What is special about water as a matrix of life?

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\textbf{Summary.} Water offers a large temperature domain of stable liquid, and the characteristic hydrophobic effects are first a consequence of the temperature \textit{insensitivity} of equation-of-state features of the aqueous medium, compared to other liquids. On this basis, the known aqueous media and conditions offer low risk compared to alternatives as a matrix to which familiar molecular biological structures and processes have adapted. The current molecular-scale understanding of hydrophobic hydration is not conformant in detail with a standard structural \textit{entropy rationalization}. That classic pictorial explanation may serve as a mnemonic, but isn’t necessary. A more defensible view is that peculiar hydrophobic effects can be comprehended by examination of engineering parameters characterizing liquid water. LA-UR-05-3081

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1 Heuristic identification of solvent systems alternative to water as a matrix of life

The title of this discussion is a question that hints at a practical interest in identifying alternative media for biomolecular processes and structures. In
addition there is the curiosity to understand precisely the special role that water plays in known biochemistry and biophysics. Thus, we would like to understand the specialness of liquid water as a matrix of life [1–3] well enough to identify close comparisons, and we would like to identify close comparisons in order to refine our understanding of the specialness of water as a matrix of life.

We are encouraged to embark on this discussion now because theories of hydrophobic effects — universally viewed as an essential feature of aqueous biochemistry and biophysics — have become more serious over the past decade [4, 5]. For many more years than that there have standard views of hydrophobic effects [6, 7] that center on tetrahedrality as a feature of the local structure of liquid water, and upon entropic contributions associated with constraints on the structure that might be imposed by hydrophobic solutes. That tetrahedrality concept, however, has been ineffective in identifying alternatives. It is defined on the basis of known structures of liquid water, and then typically leads to a view that there is no water but water.

Here we will refer to the classic views of hydrophobic effects based upon that tetrahedrality concept as pictorial theories because those words were used initially [8], and because those views often don’t proceed to a quantitative stage of molecular science. The recent progress on the problems of hydrophobic effects [4, 5, 9–17] lead in a different direction from the classic pictorial theories. The new direction avoids speculations on structurally specific molecular mechanisms, and instead focuses on engineering characteristics — such as the equation of state of the liquid water matrix — in building a theoretical description.

From the perspective of that recent progress, the pictorial theories that are side-stepped are rationalizations typical of subtle but vital chemical problems. Though the alternative direction avoids simple rationalization to achieve a fully defensible theory, it also leaves open the sources of the necessary information. We use the context of this discussion to collect some results on solvents that might offer natural alternatives to liquid water for astrobiology.

A striking feature of the biophysical structures that we know is that spatial organization is achieved by competing hydrophilic and hydrophobic interactions [18]. It is natural then to expect that an effective alternative matrix for life should support both solvophobic and solvophilic interactions. We comment on each of these issues in turn.

1.1 Hydrophobic effects

The most primitive conceptualization of hydrophobic effects is just that water and oil don’t mix [16, 19]. These phase equilibria, together with molecular-scale hydrophobic-hydrophilic amphiphilicity, result in spatially segregated mesoscopic structures with obvious utilities [18]. The driving force for oil-water phase separation is customarily viewed as a sticky interaction operating
between hydrophobic species [20, 21], but not as specifically as suggested by the archaic term ‘hydrophobic bond.’

This phase equilibrium alone is not, however, the most challenging aspect of the puzzle of hydrophobic effects. Standard solution thermodynamic studies establish that the suggested hydrophobic stickiness becomes stronger as the temperature increases. This point is experimentally clear in the phenomenon of cold-denaturation of proteins wherein cool, unfolded soluble proteins fold upon heating [22–25]. Another example of this behavior is shown in Fig. 1.

**Fig. 1.** Flory-Huggins interaction parameter for polyethylene glycol water mixtures as a function of volume fraction of water for temperatures 30 C (lower) and 40 C (upper). This interaction parameter is larger, favoring phase separation, at the higher temperature, an expected behavior for hydrophobic effects. The data are those of [26]; see [27].
It is inevitable that organized mesoscopic solution structures should come apart at sufficiently high temperatures. The fact that hydrophobic — stabilizing — interactions should become stronger with increasing temperature then stabilizes those structures over a broader range of temperatures than if this peculiar temperature behavior of hydrophobic interactions didn't obtain. The temperature at which this increase of hydrophobic attraction ceases is known as the entropy convergence temperature, and is in the neighborhood of 130 °C at moderate pressures; the upper-temperature limit of known life is in the neighborhood of 120 °C [28], so classic hydrophobic interactions get stronger throughout that upper range of temperatures.

