Interfacial Reactivity of “on Water” Reactions in the Presence of Alcoholic Cosolvents

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A detailed study of the variation in the interfacial reactivity and selectivity of “on water” reactions in the presence of increasing amounts of alcoholic cosolvents is discussed in the present work. The initial increase in the rates of “on water” reactions on the addition of alcoholic cosolvents is contrary to the sharp decrease in rates observed for homogeneous aqueous reactions. The existing theoretical framework is presented in terms of a typical “on water” process to enable a discussion of the experimental observations with reference to changing composition of the reaction medium. On the basis of the interesting observations of reactivity and selectivity variations with composition of the reaction medium, a simple “signature” characteristic for “on water” reactions is proposed.

1. Introduction

The spectacular rate-enhancing effect of water as a solvent medium is widely reported for numerous organic reactions.[1] It was the drastic effect of hydrophobic forces on the rates of Diels−Alder reactions, reported by Breslow and Rideout that provided the impetus for further research.[2] However, the marginal solubility of organic substrates in aqueous media was thought to be a major deterrent in the scaling up of aqueous reactions for practical applications. In order to overcome this limitation, considerable efforts were directed toward the functionalization of substrates or reagents[3] or toward the design of biphasic processes using phase transfer catalysts.[4] The “on water” protocol promoted by Sharpless and co-workers established that the low solubility of organic substrates in aqueous systems need not necessarily be a deterrent to the progress of the reaction.[5] Contrary to conventional views, the interfacial mechanism was observed to be the dominating pathway for most of the transformations. At the molecular level, various factors like hydrophobic packing, hydrogen bonding, enforced hydrophobic hydration, *ced*, etc., are believed to cause rate accelerations in homogeneous aqueous media.[6] For the “on water” reactions, however, Jung and Marcus proposed that the typical arrangement of water molecules with dangling −OH groups at the interface leads to greater activation by hydrogen-bonding interactions, which is absent in both the neat and homogeneous aqueous reactions.[7] Numerous workers have reported rate accelerations of organic reactions as varied as [3 + 2] cycloadditions, brominations, hydrogenations, functionalizations, Wittig reactions, etc., by employing the “on water” protocol[8] and the recent progress has been thoroughly reviewed.[9] All these reactions have been carried out with water-insoluble reactants, in the absence of phase transfer catalysts and at ambient temperature and pressure. The “on water” pathway is also known to have an influence on the regio- and stereoselectivity of the reaction.[10]

Despite these encouraging developments, the lack of in-depth understanding of the mechanistic processes at the water−organic interface hinders the industrial-scale application of the “on water” methodology. Very little is known quantitatively about the reactivity or selectivity of the substrates at the interface. It is only recently that the rate dependence of heterogeneous organic reactions in aqueous media on the polarity and mixing methods has been experimentally demonstrated.[11] This is not surprising, given the numerous practical and analytical difficulties present in studying the interface. Even when a satisfactory analytical procedure has been established for studying the interface, the interpretation of the results is not straightforward. Any interfacial reaction is affected by numerous processes like diffusion of the reactants to the interface, the variable tendency of adsorption and chemisorptions, the orientation of the adsorbed reactants at the interface, and the solubility effects. A discussion of the efficiency of the interfacial process is difficult because the respective contributions from all the above-mentioned factors have not been consistently quantified. Significant progress has been achieved in the last 2−3 decades in this direction through detailed modeling approaches and sophisticated analytical techniques.[12] The application of these techniques has resulted in the emergence of a comprehensive picture in terms of solvation and reactivity at the interface.[13] Nevertheless, the use of such sophisticated analytical techniques is limited. The introduction of simpler methods of analysis and a general “rule-of-thumb” for characterizing and differentiating the “on water” reactions from their homogeneous counterparts would be preferred.

For example, almost all the studies on the hydrophobic effects on selectivities of Diels−Alder reactions employ dienes and dienophiles in concentrations well within the solubility limits.[6] Given the low solubility of most of the reactants, this means that the concentrations are extremely low to be of any practical relevance. Thus, while the predictive models and explanations were valid for the typically homogeneous reaction systems, the inferences could not be extended to suspensions or heterogeneous reaction systems. Most of the hypotheses put forth in the studies may not be relevant for the actual scaled-up processes. Previous results from our group had indicated the superiority of water as a reaction medium over other environmentally benign solvents like ionic liquids.[14] As a part of our continued studies about the scope of environmentally benign reaction media,[15] we recently reported interesting temperature dependence of the salting-in and salting-out additives for “on water” Wittig reactions,[16] indicating that further study may be instru-

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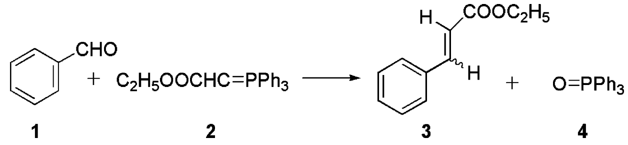

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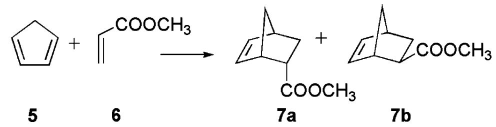

mental in unraveling the fundamental processes that govern the "on water" catalysis.

Another impediment for scale-up of "on water" reactions is the fact that the stirring power per unit volume required to produce a given value of interfacial area per unit volume increases with the volume of the reaction vessel or container. In scaled-up reaction systems, where the extension of the interface is small compared to the volume of bulk phases, the increase in the absolute rate caused by the interface may be more than compensated by the very much larger amounts of reactants present in the bulk phases. In order to ensure a smooth transition of the "on water" protocol from a chemist's flask to the reactor vessel, it is important to address these issues.

