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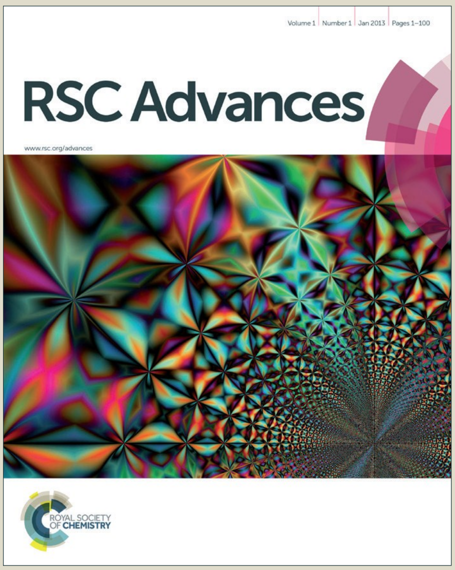

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ARTICLE TYPE

Gas Hydrates Model for Mechanistic Investigation of Wittig Reaction "on Water"

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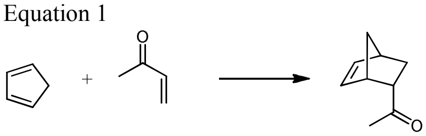
Theoretical mechanistic details for "on water" Wittig reaction of a stabilized ylide with benzaldehyde are presented and compared with a similar reaction under neat conditions. Gas hydrate structure consisting of 20 water molecules has been applied as water surface for the reaction. The model is chosen to capture non-bonding interaction over larger area in order to better account for the "on water" effect. The calculated acceleration for the cis-selective Wittig reaction is more than that for the trans-selective Wittig reaction. The "on water" acceleration for Wittig reaction is due to greater number of non-bonding interactions in the transition structure, compared to the starting material. The greater acceleration for the cis-selective Wittig over the trans-selective Wittig has been rationalized on the basis of non- bonding interaction in addition to hydrogen bonding. Besides accelerating the reaction, water also affects the pathway for reaction. Decomposition of cis OP2 to alkene is estimated as a barrierless process. Moreover OP2 is more stable than OP1 for both cis and trans-selective Wittig reactions, opposite to observed for neat reaction.

1. Introduction

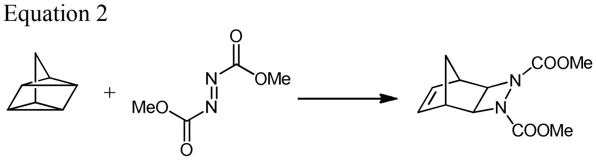
Water is a green solvent however its use in organic transformations had been quite rare until the discovery of Rideout and Breslow in 1980[1] that Diels Alder reaction between non polar substrates (Equation 1, Scheme 1) is accelerated significantly in homogeneous aqueous solution, when compared with solvent free (neat) conditions or organic solvent based reactions. The limited use of water was not only due to the classical solubility and reactivity consideration[2] but also because of the fear of hydrolysis of organic substrates, impeding catalytic activity, possible obstruction of functional groups, and side reactions caused by water.[3] Later Sharpless[4] coined the term "on water" for organic reactions which are accelerated by water but involve water insoluble reactants (Equation 2, Scheme 1). Sharpless has demonstrated that the reaction time for a heterogeneous mixture of reactants[4,5] and water is much shorter (by a factor of 300) than the reaction time for a homogeneous mixture of reactant in water.

Equation 1



1 2 3

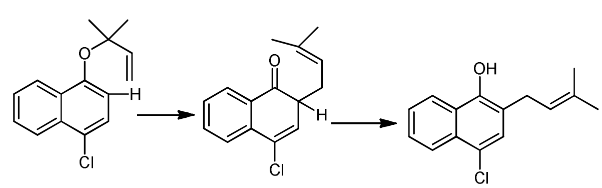
Equation 2



4 5 6

Scheme 1. Diels Alder reaction in water (equation 1) and on water (equation 2)

Water may influence the chemical reaction in different ways depending whether the reaction is "in water" or "on water".[5] For a homogeneous reaction (in water), the generally operating effects are (1) hydrophobic effect[6] (2) hydrogen bonding[7] and (3) water polarity effects. The hydrophilic effect generally enhances the rate of the reaction whereas hydrogen bonding and polarity (water) may have additive or inverse effects to the hydrophobic effect. Some other effects reported in the literature include micellar catalysis[8], solvophobicity[9], cohesive energy density[10] and ground state destabilization.[11] A heterogeneous reaction (on water), involves trans phase interaction of water with transition states and reactants. Sharpless illustrated that unique properties at the macroscopic boundary between water and organic molecules are responsible for "on water" effects. The cases mentioned above are two extremes where organic compounds are either completely miscible with water or totally insoluble in water. However in majority of cases, there exists a broad spectrum of solubilities therefore the real operating mechanism under these conditions is a combination of "in water" and "on water" reaction mechanisms

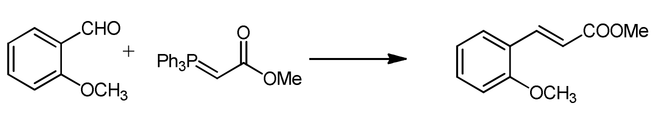


7 8 9

Scheme 2. Claisen Rearrangement of 1-(4-chloronaphthyl)-1,1-dimethylallyl ether on water, reported by Sharpless[4]

Although the early reports of acceleration of reaction "in water" and "on water" were on Diels Alder reaction however the concept has been elaborated to a number of different examples. The concept of reaction "in" or "on-water" has been described in detail in recent books,[12] reviews[13] and articles[14]. Sharpless[4] also reported that Claisen rearrangement of 1-(4-chloronaphthyl)-1,1-dimethylallyl ether **7** (Scheme 2) in aqueous suspension was completed in 5 days at 23°C. However the neat reaction took one additional day, and the reaction was even slower in organic solvents. The other reactions which are accelerated by water are "ene reaction[4, 15] Claisen/Diels Alder and more recently Wittig reaction[16] in water where reactants have very low solubility in water. On water effect is observed not only in the acceleration of organic reactions but also in altering the regio- and stereoselectivities of the reactions. For example high level of *endo* selectivity is achieved through reaction "on water". Similary, Wittig reaction which is generally favorable for *E*-olefins from a stabilized ylide and aldehyde, *E/Z* selectivity is altered for reaction on water.

