JOTCS
Journal of the Turkish Chemical Society
Section: A
Chemistry
TURKISH CHEMICAL SOCIETY

Critical Reflections on the Hydrophobic Effect, its Origins, and Manifestation: Water Structure, Chemical Reactivity, Micelles, and Gels

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Abstract: The origins of the hydrophobic effect (HE), its biological significance and its experimental basis are critically addressed in this brief review. It is argued that the mechanistic work reported on the HE in recent decades needs to be reassessed, as its conclusions are apparently debatable. Essentially, it is highly inaccurate to view the HE as a repulsive interaction, which is rather an attractive one. It appears inevitable that the HE is indeed a manifestation of the perturbation of the structure of water upon the introduction of hydrocarbon molecules into its interior. There appears to be no other satisfactory explanation for the formation of micellar aggregates and the existence of the critical micelle concentration. Also, the practical significance of the HE on the reactivity of organic compounds (*e.g.* cycloadditions) is severely limited by their minuscule solubility levels, itself a manifestation of the HE! Other related phenomena apparently include the formation of gels and the occurrence of certain esterification reactions in water, which are briefly reviewed from a conceptual viewpoint.

Keywords: Anti-hydrophobic, chaotropic, Diels Alder, denaturation, gels, micelles.

Submitted: July 17, 2017. **Accepted:** September 05, 2017.

Cite this: Chandrasekhar S. Critical Reflections on the Hydrophobic Effect, its Origins, and Manifestation: Water Structure, Chemical Reactivity, Micelles, and Gels. JOTCSA. 2017;4(3):899–914.

DOI: http://doi.org/10.18596/jotcsa.328983.

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INTRODUCTION

Origins of the hydrophobic effect

The concept of the hydrophobic effect (HE) apparently dates back to 1945, when it was proposed to explain why hydrocarbons are almost immiscible in water (1-5). The HE was later extended to the biological domain to serve as a basis for certain physicochemical properties of biological macromolecules, particularly relating to the denaturation of proteins and nucleic acids. These were composed of monomeric units of varying solubility in water, and the macromolecules adopted conformations that exposed the relatively water-soluble residues to the aqueous exterior while shielding the less soluble residues within the interior. Thus, the belief grew that the key to the overall shapes of the macromolecules lay in the incompatibility of the relatively hydrocarbon-rich regions with the aqueous medium (hence 'hydrophobic' effect).

This loaded semantic notwithstanding, the HE was earlier believed to originate in the robustness of the internal structure of water. Indeed, the unique characteristics of water are well known (*e.g.* its anomalous expansion) and believed to be due largely to its strongly hydrogen bonded structure (6-9). Thus, even if a hydrophilic solute perturbed the structure of water upon its dissolution, the resulting increase in energy was largely compensated by polar interactions (possibly including hydrogen bonding) between the solute and water. In the case of a hydrocarbon solute, however, these compensating interactions would be weak or absent, so the perturbations on the structure of water were essentially prohibitive.

Indeed, this view is evidenced by characteristic thermodynamic parameters (Table 1), essentially a substantial positive change in the Gibbs free energy (G, henceforth 'free energy') that involves negative enthalpy (H) and entropy (S) components, associated with the introduction of a hydrophobic solute into water (2). Thus, for example, the transfer of CH_4 from CCl_4 into water involves: $\Delta G = +12.1$ kJ mol^{-1}, $\Delta H = -12.5$ kJ mol^{-1} and $\Delta S = -75.8$ J K^{-1} mol^{-1}. The positive ΔG value implies a correspondingly low – although finite – concentration of CH_4 in water; however, whereas the negative ΔH value implies an attractive interaction between CH_4 and water, the negative ΔS value indicates considerable loss of molecular mobility. (In fact, analogous entropy-enthalpy compensation may well be the basis for the anomalous expansion of water occurring at 0-4 °C.)

The data thus indicate that there is a large entropic driving force for the HE, *i.e.* a considerable loss of entropy upon introducing a hydrocarbon solute into water. This likely involves not just the solute but also the water in terms of its highly ordered structure, which is believed to be disturbed by the cavity formed to host the solute molecule. (This is reminiscent of the formation of a clathrate compound, but *vide infra.*)

Table 1. Typical thermodynamic parameters for the transfer of hydrophobic solutes from an organic phase into water (at 25 °C, from ref. 2).