Water−alcohol mixtures have been employed extensively in the past as mechanistic tools to study the origin of hydrophobic acceleration of organic reactions.[17,18] These mixtures appeared to be promising solutions for the "synthetic chemist's dilemma" of choosing between the enhanced absolute reactivity at the aqueous interface against the very much larger amounts of reactants and the resultant greater conversion accessible in the bulk phases. Ironically, in all the previous studies, the concentration of the reactants in the kinetic analyses using water−alcohol systems was kept low enough to ensure complete homogeneity, even in pure water. The response of a typical "on water" system to the addition of alcoholic cosolvents and the resultant transition from heterogeneous to homogeneous reaction conditions, although of much practical significance, has not been studied.

In the present work, we attempt to study how addition of increasing amounts of an alcoholic cosolvent affects the reactivity and selectivity of C−C bond-forming reactions carried out in aqueous suspensions. We state the existing theoretical framework in terms of a typical "on water" process to enable a discussion of the experimental observations on the reactivity and selectivity with reference to changing composition of the reaction medium. We focus on two important classes of C−C bond-forming reactions—the Wittig reaction of benzaldehyde (**1**) with (carboethoxymethylene)triphenylphosphorane (**2**) (Scheme 1) and the Diels−Alder cycloaddition of cyclopentadiene (**5**) with methyl acrylate (**6**) (Scheme 2). The solvent composition is varied from that of pure water to pure alcohol. The presence of the cosolvent should alter the "local" solute−solvent interactions, while gradually leading to "homogenization" of the reaction medium. We attempt to explore the possibility of employing bulk solvent parameters to identify the dominating interactions determining interfacial reactivity and selectivity. The variation in the endo selectivity of the "on water" Diels−Alder reaction was analyzed by independent estimation of k_{endo} (rate of formation of the endo isomer) and k_{exo} (rate of formation of the exo isomer). On the basis of the interesting observations of reactivity and selectivity, a simple "signature" characteristic, which would allow preliminary investigations, without the aid of sophisticated experimental setup is proposed.

2. Experimental Section

2 (a) Materials. The aldehyde (**1**) and the dienophile (**6**) were freshly distilled prior to their use. The diene **5** was freshly cracked from its dimer and stored in a deep freeze. Deionized water and GR grade solvents were used for the experiments. The ylide **2** was synthesized as described previously.[16] The procedure for the synthesis of the polymer bound ylide was similar to that adopted for synthesizing the unbound ylide, except for the fact that polymer bound triphenlyphosphine was used as the starting material.

2 (b) Kinetic Analysis. The kinetic procedures for determining the rates of the Wittig reaction[16] and the Diels−Alder reaction[14] were identical to those reported previously. For the "on water" Wittig reaction, the concentration of the aldehyde was chosen to be within the solubility limit while the amount of the ylide added was beyond the solubility limit. Higher formal concentrations of the aldehyde would have resulted in a complicated situation due to the presence of an additional water−aldehyde (liquid−liquid) interface. For the "on water" Diels−Alder reactions, the dienophile was taken in excess to ensure a pseudo-first-order reaction.

For a typical kinetic run of the "on water" Wittig reaction, the 1 mM solution of the aldehyde **1** (1 μmol in 10 mL) was allowed to equilibrate at the desired temperature. The temperature was controlled using a constant temperature bath with an accuracy of ±0.01 K. The reaction was initiated by addition of **2** (5 μmol in 10 mL) into the above aldehyde solution. The reaction progress was monitored by following the decrease of the aldehyde concentration using UV spectrophotometry to yield the pseudo-first-order rate constants. The rate constants were reproducible to within ±3% at 298 K and ±6% at 338 K.

For determining k_{endo} and k_{exo} separately, the GC calibration was done independently for the endo and exo isomers. Separation of the isomers required for the independent calibration was achieved through the iodolactonization procedure. **5** was condensed with acrylic acid and the resultant endo and exo bicyclic acids were separated by the iodolactonization method as reported earlier by Evans et al.[19] The iodolactone was cleaved reductively with zinc and acetic acid to get pure endo acid in high yield.[20] The bicyclic acids were then individually treated with methanol and concentrated H_2SO_4 under reflux for 18 h to get the corresponding esters, carbomethoxy bicyclo[2,2,1]hept-5-ene. Identical GC response factors were observed for both the endo and the exo isomers.

For a typical kinetic run of the "on water" Diels−Alder reaction, the dienophile was added to the solvent system (5 mmol in 1 mL) and was allowed to equilibrate at the desired temperature. The reaction was initiated by addition of **5** (1 mmol in 1 mL), and the reaction progress was monitored at appropriate time intervals by extraction of aliquots with ether followed by appropriate dilution and GC analysis. The rate constants thus determined were reproducible to within ±6%.

3. Theoretical Framework

The study of an "on water" process, in accordance with the convention adopted for any interfacial process, can be represented at three different levels—the kinetic or molecular level, the local or microscopic level, and the macrokinetic or macroscopic level—each employing a separate model. The information from a lower scale model is used as an input for the model at the next scale. The kinetic model is built in accordance with the principles of formal kinetics and describes chemical interaction between the components of the system at

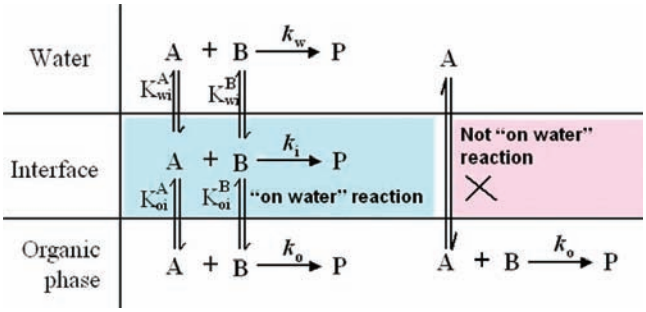

Figure 1. Local kinetic model for a general “on water” reaction.

the molecular level in terms of mechanism, energies of activation, and rate and equilibrium constants of chemical reactions.