Wittig reaction is a powerful tool for synthetic organic chemists to synthesize carbon carbon double bond with high stereoselectivity. *Z*-alkenes are preferentially formed from non-stabilized ylides whereas *E*-Alkenes are the major product from the reaction of stabilized ylides with aldehydes[17]. The reaction of stabilized ylides with aldehydes is generally slow in non-polar solvents[18]. Quite diverse strategies have been applied to accelerate/improve the reaction; increasing temperature[19], high pressures[20], irradiation with light[21] or microwave, ionic solvents[22], silica gel[18], additives Lithium salts[23] Phase transfer catalyst,[24] Cyclodextrins[25] and more recently water. The literature reveals both "in water" and "on water" acceleration for Wittig reaction. Bergdahl and coworkers[3] have studied the "on water" Wittig reaction between the stabilized ylides with aldehydes and they demonstrated that the reaction is accelerated considerably but at the cost of *E/Z* selectivity. For example, the reaction of anisaldehyde **10** (Scheme 3) with a stabilized ylide (methoxycarbonyl methylene triphenylphosphorane) **11** delivered 36 % yield with 82:18 *E/Z* selectivity whereas the same reaction under on water conditions furnished 81% yields of **12** in 1 hour with 76:24 *E/Z* ratio. Generally excellent results were obtained when hydrophobic groups were present (heterocycles). Moreover the authors have compared the reactivity of two different aldehydes (anisadehyde and 2-methoxycinnamaldehyde) with methoxycarbonyl methylene triphenylphosphorane. A general trend is reaction is accelerated in water however *E/Z* selectivity is decreased. Mostly regioselectivities were comparatively higher in organic solvents.



10 **11** **12**

Scheme 3. On Water Wittig reaction between methoxycarbonyl methylene triphenylphosphorane and ansialdehyde

Reactions in water are not only important for experimentalists but they have gained interest from theoretical chemists as well especially in understanding the mechanisms for these accelerated transformations. For example, Jorgenson modelled the Diels Alder reaction[7b, c] through ab-initio methods using one explicit molecule of water and showed that multiple hydrogen bonding in the transition states are responsible for lowering the activation barrier about 3-5 kcal mol^{-1} which is in nice agreement with the experimental 4 kcal mol^{-1} for reaction in water. For on water conditions, recently Jung and Markus[2] have applied the oil droplet model in order to explain the enhanced acceleration under "on water" conditions relative to "in water" conditions. They suggested that the enhanced acceleration can be rationalized when the transition state has more hydrogen bonding interactions with the surface water molecules than the reactants. The same oil droplet model has been used by Zhang and coworkers to explain the acceleration of aromatic Claisen rearrangement in water[26]. Wittig reaction is accelerated on water however the stereoselectivity decreases (*vide supra*). This behavior has not been addressed in any theoretical study to date. Although the Wittig reaction has long history and even the mechanistic details of a non-catalyzed reaction were still under intense investigation through nmr[27] and computational studies, although concluded to a single mechanism for salt free Wittig reaction very recently. With these facts, it becomes even more important to explore the mechanism of Wittig reaction on water, not only to address the acceleration on water but also the drop in stereoselectivity.

For mechanistic understanding, we propose here a different model in which instead of one or three water molecules, a gas hydrate of 20 water molecules is taken into account. We believe that this model is much superior to the previously taken models where a limited number of water molecules were taken into account.

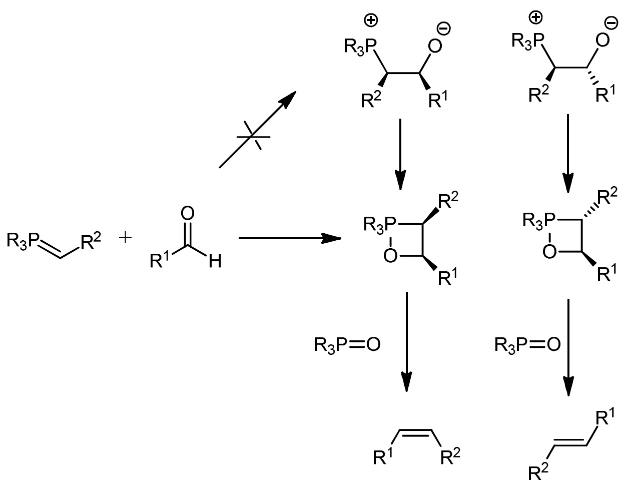
The advantage of our model is not simply based on the larger number of water molecules (20 versus 3). In the $(H_2O)_{20}$ pentagonal dodecahedral structure all water molecules are bound as at the neat water surface. It is just perfect to mimic reactions "on water". In contrast, small numbers of water molecules cannot represent the full cooperativity as present in the extended hydrogen bonding network of bulk water or at the water surface[28]. Experimental and theoretical studies on gas phase clusters showed that full cooperativity is reached for the cyclic pentamer and hexamer, whereas cyclic trimers are strongly disfavored due to enthalpic and entropic reasons[28]. Exactly twelve favorable cyclic structural motives are present in our dodecahedral water cluster. In isolated cyclic clusters only half of the OH groups are involved in hydrogen bonding, the other half is free. Such a situation is not known for water surfaces, where instead three of the two donor and two acceptors sites of each water molecule are part of the H-bond network. One free OH donor or one electron lone pair acceptor per water molecule points away from the surface and represent preferable reaction sites. Without taking boundary effects for flat water surfaces into account, the $(H_2O)_{20}$ cluster is the best model for investigating reaction "on water" because realistic H-bond strength, cooperativity and coordination numbers is taken into account.