Solute	**Solvent**	**Δ*H*** (kJ/mol)	**-*T*Δ*S*** (kJ/mol)	**Δ*G*** (kJ/mol)
CH_4	CCl_4	-12.5	22.6	12.1
C_3H_8	C_3H_8	-7.1	27.4	20.5
C_6H_{14}	C_6H_{14}	0.0	28.4	28.4

Note also that the above thermodynamic values imply relative, rather than absolute, stabilities. This may well be the reason for the element of controversy which continues to surround the idea of the hydrophobic effect (1-5)! Thus, there is the apparent anomaly of a hydrocarbon solute existing at a finite concentration in water despite the positive Δ*G* for its transfer from an organic medium. Clearly, however, this is not to be confused with the absolute heat of formation: the above Δ*G*, in fact, leads to the equilibrium constant for the partitioning of the solute between the aqueous and organic phases. (The –Δ*H* for the transfer seems to conflict with the + Δ*G*, but this is an illusion.)

In particular, it is noteworthy that the dissolution of an organic solute in water must result in an overall decrease of the free energy, as otherwise separate phases would form! It is useful to consider here the transfer of the organic solute to the aqueous phase from the gaseous phase rather than from an organic phase. Then the major interactions would arise in the aqueous solution phase, and the fact that the solute dissolves therein implies a negative free energy change for the transfer. Of course, this does not apply beyond the solubility limit of the solute, when separate phases would form. These arguments are particularly useful in the context of formation of micelles as will be considered further below.

Furthermore, the negative entropy change for the transfer of an organic solute from an organic phase into water implies an increase in the order of the system as a whole. This may apply to the structure of the water or the solute, or indeed both. The accompanying negative enthalpy change, again, could apply to the reordered water structure or the interactions of the solute with the surrounding water molecules, or indeed both. If indeed the reordered water structure is lower in enthalpy than the native form, the reordering would be accompanied by a large negative entropy change (-Δ*S*); and the favorable interactions between the solute and the water (-Δ*H*) would partly mitigate this –Δ*S* (resulting in a less unfavorable Δ*G*).

In recent decades, however, the above qualitatively straightforward explanation of the HE has been supplanted by a view that apparently considers the HE literally, *i.e.* as an essentially repulsive interaction (5, 10). This conceptual departure has been paralleled by mechanistic studies of certain organic reactions carried out in water. These were bimolecular reactions which involved the aggregation of non-polar reactants at the transition state (particularly cycloadditions), that were apparently enormously accelerated in water (relative to an organic medium). The belief thus grew that these reactions were driven by the need to minimize contact between a non-polar surface and water, which was imputed to be the basis of the HE in a general sense.

There are, however, serious problems with this view as also the interpretation of the studies reported as evidence in its support. A critical reassessment of these ideas attempted below, leads to intriguing insights into a fascinating physicochemical phenomenon that is fundamental to understanding life itself. (The HE has indeed spawned a plethora of theoretical explanations, and this focused review adopts a pragmatic approach based on the above qualitative considerations.)

The structure of liquids and of water in particular

Liquids are believed to possess short range order – of whatever type – which is stable over exceedingly short time scales (9). It is interesting to view this in terms of a dynamic and fluxional structure composed of 'micro-domains' that are characterized by internal molecular-level order (Fig. 1). As the internal order and the boundaries between the micro-domains persist over short time scales, the resulting fluxional properties bestow liquids with their characteristic fluidity.

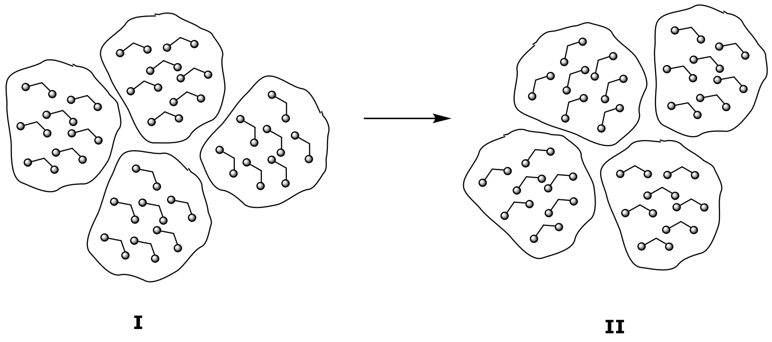


Figure 1: Cartoon representation of possible micro-domains in a liquid. The ordered structures within the micro-domains represent the molecules of the liquid. The boundaries in **I** coalesce and lead to new micro-domains as in **II.** The space between the boundaries represents pre-existing 'cavities' into which hydrophobic molecules can slip.

