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Unusual temperature dependence of salt effects for "on water" Wittig reaction: hydrophobicity at the interface†

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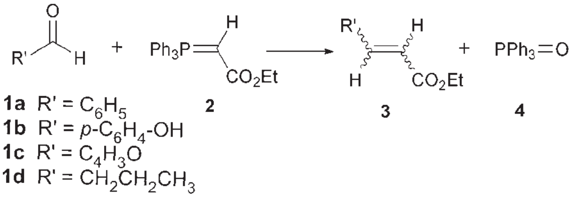
Received (in Cambridge, UK) 29th May 2008, Accepted 16th June 2008
First published as an Advance Article on the web 28th July 2008
DOI: 10.1039/b809127g

An unusual variation with temperature of the salt effects in aqueous Wittig reaction is observed, suggesting that hydrophobic acceleration of reactions comprising "on water" reactants is fundamentally different from that for reactions with small non-polar solutes.

Water is known as "Nature's solvent". The special effect of water in enhancing the selectivities and yields of organic reactions, and of Diels–Alder reactions in particular, has been appreciated only after the pioneering contribution of Rideout and Breslow.[1] Different forces such as hydrophobic packing,[2] hydrogen bonding,[3] enforced hydrophobic hydration[4] *etc*. are believed to be responsible for the origin of the special effect of water during organic and biochemical transformations. The "on water" method employed by Sharpless and co-workers recently has indicated the importance of interfacial processes in determining the progress of aqueous reactions.[5] A thorough understanding of the phenomenon of hydrophobicity at the molecular level, however is still elusive.

Recently, "on water" Wittig reactions of stabilized and semi-stabilized ylides in aqueous medium, leading to enhanced rates and yields, have been reported.[6] The use of 1.2 M aqueous LiCl further enhances the yields. The increase in rates on addition of LiCl is believed to be an evidence of the dominance of hydrophobic effects against other solvent effects.[3c] In the past, salt effects have also been employed as mechanistic tools for homogeneous aqueous reactions. Herein we highlight an unusual temperature-dependent effect of prohydrophobic additives ("salting-out" agents) and antihydrophobic additives ("salting-in" agents)[3d] on the rates of "on water" Wittig reactions. The observations are explained in terms of an interfacial process and are helpful in gaining an insight into the complex phenomenon of hydrophobicity in "on water" reactions.

The Wittig reactions of benzaldehyde (**1a**) and (ethoxymethylene)triphenylphosphorane (**2**) were carried out in water and different aqueous salt solutions (Scheme 1). Two prohydrophobic salts LiCl and NaCl were chosen in addition to an antihydrophobic salt guanidinium chloride, GnCl. The previous reports had mentioned refluxing conditions for carrying out the Wittig reactions in 1.2 M aqueous LiCl.[6] Since it was difficult to carry out the kinetic studies with good accuracy in refluxing water, an optimum temperature of 338 K was chosen in addition to room temperature (298 K).‡



Scheme 1 Wittig reaction of aldehydes **1a–d** with stabilized phosphorus ylide **2**.

At 338 K, the addition of 1 M LiCl and 1 M NaCl to the reaction medium led to an observable increase in the apparent rate of reaction of **1a** with **2** (Table 1). The presence of an antihydrophobic agent such as GnCl lowered the rate to nearly half of the magnitude in water. In contrast, at 298 K, the use of prohydrophobic additives—LiCl and NaCl decreased the rate of the reaction. This observation was contradictory to all the previous reports about the rate-enhancing effect of salts such as LiCl and NaCl.[3c]

In order to confirm that the retarding effect of additives was general, the kinetic studies were repeated for different substrates—4-hydroxybenzaldehyde (**1b**), furfural (**1c**) and butyraldehyde (**1d**) under identical conditions. Decrease in rates is observed for all the three aldehyde substrates on addition of prohydrophobic salts at 298 K. The results indicate that the effect is not substrate-specific. The magnitude of the relative rates depends on the concentration of the salt

Table 1 Relative rates k_{rel} (with respect to water) for the aqueous Wittig reaction of **1a–d** with **2** in different reaction media at 298 K[ab]

			k_{rel}[c]		
Entry	Aldehyde	T/K	1 M LiCl	1 M NaCl	1 M GnCl
1	**1a**[d]	338	1.12	1.27	0.55
2	**1a**	298	0.86	0.74	0.95
3	**1b**	298	0.64	0.52	0.98
4	**1c**	298	0.63	0.47	1.19
5	**1d**	298	0.70	0.61	0.99