We used the $(H_2O)_{20}$ pentagonal dodecahedral structure in earlier studies for showing the freezing of the "Bucky-ice" in the quantum cluster equilibrium model[29]. Combined with the tetrakaidecahedral $(H_2O)_{24}$ or the heccacaidecahedral $(H_2O)_{28}$ this structure forms the principle building blocks of gas hydrates type-I and type II, respectively[30]. Of course, gas hydrates are only stable at higher pressure and lower temperature and well supported by guest molecules. The most prominent species are methane hydrates for which giant natural methane deposits are expected in the deep ocean floor and in permafrost regions[30b]. Here, we want to show that these configurations can be used for studying reactions “on water” and that they better represent the water surface compared to a small number of not fully H-bonded water molecules.applications.

2. Results and discussion

Water Free mechanism

The mechanism of the Wittig reaction has faced several controversies over the past 60 years, since the discovery of the reaction[31]. The mechanism remained the subject of intense debates and it can be illustrated by the fact that Johnson[32] has shown eight different mechanisms that had been proposed at different times over the past six decades. This is one the great long standing investigation which has been addressed by both theoreticians and experimentalists. The controversies appeared due to improper addressing of all the contributing factors associated with the Wittig reaction.



Scheme 4. Mechanism of salt free Wittig reaction

Wittig reaction can broadly be classified into two main categories; Salt free Wittig reaction and Salt mediated (mainly Li+). The mechanism of the latter is not well documented in the literature. Thanks to Gilheany and co-workers (Experimental)[31] and Harvey, Aggarwal and co-workers (Theoretical)[33], the mechanism of salt free Wittig reaction is now almost settled to a single mechanism for unstable, semi-stabilized and stabilized ylides where oxaphosphetanes are proposed as intermediates without the involvement of betaines. According to the mechanism (Scheme 4) the oxaphosphetane formation is irreversible, quite contrary to the early literature where the high *E* selectivity of Wittig reaction has been explained on the reversible nature of oxaphosphetane formation and thermodynamic control of the reaction. However it is interesting that a few examples where the oxaphosphetane formation is genuinely reversible belong to the class of non-stabilized ylides.[31, 33]

Despite the fact that the mechanism is same for non-stabilized, semi-stabilized and stabilized ylides, the reasons for the selectivities are different. The *E*/*Z* selectivity of the Wittig reaction is mainly explained by planar or puckered nature of the addition transition states. The degree of puckering depends on C-H---O hydrogen bonding (hydrogen bonding between a C-H of P-substituent and oxygen of the aldehyde), dipole-dipole interactions, and steric interactions between ylide and aldehyde substituents (1,2) and between phosphorus and aldehyde substituents (1,3). Except for 1,2 steric interaction, all other interactions are significantly affected by substituents on phosphorus.

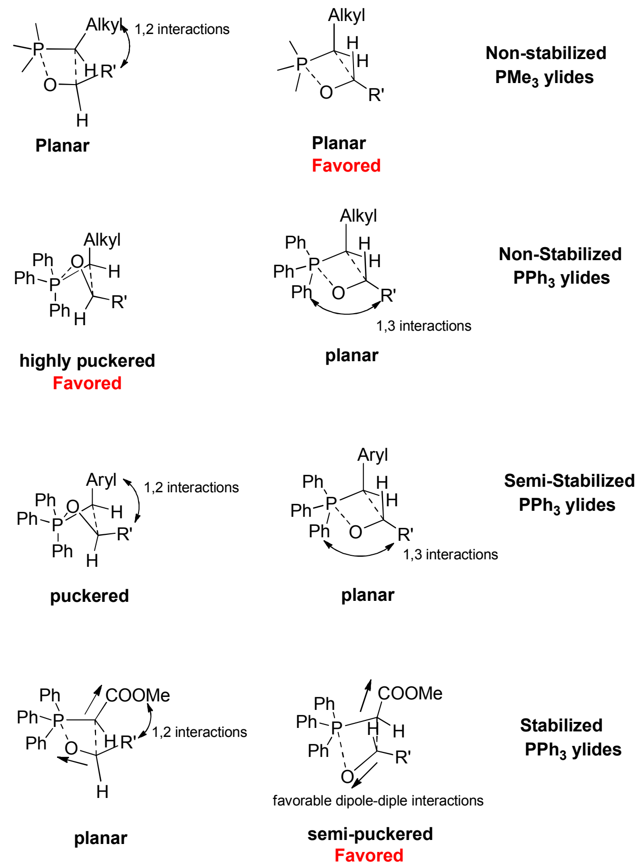


Figure 1. Origin of selectivity for trimethyl and triphenyl phosphonium ylides.

The E/Z selectivity of the Wittig reaction from non-stabilized and semi-stabilized ylides is mainly explained on the basis of steric interactions (1,2 and 1,3); however, dipole-dipole interactions play key role in reactions from the stabilized ylides. For example, in the case of non- and semi stabilized ylides, methyl and methoxy substituents on phosphorus lead to planar and semi-puckered addition transition states, respectively. Therefore, 1,2 steric interactions operate in the favour of *E*-selectivity. For the planar geometries, 1,2 steric interactions are more pronounced in the *cis* TS. Therefore, the *cis* TS is less stable compared to the *trans* TS. The relatively higher stability of the *trans* TS delivers the *E* olefin.The situation is more complex with phenyl substituents where both puckered and planar transition states are observed. The selectivity is generally governed by a complex interplay of 1,2 and 1,3 steric interactions. The Wittig reaction from non-stabilized triphenyl phosphonium ylides proceeds through *cis*-puckered and *trans* planar transition states. Low 1,3 steric interaction combined with better solvation render the *cis* puckered TS more favourable (*Z*-selective). For semi-stabilized triphenyl phosphonium ylides, the *cis* transition state is less puckered therefore 1,2 steric interaction play significant role in addition to 1,3 steric interaction. Therefore, the *Z*-selectivity is reduced (*E*/*Z* mixture). The *E*-selectivity of the Wittig reaction from the stabilized ylides is mainly explained by dipole-dipole interactions between the reactants. The recent theoretical work illustrates that transition states for *trans* addition from stabilized ylides is puckered whereas the *cis* addition TS is planar (to avoid unfavourable electrostatic interactions). The planar structure of the *cis* TS is unfavourable due to increased 1,2 interactions. The dipole-dipole interaction is favourable (dipoles orient opposite to one another) for the *trans* addition therefore, *E*-selectivity is observed. The electrostatic origin of *E*-selectivity from stabilized ylides is contrary to what was originally proposed by Vedejs.[34,35] According the earlier model proposed by Vedejs, the addition transition states from stabilized ylides are late in nature, and therefore non flexible. The planar *trans* TS is therefore more favourable due to reduced 1,2 steric interactions, compared to the *cis* TS.[34,35]