At the observed lower end of the temperature domain for metabolite activity, perhaps near −20 °C [29, 30], hydrophobic stabilization of enzymes is expected to be more delicate [31]. Though other conditions may not be entirely the same in such a comparison, the systems of initial interest are predominantly aqueous systems in the temperature range is −20 °C < T < 120 °C.

The idea followed here is that this is a large temperature range. Finding alternative solvents that might approach a temperature range this large is not expected to be easy.

A large temperature range is expected to be important because a living organism is likely to require a multitude of physical and chemical processes each with some temperature sensitivity. Optimization of individual such processes should be seen as secondary to satisfactory compromises of performance among many processes. An alternative medium that offers a wide range of possibilities for such compromises should be a preferred choice as an alternative for the known matrix of life.

Viewed contrapositively, a medium in which a significant fraction of required processes could be seriously degraded by a thermal excursion would not be expected to be a satisfactory matrix of life. Then the temperature maxima and minima that abound in physical properties of aqueous solutions — the maximum of the density in the liquid is one example, and the minimum in the compressibility shown in Fig. 4 is another example — the significance of these maxima and minima is first that the properties of liquid water have a small net variation in an extended temperature range.

1.2 Hydrophilic effects

If traditional hydrocarbon-dominated organic molecules are the carriers of one of those categories of interaction, that seems to leave classic electrostatic and chemical interactions for the other category [15]. Indeed, water is a chemically active liquid. Water is involved in standard acid-base chemistry, both through direct molecular participation, and indirectly by auto-ionization:

$$\text{H}_2\text{O} \rightleftharpoons \text{HO}^- + \text{H}^+ \quad (1)$$

This underlies the buffering that is essential to familiar biochemistry, and moderates changes in charge states of soluble macromolecules. Fig. 2 shows
temperature variation of the ion product $K_W = [H^+] \times [OH^-]$. It increases significantly with increasing temperature along the saturation curve as both the density and the dielectric constant decrease.

In the context of protein folding studies some years ago, Klotz [32] drew attention to the fact that $pK_A$ of simple carboxylic acids show extrema curiously similar to the others we have been discussing; this is exhibited in Fig. 2.

Familiar aqueous biochemistry exploits standard acid-base chemistry and mobile ions in solution. For example, the interiors of cells have a negative electrical potential relative to the exterior. This is because electrical potential differences couple to proton shuttling and ATP synthesis. Regulated electrical communication seems necessary. Mobile ionic solutes serve that purpose.

Ionic dissolution and dissociation in liquid water is associated with its high dielectric constant. Fig. 3 shows that this dielectric constant is above 50 for temperatures below 120°C; these are high values, and so high that the variation of $\varepsilon_0$ in the liquid phase here is not a dominating concern. Relative variations of hydration free energies will depend on $\delta\varepsilon_0/\varepsilon_0$. The observed high-values of the dielectric constant means that salts are satisfactorily soluble in liquid water, and that good solubility will not be critically sensitive to variations of solvent quality. Dissolution of minerals extends the $(T, p)$ domain of the liquid phase.

Liquids with dielectric constants as high as those of liquid water are not usual; results for a selection of such cases are shown in Fig. 3.

2 Current theory of hydrophobic effects

Why should hydrophobic attractions become stronger at higher temperatures? This has always been a contentious issue for molecular theories [42, 43]. But a rationalization based upon a structural mechanism has always been standard [6]: water molecules contacting hydrophobic groups are considered to be ordered, suffering an entropy penalty [44]. When hydrophobic groups are buried by phase segregation or folding, contacting water molecules are released to the bulk, regaining the penalized entropy. The demixed or folded case has a higher entropy for that reason, and is the stable outcome at higher temperatures. Viewed in the opposite temperature direction, this suggests that cold-denaturation works by water molecules prying-open folded, soluble protein molecules [45].