The local model builds on the information derived from the kinetic model, taking into account the inhomogeneous distribution of energy and reactants in the bulk phases and the interface. The local model is characterized by mass transfer rate, conversion of the transferred reactant, topology of the reaction zone, concentrations and distribution of reaction groups, etc. In order to understand the solvent effects of “on water” reactions, we adapt the pseudophase formalism, which treats the aqueous suspension as a three-layer bulk system and ignores the temporal variation in shape and size of the suspended droplets/solid particles (Figure 1). We assume that the reaction mixture consists of three distinct pseudophases: an aqueous phase (w), an organic phase (o) and the interface (i). For “on water” reactions, the organic phase consists of the water-insoluble reactant suspended in aqueous environment. The reactants are partitioned between the three pseudophases based on relative affinities and diffusion processes—denoted by the respective partition functions. A complete quantitative analysis of the kinetic or stereoselectivity data would involve estimation of the partition coefficients (*K*) and the rate constants (*k*). Care must be taken to rule out the other possible scenario wherein one of the reactants is transferred through the interface into the bulk and the reaction takes place in the bulk, near the interface but not “on the interface”.

The observed rate of the reaction is, in effect, the total of the rates at all the pseudophases and the rates of diffusion and adsorption of the reactants. Some important assumptions will be made for simplifying the application of the model to experimental kinetic data of common C−C bond-forming reactions:

(1) The diffusion of the reactants to the reaction site in the bulk or the interface in “on water” reactions is much faster than the rate of the reaction. This implies that the distribution of the reactants between the pseudophases is an equilibrium property and the process is not diffusion limited. (Exceptions include electron transfer reactions, free radical reactions, proton transfer, etc.)

(2) The reaction does not undergo a change in the mechanism from one pseudophase to another. The basic rate law describing the order of the reaction remains the same in all the pseudophases.

(3) The rates of the reaction in the three pseudophases are largely independent, affecting each other only by changing the net amount of the reactants available for the process.

In order to reduce the rates in the neat, aqueous, and interfacial conditions to the same units, we follow the approach suggested by Jung and Marcus. Let k_x, $[A]_x$, and $[B]_x$ denote the rate constant, concentration of reactant A, and concentration of reactant B, respectively, in a given pseudophase *x*. The subscript *x* can be replaced by the appropriate notation for the three pseudophases, viz., organic (o), water (w), and interface (i). Accordingly, the rates are described in terms of the number mole fraction of reactant B, n_B. Taking Z_x to be the coordination number between the two reactants in a given pseudophase, the product $Z_x n_B(t)$ is the probability that the two reactants are within the “reacting distance” at a given time instant *t*. The resulting rate expression is given by eq 2, subject to the conditions stated in eqs 3 and 4.

$$d[P]/dt = k_o[A]_o[B]_o + k_w[A]_w[B]_w + k_i[A]_i[B]_i \tag{1}$$

$$\begin{aligned} d[P]/dt &= k_o[A]_o Z_o n_{Bo} + k_w[A]_w Z_w n_{Bw} + k_i[A]_i Z_i n_{Bi} \\ &= k_o[A]_o Z_o n_{Bo} + k_w[A]_w Z_w n_{Bw} + k_i N_d \bar{A}_i Z_i n_{Bi} \end{aligned} \tag{2}$$

$$[A]_{Total} = [A]_o + [A]_w + [A]_i \tag{3}$$

$$(n_B)_{Total} = n_{Bo} + n_{Bw} + n_{Bi} \tag{4}$$

N_d is the total number of suspended droplets or particles in the reaction mixture and $\bar{A}_i$ is the average number of molecules of species A on the surface of one droplet or particle at time *t*. The model is general enough to accommodate multicomponent or multistep reactions, although only the case of an irreversible single-step bimolecular reaction is pictorially represented in Figure 1. Since the model does not contain any a priori dependence on the shape of the interfacial entities, it can be applied to highly agitated systems as well.

The results thus obtained lead to the macroscopic or macrokinetic model, which predicts the evolution of the characteristics of the reaction system as a whole in terms of the bulk properties of the solvent systems and measurable properties of the interface. In the case of systems with intensive stirring, the macroscopic model is often the only tool for establishing the relation between the experimentally observed characteristics and the processes occurring at the interface. For macrokinetic modeling of the interface, the two intrinsic properties of interfaces, also known as intensity factors, the interfacial pressure and the interfacial potential, are generally known to influence the reaction rate. The role of interfacial pressure, Π, is conventionally represented as

$$[\partial(\ln k)/\partial \Pi] = \Delta A^*/RT \tag{5}$$

where ΔA^* is the difference in area between the transition complex and the reactant molecules, i.e., area of activation. It can be seen that the effect of interfacial pressure on reaction velocity depends on the sign as well as the magnitude of ΔA^*. When the intensity factor is electrical potential, *V*

$$[\partial(\ln k)/\partial V] = \Delta q^*/RT \tag{6}$$

where Δq^* is the difference in the electric charge (or more appropriately, the dipole moment) between transition complex and the reactant molecules. Provided that *q* and *V* are of the same sign, the rate of the reaction will increase or decrease as *V* is increased or decreased. It should be noted that eqs 5 and 6 represent a general situation. Since the reactants in this study are uncharged species, the contribution of the potential to the rate of the interfacial reaction will be insignificant.

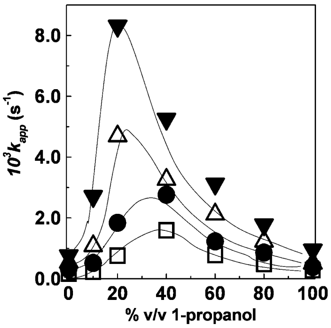

Figure 2. Apparent rate constant, k_{app} for the Wittig reaction of **1** + **2** against composition of the reaction medium at 278 K (□), 288 K (●), 298 K (Δ), and 308 K (▼). (The lines are drawn to guide the reader's eye.)

Understanding the macrokinetic behavior of the system can also help to increase efficiency of laboratory and industrial synthetic processes. We attempt to develop a macroscopic scenario relating the change in stereoselectivity at the interface as a function of solvent composition to the bulk solvent properties in the following sections.