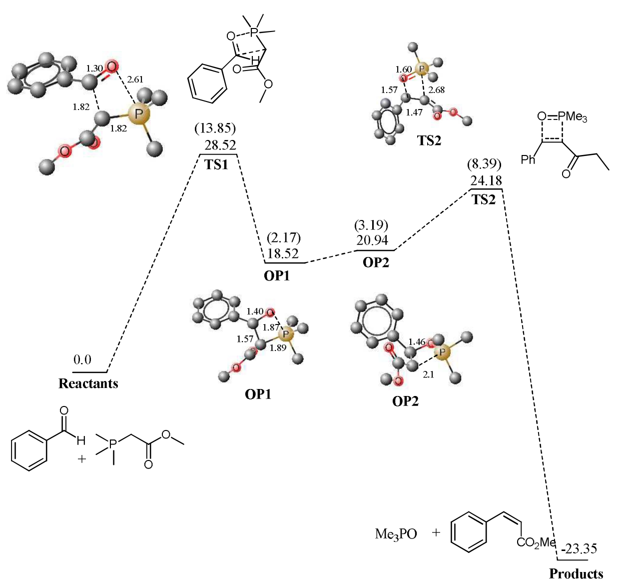


Figure 2. Gibbs and electronic (parentheses) energy profile for *cis*-selective Wittig reaction in neat conditions. All energies are relative to benzaldehyde and ylide. Unimportant hydrogen atoms are removed for clarity

It is worth mentioning here that in this study, we have truncated the system from the original report of Bergdahl and coworkers[3]. The ortho methoxy group on the aldehyde is removed, and the phenyl groups on the phosphorus of the ylide are replaced with methyl groups, in order to reduce the computational cost. This truncation is believed not to affect our study aimed at investigating on water mechanism of the Wittig reaction. The steric and electronic effects (if any) from phenyl and methoxy groups are believed to be comparable for both *cis* and *trans* product formation and therefore not expected to affect the energy profile significantly. To prove that the replacement of phenyl by methyl groups on the phosphorus of the ylide has only minor effects on the energy profiles, we have also investigated the energy profile for water free *trans*-selective Wittig reaction of triphenylphosphonium ylide, and compared with the energy profile of the same reaction "on water". Moreover, we have also calculated the activation barrier for *cis* and *trans* addition of triphenylphosphonium ylide on benzaldehyde. As shown in the Supporting Information, the energy profiles are comparable. The reactions for both ylides show similar acceleration behaviour on water.

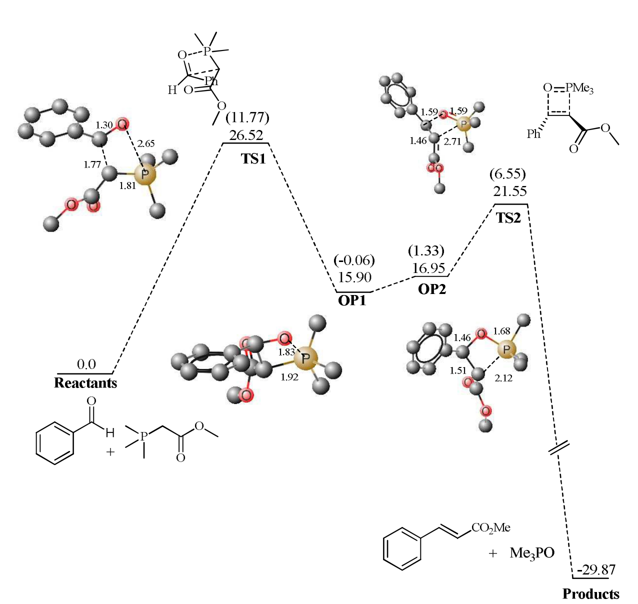


Figure 3. Gibbs and electronic (parentheses) energy profile for *trans*-selective Wittig reaction in neat conditions, all energies are relative to benzaldehyde and ylide. Unimportant hydrogen atoms are removed for clarity.

For a true comparison for reaction on water, an exactly identical system must have been theoretically studied in neat conditions as well. Fortunately Aggarwal, Harvey and coworkers[33,36] have theoretically studied the reaction under neat and THF solvent conditions. However they reported only the results based on total energies without any zero point correction. We believe that Gibbs free energies are more meaningful for reactions involving reaction between more than one species because entropic factors are included in Gibbs free energy. We have calculated frequencies on the structures optimized by Agarwall and coworkers and the results here are described and compared with "on water" study in terms of Gibbs free energy. The transition states were reported at barrier of 14.52 and 11.58 kcal mol^{-1} (total energies) for the *cis* and *trans* oxaphosphetane formation, respectively from the ylide and benzaldehyde. However the Gibbs free energies are 28.52 and 26.51 kcal mol^{-1} for the *cis* and *trans* oxaphosphetane formation respectively. In the transition state for *cis* oxaphosphetane formation **TS1** (Figure 2), C-C and P-C bond lengths are 1.82 A (Figure 2) whereas the O-P bond length is 2.61 angstroms. One can observe that in the transition state C-C is formed considerably which indicates the late nature of the transition state, and it is consistent with the reports of Harvey and coworkers that the transition states from stabilized ylides and aldehdyes are late in nature. For the transition state leading to *trans* oxaphosphetane (Figure 3), bond lengths are not much different. Since the ylides are stabilized therefore the formation of oxaphosphetane is endergonic by 18.52 (2.17) and 15.90 (-0.06) kcal mol-1 for the *cis* and *trans* oxaphosphetane formation, respectively. Oxaphosphetanes from non- and semi-stabilized ylides are lower in energy than the reactants (exothermic reaction) whereas oxaphosphetanes from stabilized ylides are higher in energy (endothermic).