[a] Reactions carried out with 1 μmol aldehyde and 5 μmol of **2** in 10 mL of reaction medium. [b] The isolated yields (and $E:Z$ ratios) at 298 K after a reaction time of 3 h are 92% (93 : 7) in water, 89% (91 : 9) in aq. LiCl, 89% (91 : 9) in aq. NaCl, 71% (82 : 18) in aq. GnCl and 84% (83 : 17) in aq. $LiClO_4$. [c] $k_{\mathrm{rel}} = k_{\mathrm{obs}}/(k_{\mathrm{obs}})_{\mathrm{water}}$. The rate constants agreed within an experimental error of ±3%. [d] The rates agreed within an error of ±6%.

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† Electronic supplementary information (ESI) available: Detailed procedure, kinetic analysis, representative plots for rate determination. See DOI: 10.1039/b809127g

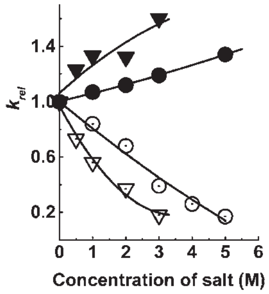

Fig. 1 Relative rates for the Wittig reaction of **1a** with **2** in (▼) 1 M NaCl at 338 K, (●) 1 M LiCl at 338 K, (○) 1 M LiCl at 298 K and (▽) 1 M NaCl solution at 298 K.

added. The effect of addition of LiCl and NaCl on the rates is exactly opposite at the two temperatures: 298 K and 338 K (Fig. 1). This contrasting effect of salt additives on the rates in water and aqueous salt solutions cannot be explained by an extension of current notion of "salting-out" and "salting-in" behaviour.[1a,7] Since the rate acceleration on addition of LiCl or NaCl is attributed to the enhancement of hydrophobic effects, the contrasting results at 298 K underline the need for further investigation of the role of hydrophobicity as a driving force for the reaction.

The temperature dependent studies of the rates were carried out in water and 3 M aqueous LiCl for the reaction of **1a** with **2**. The rate enhancing effect of LiCl gradually appears to become smaller in magnitude and at a temperature of ~318 K, the rates are similar in both the media. LiCl then acts as a retarding additive if the temperature is decreased further (Fig. 2).

Since the ylide particles are not completely soluble in water or the aqueous mixtures, the reaction can take place either at the interface *i.e.* it takes place at the surface of the ylide particle or in the bulk solution. In order to understand this aspect, the rates were compared for an exclusively homogeneous system and an identical but heterogeneous reaction mixture. The concentration of **1a** did not change much after 40 min for the homogeneous reaction (*i.e.* when the ylide **2** was dissolved by overnight stirring) at 298 K (Fig. 3). Under identical but heterogeneous conditions, more than 25% of the **1a** had undergone conversion to the product within 35–40 min. The rates were determined for ylide samples having different particle size. (Table 2) A smaller particle size leads to a greater surface area exposed to the reaction medium, and hence, is reflected in the higher apparent rate constants. The observations are a strong evidence for the predominantly interfacial mechanism of the reaction. This is a characteristic feature of "on water" reactions.[5] In such cases, the heterogeneous conditions are actually found to "catalyze" the reactions by a notable magnitude. In a recent report, Jung and Marcus have proposed that the H-bonding between the substrate and the free OH groups of the water molecules at the interface might be the basis for the superior rates observed for "on water" reactions.[8] The drastic variations in the rates for aqueous interfacial reactions can be explained on the basis of the difference in the spatial arrangement of water molecules around a hydrophobically hydrated solute and that around an extended macroscopic interface.[9]

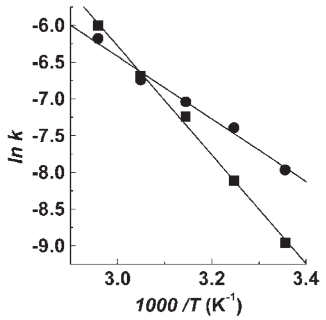

Fig. 2 Eyring plots for the Wittig reaction of **1a** with **2a** in water (●) and 3 M LiCl (■).

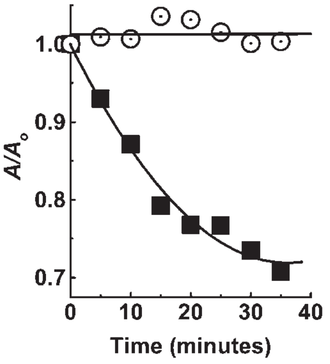

Fig. 3 Relative absorbance (an indicator for the extent of conversion) against time plotted for the reaction of **1a** with **2** at 298 K under (○) homogeneous conditions and (■) heterogeneous conditions.