4. Interfacial Reactivity of "on Water" Reactions

The reactivity of substrates at the interface may be intrinsically different from that of an analogous reaction in the homogeneous phase due to energetic and geometric factors. For some reactions, the reduction of dimensionality of diffusion is known to induce rate acceleration under specific conditions.[21] The interface can influence the progress of a reaction by affecting the rate of adsorption of the reactant and availability of reactive sites, changing the concentration and orientation of the reactants with respect to the bulk, etc.[22] This makes a quantitative discussion of the constituent processes difficult.

Not surprisingly, very few kinetic studies at interfaces have been reported[12,23] since the first study by Bell regarding the kinetics of oxidation of benzoylotoluidide with aqueous potassium permanganate at a flat liquid−liquid interface.[24] The systematic study of solvent effects on the products of interfacial polycondensation reactions was carried out by Morgan and coworkers[25] when they demonstrated that the molecular weight of the polymer product was dependent on the solvent used.

4 (a) Solid−Liquid Interface: Wittig Reaction. The rates of the Wittig reaction between the aldehyde **1** and ylide **2** were studied in a series of water−1-propanol mixtures at four different temperatures. The apparent pseudo-first-order rate constants, k_{app}, plotted as a function of the solvent composition is shown in Figure 2. The rates show a sharp increase when a small amount of 1-propanol is added initially, reaching a maximum before decreasing with further addition of the cosolvent. The sensitivity of the k_{app} to the composition of the medium increases with increasing temperature. For example, the rate constant is observed to increase from a value of $1.7 = 10^{-4}$ s^{-1} in pure water at 278 K to $15.9 = 10^{-4}$ s^{-1} in 40% v/v aqueous propanol. This corresponds to an increase in rates by a factor of 9. At 309 K, the magnitude of k_{app} increases from $7.6 = 10^{-4}$ s^{-1} in pure water to $83.1 = 10^{-4}$ s^{-1} at just 20% aqueous 1-propanol, which corresponds to rise in rates by a factor of 11 times. The position of the maximum in rate constants also shifts to lower values of the cosolvent volume fraction with increasing temperature.

In order to explain these remarkable results, we must take into account the different ways in which the addition of a cosolvent can affect the "on water" process and compare the same with the cosolvent effects observed for homogeneous reactions carried out in binary aqueous mixtures. For aqueous reactions in purely homogeneous conditions, the addition of cosolvents is known to give rise to a number of additional interactions. It is known that the addition of small amounts of cosolvents like alcohols enhances the local three-dimensional hydrogen bonding of water and thus makes the hydrophobic interactions entropically more favorable. At the same time, the favorable interactions of the cosolvent with the reactant effectively stabilize the initial state. At higher mole fractions of the alcoholic cosolvent, highly dynamic clusters of the cosolvent molecules are formed.[26] The composition of the microenvironment around the reactants is different from the bulk composition. Engberts and co-workers have attempted to quantitatively explain the reactivity in such binary mixtures on the basis of the resulting "preferential solvation" of the organic reactants by either of the solvent components.[17] Beyond a particular limit, the binary mixtures start to behave like conventional organic solvent, exhibiting smooth variation in the rate and stereoselectivity trends.

Unlike the previous examples in literature for homogeneous aqueous systems, the analysis of the cosolvent effect is complicated in the present work since the aqueous reaction is initially carried out in a heterogeneous environment and is largely interfacial in nature. Small amounts of the added cosolvent should affect the composition of the bulk phases as well as the interface. It may also affect the orientation and mutual interaction of the water and reactant molecules at the interface. Increasing mole fraction of the cosolvent induces a heterogeneous to homogeneous phase change for the reaction. Thus, the observed enhancement of the reactivity is the combined outcome of numerous contributing factors.

In terms of Figure 1, the cosolvent is expected to influence to overall process by affecting the partition of the reactants and by influencing the rate constants. The "on water" Wittig reaction involves a solid−liquid interface and, hence, can be termed as the simplest possible variant of the model in Figure 1, since $k_{\mathrm{o}} = 0$. The insoluble ylide suspended in the aqueous phase is a solid, and hence the absence of the other reactant in the organic phase precludes any reaction in the organic phase. Initially, under "on water" conditions, the reaction is plausible only at the interface (k_{i}) or in the bulk water phase (k_{w}). Kinetic studies in our group have provided evidence that in pure water, $k_{\mathrm{i}} \gg k_{\mathrm{w}}$.[16] Hence the reaction can be modeled as a system where both the reactants are confined to the interface. For all practical purposes

$$(\mathrm{d[P]/d}t)_{\mathrm{water}} = k_{\mathrm{i}}N_{\mathrm{d}}\bar{A}_{\mathrm{i}}Z_{\mathrm{i}}n_{\mathrm{Bi}} \tag{7}$$

It is reasonable to assume that the addition of cosolvent will affect the process in one or all of the following ways:

1. Increasing cosolvent concentration leads to an increased solubility of the ylide, thus shrinking the ylide particles. Since the factor (N_{d} $\bar{A}_{\mathrm{i}}/A$) is inversely proportional to the radius of the ylide particle (r),[7] the initial decrease in the radius of the solid particle—provided all other factors including N_{d} are constant—can increase in the rate of the interfacial process.

The dissolved ylide increases the contribution of the reaction in the bulk aqueous medium. One of the possibilities is that as more and more cosolvent is added, increasing amounts of ylide should be dissolved in the water−cosolvent medium, making the homogeneous process more and more feasible (i.e., the influence of the solubility factor). The overall process in aqueous mixture has to be described as the sum of the second and third terms in eq 1, with the difference that the k_w term should be replaced by the k_{aq} term, indicating the fact that the reaction medium is not pure water but a binary aqueous mixture.

2. Alternatively, the increase in the rates observed may also partially result from enhanced local structure of the reaction medium at the reaction site induced by the cosolvent; i.e., apart from the effect on the partition or distribution of the reactants between the pseudophases, a direct effect of solvent composition on the magnitude of k_i and k_w will also play a role.