The oxaphosphetane generated from the Wittig addition **OP1** undergoes conformational changes to generate oxaphosphetanes-2 **OP2** and the thermodynamic cost for the step is 2.42 (*cis*) and 1.05 (*trans*) kcal mol^{-1}. Characteristic bond lengths for the intermediates and transition states are shown in figures 1 and 2. Transition states for retero (2+2) are located at barrier of 3.24 and 4.60 kcal mol^{-1} from the *cis* and *trans* oxaphosphetane-**2**, respectively.

Reaction "on water"

For the study of Wittig reaction on water we have chosen gas hydrates where twenty water molecules are used a model. The gas hydrates describe hydrogen bonding interactions in reactants and transition states more accurately because a number of water molecules are present all round to encompass the maximum number of interactions. This fact has been described to some extent by Zhang and coworkers in their study of benzene Claisen rearrangement where three water molecules provide much better illustration of hydrogen bonding than a single water molecule, and the result in the former case were very close to the experiment. We have extended the concept to twenty water molecules with the belief that the results will be further improved.

Binding energy of ylide with water cluster

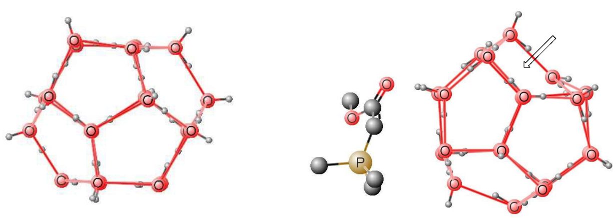


Figure 4. illustration of pentagonal motifs of $(H_2O)_{20}$ gas hydrate before and after binding with ylide.

Our study for Wittig reaction "on water" begins with the formation of a complex between the ylide and gas hydrate. Gas hydrate complexes containing both ylide and benzaldehyde are insignificant in this study, and a brief discussion can be found in the supporting information. Since we proposed that 20 water molecule gas hydrate should better represent water surface for the reaction then one necessary condition for the validity of our hypothesis is that the gas hydrate structure is not affected significantly during the reaction. Therefore, immediately after complexation of the ylide with the gas hydrate, the structure of the complex (Figure 4, right) was analyzed and compared with the gas hydrate before complexation (Figure 4, left). The complexation of the ylide with the gas hydrate does not significantly affect the structure of the latter. One can observe that the pentagonal motifs, characteristic of the gas hydrate, are mostly retained except one pentagon which is transformed into an envelope like structure (shown by a directed arrow). But this pentagon is far away from the reaction center therefore this slight perturbation in structure of the gas hydrate does not influence the validity of our hypothesis. The Ylide-gas hydrate complex is 17.59 kcal mol^{-1} more stable than the reactants. However the free energy of complexation is only -0.22 kcal mol^{-1}. The high stability of the ylide-water20 complex is due to multiple hydrogen bonding interactions (Figure 5). In Figure 5a, unnecessary hydrogen atoms are removed for clarity however Figure 5b displays all hydrogen bonding interaction including inside the gas hydrates, and between the gas hydrate and the ylide. The structures of the gas hydrates have already been discussed in the literature in fair detail therefore only interactions with ylide are discussed here.

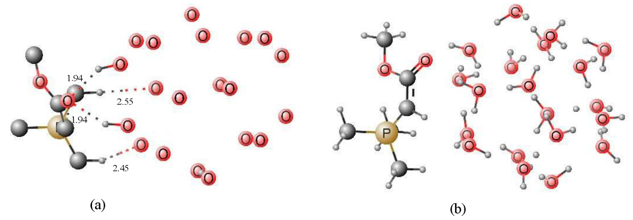


Figure 5. Gas hydrate-ylide complex (a) unimportant hydrogen atoms removed (b) all hydrogen atoms included

The carbonyl oxygen of the ester moiety in the ylide acts as hydrogen bond acceptor from two water molecules in the gas hydrates. The bond distances are 1.94 angstrom for both. Protons from two methyl groups of PMe_3 group behave as hydrogen bond donor for gas hydrates. The interaction distances are 2.45 and 2.55Å (Figure 5a). These interaction are relatively weak compared to the interactions from the carbonyl oxygen, and this may be primarily attributed to the in space orientation of the ylide on the gas hydrate surface. Hydrogen bonding interactions between the ylide and gas hydrate also affects the hydrogen bonding interaction inside the gas hydrate (*vide supra*) therefore the binding energies can be used to measure the strength of hydrogen bonding established between the ylide and gas hydrates.

***Cis* addition (2+2)**

The transition states for "on water" Wittig reaction has been located for both *cis* and *trans* addition. A transition state for the *cis* addition of ylide – water complex **TS1** (Figure 6 and 6) to benzaldehyde is located at a barrier of 26.24 kcal mol^{-1} (Gibbs free energy of activation) and this is about 2.3 kcal mol^{-1} lower than the free energy of activation for the *cis* addition without water (neat). The lower activation barrier under "on water" conditions is very much consistent with the experimental observations. The non-bonding interactions of Wittig complex with gas hydrate are changed considerably from the interaction in the starting complex. The transition state shows more hydrogen bonding interaction when compared with the starting material and it supports the earlier concept by Sharpless[4] that more hydrogen bonding interactions in the transition state compared to the starting materials lead to low activation barrier for the reaction carried out in or on water. The stability of the gas hydrate during the reaction is also investigated at the stage of TS1, by looking into pentagonal motifs of the gas hydrates. It can be easily seen in Figure 7b, that the gas hydrate component retains most of its pentagons except one which is influenced by the approach of the aldehyde (may be a steric effect)

