

Topics in Current Chemistry

128

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Ion-Selective Bulk Membranes as Models for Biomembranes



Biomimetic and Bioorganic Chemistry

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With Contributions by
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E. Kimura, Y. Matsui, Y. Nakatsuji,
T. Nishioka, K. Ogino, M. Okahara,
W. Tagaki, D. W. Urry

With 111 Figures and 45 Tables



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Biochemistry and Physiology of Herbicide Action

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C. Fest, K.-J. Schmidt

The Chemistry of Organophosphorus Pesticides

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Chemical Section. – Biochemistry. – Appendix.

Internationally acclaimed in its first edition, this renowned reference work has been expanded and completely revised to cover recently developed and improved organophosphorus fungicides, herbicides and insecticides. These include relatively non-toxic compounds that can be metabolized into inorganic phosphates and still meet the demands for efficiency, economy and ecological safety. The organophosphorous pesticides covered herein are considered according to their

- preparation
- industrial production
- modes of action



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With its comprehensive and detailed coverage, **The Chemistry of Organophosphorus Pesticides**, 2nd Edition will prove an indispensable reference not only for organic chemists in industry and research, but also for biologists, entomologists, mycologists, botanists, farmers, and administrative bodies dealing with agricultural research, pest control and environmental studies.

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Solvation and Ordered Structure in Colloidal Systems

Gotthold Ebert

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1 Introduction

As a contribution to the topic "Biomimetic and Bioorganic Chemistry" this review deals mainly with colloidal systems consisting of biomolecules forming association colloids or existing as macromolecular colloids (biopolymers). The associated monomolecular units are in a more or less ordered state in micelles, vesicles or in the membrane itself. However the molecular order of solubilized molecules is also strongly influenced. Biopolymers are able to attain highly ordered, periodic structures depending on various parameters e.g. temperature, pH, electrolyte concentration etc. Usually the solvation effects or changes in the solvation of these molecules are involved in the formation of ordered structures.

Because biomolecules normally exist in liquid water, this article will be largely concerned with their ordered structures in aqueous media and therefore with hydration effects. In order to understand better the influence of solute-solvent interactions on molecular order, also solvation in organic liquids will be considered to some extent.

"Solvation" and especially "hydration" are rather complex phenomena and little is known about them. Depending on the kind of molecular groups, atoms or ions interacting with the solvent, one can differ between lyo- or hydrophilic and lyo- or hydrophobic solvation or hydration. Due to these interactions the so-called "liquid structure" is changed. Therefore it seems to be unavoidable to consider, at least very briefly, the intermolecular interactions and the main features of liquids, especially "water structure" before dealing with solvation/hydration and their effects on the formation of ordered structures in the colloidal systems mentioned above.

2 Intermolecular Forces and Structures in Liquids

2.1 Apolar Liquids

This type of liquid is characterized by direction independent, relatively weak dispersion forces decreasing with r^{-6} , when r is the distance between neighbouring molecules. A simple model for this type of liquid, which accounts for many properties, was given by Luck^{1,2}: it is represented by a slightly blurred lattice-like structure, containing hole defects which increase with temperature and a concentration equal to the vapor concentration. Solute molecules are trapped within the holes of the liquid thus reducing their vapor pressure when the latter is negligible.

2.2 Interactions in Polar Liquids

In this case the interaction between neighbouring molecules is not only stronger but also orientation dependent. The mean statistical energy of dipole-dipole interactions \bar{U}_{dd} also decreases with r^{-6} , but depends on μ^2 (μ : dipole moment) according to³⁾

$$\bar{U}_{dd} = \frac{2\mu_1^2\mu_2^2}{3r^6kT} \quad (1)$$

As a consequence of such interaction there are some preferential mutual orientation disturbed by the thermic motion of the molecules.