The internal structure of liquid water has also been well studied and understood in considerable detail (6-8). A tetrahedral model, in which each water molecule is hydrogen bonded to four other water molecules at the corners of an irregular tetrahedron, was for long a favored structure. In this, each water molecule acts as both hydrogen bond donor (at the two hydrogen atoms) and acceptor (at the two lone pairs). Relatively recently, however, a string based structure has been proposed, involving hydrogen bonded chains and rings (9).

All the same, it would appear that water in general is not much different from other liquids, likely composed of the above-mentioned fluxional micro-domains. The difference, perhaps, is that the internal structure of the micro-domains is stronger in the case of water, by virtue of extensive hydrogen bonding. (This model of the structure of liquid water is also most useful in understanding the formation of gels, as will be discussed further below.)

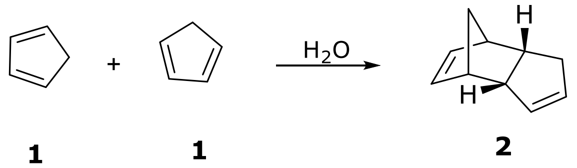
RESULTS AND DISCUSSION

General considerations: On the nature of the HE

Firstly, the view that the HE is a repulsive interaction between a non-polar molecular surface and water is apparently unviable, as it implies that a non-polar solute would have essentially zero solubility in water. Clearly, the solubility of a hydrocarbon solute in water – even if it is minuscule – is measurably finite. The above mentioned thermodynamic parameters indicate that the relatively low solubility of a hydrocarbon solute in water is largely due to the resultant perturbation of the structure of water.

Consequently, the acceleration of certain organic reactions in water is to be viewed as resulting from the high energy of the reactant ground state (relative to the case of an organic solvent). Importantly, this also implies that the transition states of these reactions are thus less destabilized in water than are the corresponding ground states. Reaching an understanding of these 'hydrophobic accelerations' thus requires an explanation for this differential destabilization of ground and transition states in water.

The current view appears to be that these trends originate in the need to minimize the molecular surface area, apparently based on the presumption that the HE is essentially repulsive in nature. Thus, for example, in the Diels-Alder dimerization of cyclopentadiene (Scheme 1) the surfaces of two reactant molecules are exposed to water in the ground state; in the transition state, however, the overall surface area exposed to water is reduced by about half, with a corresponding reduction in the HE (5, 10, 11).



Scheme 1: The Diels-Alder dimerization of cyclopentadiene (**1**) to dicyclopentadiene (**2**) in aqueous medium (from refs. 5 and 10).

Kinetic studies with antihydrophobic additives

Antihydrophobic additives and their effect on the HE

In fact, recent mechanistic approaches attempt to define the relative reduction of the surface area at the transition state with quantitative precision (10). These studies involve the use of so-called antihydrophobic (or 'chaotropic') additives which are proven to mitigate the HE. Many of these are simple organic compounds (*e.g.* the lower alcohols), but they also include urea and salts such as guanidinium chloride (GdmCl) or $LiClO_4$. These are known to increase the solubility of hydrocarbon solutes in water by a 'salting in' effect, although the mechanism of action is not always clear.

All the same, in depressing the HE, these additives lower the rate accelerations normally observed in water for reactions such as the dimerization of cyclopentadiene (Scheme 1). This then indicates that the additives enhance the relative solubility of the ground state more than that of the transition state in water. This – apparently – reinforces the view that the HE itself is based on the minimization of the molecular surface area that is exposed to contact with water. This conclusion, however, is predicated on the view that the additives minimize the area of contact by providing an interface between the molecular surface and water.

This seems reasonable enough, although the mechanism of action is often unclear. Thus, additives can be either 'salting-in' (GdmCl, urea, $LiClO_4$, Bu_4NCl) or 'salting-out' (LiCl) agents (the former decreasing the HE and the latter increasing it). However, members of either group can increase the surface tension of the resulting solution (GdmCl, urea, $LiClO_4$, LiCl) or decrease it (Bu_4NCl)! All the same, it was concluded that the action of salting-in agents cannot involve cavity formation as they generally lead to an increase in the surface tension. (However, it could equally be argued that an increase in surface tension leads to a strengthening of the walls of the cavity!)

On the nature of solvent cavities

The formation of cavities is a possible way in which hydrophobic solutes could be accommodated in the aqueous medium. Thus, the finite solubility of an organic solute in water implies an inherent tendency towards cavitation, which (perhaps) can be fortified by increasing the surface tension. However, the meaning of 'cavity' is likely subtle in these cases and possibly depends on the nature of the structure of liquids in general and of water in particular (6-9). In fact, it is difficult to deal with the HE in any depth or detail without referring to the structure of water in some way (certain aspects of the structure of liquids having been briefly dealt with above).