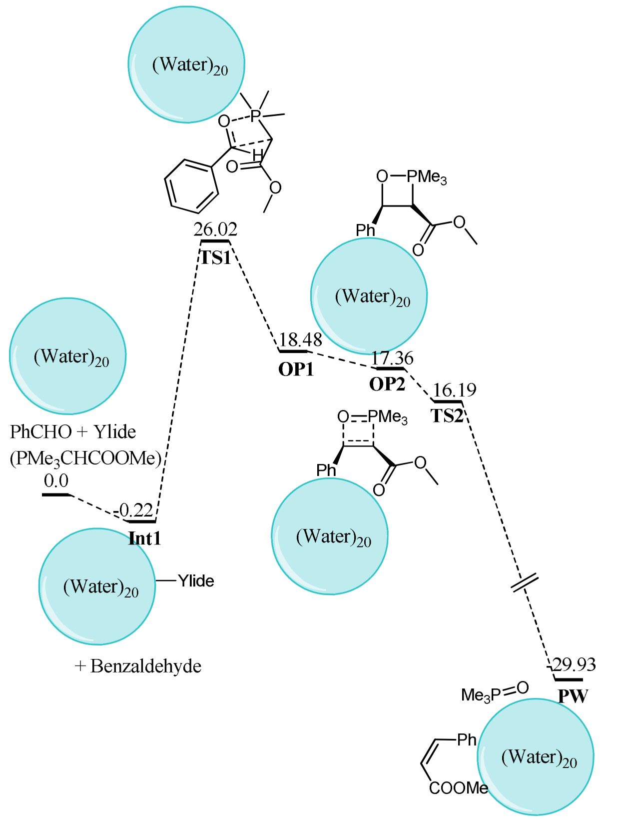


Figure 6. Gibbs free energy profile for *cis*-selective Wittig reaction on water, all energies are Gibbs free energies relative to benzaldehyde, ylide and water 20 molecule.

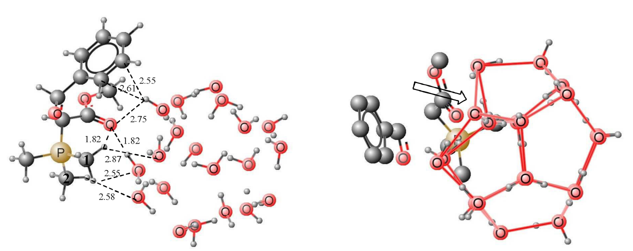
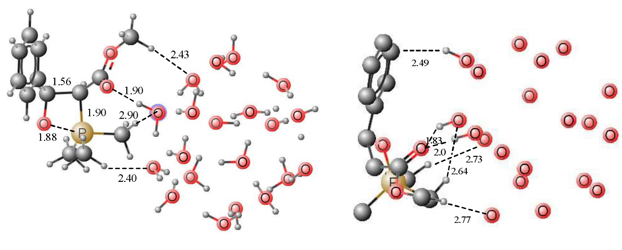


Figure 7. TS1 for *cis* Wittig addition (a) illustrating non-bonding interactions (b) illustration of pentagonal motifs of the gas hydrates

Two hydrogen atoms on the methyl carbon 1 (see Figure 7) act as hydrogen donor to gas hydrate in the transition state, compared to one in the starting material. The H---O bond lengths are 2.55 and 2.87 Å. However the methyl 2 of PMe_3 (see Figure 7) has only one hydrogen bond interaction with the gas hydrate (2.58Å), both in the transition state and the starting ylide water complex. The increased number of interactions from carbon 1 (see Figure 7) may be considered as a consequence of the approach of the aldehyde. With the approach of the aldehyde, the change in the geometry of phosphorus causes the methyl groups to come close in space among them as well close to the gas hydrate. However the hydrogen bond acceptor interactions of the carbonyl oxygen with water molecules are slightly diminished compared to the starting material. The O---H bond lengths are 1.82 and 2.75 Å. A hydrogen from C1 of PMe_3 acts as a hydrogen bond donor for the carbonyl oxygen (1.82 Å) which compensates for the diminished interaction of the carbonyl oxygen with the hydrogens of the gas hydrates. In the transition state, some interesting interactions are also observed besides the above mentioned hydrogen bonding interactions. The benzene moiety of benzaldehyde interacts with the hydrogen atoms of the water. A hydrogen atom from the gas hydrate water molecule interacts with two carbons of benzaldehyde (2.55 and 2.61 Å). Although significant interactions between gas hydrate and transition states are observed however the nature of the transition state and associated bond lengths are not affected much. For example, C-C bond being generated has bond length of 1.81Å in both transition states (neat and on water). A slight difference in the bond length of P-O is observed between neat (2.61Å) and on water (2.56Å). The (2+2) addition of ylide-water complex with aldehyde is endergonic (E_R=18.7 kcal mol^{-1}(free energy of reaction), whereas the energy of reaction 3.82 kcal mol^{-1}). The reaction is endergonic and it is consistent with the reports of Harvey, Aggarwal and coworkers[33,36] that (2+2) addition of benzaldehyde and ylide in Wittig reaction is endothermic for stabilized ylides. The intermediates generated from the addition, **OP1**-gas hydrate (written as **OP1** and so for other oxaphosphetanes in this discussion) is an oxaphosphetane. Bond distance for the C-C bond generated in the Wittig reaction is 1.56Å and O-P bond is 1.88Å. The C-P bond distance is 1.90Å. All these bond lengths are characteristic of an oxyphosphatine. Non-bonding interactions are considerably reduced in the product when compared with the transition state. For example, non-bonding interactions between the phenyl ring and water molecules are absent altogether. Moreover the carbonyl oxygen of the ester moiety is an acceptor of only one hydrogen bond (1.90A) between the complex and gas hydrate compared to two for **TS1**. However the interactions between methyls of PMe_3 and gas hydrate structure are almost similar.