Ion-dipole interactions interact over longer distances. Their mean interaction energy \bar{U}_{id} decreases with r^{-4} ³⁾:

$$\bar{U}_{id} = \frac{e_0^2 \mu^2}{3r^4 kT} \quad (2)$$

Ion-ion interactions are long-range interactions decreasing only with r^{-1} and their mean interaction energy \bar{U}_{ii} is given by ³⁾

$$\bar{U}_{ii} = \frac{1}{\epsilon} \frac{z_i z_j e_0^2}{r} \quad (3)$$

Hydrogen bonds play a very important role in the formation of structures in liquids. Their interaction energy is relatively high (3–10 kcal/mole) and is strongly dependent on the direction between donor and acceptor ^{1,3-7)}. The maximum of hydrogen bond energy is attained if proton donor and acceptor are arranged linearly and the angle β between both is zero. Deviations from the linear arrangement up to $\beta = 30^\circ$ have only a negligible influence on the bonding energy ^{1,4-7)} and in fact discrete values of β characteristic for ring shaped associates have been observed ¹⁾. Therefore, in order to enable dipole molecules to participate in hydrogen bonding, the maximum of intermolecular interaction must occur in the O—H ... O-direction and not in that of the dipole moment which lies in the direction of the H—O—H angle bisector, as in the case of water.

The typical properties of water arise from the ability of the water molecule to participate in four hydrogen bonds due to its two protons and its two lone electron pairs ($2s$)²($2p_z$)² which act as proton acceptors. In the condensed state, the angle between the $2p_x$ and the $2p_y$ orbital of oxygen is enlarged by hybridisation to a mixture of s- and p-state to 109° . Because both of the free electron pairs are situated in a plane

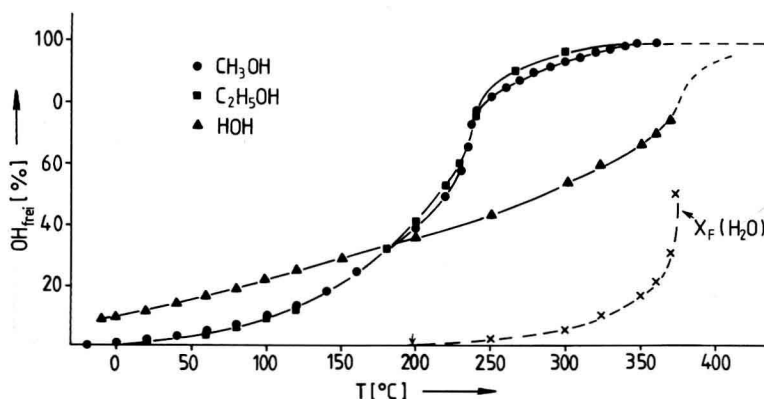


Fig. 1. Fraction of non-hydrogenbonded ("free") OH-groups in water, methanol and ethanol determined by IR-spectroscopy. x_F is the fraction of hole defects for water ⁷⁾

perpendicular to that of the H—O—H, each water molecule in the ice modification ice I is surrounded tetrahedrally by four others, so forming a hexagonal lattice similar to the SiO₂-tridymite containing large holes. When the ice melts, it is only the long-range order which is lost, whereas a remarkable degree of short-range order is maintained over a wide temperature range. This was shown by X-ray analysis^{8,9)}, IR-, Raman-, NMR-spectroscopy¹¹⁻¹³⁾, dielectric measurements¹⁴⁾, thermodynamical considerations^{1,6,15)} etc. reviewed by several authors.

For this reason the number of "free", non-hydrogen bonded molecules is on the average of time at near room temperature rather small, not only in water but also in alcohols. This is shown in Fig. 1, in which the fraction of "free" OH-groups is plotted against temperature⁷⁾. There are many theories on the structure of liquid water^{5,6,16)}, but no one is able to offer an interpretation of all the properties of liquid water. One of the most advanced theories on liquid water is offered by Nemethy and Scheraga¹⁷⁾ and allows for the evaluation of many of its thermodynamic properties. The authors assume "flickering clusters" with life-times of $\approx 10^{-11}$ sec and a size of ≈ 60 water molecules at 20 °C in equilibrium with "monomeric" water. Unsatisfactorily the number of broken hydrogen bonds in this model is too high in comparison with experimental results. According to a model developed recently by Luck⁷⁾ and valid up to 180 °C, there are structures of "liquidified ice" and hydrogen bond defects which have the tendency to attain a packing as in apolar liquids by means of a cooperative mechanism.