In the case of water, hydrophilic solutes are likely included within the micro-domains, whereas hydrophobic solutes are likely accommodated at the boundaries between the micro-domains (Fig. 1). The latter arrangement would clearly disturb the internal structure of water (within the micro-domains) to a minimal extent. The boundaries between the micro-domains would then serve as pre-existing 'quasi-cavities' into which solute molecules can slip. Weak dispersive interactions between the solute and the surfaces of the micro-domains, which stabilize the above arrangement, may also be envisaged.

Furthermore, it is possible that different additives affect the HE by different mechanisms. Thus, simple alcohols would likely bind at the 'quasi-cavities,' with the alcohol hydroxyl group within the micro-domains and the hydrocarbon part in the 'quasi-cavity' (for obvious polarity reasons). The hydrophobic solute could then bind alongside the alcohol hydrocarbon moiety. Polar additives (GdmCl, urea, $LiClO_4$, Bu_4NCl), however, are likely included within the micro-domains where they could stabilize the structure of water: this additional stabilization would offset the effect of accommodating the hydrophobic solute within the 'quasi-cavities.'

Kinetic studies: interesting results but intriguing interpretations

The kinetic effects of anti-hydrophobic additives on various reactions have been the subject of intensives studies, although the conclusions are debatable (5, 10). They are essentially based on a putative linear free energy relationship between the transition state and the ground state, in certain cycloaddition and related reactions. Although a number of reaction classes were intensively studied with various additives, the dimerization of cyclopentadiene is exemplary and bears particular mention.

Dimerization of cyclopentadiene (Scheme 1). Thus, for the Diels-Alder dimerization of cyclopentadiene in water, the logarithm of the rate constant (k) was plotted against the logarithm of the solubility (S') of the reactant at various concentrations of the additive (a low molecular weight alcohol). This led to a straight line with a negative slope, implying that the reaction is decelerated with increasing concentration of the additive. However, although this appears to be due to the additive decreasing the HE, the mechanism is likely complex, as argued below. In fact, there are two serious methodological problems with this approach, which render the conclusions dubious.

Firstly, log$k$ relates to the free energy of activation, not the free energy of the transition state. As originally conceived, the above slope was believed to lead to the ratio of the hydrophobic surface area of ground and transition states. This was apparently based on the assumption that the x and y axes relate to the increasing stabilization of the ground and transition states respectively, *via* the binding of the antihydrophobic additive to the molecular surface. In the event, however, the x axis represents the surface area of the ground state whereas the y axis represents the difference in the surface area between the ground and transition states.

Thus, the x axis was believed to represent the four faces of the two cyclopentadiene reactant molecules, and the y axis the two faces of the transition state that are exposed to the solvent medium. The stabilization afforded by the additive at the transition state would be half that at the ground state (assuming equal binding strength). On this basis, the expected slope of the above plot should be ±0.5: -0.5 if log$k$ were plotted, and +0.5 if the free energy of activation were plotted, along the y axis.

Secondly, the solubility of the reactant was considered to be the saturating concentration obtained at various concentrations of the additive. Apparently, there is an interesting logarithmic relationship between the percent additive content of the solvent and the amount of cyclopentadiene extracted into it. However, the saturating concentrations of cyclopentadiene are considered to reflect the stability of the solutions in terms of their free energy content (solubility being viewed as an equilibrium constant).

In the particular case of the dimerization of cyclopentadiene, the plot of -log*k* *vs.* log*S′* led to a straight line of slope 0.92 [Fig. 2 (i) is a qualitative representation of the results reported in ref. (10)]. This was intriguingly interpreted in terms of a corresponding loss (of 92%) in the stabilization of the transition state relative to the ground state. This was believed to reflect the loss of hydrophobic surface area at the transition state and a corresponding diminution in the amount of bound additive.

However, as pointed out above -log*k* relates to the free energy of activation, not the free energy of the transition state. On this basis, the above slope (0.92) indicates that practically all of the increase in the free energy of activation is accounted for by the increase in the stability of the ground state! And fascinatingly, this implies that the anti-hydrophobic additive binds minimally (if at all) to the transition state! The reasonable conclusion, then, is that the reaction occurs *via* the reactant that is not bound to the additive, *i.e.* the additive is stripped from the reactant before this can reach the transition state.