Single point energy calculations are performed at higher level of theory to refine the free energies of activation (See supporting information). The results from higher level are consistent with the results from B3LYP/6-31G(d) that the *cis* Wittig addition is accelerated on the surface of water. The calculated acceleration effect for cis Wittig reaction at B3LYP/6-311++G(d,p) is much higher (about 5 kcal mol^{-1}) than then one predicted at B3LYP/6-31G(d). The calculations have also been performed at Minnesota functional M05-2X (with 6-31G(d)) which is well known to account for non-bonding interactions. The results here also suggest much pronounced acceleration of *cis* Wittig reaction on water (see Supporting information). These results suggest that B3LYP/6-31G(d) level of theory is probably illustrating the minimum limit of acceleration of Wittig reaction.

The oxaphosphetane **OP1**-Water 20 undergoes slight changes in the geometry prior to it decomposition into alkene however we have not modeled the transition state for this step because it is almost insignificant in our studies of “on water” Wittig reaction mainly because of the fact that the activation barrier for this process is insignificant. The **OP2** generated is more stable than **OP1** and this behavior is opposite to the observed for neat reaction. In reactions without water, **OP2** is 2.42 kcal mol^{-1} higher in energy than **OP1**. The higher stability of **OP2**-water complex over OP1 complex may be rationalized on geometric analysis. **OP2** has more non-bonding interactions with Water-20 complex compared to **OP1**-water complex.



OP1-Gas hydrate **OP2-Gas hydrate**

Figure 8. *Cis* **OP1** and **OP2**-Gas hydrate complexes

For example, carbonyl oxygen is one hydrogen bond acceptor in **OP1** whereas in **OP2**, it accepts two hydrogen bonds from the gas hydrate (Figure 8 for details). Moreover the hydrogen bond are 2.0 and 1.83Å in **OP2** compared to 1.90Å in OP1. In addition, methyl groups on PMe_3 are three hydrogen bonds donor in **OP2** compared to two hydrogen bonds donor in **OP1**. More interestingly, the phenyl ring of the aldehyde fragment is far away from the gas hydrate in **OP1** whereas this phenyl ring is in close proximity to a hydrogen from the gas hydrate and has a favorable interaction between a *meta* carabon and a hydrogen from the gas hydrates. The enhanced interaction between the Wittig complex with the gas hydrate in **OP2** compared to **OP1**, make the former thermodynamically more stable. All attempts to locate a transition state for retro (2+2) from **OP2** met with failure. However we isolated a structure during the optimization of **TS2** with RMS gradient 4.2 x 10-4 which has the right frequency for the retro (2+2) but this structure now called as **TS2** is lower in energy compared to **OP2** which indicates that this process is a barrierless process. A low activation barrier is generally expected for retro (2+2) in *cis* oxaphosphetane however its barrierless nature has not been reported to date, to the best of our knowledge. The transition state may be taken as a stationary point on PES if the convergence criteria reported by Aggarwal, Harvey and co-worker is taken into account. In their report of mechanistic study of Wittig reaction, structures with RMS gradient of 0.0015 were taken as stationary point on PES (they used loose optimization under Jaguar formalism).

The product of the reaction is a complex in which phosphoxide and Wittig product (olefin) are bound to gas hydrate, and this structure is called product water complex (**PW**). The **PW** complex is highly stable and lies about 47.29 kcal mol^{-1} lower in energy than the **OP2**-hydrate complex. The high thermodynamic stability of the **PW** is also a factor for difficulties in locating **TS2**, and even **OP2** because any attempt leads to the optimization of **PW**. Since the reaction is thermodynamically highly exergonic therefore the transition state is an early transition state according to the Hammond Loeffler postulate.

Trans Addition

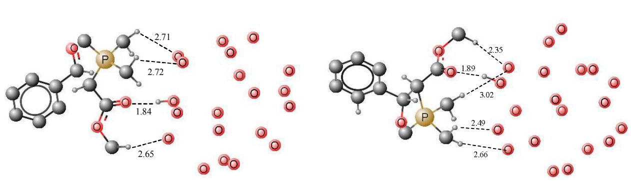


Figure 9. Optimized geometries of *trans* **TS1** and *trans* **OP1**. All bond lengths are in Angstrom. Hydrogen atoms are removed for clarity

For the *trans* (2+2) addition of benzaldehyde and ylide under on water conditions, a transition state has been located at a barrier of 25.12 kcal mol^{-1} from the ylide water complex. This activation barrier is about 1.4 kcal mol-1 lower compared to the activation barrier for the neat reaction (without any water molecules, 26.52 kcal mol^{-1}). A few important hydrogen bonding interactions in the transition state are shown in Figure 9. A proton from the methyl of the ester moiety acts as hydrogen donor for a water molecule in the gas hydrate. The carbonyl oxygen accepts only one hydrogen bond from the hydrate whereas the transition state for the *cis* addition displayed two interactions from the carbonyl oxygen. The other interactions were almost comparable between the *cis* and *trans* transition states. An oxaphosphetane is generated from the *trans* addition of ylide and benzaldehyde and the reaction is endergonic by 14.23 kcal mol^{-1} compared to 18.48 kcal mol^{-1} for the formation of *cis* oxaphosphetane. In the case of *trans* addition, no significant difference in non-bonding interaction is observed between **TS1** and oxaphosphetane. The number of interactions and interacting atoms are same in **TS1** and oxyphosphantine. The bond lengths at the reaction center change, for example, C-C bond generated has bond length of 1.74Å in the transition state which reduced to 1.54Å in **OP1**. Similarly P-O bond reduces in length from 2.64Å in **TS** to 1.84Å in **OP1**.

Although the calculations at B3LYP/6-31G(d) suggest acceleration of trans Wittig reaction as well, but the results from B3LYP/6-311++G(d,p) and M05-2X/6-31G(d) are quite opposite. The level of theories suggest deceleration of *trans* Wittig reaction (see supporting information). These calculations would suggest that E/Z ratio should be small because cis Wittig is accelerated but *trans* is decelerated (contrary to the experimental observations). These results forced to look deep into the experimental conditions for Wittig reaction. We could realize that they added HCl to the water reactions before work up! Their idea was to make sure no more Wittig reaction occurred during work up in the organic solvent extraction. This was a good idea in principle but acid could have isomerised a portion of the Z-isomer to the *E*-isomer. So their reported *E/Z* ratios could be artificially high in *E*-isomer.