It should be mentioned that in the last few years super-cooled water has attracted the interest of many scientists because of its exceeding properties and life at temperatures below 0 °C^{18,19)}. Speedy recently published a model which allows for the interpretation of the thermodynamic anomalies of supercooled water²⁰⁾. According to this model there are hydrogen bonded pentagonal rings of water molecules which have the quality of self-replication and association with cavities.

Pentagonal rings and other cyclic structures have been suggested not only for liquid water^{22a-c)} but also for clathrate hydrates²¹⁾.

2.3 Water Structure in Aqueous Solutions

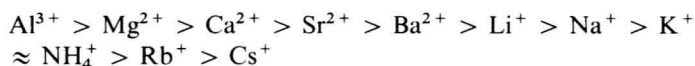
More complicated and less known than the structure of pure water is the structure of aqueous solutions. In all cases, the structure of water is changed, more or less, by dissolved substances. A quantitative measure for the influence of solutes on the structure of water was given in 1933 by Bernal and Fowler²³⁾, introducing the terminus "structure temperature, T_{st} ". This is the temperature at which any property of pure water has the same value as the solution at 20 °C. If a solute increases T_{st} , the number of hydrogen bonded water molecules is decreased and therefore it is called a "water structure breaker". Vice versa, a T_{st} decreasing solute is called a "water structure maker". Concomitantly the mobility of water molecules becomes higher or lower, respectively.

2.3.1 Hydrophilic Hydration

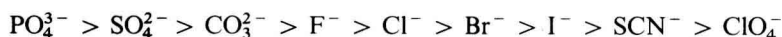
Hydrophilic hydration signifies that a strong energetically favored direct interaction exists between dissolved polar or ionic particle and the surrounding water molecules by ion-dipole-, dipole-dipole-interactions and/or hydrogen bonds.

It is possible to indicate by thermodynamic considerations^{24, 25, 27)}, by spectroscopic methods (IR²⁸⁾, Raman²⁹⁾, NMR^{30, 31)}, by dielectric³²⁾ and viscosimetric measurements²⁶⁾, that the mobility of water molecules in the hydration shell differs from the mobility in pure water, so justifying the classification of solutes in the water structure breaker and maker, as mentioned above.

The order of cations and anions regarding these structure breaking and making properties is related to their position in the lyotropic or Hofmeister series, such as



and



On the left-hand side there are strong hydrated multivalent ions with a high charge density on the ion surface responsible for the strong ion-dipole interaction. On the right hand side one finds large monovalent ions with a lower charge density. This is shown in Table 1 for the cations³³⁾.

Table 1. Ionic radii and charge densities of alkali and alkali earth cations (Hilgenfeld, R., Saenger, W.³³⁾)

Ion	r [Å]	Charge/density $\times 10^{20}$ [Coulomb/Å ²]
Li ⁺	0,68	12,1
Na ⁺	0,95	4,46
K ⁺	1,33	1,62
Rb ⁺	1,48	1,18
Cs ⁺	1,69	0,79
Be ²⁺	0,35	178
Mg ²⁺	0,66	26,8
Ca ²⁺	0,99	7,90
Sr ²⁺	1,12	5,46
Ba ²⁺	1,34	3,17

It should be emphasized that the position of some ions in the series mentioned above depends somewhat on the method used for its determination^{5, 34)}. Recently it was shown by Lang that in supercooled water and under low pressure all kinds of ions, e.g. Mg²⁺ and Li⁺ act as water structure breaker^{35, 36)}. Besides ions, non-ionic but polar solutes also influence the mobility of H₂O molecules by mutual interactions which change the water structure^{24, 31)}. Solutes containing proton acceptors or proton donators are especially able to form hydrogen bonds with water molecules and act as water structure makers or breakers³⁷⁻⁴⁰⁾.

2.3.2 Hydrophobic and Lyophobic Solvation

As shown by Frank and Evans⁴¹⁾, solutions of apolar substances in water are characterized by a large entropy of mixing, leading to a high positive free energy of dissolving.

