in the absence of transition metals, or strong acids or bases. Quite recently, Connon's group developed a novel convenient methodology for the preparation of β-alkoxycarbonyl compounds with the amine-catalyzed hydroalkoxylation process.[8]

Clearly, the mechanisms of phosphine-catalyzed oramine-catalyzed hydroalkoxylation reactions are very interesting because they should be different from the general based-catalyzed mechanism.[7] Although some experiments have been employed to probe the possible mechanisms of this reaction,[5] a detailed theoretical investigation on this reaction is still valuable. To the best of our knowledge, this has not been done so far. In this paper, we report a theoretical investigation on the mechanism of this phosphine-catalyzed reaction. The model reaction we chose is the hydroalkoxylation of methyl vinyl ketone catalyzed by trimethylphosphine (PMe_3). The possible low-energy pathways are explored and the bulk solvent effects on the reaction are discussed.

SCHEME 1



2. Computational Details

All the calculations are performed with the second-order Møller−Plesset perturbation theory (MP2),[9] using the Gaussian 03 package.[10] The 6-31+G(d) basis set (basis set I) is used for all geometry optimizations, then more accurate energetics of reaction energy profiles are obtained by performing single point calculations with the 6-311+G(2df,2p) (basis set II) basis set. For each species, the harmonic vibrational frequencies are calculated with basis set I to obtain the zero point energies (ZPE) and verify whether it is a minimum or a transition state. Unless stated specifically, the energies of all species discussed in the following sections are calculated with basis set II, including the thermal corrections obtained with basis set I.

In the studied reaction, ionic complexes and anions are possible intermediates. Recent investigations[11] show that the

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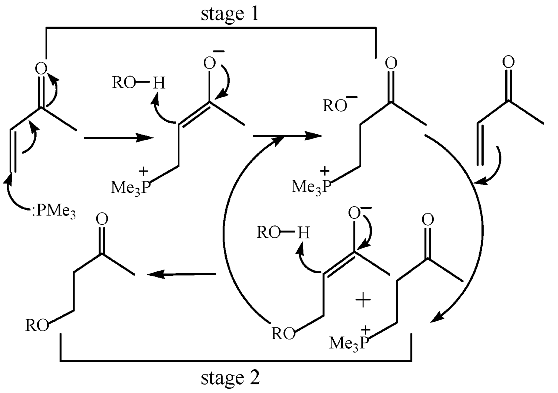
SCHEME 2: Proposed Catalytic Cycle



solvent has little effect on the optimized structures of the neutral species, but has a significant effect on the geometries of ionic species. To better estimate the bulk solvent effects on the reaction, each stationary point has been optimized in methanol at the MP2/6-31+G(d) level, using the conductor-like polarized continuum model (CPCM)[12] with UAHF parametrization (denoted CPCM-MP2/6-31+G(d)). In the Gaussian 03 program, the calculated solvation free energies use a reference state of 1 mol/L (M), but the calculated Gibbs free energies (G) for gas-phase species use a reference state of 1 atm. To obtain the free energy in the solution phase, it is necessary to convert the gas-phase free energies with the reference state of 1 atm into the corresponding free energies with the reference state of 1 M, which can be done by using the following equation:[13] $G_{gas}(1\ M) = G_{gas}(1\ atm) + RT\ \ln(24.46)$. This additional term is numerically equal to 1.90 kcal/mol at 298 K. Throughout this paper, the Gibbs free energies with the reference state of 1 M at 298 K will be used in discussing the reactivity in the solution phase.

3. Results and Discussion

On the basis of the related experiments, a possible mechanism, which is shown in Scheme 2, has been suggested for the studied reaction.[5] The whole reaction can be divided into two stages. In stage 1, a strong base, an alkoxide anion, is generated. In stage 2, the formed base acts as a catalyst and catalyzes the reaction to yield the β-alkoxy carbonyl product. We will investigate four possible reaction pathways in stage 1 and stage 2, as shown in Scheme 3. In stage 1, the formation of the methoxide anion may occur via the phosphine-induced base-formation mechanism (pathway I) or the direct base-formation mechanism (pathway II). In stage 2, the catalytic cycle may proceed through the base-catalyzed mechanism (pathway III) or the S_N2 mechanism (pathway IV).