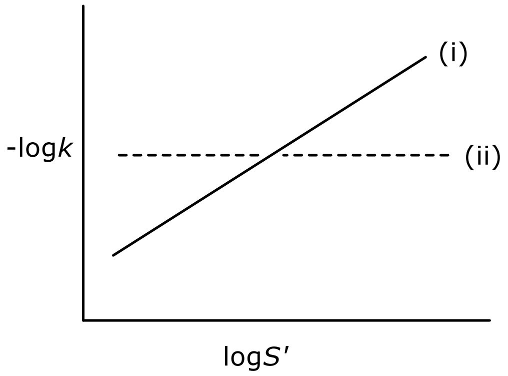


Fig. 2. Observed plot (i) of the logarithm of the rate constant (log*k*) *vs.* the logarithm of the solubility (log*S′*) of cyclopentadiene for its dimerization (Scheme 1, *cf.* ref. 10); (ii) indicates the putative plot if the *y* axis in the case of plot (i) represented the free energy of the transition state.

And indeed – with hindsight – this is eminently reasonable as the two reactant molecules need to come out of their solvent shells before they can react together! Although one might argue that only one face of each cyclopentadiene reactant molecule needs to be stripped of the additive for reaction to occur, the observed results seem to indicate otherwise. Thus, the binding of the additive to even one face of the cyclopentadiene molecule apparently prevents reaction. (It is also possible that the additive initially binds to only one face of the cyclopentadiene reactant, which is already aggregated in the ground state.)

It also bears mention that a plot of the free energy of the transition state (along the *y* axis) *vs.* that of the ground state (along the *x* axis) for the dimerization of cyclopentadiene, would lead to rather different conclusions to those reached above. Indeed, if the slope of such a plot were ~ 1, it would imply that every unit increase in the stability of the ground state is matched by a unit increase in the stability of the transition state. Thus, the free energy of activation would remain constant (with additive concentration), hence log*k* would remain unchanged [Fig. 2 (ii)]!

Other cycloaddition reactions. Analogous studies on several other reactions were also reported, *e.g.* the cycloaddition of 9-hydroxymethylanthracene with various N-alkyl maleimides (5, 10). In these cases, a plot of -log*k* *vs.* log*S′* apparently led to a straight line with a slope < 1, implying that the additive is also bound to the transition state. (A slope < 1 implies that the stabilization of the ground state is partly offset by the stabilization of the transition state.) It seems likely that the 9-hydroxymethyl group complexes with the alcohol additive *via* hydrogen bonding, leading to a relative diminution of the anti-hydrophobic deceleration (*vide supra*). (The other cases reported are also complicated by competing ground and transition state effects, apparently.)

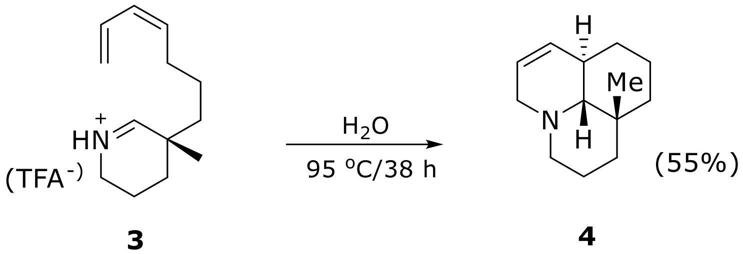
Clearly, the above studies are beset by ambiguities. Thus, that there is a reduction in the overall surface area, in all the reactions reported in the studies discussed above, is apparent by mere inspection of the ground and transition states! The attempt to probe this *via* anti-hydrophobic additives is interesting, but plagued by flawed analyses of the results obtained. In any case, the studies do not lead to an understanding of the origins of the HE itself, but apparently perpetuate the dubious view that the HE is essentially a repulsive one. (The statement ‘The HE reflects the high energy of a water hydrocarbon interface..’ raises the question ‘What is the origin of the high energy of the interface?)!

The problem of accelerations: Rate constant vs. rate

It is often stated that the HE leads to enhanced rates of certain reactions (5, 10, 11). In these, there is a significant reduction in the overall surface area in contact with water when the transition state is attained (*vide supra*). A problem with this view, however, is that it is valid only with reference to the rate constant but not the reaction rate (12). This is because of the poor solubility of the reactant in the aqueous medium and its consequent low concentration. In fact, the diminution in concentration would correspond in magnitude to the HE (5, 10), which thus enhances the rate constant while correspondingly diminishing the rate. Intriguingly, therefore, the HE nullifies itself overall!

This is the main reason why ‘hydrophobic acceleration’ has found hardly any practical application, say in synthesis (12). Although it may appear that a biphasic system involving the hydrophobic solute and water could evidence a hydrophobic rate effect, it is likely stymied by a very slow transfer of the solute into the water phase. Again, this is due to the HE, which thus appears 'self-limiting' and apparently of little practical utility as yet in conventional chemistry.