Table 2. Partial excess quantities for mixing pure solvent and pure solute to infinitely diluted solution according to Chan et al. ⁴²⁾

Quantity	Hydrophobic	Normal
$\Delta\mu_2^E$ (cal · mol ⁻¹)	≥ 5000	$\approx \pm 600$
ΔH_2^E (cal · mol ⁻¹)	$\approx \pm 1000$	$\approx \pm 1000$
ΔS_2^E	$T \Delta S_2^E \gg \Delta H_2 $	$T \Delta S_2^E < \Delta H_2 $
ΔC_{p2}^E (cal · mol ⁻¹ deg ⁻¹)	≥ 50	± 3
ΔV_2^E (cm ³ · mol ⁻¹)	≤ 15	± 1

This effect is explained by a structuring of the solvent surrounding the apolar solute. Table 2 shows a comparison of the thermodynamical excess quantities for mixing the pure solvent with the pure solute to an infinitely diluted solution for hydrophobic and non-hydrophobic solutes, according to Chan et al. ⁴²⁾.

Besides the large partial excess free energy $\Delta\mu_2^E$ due to the highly negative excess entropy ΔS_2^E , the large excess heat capacity ΔC_{p2}^E indicates that there is a remarkable energy necessary for “melting” the ordered solvent structure by raising the temperature. Therefore, a clustering of apolar solutes is favored by gaining entropy due to a decrease in the number of ordered water molecules. Theoretical treatment of the hydrophobic effects have been given by several authors ^{20, 24, 42–46)}.

The question is raised as to whether lyophobic effects also occur in nonaqueous, high polar solvents. As a result of energy and interfacial energy measurements on mixtures of polar, aprotic solvents and n-decane, Greco ⁴⁷⁾ comes to the conclusion that at a colloidal level hydrogen bonds are unnecessary for entropy losses as in the case of hydrophobic effect. Indeed there seems to be a higher degree of order in the solvation shell of polar molecules surrounding an apolar one because, for energetical reasons, the self-interaction of these solvent molecules is favored compared with the polar-apolar interaction. For this reason the extent of the freedom of orientation in the solvation shell may be decreased according to a loss in entropy.

3 Solvation of Amphiphilic Molecules and Ordered Structures

3.1 Solvation and Ordered Structures in Reversed Micelles

Molecules consisting of polar and apolar moieties behave as amphiphiles: they are simultaneously hydro- and lipophilic or hydrophilic and hydrophobic. Due to this fact, such molecules are able to associate equally well in both aqueous and hydrocarbon solutions above a certain concentration — the critical micelle concentration (c.m.c.) — forming thermodynamic stable micelles in water or reversed micelles in hydrocarbons. Detailed reviews of these phenomena were published a few years ago in this series ^{48, 49)}.

Micelles and reversed micelles are able to solubilize substances which are insoluble in the bulk phase of the system considered. This solubilization is due to a solvation by the amphiphile and concomitantly a change in the order of the solubilized molecules may occur as a consequence of its modified solvation shell. In this sense reversed micelles of detergents in hydrophobic solvents with solubilized water in the core are

of special interest. A detailed molecular model of reversed micelles has been published by Kitahara and Kon-No⁵⁰⁾.

Inside the small water pool there are strong interactions of the water molecules with the ionic head groups of the surfactant and between the water molecules themselves. Eicke and coworkers^{51,52)} have studied the role of water for the formation of reversed micelles experimentally and theoretically in detail. They have shown for AOT (bis-(2-ethyl-hexyl)-2-sulfonatosuccinate)/isooctane/water-systems, that hydrogen bonding is very important for micellisation of surfactants in hydrocarbons⁵¹⁾. From photon correlation spectroscopy measurements between -85 and $+95$ °C, an unexpected high thermal stability of AOT reversed micelles was found⁵²⁾. This is probably due to the reinforced formation of extended networks by hydrogen-bonded water molecules in the water pool.