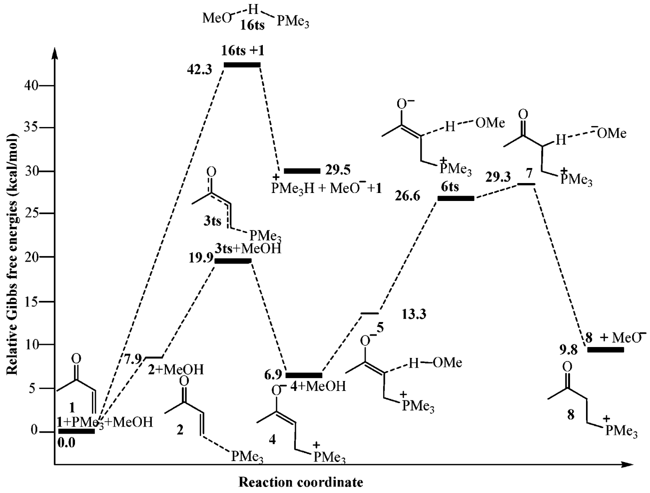
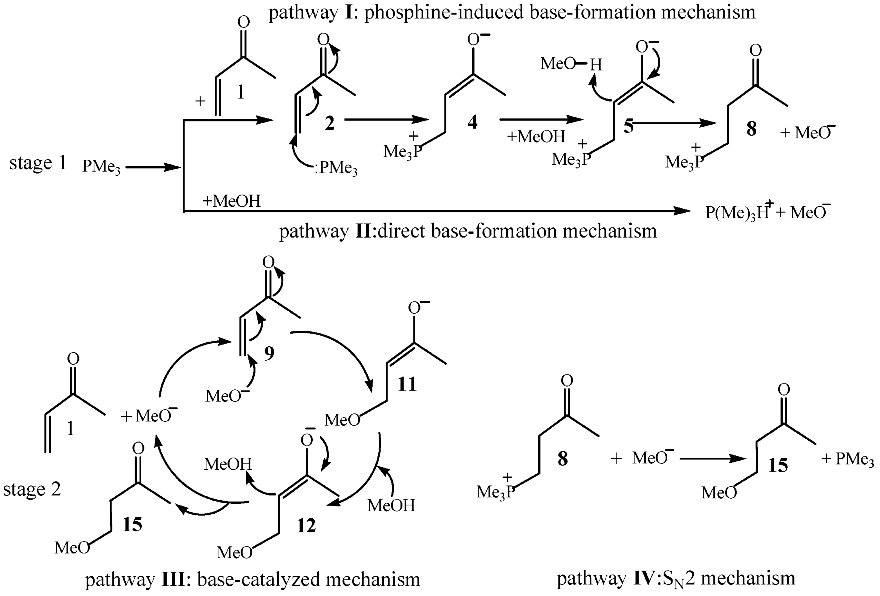


Figure 1. Free energy profiles of the pathways I and II in stage 1 at the CPCM-MP2/6-311+G(2d,2p)//CPCM-MP2/6-31+G(d) level. Species **2**, **5**, and **7**, denoted by short thin lines, are molecule−molecule or ion−molecule complexes, and should not be considered as "real" intermediates for the studied reaction in solution.

In this section, we will discuss the free energy reaction profiles in the solution phase and correlate our results with related experimental results in subsection 3.1, and then discuss the solvent effects on the reaction in subsection 3.2.

3.1. Free Energy Reaction Profiles in the Solution Phase. The free energy reaction profiles of the reaction in solution are shown in Figures 1, 2, and 3. The MP2 energies and thermal corrections to Gibbs free energies for all species in the reaction are given in the Supporting Information. The optimized geometries of intermediates, transition states, and products are displayed in Figure 4. The calculated relative electronic energies, the enthalpies, and the free energies at 298 K for all stationary

SCHEME 3: Possible Pathways of the Reaction



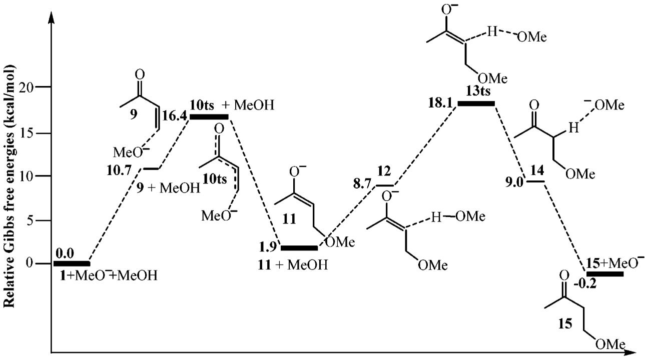


Figure 2. Free energy profile of pathway III in stage 2 at the CPCM-MP2/6-311+G(2d,2p)//CPCM-MP2/6-31+G(d) level. Species **9**, **12**, and **14**, denoted by short thin lines, are ion−molecule complexes, and should not be considered as “real” intermediates for the studied reaction in solution.