Upon further addition of the cosolvent, the interface vanishes (the ylide completely dissolves), at a particular composition and then the kinetic trend is similar to that observed for the homogeneous water–organic cosolvent systems. The overall rate is now a function of the rate in the bulk aqueous–organic phase, k_o.

$$(\mathrm{d}[\mathrm{P}]/\mathrm{d}t)_{\text{water+cosolvent}} = k_{w+o}A_{w+o}Z_{w+o}n_{Bw+o} \qquad (8)$$

(note: k_{w+o} stands for the rate in aqueous − organic phase)

Increasing the concentration of cosolvent further results in the reaction becoming less hydrophobically accelerated. The reaction medium loses its typically aqueous character while the reactants and transition state are being preferentially solvated by the 1-propanol molecules. Finally, the binary mixture starts resembling a conventional organic solvent as reflected in the conventional decrease in rates observed for such solvent environments. In terms of the model in Figure 1

$$k_{w+o}A_{w+o}Z_{w+o}n_{Bw+o} \rightarrow k_oA_oZ_on_{Bo} \qquad (9)$$

The maximum in the rate-composition curve depicts the point where the system departs from complex interfacial behavior to the conventional homogeneous kinetics. The shift in the position of the maximum with temperature also implicates the role of phase transitions in the observed kinetic trends. The initial increase in rates may be the result of increased solubility or a change in the solvation at the interface upon the addition of 1-propanol or a combination of both factors.

In order to elucidate the role of solubility, the kinetic experiments were repeated with polymer-supported ylide under identical conditions at 298 K.[16] The ylide was covalently bound to the surface of the polymeric beads, and hence, dissolution in the reaction medium could be ruled out. All the other conditions were identical to those used for the kinetic studies of the other "on water" Wittig reactions. The maximum in the rate was still observed when the role of solubility was completely excluded (Figure 3), thus indicating that the initial increase in rates originated predominantly due to the change in the interfacial structure of the reaction medium upon addition of alcohol.

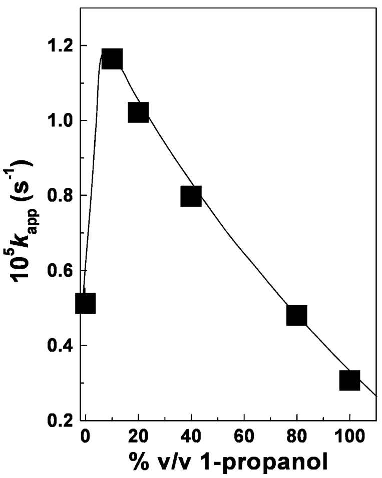

Figure 3. Apparent rate constants, k_{app} for the Wittig reaction of **1** + polymer-supported ylide **2** in water−1-propanol mixtures at 298 K. (The line denotes smoothening of the data.)

The microscopic arrangement of water molecules around an extended hydrophobic surface is different from that around a single hydrophobic molecule due to the length scale dependence of hydrophobicity.[27] The dewetting arrangement and the typical orientation of water molecules at extended interfaces manifest in the typical properties of the aqueous interface which can be exploited for better interfacial transformations. Ab initio calculations have shown that the air–water interface is typified by the presence of free or "dangling" −OH bonds, which are estimated to constitute 36% of the interface.[28] In comparison, the sum frequency generation (SFG) spectra for the air–water interface showing a sharp feature at 3700 cm^{-1} for the free −OH bonds indicate that these bonds occupy approximately 20% of the interface.[29] The simulations also showed that the lowering of the HOMO for each water molecule near the interface results in increase in the number of "reactive sites" as compared to the bulk.

Vibrational sum frequency spectroscopy (VSFS) and molecular modeling studies to complement the experimental observations are frequently employed to investigate the effects of ions and molecules on the interfacial orientations for the aqueous systems.[30] The characteristic orientations of alcohol and water molecules at the water–vapor interface and their effect on the surface characteristics have been studied by sum frequency generation spectroscopy[31] and molecular modeling studies.[32] The linear increase of the number of ethanol–ethanol hydrogen bonds and linear decrease of water–water hydrogen bonds at the interface indicates that the addition of ethanol enhances the self-clustering of ethanol and breaking of the hydrogen-bonded network of water at the interface.[32b] This effect at the interface is in contrast to the effect that introduction of ethanol molecules would have in the bulk of the solution. The most probable angle between the H_2O dipole at the liquid/vapor interface and the surface normal is 67.5° at a 0.059 mol fraction of ethanol as compared to 74° for pure water, signifying enhanced orientation ordering on addition of ethanol. After the initial increase, the orientation of the surface H_2O molecules starts decreasing from 0.11 mol fraction of ethanol until it is sharply peaked at about 141.5° for 0.40 mol fraction of ethanol with no predominate orientation existing 3 Å below the interface.[32a] These observations suggest that the addition of alcohols initially tends to enhance the surface characteristics of water, before further addition depletes those features.

More accurate representations of the interfacial orientations have been achieved by Chen et al. using direct polarization null angle (PNA) measurements.[33] The results have shown that the vapor/water–methanol interface has an antiparallel doube layered structure with a laterally extended hydrogen bonding network. This typical behavior may hold the explanation for the anomalous increase in the rates observed. Monte Carlo simulations agree well with the experimental observations and show that the orientational preference of interfacial water molecules is extremely sensitive to the presence of methanol component.[34] The peak corresponding to the "free" −OH bonds at the interface disappears with increasing methanol concentration. However, further evidence in the form of experiments and

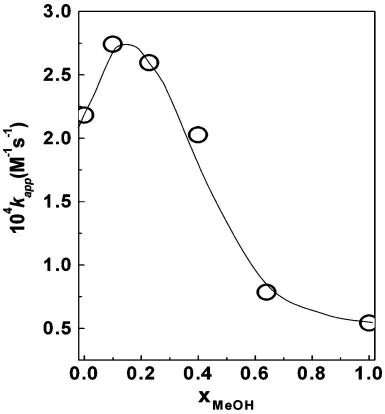

Figure 4. Apparent rate constants, k_{app}, for the Diels−Alder reaction of **5** + **6** in water−methanol mixtures as a function of the mole fraction of methanol, x_{MeOH} at 298 K. (The line represents the general trend in data.)

theoretical calculations would be required to explain the phenomenon satisfactorily for a thorough explanation of the observed interfacial reactivity.