Senō et al.⁵³⁻⁵⁶⁾ have studied the properties of water solubilized in the core of reversed micelles of various surfactants such as dodecylammoniumpropionate (DAP), hexadecyltrimethylammoniumbromide (HTAB) and sodium bis-(2-ethylhexyl)-2-sulfonatosuccinate (AOT or SBSS) in different organic solvents (CH_2Cl_2 , CHCl_3 , C_6H_6 , $n\text{-C}_6\text{H}_{14}$) by IR and NMR-spectroscopy. It was found that there are two kinds of water molecules within the water-pool: one of them (type A) interacts quite strongly with the ionic head groups of the surfactant, the other kind (type B) is less bound and interacts with the Type A water molecules of the primary hydration layer. According to Senō et al.^{54,55)} the properties of these solubilized water molecules are closely related to the enzyme-like behaviour of DAP/hexane/water systems. This becomes obvious by the hydrolysis of adenosine-5'-triphosphate (ATP) greatly enhanced by Mg^{2+} in reversed micelles⁵³⁾. FT-IR studies⁵⁶⁾ have shown that the maximum of the bands of water associated with Na-sulfonate and tetrabutylammoniumbromide (TBAB) are close to that of AOT and HTAB. This seems to indicate that the interactions of water with the ionic head groups in reversed micelles are very similar to those in the hydration shell of ions in aqueous solution. From difference-spectra obtained by subtracting the spectra of the NaBr solution from that of the TBAB-solution it is possible to estimate the approximate frequencies of water associated with Na^+ and TBA ions. A band at $\approx 3400\text{ cm}^{-1}$ is most likely caused by water molecules interacting with ammoniumgroups. Probably due to the structure-making effect of quaternary alkylammonium ions the O—H stretching band of the solubilized water is shifted to lower frequencies.

The strong interactions between the water molecules also become obvious from NMR measurements by Tsujii et al..⁵⁷⁾ ^{13}C -NMR experiments were used for determining the microviscosity of water in reversed micelles of dodecylammonium-propionate with ^{13}C glycine cosolubilized. It was found that the apparent viscosity of the water-pool corresponds to the viscosity of a 78 % aqueous glycerol solution, obviously as a consequence of the extended network formation by strong hydrogen bonding.

Similar conclusions were obtained from ^1H and ^{31}P NMR and also from IR studies of egg phospholipid reversed micelles in benzene by Boicelli et al.⁵⁸⁻⁶¹⁾. According to the results of these experiments the water structure within the reversed phospholipid micelles alters considerably compared with water in bulk. This becomes evident from the shortening of the relaxation time T_1 of the water protons split into two relaxation times T_{1A} and T_{1B} , indicating that there are at least two

populations, A and B, of water molecules⁶⁰). This is in agreement with Senō et al.^{54, 55}). If amino acids or small peptides are cosolubilized, the relative amounts of A and B are changed. One can assume that due to the hydration of the solute the number of water molecules available for one polar head group will be decreased. As can be easily understood, the solute molecules prefer to interact with water molecules belonging to population B, rather than with those of population A firmly bound to the phospholipid polar head-groups.

With increasing water content the reversed micelles change via "swollen micelles"⁶²) into a lamellar crystalline phase, because only a limited number of water molecules may be entrapped in a reversed micelle at a distinct surfactant concentration. Tamamushi and Watanabe⁶²) have studied the formation of reversed micelles and the transition into liquid crystalline structures under thermodynamic and kinetic aspects for AOT/isooctane/water at 25 °C. According to the phase-diagram, liquid crystalline phases occur above 50–60% H₂O. The temperature dependence of these phase transitions have been studied by Kunieda and Shinoda⁶³).

Sodium octanoate (NaO) forms reversed micelles not only in hydrocarbons but also in 1-hexanol/water. The hydration of the ionogenic NaO headgroups plays an important role in this case too. For this reason Fujii et al.⁶⁴) studied the dynamic behaviour of these headgroups and the influence of hydration-water with ¹³C and ²³Na NMR measurements. Below $w_0 = [\text{H}_2\text{O}]/[\text{NaO}] \approx 6$ the ²³Na line-width