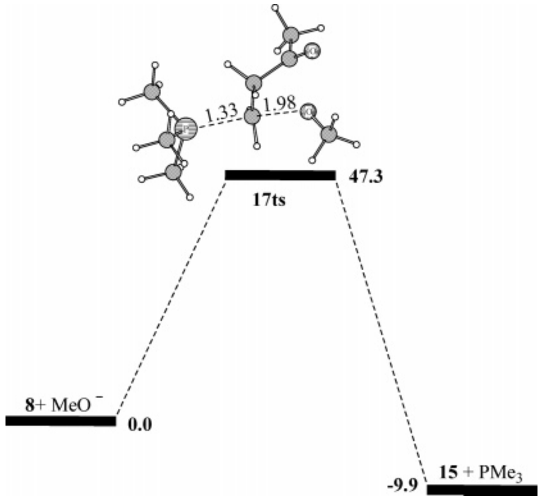


Figure 3. Free energy profile of pathway IV in stage 2 and the transition-state structure obtained at the CPCM-MP2/6-311++G-(2d,2p)//CPCM-MP2/6-31+G(d) level. The bond distances are in angstroms.

points are collected in Tables 1 and 2. Hereafter we will discuss the reactivity of the studied reaction using the Gibbs free energies with the reference state of 1 M at 298 K.

3.1.1. Pathways I and II in Stage 1. In pathway I, initially, a trialkylphosphine molecule (PMe_3) is added to the methyl vinyl ketone **1** to form the phosphonium enolate **4** through a 1,4-Michael addition. Our geometry optimizations also located an encounter complex **2**, whose electronic energy is 3.1 kcal/mol below that of the reactants. Since its Gibbs free energy is 7.9 kcal/mol higher than those of the reactants in solution, this weakly bound encounter complex is thermodynamically unstable in solution. As a result, the activation free energy from the reactants to **4** through a transition state **3ts** is 19.9 kcal/mol. In the transition state **3ts**, the distance between the phosphorus atom and the carbon atom is 2.29 Å. By comparing the natural charges on the phosphorus and oxygen atoms in the reactants and **4**, we found that the charges are transferred from trialkylphosphine to ketone. After **4** is formed, it will deprotonate a methanol molecule to generate a methoxide anion and a β-phosphonium ketone cation **8** through a transition state **6ts**. The free energy barrier for the generation of MeO^- and **8** should be 19.7 kcal/mol. During this step two other encounter complexes, **5** and **7**, could also be located on the potential energy surface, but their calculated free energies are significantly higher than those of the corresponding separated species in solution. Thus, these encounter complexes should not be considered as “real” intermediates in the studied reaction, which are in accord with the generally accepted viewpoint that these weakly bound ion−molecule complexes are not important in protic solvents. For this reason, we will not discuss the role of these weakly bound complexes for the studied reaction in the following section. Nevertheless, it should be pointed out that the ion−molecule or molecule−molecule interaction may still play a role in accelerating the reaction between an ion and a molecule (or between two molecules).

Along pathway II, a trialkylphosphine molecule deprotonates a methanol directly to form a methoxide anion. Since the free energy of the transition state in this step is significantly higher than those of transition states along path I, the reaction in stage 1 is more likely to proceed through pathway I.

3.1.2. Pathways III and IV in Stage 2. Following pathway III, the MeO^- anion generated from stage 1 could add to the methyl vinyl ketone **1** to form a methoxyl enolate anion **11** through a transition state **10ts** with a free energy barrier of 16.4 kcal/mol. Then, **11** would deprotonate a methanol molecule through a transition state **13ts** to yield the β-alkoxy carbonyl product **15** and regenerate a MeO^- anion, which completes the catalytic cycle. The activation free energy for this proton-transfer step is calculated to be 16.2 kcal/mol. Thus, the two steps have comparable activation free energies.