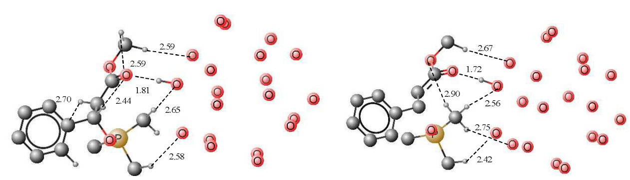


Figure 10. Optimized geometries of *trans* **OP2** and **TS2**, hydrogen atoms are removed for clarity and all bond lengths are in Angstroms

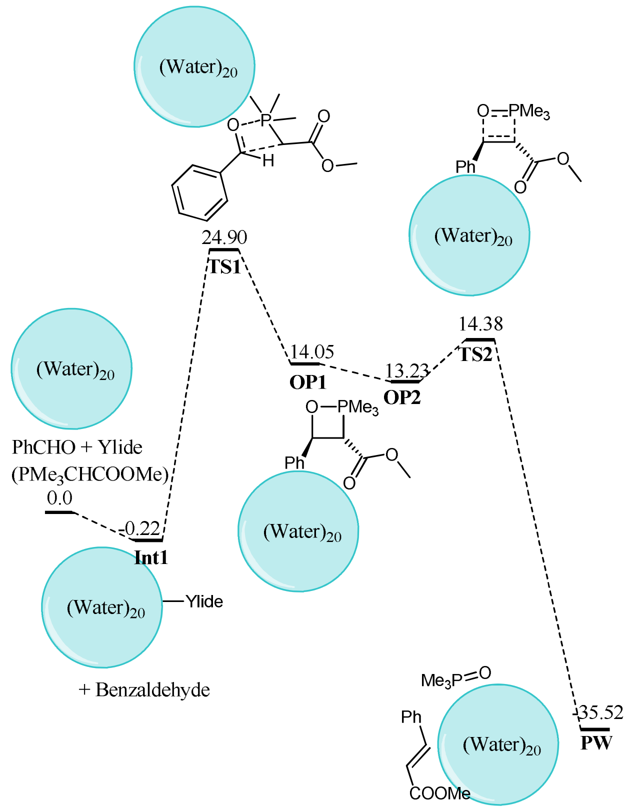


Figure 11. Gibbs free energy profile for *trans*-selective Wittig reaction on water, all energies are Gibbs free energies relative to benzaldehyde, ylide and water 20 molecule.

OP1 gets transformed into **OP2** and the process is thermodynamically favorable, quite similar to the case of *cis* **OP2** from **OP1**. The higher stability of **OP2** relative to **OP1** is common for both *cis* and *trans*-selective Wittig reaction on water. The *trans* **OP2** is of higher energy compared to **OP1** (by 1.39 kcal mol-1) in neat conditions. The *trans* **OP2** is a stable species on the potential energy surface. A transition state for the retro (2+2) from **OP2** has been located at a barrier of 1.15 kcal mol^{-1}. Although this activation barrier is negligible for *trans* retro (2+2) but still it represents a marked difference from the behavior of *cis* **OP2** where the cleavage has been shown to be a barrierless process. In the transition state the P-C bond which is being broken has bond length of 2.21Å and the C-O bond is 1.46Å (Figure 10). The retro (2+2) reaction from **OP2** to form *E* product complex **PW** is thermodynamically highly favorable (49.75 kcal mol-1). The overall process is also thermodynamically favorable one by 35.2 kcal mol^{-1}.

3. Conclusions

In summary, we have shown that gas hydrate model consisting of 20 water molecules nicely illustrates the acceleration of the Wittig reaction on water. Water not only affects the reaction rates for both *cis* and *trans* Wittig reaction but also affects the relative stabilities of different intermediates during the course of the reaction. Low activation barrier for the rate determining formation of oxaphosphetane illustrates that Wittig reaction for the formation of both *cis* and *trans* olefins is accelerated, however the former is accelerated more than the latter. Another remarkable difference between the neat and "on water" reaction is the higher stability of **OP2** than **OP1** in the latter case whereas the reverse is true for neat reaction. For the *cis*-selective Wittig reaction, the retro (2+2) from oxaphosphetane **OP1** is a barrier less process however a barrier of 1.38 kcal mol^{-1} is the calculated from **OP2** (*trans*).

4. Experimental Section

All calculations were performed with Gaussian 09[37]. Geometries of the structures were optimized without any symmetry constraints at hybrid B3LYP method of DFT at 6-31G* basis set[38]. The B3LYP method is quite effective at predicting the behavior and geometries of neutral[39] and charged species[40] including study of reaction in and on water. The method has also been used for the study of Diels Alder and aromatic Claisen[26] rearrangement under on water conditions. Each optimized structure was confirmed by a frequency analysis at the same level of theory as a true minimum (no imaginary frequency) or a transition state (one imaginary frequency). The imaginary frequencies were also evaluated to confirm that their associated eigenvector correspond to the motion along the reaction coordinates. The reported energies are Gibbs free energies and are in kcal mol^{-1}. Total energies and zero point energies can be found in the supporting information

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Keywords: Reaction "on water" • Wittig Reaction• DFT studies • Gas hydrate model • stereoselectivity

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Table of Contents Entry

Water in action! A gas hydrate model consisting of 20 water molecules nicely illustrates the acceleration of the Wittig reaction "on water". Water not only influences the reaction rates for both the cis-selective and the trans-selective Wittig reaction but also affect the relative stabilities of different intermediates during the course of the reaction. Water decreases the E-Z ratio in accordance with the experimental observation. Overall it is shown that "bucky" water is a perfect model for describing chemical reactions "on water".