This entropy rationalization might have a fractional truth. But it has never been developed in a conclusive way and proved. An appreciation of this gap between molecular theories and common rationalizations seems to be growing more widely [46].

Furthermore, experimental counter-examples are readily available, simple, and troubling. A particularly clear counter-example is due to Friedman & Krishnan [47]: the sum of the standard hydration entropies of $K^+(aq)$ and $Cl^-(aq)$ is about twice the standard hydration entropy of Ar(aq). The case
Fig. 2. Upper: the ion product $K_W = [H^+] \times [OH^-]$ with concentrations in units of mol/l, for liquid water along the vapor saturation curve [33]. The dotted curve is a model of the form $-\log_{10}[H_2O] + a + b/T$ fitted to the data below 150°C. The analogous ion product for liquid ammonia, $[H^+] \times [NH_2]$, is reported to be about $10^{-33}$ [34]. Lower: From [35]. Except for the n-butyric case, the magnitudes of the standard enthalpies for these dissociation reactions are substantially less than the thermal energy here.
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**Fig. 3. Upper:** the static dielectric constant of fluid water along the liquid-vapor coexistence curve [36], and liquid methanol [37] and liquid ammonia [38]. The blue dotted curves are fitted models $\propto \rho_{\text{liq}}/T$, suggesting that the qualitative behavior is simply understood on the basis of equation of state variables. Measurement of the dielectric constant of liquid H$_2$S as a function of temperature has been sketchy; but the value at its normal freezing point, about 9.3, gives a typical magnitude. The static dielectric constant of liquid ammonia is about 23 for the lowest temperature liquid state. **Lower:** Static dielectric constants as a function of $T$ at ambient pressures for several high-dielectric-constant liquids; see [39]. Hydrogen cyanide might be the highest-dielectric-constant molecular liquid, but with the most rapid decrease with $T$ through these thermodynamic states [40]. The electrical conductivity of HCN is lower than that of liquid water. Formamide has a higher dielectric constant than liquid water here, and that dielectric constant doesn’t decrease faster than does the dielectric constant of water [41]. A variety of amides, and also urea and thiourea, are likely to exhibit similarly high dielectric constants. Liquids with static dielectric constants above 30 are fairly common, and some of those cases are shown.
of methanol as solvent is qualitatively different. If hydrophobic effects are conceptualized on the basis of hydration entropies and specific hydration structures, this is paradoxical: according to the measured entropies \( \text{Ar(aq)} + \text{Ar(aq)} \) is about as hydrophobic as \( \text{K}^+(\text{aq}) + \text{Cl}^-(\text{aq}) \), but the hydration structures neighboring \( \text{K}^+(\text{aq}), \text{Cl}^-(\text{aq}) \), and \( \text{Ar(aq)} \) are clearly qualitatively different, both in structures observed and numbers of water molecules affected. A speculation how this might happen was offered recently [48], but couldn’t be considered yet proved.

This example should not be interpreted to suggest that \( \text{K}^+(\text{aq}) + \text{Cl}^-(\text{aq}) \) is hydrophobic. The point is that the classic entropy rationalization is not a necessary explanation why \( \text{Ar(aq)} \) is hydrophobic.

The proved theories of classic hydrophobic effects [4, 5, 7, 9] — leaving aside the cases of ionic solutes or of hydrophobic effects in the context of amphiphilic solutes — establish something more subtle and more general than the structural entropy rationalization discussed above: the entropic effects that are characteristic of hydrophobic phenomena are closely tied to peculiarities of the equation of state of liquid water. This is the engineering perspective that we noted at the outset of this discussion.

2.1 Equation-of-state features that govern primitive hydrophobic effects

Fig. 4 then grounds our description of these engineering aspects of the present problem [7, 16]. The upper-left panel there shows measured compressibilities for liquid water and several organic solvents. Water is qualitatively stiffer. Current theory [4, 5] suggests that the low solubility of inert gases in liquid water is first a reflection of this stiffness. Notice that this stiffness is only weakly sensitive to temperature along the vapor saturation curve, in contrast to the stronger temperature dependence of the compressibilities of the other solvents.