Along pathway IV, the phosphonium ketone cation **8** converts into the β-alkoxy carbonyl compound **15** directly by an S_N2 pathway.[6a] The free energy barrier of this step is 47.3 kcal/mol, which is much higher than those in pathway III. Thus, the reaction in stage 2 would take place along pathway III.

3.1.3. Correlation of Our Results with Experimental Results. From the results above, one can see that the overall reaction may proceed through the phosphine-induced base-formation pathway in stage 1 and the base-catalyzed pathway in stage 2. In stage 1, both the nucleophilic addition of trialkylphosphine to **1** and the proton transfer from a methanol molecule to **4** have comparable free energy barriers (about 20 kcal/mol), while the similar two steps in stage 2 have activation free energies of about 16 kcal/mol. Trialkylphosphine plays a very important role in generating the base (the methoxide anion), which acts as a catalyst in stage 2. The results shown in Figure 2 and Table 2 show that the catalytic reaction in stage 2 is exothermic with ΔH_{298} of 10.2 kcal/mol, but entropically unfavorable. The free energy change in stage 2 is slightly negative, indicating that the catalytic reaction is thermodynamically possible. These results are in good agreement with the experimental facts.[5] However, one can also notice that in stage 1 the transition state **6ts** and the products (**8** + MeO^-) along pathway I have relatively high Gibbs free energies relative to the reactants, which are not quite consistent with the fact that the studied reaction would occur under mild conditions.[5] In fact, this inconsistency may be ascribed to the underestimation of the CPCM method for the solvation free energies (ΔG^o_{sol})[14] of some ionic species. Previous theoretical studies[11d,15,16] showed that ΔG^o_{sol} of neutral molecules could be obtained by the CPCM method with good accuracy (noticeably less than 1.0 kcal/mol), but ΔG^o_{sol} of anions or cations may be underestimated by several kcal/mol in some cases. For example, for MeO^- in water Takano and Houk[11d] showed that its ΔG^o_{sol} computed by the CPCM model is 7.5 kcal/mol below the corresponding experimental data (95.2 kcal/mol[17]), while our calculations indicate that its ΔG^o_{sol} is also underestimated by 4.7 kcal/mol at the CPCM-MP2/6-311+G(2df,2p)//CPCM-MP2/6-31+G(d) level. Since the reactants (**1** + PMe_3 + MeOH) on