In fact, although a large number of cycloaddition reactions have been carried out in water as part of complex synthetic strategies (*cf.* Scheme 2), the purported accelerations are apparently not due to the HE (12-14). This is because the substrates employed were hydrophilic (**3**) rather than hydrophobic, so the observed reactions were most likely driven by water catalysis, *i.e.* a medium effect (*vide infra*).



3 **4**

Scheme 2: Intramolecular cycloaddition of the iminium diene **3** to form the tricyclic amine **4** in water (TFA⁻ is the trifluoroacetate counterion; from ref. 14).

Alternative interpretation of hydrophobic accelerations: Polarity of water

The discussion so far raises the possibility that the reduction in the surface area of the reactants upon reaching the transition state may not be a major contributor to the observed hydrophobic rate enhancements. In particular, the favorable enthalpy change accompanying the transfer of organic solutes into water indicates enhanced attractive interactions in water relative to an organic medium! Of course, an unfavorable entropy change essentially stymies this effect, hence the poor solubility of hydrocarbon solutes in water. The entropic effect is believed to reflect restricted motions of both the solute and the reorganized water phase (*vide supra*).

The observed rate enhancements of certain reactions in aqueous media, therefore, must reflect a diminution of the above effects at the transition state relative to the ground state. Thus, in the case of the dimerization of cyclopentadiene, the transition state is – perhaps arguably – compact relative to two free cyclopentadiene reactant molecules. This may well considerably diminish the above entropic effects, as the transition state is accommodated relatively easily by the water structure.

This reflects the prevailing view of hydrophobic rate enhancements (5). However, as seen above, the view that the enhancements are driven by the need to minimize the surface area of the reactants is not entirely free of ambiguities. It would appear that – at most – this view is partially valid, so alternative explanations are worth seeking.

An interesting possibility is that the high polarity of water plays a major role in the observed enhancements. Thus, water is the most polar of the common solvents, possessing a high dielectric constant of 78.54 (15). Also, Diels-Alder reactions are known to be accelerated *via* electrophilic activation. Such a mechanism is a distinct possibility in the case of the dimerization of cyclopentadiene, involving activation of the dienophilic reactant molecule *via* hydrogen bonding of the *π* cloud with the surrounding water molecules.

Interestingly, in fact, it is also possible that the binding of anti-hydrophobic additives to the reactant leads to decelerations by simple steric and electronic effects. Thus, although these additives increase the solubility of the reactant and thus its concentration, a smaller fraction of the reactant may then be available for reaction in unbound form. This can happen if the solubility of the reactant 'plateaus out' at higher additive concentrations, as was indeed reported and mentioned above (10). It was also seen above that the transition state is likely bereft of the additive, thus indicating that the additive-bound reactant is essentially unreactive. The ultimate origin of these effects, however, is apparently open to debate: Indeed, a number of the above effects may operate together although to unknown extents in each case.

Micelles and the significance of the critical concentration

One of the earliest and most significant manifestations of the HE is related to the formation of micelles (16, 17). Micelles are generally water-soluble aggregates of long chain hydrocarbon molecules that possess a polar head-group (the solute). The hydrocarbon chains aggregate towards the center of the micelle, with the polar groups being pointed outward into the aqueous medium. An important characteristic of the formation of micelles is that it requires a minimum concentration of the solute, the so-called 'critical micelle concentration' (CMC). This implies that below the CMC the solute molecules are essentially fully soluble, and hence do not need to aggregate.

The most likely explanation for this is that the perturbation of the structure of water becomes prohibitive beyond the CMC. This implies that below the CMC the solute molecules are accommodated within cavities in the aqueous medium that essentially pre-existed as features of the water structure (*vide supra*). Thus, at the CMC all the cavities are filled with molecules of the largely non-aggregated solute.

Aggregation of the solute molecules at the CMC reduces their effective molecular volume by increasing their density, so they can still be accommodated within the above cavities. However, the reduction of the molecular volume also implies a reduction of the molecular surface area, leading to the notion that this is the causative factor driving the aggregation! In fact, the aggregation must be accompanied by a decrease in free energy of the system as a whole as otherwise separate phases would result.

Indeed, this appears to be the key problem in understanding the origins of the HE. As was discussed at some length above, explanations based on the reduction of the surface area apparently imply that the HE is repulsive. Rather conversely, once it is recognized that the interaction between a hydrocarbon solute and water is weakly attractive, it becomes apparent that aggregation is based on the reduction of the molecular volume. (Anti-hydrophobic additives apparently provide an interface that enhances the attractive forces between the solute and water.) Apparently, the formation of micelles provides the clearest enunciation of these arguments about the nature of the HE. (The folding and aggregation of biological macromolecules into tertiary and quaternary structures is indeed a related phenomenon.)