According to the Lum–Chandler–Weeks (LCW) theory, the hydration of a mesoscopic surface (radius $r > 100$ Å) involves a "dewetting" of the surface.[10] The local density of water at such an interface is less than the bulk density of water. In fact, the length-scale dependence of hydrophobic hydration is a widely accepted physical phenomenon, which has been predicted theoretically[11] and proved experimentally.[12]

The medium effects for "on water" reactions could be explained on the basis of such size-dependent hydration thermodynamics. The surface of the solid ylide particles, which is the "site" of the interfacial Wittig reactions, can be considered as a macroscopic surface. Thus the orientation of water molecules around the ylide particles will be very different from the structured "iceberg"-like model used for the study of hydrophobicity of small non-polar solute molecules.[13] Addition of salts such as NaCl that are known to enhance the structure of water (structure-making or kosmotropes)[14] should lead to an increase in the cost of hydration of the ylide particle,

Table 2 Apparent rate constants (k_{obs}) for Wittig reaction of **1a** with **2a** samples having different particle size at 298 K

Particle diameter[a]/μm	$10^4 k_{obs}{}^b/s^{-1}$
162.7	3.47
131.7	5.28
70.5	5.37
64.8	5.51
39.4	5.95

[a] Samples of different particle size prepared by using a rolling ball mill and their diameter determined using a particle size analyzer. [b] Reactions carried out with 1 μmol of **1a** and 5 μmol of **2** in 10 mL of reaction medium.

as reflected by the greater free energy of cavitation for the "more structured" salt solutions.[15]

This may cause a further depletion of the water density around the surface, or in other words, a greater extent of "dewetting". The addition of NaCl is reported to increase the free energy of hydration per unit surface area, $\Delta G_{\text{hydration}}/A$ (A is the surface area).[12b] On the basis of SFM experiments measuring hydrophobic adhesion forces, Kurutz and Xu stated that addition of NaCl had no effect on the hydrophobic force experienced by the "supramolecular" surface, in contrast to its solution-phase effect on solubility of small solute molecules.[16]

Applying the same logic to the "on water" reaction kinetics, the addition of salts such as NaCl and LiCl might lead to a lesser number of water molecules at the interface available for H-bonding. The resultant change in the extent of interaction (wider "dewetted" region or fewer water molecules at the interface) may lead to a weaker "on water" effect, provided the reaction is indeed accelerated by the highly specific interfacial arrangement of water molecules. The fewer number of water molecules at the interface will translate into a lower extent of "catalysis" by dangling –OH groups and hence, a net slowing down of the reaction at 298 K.

At higher temperature, water is intrinsically "less structured" *i.e.* at 338 K as compared to 298 K. The interfacial arrangement of water molecules is greatly disturbed at such temperatures. Consequently, although salts such as NaCl or LiCl will still continue to perturb the interfacial structure but to a weaker extent. In this case, the effect of additives on the rates can possibly be dominated by other physicochemical processes. For example, at higher temperatures, it is probable that the salts exert their effect through controlling the solubility equilibrium of the ylide. The addition of LiCl or NaCl should increase the proportion of the undissolved ylide—favouring the faster "on water" reaction as compared to the sluggish homogeneous reaction of the dissolved ylide. Preliminary solubility studies in our laboratory have indicated that presence of LiCl and NaCl lead to a decrease in the solubility of the ylide as compared to that in water alone, in accordance with the conventional picture. This means that the addition of NaCl, LiCl should "salt-out" the ylide. However a thorough kinetic and solubility analysis is required for any conclusive explanation of the phenomenon. The effect of antihydrophobic additives also needs a closer examination.

In conclusion, the results show that the presence (or absence) of rate acceleration on addition of prohydrophobic salts at any temperature need not be a conclusive evidence for the predominance of (or lack of) "hydrophobic effect", at least for heterogeneous aqueous reactions. The salting effects on the kinetics of "on water" reactions differ significantly from those observed for homogeneous aqueous reactions. The length-scale dependence of hydrophobicity must be considered before interpreting any salting phenomenon. This observation is relevant to numerous chemical processes which are known to take place at a 'hydrophobic' interface. The results give an indication of the complex manner in which the presence of prohydrophobic and antihydrophobic salts is capable of influencing hydrophobicity at the interface.