4 (b) Liquid−Liquid Interface: Diels−Alder Reaction. The Diels−Alder reaction was one of the first organic reactions that were observed to be hydrophobically accelerated.[2] Since the mechanism of the reaction was a one-step mechanism and fairly well understood, the rates and selectivity of typical Diels−Alder reactions were used as mechanistic tools to study hydrophobicity and other solvent effects.[35] One of the earliest reports on Diels−Alder reactions carried out in aqueous suspensions coincided with the initial reports on hydrophobic acceleration of Diels−Alder reaction.[36] Breslow and co-workers demonstrated that the hydrophobic effect on the endo/ exo selectivity persists even in water-insoluble systems—i.e., when the relatively high concentration of the diene or dienophile, beyond its solubility limit, led to the formation of a distinct organic phase. The origin of the high selectivity ratios was proposed to be related to the known effects of polar media and the need to minimize the transition state surface area at the organic−water interface.

The only reports on interfacial Diels−Alder reactions are based on either the microemulsions[37] or supported dienophile.[38] Gawalt et al. used substituent effects to study the mechanism of a Diels−Alder reaction between the diene and chemisorbed mercaptobenzoquinone as the dienophile.[38] (Figure 4)

Kinetic studies of the Diels−Alder cycloaddition reaction of **5** with **6** in water−methanol mixtures at 298 K showed a trend similar to that observed for the Wittig reaction. The rate constants apparently increase initially with the addition of methanol. However, further increase in the amount of methanol led to a decrease in the apparent rate of the reaction. These observations are unlike the reported trend of reactivity in homogeneous aqueous mixtures. Blokzijl and co-workers determined the kinetic parameters for intra- and intermolecular Diels−Alder reactions in highly aqueous solutions of monohydric alcohols.[17] On the basis of the quantitative analysis, a model was developed in terms of enforced pairwise hydrophobic interactions between the diene and the dienophile. Previous studies of the kinetics of the Diels−Alder reaction in aqueous alcohol mixtures reported an initial sharp decrease followed by a gradual decrease in the rates.

Marginal increase in the rate was observed for the reaction of **5** with naphthaquinone at 298 K when a small amount of cosolvent (ethanol, 1-propanol, 2-methyl-2-propanol) was added.[17] On the basis of the kinetic studies, Engberts and co-workers claimed that while the rates in pure water were observed to be entirely entropic in origin, the rates observed in 10 mol % of 1-propanol were entirely of enthalpic origin. They further asserted that the initial rise in reactivity could be attributed to the enhanced structure of water upon addition of small amounts of cosolvent. This feature was lost as the proportion of cosolvent was increased until the rate effects in the medium reflected those for a predominantly organic environment.

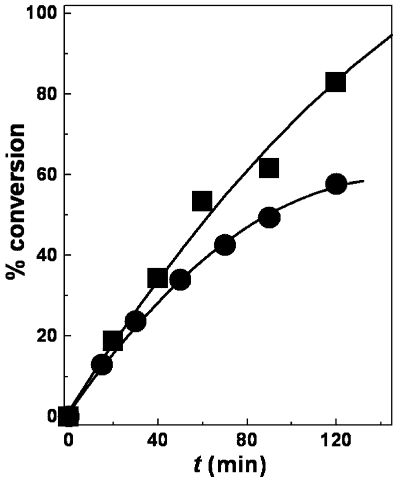

Figure 5. Percent conversion to product against time, t, for the Diels−Alder reaction of **5** + **6** in neat medium (■) and "on water" conditions (●) at 298 K. The formal concentration of the diene and dienophile was taken to be 1.0 M each for the "on water" kinetic experiment.

The approach required for the interpretation of results would be similar to that adopted for the Wittig reaction, except for the fact that the system is a more complex liquid−liquid interface, wherein $k_o \neq 0$. The initial reaction in purely "on water" conditions, is no longer dependent on exclusively one term—the processes in the organic and aqueous phase also have to be taken into account. Also, the vigorous agitation in the reaction medium entails that the system is phase-dispersed rather than phase separated. In such cases, not only is the interfacial area unknown, but it may also vary from experiment to experiment, depending on the variations in hydrodynamic conditions and/or physical properties of the system unlike the solid−liquid interface.

As stated previously, it is important to determine the relative magnitude of k_i, k_o, and k_w. Since the solubility of **5** is less than 10 mM in pure water, the initial contribution from k_w should be very small. The organic pseudophase in this case would be analogous to the "neat" medium. A comparison of the percent conversion observed for the neat (no water) and "on water" reactions, is shown in Figure 5. Despite the fact that the effective amount of diene and dienophile at the liquid−liquid interface and hence available for the interfacial reaction pathway is very less as compared to that available for the neat reaction, the conversion is comparable. This indicates that $k_o < k_i$. The higher endo/exo ratios obtained for the "on water" reaction (4.832 for 0.1 M of **5** and 0.5 M of **6**) as compared to that in the neat medium (2.67) is additional evidence for the higher magnitude of the interfacial rate constant. Thus, the reaction is predominantly interfacial when carried out in pure water only.

The addition of methanol changes the composition of the aqueous and the organic phase simultaneously, along with the effects on the interfacial structure and homogeneity as listed previously for the Wittig reaction. Since, the role of the

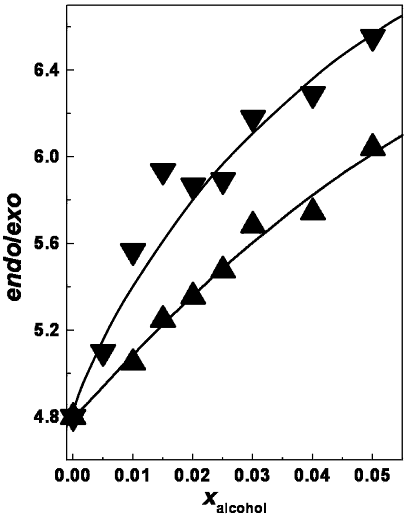

Figure 6. Variation in endo/exo ratio of the Diels−Alder reaction between **5** and **6** against mole fraction of methanol (▲) and 1-propanol (▼) at 298 K.