Formation of gels and the possible role of solvent cavities

A fascinating phenomenon that is somewhat obliquely related to the HE is the formation of gels, in both aqueous and organic media (hydrogels and organogels, respectively) (18, 19). Although gels have been widely known and employed for long (*e.g.* in culinary preparations), their scientific study has only been undertaken relatively recently. Indeed, recent decades have witnessed increasing numbers of new gels being reported with a variety of gelling agents.

A particularly intriguing aspect of the formation of gels is that the gelling agent is generally employed in minuscule amounts. Thus, typically, < 1.0 mol% of the gelling agent is sufficient to gel an entire body of the solvent! The gelling agent is usually an organic compound that can self-aggregate, gel formation being a consequence of the partial immobilization of the molecules of the solvent employed. Hence, the question arises as to how this is accomplished by an extremely small quantity of the gelling agent. Thus, each molecule of the gelling agent immobilizes more than a 100 molecules of the solvent: clearly intriguing!

An interesting possibility is that the gelling agent forms membranous structures *via* self-aggregation, and along the cavities existing between the micro-domains of the solvent. This would disturb the internal structure of the micro-domains minimally, and is the possible driving force for the self-organization. The resulting three-dimensional membranous structures may well be robust enough to function as sacs within which a relatively large number of solvent molecules are trapped. The membranous structures would also freeze the boundaries between the micro-domains, so the fluid nature of the original solvent is lost.

Electron micrographs of gels have revealed filamentous structures that are further entwined among themselves (18, 19). The resolution of the micrographs is of the order of tens of nanometers. Hence the observed filaments cannot correspond to the sacs mentioned above. However, the filaments may be formed from an agglomeration of the sacs, indicating various levels of structural ordering with the sacs as fundamental units.

This model of the gel thus depends critically on the structure of the liquid state, in particular the idea that the fluxional character of the micro-domains lends to liquids their quintessential fluidity.

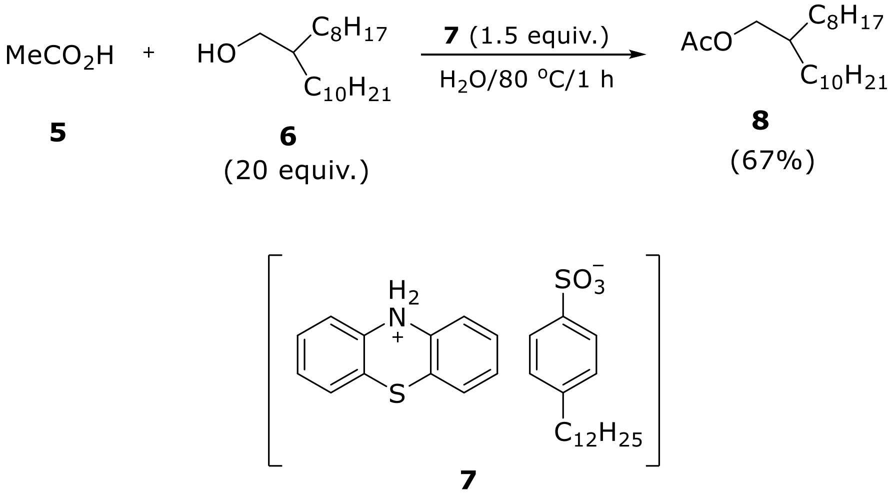
The model also explains satisfactorily how a minuscule amount of the gelling agent can be so effective in immobilizing a relatively large quantity of solvent.

Esterification reactions in aqueous media

In a remarkable development of recent years, certain dehydrative reactions have been performed in water as solvent. For instance, the esterification of low molecular weight carboxylic acids with branched long chain alcohols was effected in reasonable yields in water (20), by employing long chain sulfonic acids and their derivatives as catalysts. (These studies were directed towards the recovery of low molecular weight carboxylic acids, *e.g.* acetic acid, from waste waters.)

Intriguingly, yields as high as 67% were obtained in an aqueous medium (Scheme 3). (However, this required excess amounts of catalyst and alcohol, lower yields being obtained otherwise.) In any case, it is remarkable that these and other reactions (including aldol and Mannich reactions) could be effected in aqueous media. It is possible that the esterification reactions (in particular) are driven by the HE in some way, as long chain reactants are involved. This would imply – apparently unjustifiably – that the product esters are less hydrophobic than the reactants (acids and alcohols). The fact that the catalysts also contain hydrophobic moieties is noteworthy; although this cannot determine the direction of the equilibrium, a lowered HE at the transition state *via* aggregation of the catalyst with the reactants is indicated.