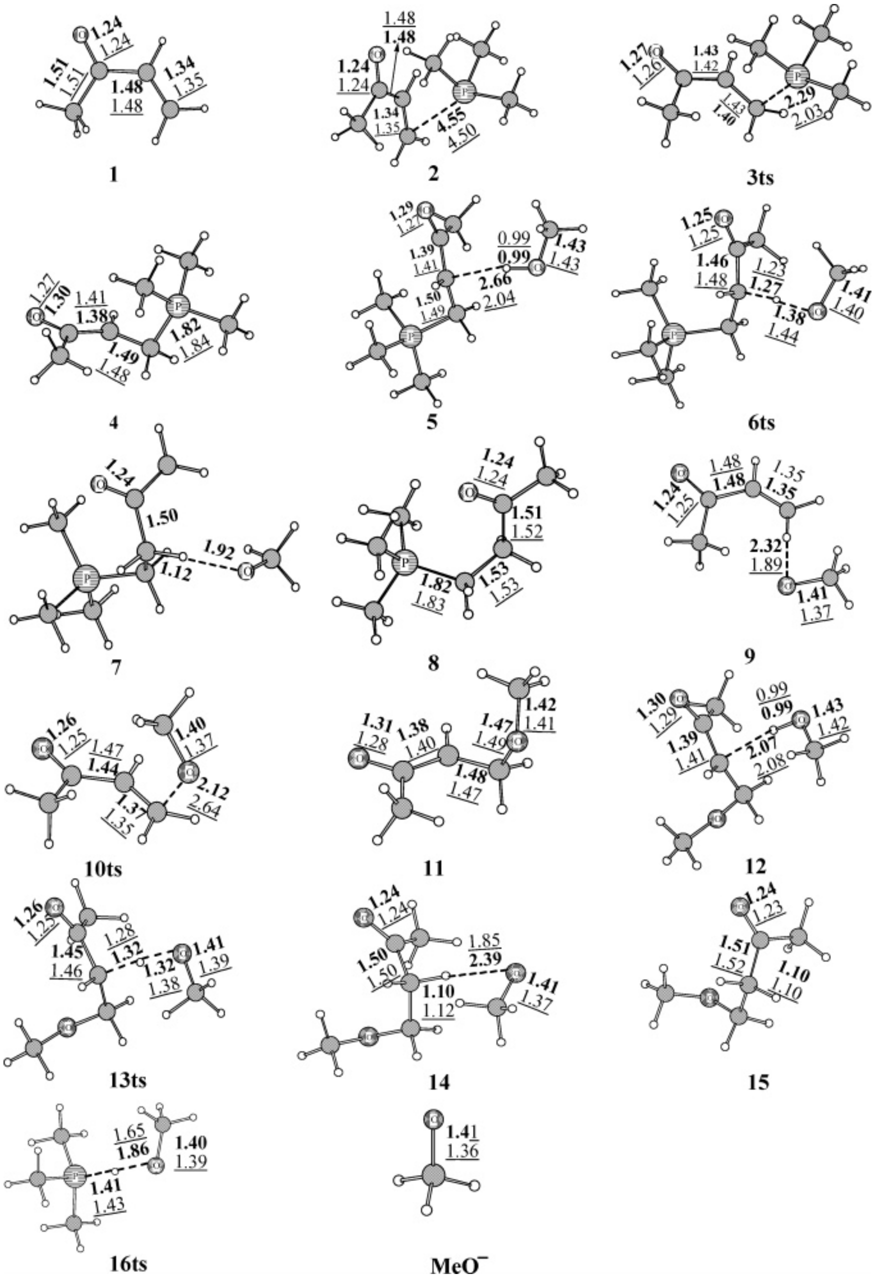


Figure 4. Optimized structures of intermediates and transition states involved in the studied reaction. The bond distances are in angstroms. The geometrical parameters in the solution phase and the gas phase are denoted in bold and underlined, respectively. For all species, their CPCM-optimized geometries in Cartesian coordinates can be found in the Supporting Information.

pathway I are all neutral species, while the species **6ts** and the products (**8** + MeO^-) contain weakly bound MeO^- or MeO^-, it can be expected that the Gibbs free energies of **6ts** and (**8** + MeO^-) (shown in Figure 1) are overestimated by approximately 5.0 kcal/mol (or even more). By taking the significant errors for ΔG^{o}_{sol} of MeO^- into account, the relative free energies of **6ts** with respect to the reactants could be reduced to about 21 kcal/mol, and the free energy change from the reactants to the products (**8** + MeO^-) could be reduced to about 5.0 kcal/mol. Therefore, the reconciliation between the resulting free energy profile of pathway I with the observed experimental facts is much improved. If more accurate solvation energies can be obtained soon, better agreement could be achieved.

To conclude, our calculations have verified the base-generation mechanism (Scheme 2) derived from related experiments.[5] This mechanism is different from that of the base-catalyzed hydration of α,β-unsaturated ketones, in which retro-aldol or ketalization products were observed.[7] In addition, it is worthwhile to make a comparison between the results described above with theoretical results from others for some similar reactions.[18−20] For example, the reaction energy profiles for the nucleophilic addition of cyanide anion to acrolein explored by Wong and co-workers[18] are also similar to our results on the reaction in stage 2. In the present reaction, some ion−dipole complexes such as **7**, **9**, and **12** are thermodynamically unstable in solution. Similar situations were also observed in the theoretical investigation on nucleophilic substitutions by a hydroxide ion at vinylic carbons.[19] The optimized transition structure **10ts** is structurally analogous to that of the addition of MeO^- to acrolein in a previous theoretical investigation.[20]

3.2. The Solvent Effects on the Reaction. Since the solvent has a strong influence on the structures and energetics of ionic species, which are intermediates in the studied reaction, it is helpful to provide a detailed analysis of the solvents of the