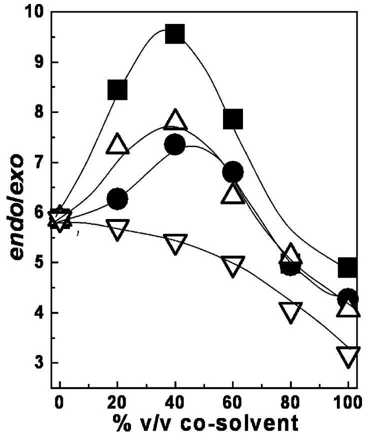

Figure 7. Plots of endo/exo ratios against solvent composition (% v/v) of water + cosolvent methanol (■), DMSO (Δ), dioxane (●), and tetrahydrofuran (∇) for the Diels−Alder reaction **5** + **6** at 298 K. (The lines indicate the average trend of the data.)

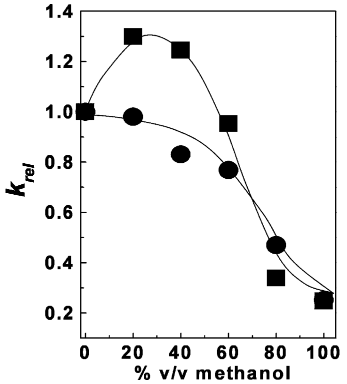

Figure 8. Plots of relative rates, k_{rel} ($=k/k_{water}$), for the formation of the endo (■) and the exo (●) isomers against % v/v of methanol in water at 298 K.

interfacial pathway is less significant as compared to that for the Wittig reaction, the observed sensitivity of the rates to the solvent composition in this reaction system is also lower. Thus, the results demonstrate the “on water” reaction systems show an initial increase in the rates when small amounts of alcohols are added as cosolvent. This observation might be considered the signature of “on water” reaction kinetics. Figure 6.

The endo/exo ratios for the reaction **5** + **6** were examined in a series of aqueous mixtures of methanol and 1-propanol at 298 K (Figure 6). The concentration of the alcoholic component was kept low enough to ensure that the heterogeneity and, hence, the “on water” characteristic of the system is least perturbed. The endo selectivity of the reaction increases when small amounts of alcoholic cosolvents are added to the system. This observation is contrary to that made by Engberts for the reaction of **5** with methyl vinyl ketone in aqueous solutions of a series of monohydric alcohols.[17b] However, the concentrations of diene and dienophile employed were very low (in the millimolar range) and, hence, were homogeneous in nature. It was observed that in case of such homogeneous aqueous reactions, the endo/exo ratio decreased sharply on addition of small quantities of alcohol.

The kinetic control of the endo selectivity of the Diels−Alder reaction over the transition from the “on water” to the homogeneous phase was confirmed by the fact that the endo/exo ratio reflected the trend in reactivity—increasing initially before decreasing to the value of the organic cosolvent (Figure 7). The choice of cosolvents was based on the nature of the plausible solute−cosolvent and water−cosolvent interactions as per the structural features of the cosolvent. The selectivity was thus studied in mixtures of a polar protic solvent, methanol, a polar aprotic solvent, dimethyl sulfoxide (DMSO), a weakly polar solvent, tetrahydrofuran (THF), and a nonpolar solvent, 1,4-dioxane. The composition of the reaction medium spanned the range from pure water to pure cosolvent. The change in stereoselectivity was, in effect, monitored from that in the heterogeneous or “on water” conditions at one extreme to that in entirely homogeneous medium at the other extreme.

Higher selectivities were obtained in aqueous binary mixtures than in water or cosolvent alone, except for water−THF mixtures where a smooth decrease in selectivity was seen. For example, the endo/exo ratio increased by 65% on the addition of 40% v/v methanol. This observation was drastically different from the previous studies of the effects of cosolvents on the ratio of the endo and exo products. Blokzijl et al. reported a dramatic decrease in the endo/exo product ratio for the aqueous reaction of cyclopentadiene with methyl vinyl ketone on addition of simple aliphatic alcohols.

A thorough kinetic analysis was necessary to understand the molecular basis of solvent interactions leading to higher stereoselectivity. In the kinetic analysis, the second-order rate constants of formation of the endo isomer (k_{endo}) and the exo isomer (k_{exo}) were determined independently for each solvent composition. The endo and the exo isomers were separated by the iodolactonization procedure (see Supporting Information for a detailed procedure) and the gas chromatograph was calibrated independently for both the isomers (Figure 8). While k_{exo} did not change on addition of 20% v/v methanol, k_{endo} increased by 36% of its value in pure water in the presence of 20% v/v methanol. The results indicate that k_{endo} is more sensitive to the change in solvent composition as compared to the k_{exo}. The change in stereoselectivity observed, thus, results from a greater stabilization of the endo transition state at the interface.

5. Macrokinetic Analysis of Interfacial Selectivity

Due to the difficulties involved in studying the liquid−liquid interfacial reaction systems, an empirical approach based on multiple linear regression was adopted. Such analysis has been previously reported for studying the endo/exo selectivity of

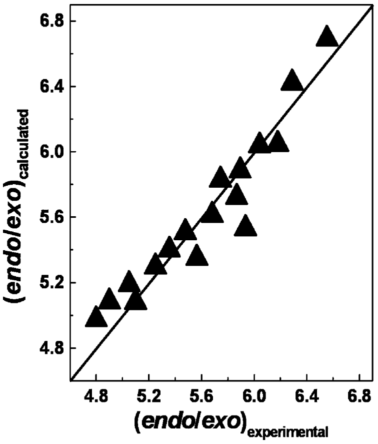

Figure 9. Plot of $(\mathrm{endo/exo})_{\mathrm{calculated}}$ against $(\mathrm{endo/exo})_{\mathrm{experimental}}$ for the Diels−Alder reaction of **5** + **6**. $(\mathrm{endo/exo})_{\mathrm{calculated}}$ obtained from multiple linear regression analysis with P_i and ε.