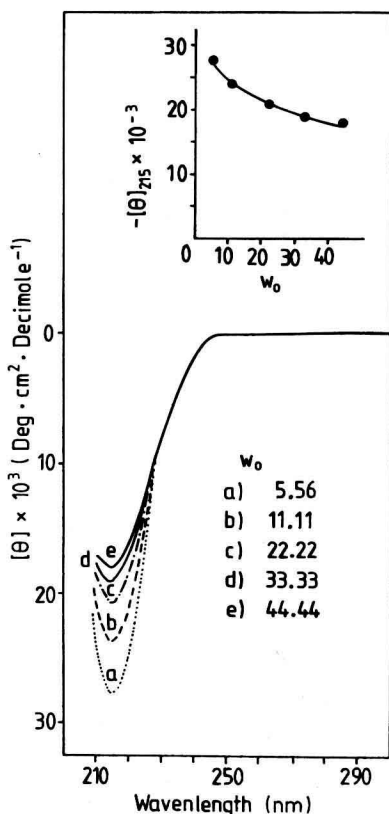


Fig. 2. CD-spectra of $(\text{L-Lys} \cdot \text{HBr})_n$ in reversed micellar systems of AOT/octane/H₂O at different w_0 -values⁶⁵). T: 20 °C

increases very steeply due to a restricted mobility of the Na^+ in the water pool. Furthermore it was found that the OH-group of 1-hexanol is probably in contact with water molecules entered among the polar NaO headgroups and that the mobility of methylen carbons 5 and 6 of NaO is affected by these water molecules.

As mentioned above, water structure in reversed micelles deviates considerably from the structure in the bulk-phase. Therefore, the hydration shell of macromolecules entrapped in reversed micellar systems should be changed and thus also their conformation. According to the results of several authors this is indeed the case.

Senō et al.⁶⁵⁾ have used basic poly- α -aminoacids (BPAA) and copolymers of basic aminoacids with L-leucin as model substances cosolubilized in a reversed micellar system AOT/octane/water. As a result the basic homopolyaminoacids $(\text{Orn})_n$, $(\text{Lys})_n$ and $(\text{Arg})_n$ form I β conformation in reversed AOT micelles (Fig. 2) whereas in AOT solutions at low concentrations $\approx 10^{-4}$ to $\approx 10^{-3}$ mol/l CD spectra similar to a superposition of II β and α -helix are observed (Fig. 3). With increasing w_0 value ($[\text{H}_2\text{O}]/[\text{AOT}]$ ratio), *i.e.* increasing water content of the reversed micelles, the specific ellipticity $[\theta]_{218}$ decreases. This may be explained by a weakening of the interactions between the $-\text{SO}_3^-$ and the basic side group of the BPAA responsible for β -structure formation by electrostatic shielding. A copolymer $(\text{L-Lys HBr}^{0.50}, \text{L-Leu}^{0.50})_n$ shows CD spectra similar to that of α -helix in $5 \times 10^{-5} - 9.4 \times 10^{-4}$ M AOT solutions,

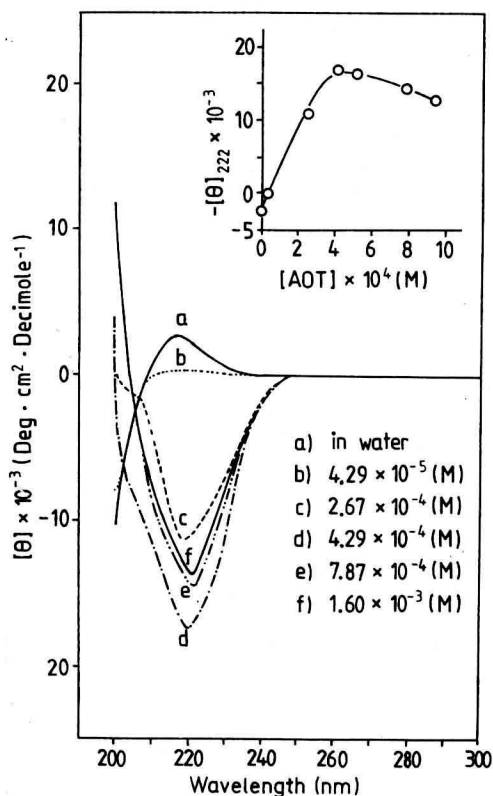


Fig. 3. CD-spectra of $(\text{L-Arg} \cdot \text{HBr})_n$ in water and in AOT-solutions at pH 6.2, $T: 20^\circ \text{C}$