Compressibilities of 150 liquids at ambient conditions of \( T = 298.15 \text{ K} \) and \( p = 1 \text{ bar} \) were surveyed in [53]. In that collection, liquid water does indeed have a low compressibility: glycerol had the lowest compressibility in that listing. Working from lowest compressibilities upward those liquids are ordered as glycerol, diethylene glycol, ethylene glycol, formamide, 2-aminoethanol, 1-4 butanediol, 1-5 pentanediol, and water, with the last two noted cases tied. This ordering suggests that all of the named liquids would be of interest for further study in an astrobiology context. Formamide not only is less compressible than liquid water, it also has a compressibility minimum near 25 C at low pressure [54].

The lower-left panel of Fig. 4 makes a similar comparison of the thermal expansions of our standard organic solvents along the saturation curve. We are principally interested in the circumstances that the density decreases with increasing temperature, but that decrease is qualitatively slower for liquid water than for the other solvents shown. Current theory [7, 16] suggests that the
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Fig. 4. Key thermodynamic parameters associated with the modern theory of hydrophobic effects, variation with temperature along the vapor saturation curve. 

*Upper-left:* compressibility, \( \kappa_T \equiv (\partial \ln \rho / \partial p)_T \). Water is stiffer than comparable organic solvents, and doesn’t appreciably soften in this temperature range.

*Lower-left:* thermal expansion coefficient, \( \alpha_\sigma \equiv - (\partial \ln \rho / \partial T)_\sigma \). Water expands less rapidly with temperature than comparable organic solvents.

*Upper-right:* the product of the liquid-vapor surface tension and the liquid compressibility, \( \gamma_{lv} \times (\partial \ln \rho / \partial p)_T \). The temperature dependence of this correlation length for water is qualitatively different from these organic solvents.

*Lower-right:* The internal pressure, \( (\partial U / \partial V)_T \). The hydrocarbon liquids qualitatively conform to the van der Waals expectation that this should be proportional to \( \rho^2 \), but water is qualitatively different. Data from [50] and [51, 52].
inverse of the thermal expansion coefficient \(-\frac{\partial T}{\partial \ln \rho}\)_\(\sigma\) should be considered a characteristic temperature for hydrophobic hydration; in the most fortunate cases \([7,16]\), it is — roughly but clearly — a small multiple of the entropy convergence temperature observed experimentally with the solubilities of inert gases in water \([55,56]\). Where this entropy convergence behavior is well-developed, the entropy convergence temperature is the temperature at which the hydrophobic stickiness stops increasing in strength with increasing temperature. Following the interpretation of \(-\frac{\partial T}{\partial \ln \rho}\)_\(\sigma\) as an important temperature scale, that temperature — see Fig. 4 — is higher for liquid water than for the other solvents shown.

It is often guessed that the surface tensions associated with water interfaces should be involved in the description of hydrophobic effects \([7,57]\). A nice way to consider what might be the implications of liquid-vapor interfacial tensions, \(\gamma_{lv}\), is to consider the product \(\gamma_{lv} \times (\frac{\partial \ln \rho}{\partial p})_T\); this is a reduced correlation length \([7,49]\), and is shown for the same cases in the Upper-right panel of Fig. 4. For the organic solvents the tensions decrease and the compressibilities increase with increasing temperature. In those cases, the compressibility-increases dominate, and the correlation lengths increase. For liquid water, in contrast, the compressibility scarcely changes, and the interfacial tension decreases with increasing temperature. Thus, this correlation length decreases with increasing temperature. Recent theories suggest that a multiple — roughly a factor of ten — of this reduced correlation length identifies a length-scale on which macroscopic considerations can be directly exploited in proved theories \([7]\).

There are two points of interpretation of the results for the reduced correlation length. The first point is that though liquid water has a relatively high interfacial tension with its vapor, when viewed in this scale the magnitudes are not unusual. It is the temperature dependence that is unusual, and that unusual temperature dependence is mostly associated with the compressibility. The second point of interpretation is that the contraction of this correlation length with increasing temperature naturally would be viewed as a breakdown of the more open architecture of liquid water at lower temperatures. This correlation length is apparently a sensitive diagnostic of this break-down behavior; the more detailed current theory also predicts a contraction with increasing temperature of a corresponding natural length scale \([7]\).