Diels−Alder reaction. Schneider and Sangwan correlated the log (endo/exo) for the Diels−Alder reaction between **5** and various dienophiles with the solvophobicity parameter, Sp, while demonstrating the role of the E_T^N parameter to be less important.[39] This was in contrast to the observations by Cativiela et al. regarding the selectivity of the reaction between **5** and α-cyanocinnamate who concluded that apart from solvophobicity the polarity of the medium also played a significant role.[40] Further work based on Diels−Alder reactions of **5** with **6** in a series of organic and aqueous−organic solvents led to the development of a model based on the influence of both solvophobicity and polarity of the medium on the stereochemical outcome of the reaction.[41] The interpretation of the results was hampered by the fact that for the solvent chosen in the study both Sp and E_T^N appeared to be correlated parameters, the highly solvophobic solvents had a higher polarity as well. A comprehensive report on how different solvent parameters (for example, polarity, Gutmann's acceptor number, solvophobicity, cohesive energy density, etc.) of organic solvents influence kinetics of several Diels−Alder reactions, is published by Cativiela and co-workers.[42]

Apart from the use of empirical polarity scales to explain the stereoselectivity of Diels−Alder reactions, the internal pressure of the reaction medium has also been considered to be a dominating factor.[43] One of us was able to successfully predict the reactivity and selectivity of a number of reactions in aqueous and organic salt solutions using equations based on nonadjustable parameters.[44]

In the present case, it would be difficult to extend the previous models to explain the selectivity since the study includes "on water" as well as homogeneous data points. Nevertheless, we attempted a preliminary multiple regression analysis for the purely "on water" endo/exo values in aqueous alcohols (shown in Figure 9) with the internal pressure, P_i, and the dielectric constant, ε, of the medium. The choice of the two properties is based on the correlation of the rates of interfacial reactions with interfacial pressure, Π, and interfacial potential, V. The interfacial pressure is a function of the interfacial tension, which can be deduced from the internal pressure. The dielectric constant is included to account for the influence of the electric potential. Both the quantities are not empirical and can be determined by simple models, which enhances their usefulness as fitting parameters. The results (Figure 9) show that the regression yields good results, at least for the homologous series of water + alcohols in the strictly heterogeneous limits. The regression equation employed for determining (endo/exo) calculated was

TABLE 1: Results of the Multiple Regression Analysis of k_{endo} and k_{exo} Involving P_i and ε for the Diels−Alder Reaction of 5 + 6

	$\ln k_{\mathrm{endo}} = \ln k_{0,\mathrm{endo}} + BP_i + C\varepsilon$			
cosolvent	$\ln k_{0,\mathrm{endo}}$	10^3B	10^2C	r^2
methanol	−12.83 ± 0.70	3.90 ± 1.33	4.65 ± 0.65	0.944
DMSO	−23.59 ± 0.73	4.62 ± 0.54	17.92 ± 0.81	0.994
dioxane	−12.72 ± 0.22	7.73 ± 0.57	3.58 ± 0.20	0.992
tetrahydrofuran	−12.43 ± 0.43	3.17 ± 0.88	4.16 ± 0.35	0.981
	$\ln k_{\mathrm{exo}} = \ln k_{0,\mathrm{exo}} + BP_i + C\varepsilon$			
	$\ln k_{0,\mathrm{exo}}$	10^3B	10^2C	r^2
methanol	−13.67 ± 0.24	2.37 ± 0.46	3.55 ± 0.23	0.988
DMSO	−23.96 ± 1.07	4.34 ± 0.79	16.04 ± 0.12	0.984
dioxane	−13.78 ± 0.25	6.29 ± 0.62	2.79 ± 0.22	0.985
tetrahydrofuran	−13.27 ± 0.34	2.49 ± 0.69	3.06 ± 0.27	0.978

$$(\mathrm{endo/exo})_{\mathrm{calculated}} = 35.88(\pm 7.61) - 0.0076(\pm 0.0025)P_i - 0.377(\pm 0.087)\varepsilon \quad (9)$$

$$(r^2 = 0.986)$$

The approach failed to explain the rate effects due to addition of cosolvents like DMSO, dioxane, and THF as well as methanol. It is observed that the k_{endo} and k_{exo} can be expressed in terms of the two properties for one water−cosolvent system at a time but not for all the systems together. The correlation gives good agreement when data from one system only are used (Table 1) but fails when all the data from all the cosolvents are used for the multiple regression analysis simultaneously.

This is not surprising since the number of contributions from different factors in a complex manner and the change in the "site" of the reaction from the interface to the bulk with gradual increase in the cosolvent proportion make a simplistic analysis difficult. The observations, nevertheless, are valuable reference points for any future investigations toward the multiparameter analysis.

6. Conclusions

The characteristic response of the reactivity and selectivity of "on water" reactions to the addition of alcohols as cosolvents have been presented. Some of the salient features of the work can be summarized as:

1. The unconventional increase in rates in the presence of small amounts of alcoholic cosolvents can serve as a preliminary "signature" test for the "on water" reaction systems, where the interfacial pathway dominates.
2. The results also underline the fundamental differences between the solvent effects in homogeneous and the interfacial pathways, which have not been completely explained.
3. The selectivity of the Diels−Alder reaction is enhanced on addition of small amounts of organic solvents in small amounts.
4. A model has been attempted in order to explain the interesting trends for the interfacial organic reactions.

Since the present work is limited to the study of two "on water" reactions, it is hoped that the inferences drawn could be developed into broad generalizations when more data become available. Further studies to unravel the mysteries of the "on water" reactions are planned with the dual aims of enhancing the fundamental understanding and translating the information into viable “green” technology.

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Supporting Information Available: NMR spectra for the iodolactone intermediates and phosphorus ylide, GC parameters for the Diels−Alder reaction, representative kinetic plot, and literature used for computing the physicochemical properties of binary mixtures. This material is available free of charge via the Internet at http://pubs.acs.org.

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