TABLE 1: Calculated Relative ZPE-Corrected Energies,[a] Enthalpies, and Gibbs Free Energies for All Species in Stage 1 at 298 K

	solution phase[b]			gas phase[c]		
species	E_0	H_{298}	G_{298}	E_0	H_{298}	G_{298}
1 + PMe_3 + MeOH	0.0	0.0	0.0	0.0	0.0	0.0
2 + MeOH	−3.1	−2.9	7.9	−2.7	−2.7	4.2
3ts + MeOH	7.8	7.3	19.9	16.0	16.0	25.7
4 + MeOH	−5.6	−6.1	6.9	14.1	14.1	23.9
5	−9.3	−9.5	13.3	4.3	4.3	22.8
6ts	3.7	3.2	26.6	22.0	22.0	42.4
7	5.3	4.5	29.3	36.3	36.3	9.9
8 + MeO^-	−1.7	−1.7	9.8	115.3	115.3	125.6

[a] The E_0, H_{298}, and G_{298} of **1** + PMe_3 + MeOH are taken to be zero. [b] The calculations are performed at the CPCM-MP2/6-311+G(2df,2p)//CPCM-MP2/6-31+G(d) level. [c] The calculations are performed at the MP2/6-311+G(2df,2p)//MP2/6-31+G(d) level.

TABLE 2: Calculated Relative ZPE-Corrected Energies,[a] Enthalpies, and Gibbs Free Energies for All Species in Stage 2 at 298 K

	solution phase[b]			gas phase[c]		
species	E_0	H_{298}	G_{298}	E_0	H_{298}	G_{298}
1 + MeO^- + MeOH	0.0	0.0	0.0	0.0	0.0	0.0
9 + MeOH	2.3	2.5	10.7	−22.6	−22.6	−13.2
10ts + MeOH	6.1	5.3	16.4	−18.9	−19.4	−7.8
11 + MeOH	−7.8	−8.7	1.9	−35.3	−36.0	−24.3
12	−11.0	−11.9	8.7	−49.1	−49.6	−28.9
13ts	−1.8	−2.4	18.1	−39.8	−40.9	−18.1
14	−9.3	−9.8	9.0	−37.3	−37.9	−16.9
15 + MeO^-	−9.8	−10.2	−0.2	−13.3	−14.3	−1.7

[a] The E_0, H_{298}, and G_{298} of **1** + MeO^- + MeOH are taken to be zero. [b] The calculations are performed at the CPCM-MP2/6-311+G(2df,2p)//CPCM-MP2/6-31+G(d) level. [c] The calculations are performed at the MP2/6-311+G(2df,2p)//MP2/6-31+G(d) level.

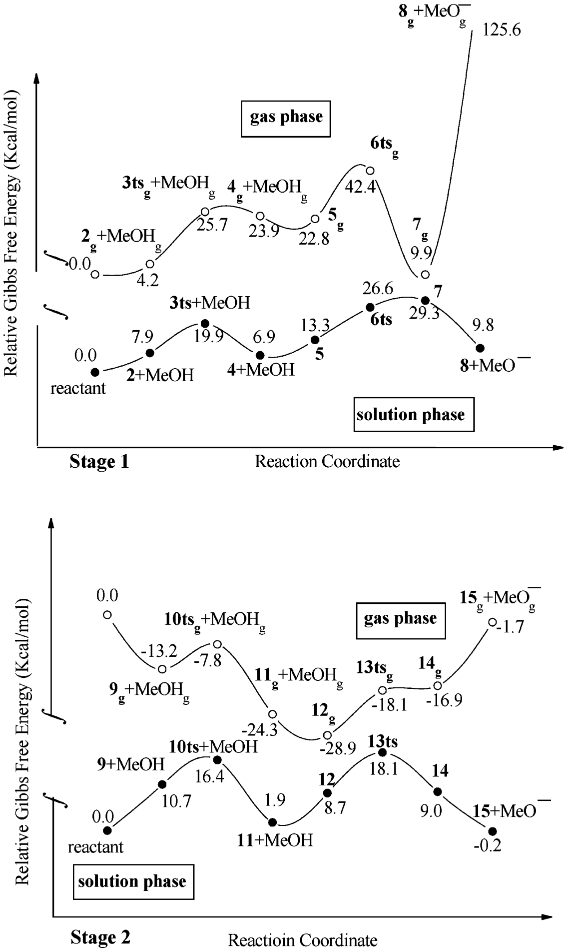


Figure 5. Free energy profiles for pathways I and III in the gas phase and the solution phase.

reaction. For this purpose, the optimized structures of all species in the gas phase and in the solution phase are shown in Figure 4, and the free energy reaction profiles in the gas phase for pathways I and III are depicted in Figure 5. As seen from Figure 4, the solvent effect has little effect on the structures of neutral species such as **1**, **8**, and **15**, but has significant effects on those of some anions (MeO^-, **10ts**) and some zwitterionic species (**3ts**, **6ts**). For instance, the O−C bond (connecting the oxygen atom of MeO^- with the terminal carbon atom (sp^2-hybridized) in **10ts**) is 2.12 Å in the solvent, but 2.64 Å in the gas phase. Nevertheless, as discussed below, the structural changes in the two phases are not mainly responsible for the difference in the free energy profiles in the two phases.