The final frame of Fig. 4, Lower-right, shows the internal pressure, \((\frac{\partial U}{\partial V})_T\). Following a van der Waals model \((\frac{\partial U}{\partial V})_T \approx a \rho^2\), with \(a\) the van der Waals parameter describing the effects of attractive intermolecular interactions on the equation of state. This contribution stabilizes the liquid at low pressure. Water is clearly qualitatively different from the organic solvents in this respect. Because of the expectation of a van der Waals model, the behavior seen for liquid water might suggest that this liquid is becoming better bound at higher temperatures, definitely counter-intuitive and a paradoxical view.

This example illustrates how a counter-intuitive temperature dependence can arise. This internal pressure can be expressed as
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\[
\left( \frac{\partial U}{\partial V} \right)_T = T \left( \frac{\alpha_p}{\kappa_T} \right) - p,
\]

where \( \alpha_p \equiv - \langle \partial \ln \rho / \partial T \rangle_p \) here is quantitatively only slightly different from the \( \alpha_\sigma \) of Fig. 4, and the compressibility \( \kappa_T \) was defined there also. For the case of liquid water, \( \kappa_T \) is small, and since \( \alpha_p \) is also comparatively small the density changes are small. The change of \( \kappa_T \) with \( T \) is thus also small, the ratio \( \alpha_p / \kappa_T \) is, above 4°C, then a substantial factor with weak \( T \) dependence, and the \( p \) contribution of Eq. (2) is a secondary magnitude. The formal multiplier of \( T \) in Eq. (2) then causes a steep increase with increasing temperature. Thus the literal description of the counter-intuitive behavior is that with increasing temperature

1. the density is decreasing but only slowly,
2. the low compressibility is scarcely changing,
3. and the kinetic energy — the explicit factor of \( T \) — is increasing.

This combination produces the counter-intuitive result which is still an amazing trick, but at least somewhat clearer. The counter-intuitive temperature dependences of hydrophobic effects such as that shown in Fig. 1 eventually acquire a practically identical explanation [4, 14]. Consequently, simple theories of hydrophobic effects that incorporate equation-of-state information properly — and scarcely anything else — can be qualitatively correct in describing many of these unusual temperature dependences.

Note that this distinctive temperature dependence continues to temperatures near the currently known upper-temperature limit of life.

2.2 Water compared to other possibilities

We can take a broader view of these characteristics of liquid water by comparison with some other fluids that might be considered in the context of astrobiology. Fig. 5 shows phase diagrams for a selection of interesting cases. The oft-noted point that water has a high critical temperature compared to other small molecule liquids is emphasized by these results. That critical temperature is well above the temperatures of first interest here, so it is probably not specifically relevant. But water achieves this high critical temperature by exhibiting a relatively long temperature domain for the liquid phase; and then the density of liquid water decreases comparatively slowly with increasing temperature. This is consistent with the results of Fig. 4.

3 Discussion

In view of the intricate beauty of molecular bioscience, a common attitude is the biomolecular structures and processes are delicately tuned to the aqueous medium and conditions we know. The discussion here suggests that the
Fig. 5. Liquid-vapor coexistence densities for several fluids compared to liquid water; from [58] except for the methylamine case which comes from [59]. The vertical axis is the density relative to the critical density in each case. The temperature domain of the liquid water phase is larger than the other cases here. The variation of the density of liquid water is slower than the other cases, consistent with Fig. 4.
familiar molecular biology has adapted to the known medium and conditions that offer low risk compared to alternatives. Water offers a large temperature domain of stable liquid, and the characteristic hydrophobic effects are first correlated with the temperature insensitivity of engineering properties of the aqueous medium, compared to other liquids.

This suggests that molecular biological structures and processes often could be isolated to function satisfactorily in alternative milieu. But it is likely that the conditions would require more careful control than in the original aqueous setting. Transplanting successively more biochemical processes to function satisfactorily at the same time in the same alternative milieu and conditions naturally should be considered as increasingly hazardous.

4 Conclusions

The current molecular-scale understanding of hydrophobic hydration is not conformant in detail with a standard structural entropy rationalization. That standard pictorial explanation may serve as a mnemonic, but isn’t necessary. A more defensible view is that peculiar hydrophobic effects can be comprehended by examination of engineering parameters characterizing liquid water. This is even simpler than the standard pictorial theory.

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