Notes and references

‡ *Brief experimental procedure for kinetic analysis*: For a standard kinetic run, the 1 mM aldehyde solution (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. (See ESI† for details of analytical method used). The reaction mixture was heterogeneous in nature and vigorous stirring was required to minimise aggregation. The pseudo first-order rate constant thus obtained is, in fact, an apparent rate constant due to the heterogeneity of the medium. The rate constants were reproducible to within ± 3% at 298 K and ± 6% at 338 K.

1 D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, 1980, **102**, 7816.
2 R. Breslow and U. Maitra, *Tetrahedron Lett.*, 1983, **24**, 1901; R. Breslow, *Acc. Chem. Res.*, 1991, **24**, 159 and references cited therein; for "prohydrophobic" and "antihydrophobic" terminology, see: R. Breslow and R. V. Connors, *J. Am. Chem. Soc.*, 1995, **117**, 6601; R. Breslow and T. Guo, *J. Am. Chem. Soc.*, 1995, **117**, 9923.
3 J. F. Blake and W. L. Jorgenson, *J. Am. Chem. Soc.*, 1991, **113**, 7430.
4 W. Blokzijl, J. B. F. N. Engberts and M. J. Blandamer, *J. Am. Chem. Soc.*, 1990, **112**, 1197; W. Blokzijl and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, 1991, **114**, 5440; W. Blokzijl and J. B. F. N. Engberts, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1545; J. W. Wijnen and J. B. F. N. Engberts, *J. Org. Chem.*, 1997, **62**, 2039; A. Maijer, S. Otto and J. B. F. N. Engberts, *J. Org. Chem.*, 1998, **63**, 8989; S. Otto, J. B. F. N. Engberts and J. C. T. Kwak, *J. Am. Chem. Soc.*, 1998, **120**, 9517; S. Otto and J. B. F. N. Engberts, *Pure Appl. Chem.*, 2000, **72**, 1365; J. B. F. N. Engberts and M. J. Blandamer, *Chem. Commun.*, 2001, 1701; T. Rispens and J. B. F. N. Engberts, *J. Org. Chem.*, 2002, **67**, 7369.
5 S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275.
6 J. Dambacher, W. Zhao, A. El-Batta, R. Anness, C. Jiang and M. Bergdahl, *Tetrahedron Lett.*, 2005, **46**, 4473; J. Wu, D. Zhang and S. Wei, *Synth. Commun.*, 2005, **35**, 1213; J. Wu and D. Zhang, *Synth. Commun.*, 2005, **35**, 2543; A. El-Batta, C. Jiang, W. Zhao, R. Anness, A. L. Cooksy and M. Bergdahl, *J. Org. Chem.*, 2007, **72**, 5244.
7 W. F. McDevit and F. A. Long, *J. Am. Chem. Soc.*, 1952, **74**, 1773; M. R. J. Dack, *Chem. Soc. Rev.*, 1975, **4**, 211; R. Breslow and T. Guo, *Proc. Natl. Acad. Sci. USA*, 1990, **87**, 167.
8 Y. Jung and R. A. Marcus, *J. Am. Chem. Soc.*, 2007, **129**, 5492.
9 F. H. Stillinger, *J. Solution Chem.*, 1973, **2**, 141.
10 K. Lum, D. Chandler and J. D. Weeks, *J. Phys. Chem. B*, 1999, **103**, 4570; D. M. Huang and D. Chandler, *Proc. Natl. Acad. Sci. USA*, 2000, **97**, 8324.
11 D. Chandler, *Nature*, 2005, **437**, 640; S. Rajamani, T. M. Truskett and S. Garde, *Proc. Natl. Acad. Sci. USA*, 2005, **102**, 9475; G. Graziano, *J. Phys. Chem. B*, 2006, **110**, 11421.
12 A. Poynor, *Phys. Rev. Lett.*, 2006, **97**, 26601; M. Mezger, H. Reichert, S. Schroder, J. Okasinski, H. Schroder, H. Dosch, D. Palms, J. Ralston and V. Honkimaki, *Proc. Natl. Acad. Sci. USA*, 2006, **103**, 18401.
13 H. S. Franks and M. W. Evans, *J. Chem. Phys.*, 1945, **13**, 507.
14 R. Leberman and A. K. Soper, *Nature*, 1995, **378**, 364.
15 S. S. Pawar, U. Phalgune and A. Kumar, *J. Org. Chem.*, 1999, **64**, 7055.
16 J. W. Kurutz and S. Xu, *Langmuir*, 2001, **17**, 7323.