As shown in Figure 5, the free energy profile in the gas phase is much different from that in the solution phase. For instance, in stage 1 the free energy barrier from (**1** + PMe_3) to **4** is 25.7 kcal/mol in the gas phase, but 19.9 kcal/mol in solution. Thus, the solvent effects appreciably reduce the barrier of this step. As expected, those anions and zwitterionic species have quite large solvation free energies (ΔG^{o}_{sol}), but those neutral species have significantly small ΔG^{o}_{sol}. The solvation free energies of all species are provided in Table S1 in the Supporting Information. For example, the ΔG^{o}_{sol} values of MeO^- and **6ts** are −89.5 and −31.2 kcal/mol, respectively, being much larger than the −6.9 kcal/mol value for methanol. The total ΔG^{o}_{sol} of MeO^- and **8** is −135.1 kcal/mol, being 118.8 kcal/mol lower than that of the reactants. The free energy change from the reactants to (**8** + MeO^-) is 125.6 kcal/mol in the gas phase, while it is only 9.8 kcal/mol (if the underestimation of ΔG^{o}_{sol} for MeO^- is not corrected) in the solution phase. Thus, the generation of the methoxide anion is thermodynamically very unfavorable in the gas phase. The presence of the solvent leads to a drastic increase in the thermodynamical stabilities of the methoxide anion and other ionic species, which makes the reaction in stage 1 become thermodynamically possible in solution. For the reaction in stage 2, one can see that the free energies of all species are all significantly lower than that of the reactants in the gas phase. The free energy change for this stage is a small negative value in the gas phase, similar to that in the solution phase. However, in the solvent the shape of the free energy profile of this stage is quite different from that in the gas phase, because the intermediate (**11** + MeOH) and two transition states (and other encounter complexes) all have positive free energies relative to the reactants. This can be ascribed to the fact that relative to the reactants (**1** + MeO^- + MeOH) other species in this stage have relatively smaller solvation free energies. To conclude, for the studied reaction a large difference in the solvation free energies of intermediates and transition states is responsible for quite different free energy reaction profiles in the gas phase and the solution phase. The studied reaction should be sensitive to the solvents.

4. Conclusions

MP2 calculations have been carried out to investigate the mechanism of thephosphine-catalyzed hydroalkoxylation of the methyl vinyl ketone. Four reaction pathways have been examined, and the geometries of intermediates, transition states, and products along these pathways have been optimized in the gas phase and in methanol with the conductor-like polarized continuum model, respectively. Our results suggest that trialkylphosphine plays a very important role in generating the base (the methoxide anion), and the hydroalkoxylation of methyl vinyl ketone catalyzed by this base follows a general base-catalyzed pathway. In the generation of the methoxide anion, trialkylphosphine first adds to the methyl vinyl ketone to form a phosphonium enolate intermediate and then this intermediate deprotonates a methanol molecule to generate a methoxide anion. Both steps have free energy barriers of about 20 kcal/mol. For the subsequent catalytic reaction the addition of the methoxide anion to the methyl vinyl ketone and the proton transfer process from methanol to the methoxyl enolate anion intermediate have comparable free energy barriers of about 16 kcal/mol. The hydroalkoxylation of the methyl vinyl ketone catalyzed by the methoxide anion is calculated to be exothermic by 10.2 kcal/mol at room temperature. An analysis of the solvent effects on the reaction demonstrated that the generation of the methoxide anion could only occur in the presence of the polar solvents. The mechanism suggested from the present work is in reasonable agreement with the known experimental facts.

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Supporting Information Available: The MP2 energies and thermal corrections to Gibbs free energies for all species in the reaction and the Cartesian coordinates of all stationary points obtained in solution phase and gas phase. This material is available free of charge via the Internet at http://pubs.acs.org.

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