It is also possible that the products form a separate phase, leading to a more thermodynamically stable state overall, relative to the reactants (which would be destabilized by the HE). Alternatively, the catalyst could be altering the structure of the water employed as the medium, rather in the manner of the formation of gels (*vide supra*). Further studies are indicated to clarify these mysterious but fascinating reactions!



Scheme 3: The esterification of acetic acid (**5**) with the branched long chain alcohol **6** to yield the acetate **8,** employing the long chain sulfonate catalyst **7** in water (from ref. 20).

CONCLUSION

Despite its apparently humble origins, the HE has evolved a sophisticated and complex theoretical underpinning. The early assessment that the HE is involved with the structure of water gradually ceded to a view based on the minimization of the hydrophobic surface area of organic solutes in water. This model has been employed to explain certain kinetic results leading to the idea of the hydrophobic rate acceleration. However, it appears these studies are plagued by various ambiguities, and also, the enhancements observed apply to rate constants rather than rates. Thermodynamic parameters also indicate a considerable attractive interaction between an organic solute and water as solvent. It thus appears that the HE cannot be understood without recourse to the structure of liquids and water in particular. The existence of micelles and gels – not to mention the folding of biological macromolecules – may only be satisfactorily explained on these bases.

REFERENCES

1. Biedermann F, Schneider H-J. Experimental Binding Energies in Supramolecular Complexes. Chem. Rev. 2016;116:5216−5300.

2. Silverstein TP. The real reason why oil and water don't mix. J. Chem. Educ. 1998;75:116-8.

3. Wenneström H. Interfacial interactions. In: Baszkin A, Norde W, editors. Physical chemistry of biological interfaces. New York/Basel: Marcell Dekker, Inc.; 2000. 85 p.

4. Reichardt C, Welton T. Solvents and solvent effects in organic chemistry 4th ed. Weinheim: Wiley-VCH; 2011. 31 p.

5. Breslow R. The hydrophobic effect in reaction mechanism studies and in catalysis by artificial enzymes. J. Phys. Org. Chem. 2006;19:813–22.

6. Ball P. Water – an enduring mystery. Nature 2008;452:291-2.

7. Ball P. Water as an active constituent in cell biology. Chem. Rev. 2008;108:74–108.

8. Shultz MJ, Vu TH, Meyer B, Bisson P. Water: a responsive small molecule. Acc. Chem. Res. 2012;45:15-22.

9. Nordlund K, Ashkenazy Y, Averback RS, Granato AV. Strings and interstitials in liquids, glasses and crystals. Europhys. Lett. 2005;71:625-31. (DOI: 10.1209/epl/i2005-10132-1)

10. Breslow, R. Determining the geometries of transition states by use of antihydrophobic additives in water. Acc. Chem. Res. 2004;37:471-8.

11. Sangwan, N K, Schneider, H-J. The kinetic effects of water and cyclodextrins on Diels-Alder reactions. Host-guest chemistry. Part 18. J. Chem. Soc. Perkin Trans 2. 1989;1223-7.

12. Shrinidhi A. Organic transformations in water: synthetic and mechanistic studies towards green methodologies. PhD Thesis, Indian Institute of Science, Bangalore (India); 2014.

13. Otto S, Engberts JBFN. Diels-Alder reactions in water. Pure. Appl. Chem. 2000;72:1365–72.

14. Grieco PA, Kaufman MD. Construction of carbocyclic arrays containing nitrogen via intramolecular imino Diels-Alder reactions in polar media. A comparative study: 5.0 M lithium perchlorate-diethyl ether versus water. J. Org. Chem. 1999;64:6041-8.

15. Atkins P. Physical chemistry 5th ed. Oxford: Oxford University Press; 1995. C19 p.

16. Rusanov AI. The wonderful world of micelles. Colloid J. 2014;76:121–6.

17. La Sorella G, Strukul G, Scarso A. Recent advances in catalysis in micellar media. Green Chem. 2015;17:644–83.

18. Terech P, Weiss RG. Low molecular mass gelators of organic liquids and the properties of their gels. Chem. Rev. 1997;97:3133-59.

19. Zhang M, Weiss RG. Self-assembled networks and molecular gels derived from long-chain, naturally-occurring fatty acids. J. Braz. Chem. Soc. 2016;27:239-55.

20. Igarashi T, Yagyu D, Naito T, Okumura Y, Nakajo T, Mori Y, Kobayashi S. Appl. Catal. B. 2012;119–120:304–7.