This article was downloaded by: [Tomsk State University of Control Systems and Radio]
On: 23 February 2013, At: 07:01
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954
Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK

Molecular Crystals and Liquid Crystals
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl16

Occurrence, Fluctuations and Significance of Liquid Crystallinity in Living Systems

R. K. Mishra [a] [b]

[a] College of Engineering, University of Akron and Lymph Research Laboratory, Akron City Hospital, Akron, Ohio

[b] Department of Biophysics, All-India Institute of Medical Sciences, New Delhi, 16, India

Version of record first published: 21 Mar 2007.

To cite this article: R. K. Mishra (1975): Occurrence, Fluctuations and Significance of Liquid Crystallinity in Living Systems, Molecular Crystals and Liquid Crystals, 29:2, 201-224

To link to this article: http://dx.doi.org/10.1080/15421407508083201

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.tandfonline.com/page/terms-and-conditions

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be

independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

Mol. Cryst. Liq. Cryst., 1975, Vol. 29, pp. 201–224
© Gordon and Breach Science Publishers, Ltd.
Printed in Holland

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

Occurrence, Fluctuations and Significance of Liquid Crystallinity in Living Systems

R. K. MISHRA†

College of Engineering, University of Akron and
Lymph Research Laboratory, Akron City Hospital, Akron, Ohio.

(*Received September 28, 1972; in final form June 3, 1974*)

Many molecules and macromolecules present in the living systems are known to exhibit the mesomorphic or the so-called liquid crystalline state under appropriate conditions. This state is characterised by relative mobility when compared with true solids and by association and alignment in one crystallographic axis or in one plane when compared with true liquids. It may be brought about by the variation of temperature yielding thermotropic liquid crystals or by the variation of amount and properties of the solvent giving rise to the lyotropic ones. Of these the former mechanism is obviously unimportant for the living systems, particularly for the homeothermic organisms, since there are but few compounds which undergo liquid crystalline transitions at the body temperature within the range of probable local temperature fluctuations in the tissues and body surfaces. However, many molecular species of biological relevance, including some which form thermotropic mesophases, are capable of associating into a lyotropic mesophase under the influence of the water which is the common solvent in the living systems. This association has been hitherto recognised in the case of relatively small molecules like phospholipids, or large natural macromolecules and discrete globular units like sickel cell hemoglobin, or virus particles.

Although the existence of mesophases is accepted it has not been critically investigated if the state is essential for the characteristic features of the living state. It is contended here that the association of segments of biological macromolecules in the case of quaternary structures and the association of whole molecules with others follows the same essential rules as do lyotropic liquid crystals in general. The conformation of molecules resulting from intramolecular attractions and repulsions seem also to be governed similarly to a considerable extent. Thus the

---

† Permanent address: Department of Biophysics, All-India Institute of Medical Sciences, New Delhi 16, India.

Substance of this paper was presented at the 4th International Liquid Crystal Conference, Kent, Ohio, August 23, 1972.

"liquid crystallinity," in this sense, is perhaps of general occurrence. In essence, the associations are a consequence of the balance between interatomic or intermolecular affinity within the molecule or molecules and the affinity toward the solvent. Correlation amongst electrons in associated molecules establishes basic continuity. By this is implied that the electrons in one molecule induce appropriate states in the electrons in the neighbouring molecules across distances commonly found in the living systems and in the liquid crystals.

Since the lyotropic systems undergo fluctuations of internal energy and structure as a consequence of the input of quantum chemically defined species or of mass or momentum, or electromagnetic fields it is suggested that this state, in the manner defined, is essential for the following features of the living state: specificity, asymmetry, dynamic transformations, rhythmicity, control and communication in immediate molecular domains and evolution. The advantage of this statement, is that it permits the application of the concept of mesophase and electron correlation to biologic systems. Also, in the reverse, the large body of data pertaining to the molecules in the living systems can help us to understand the liquid crystalline state where data on numerous physical parameters of the mesomorphogenic molecules have been accumulated but there is as yet no direct link between them and the dominant concept in the liquid crystal field: the behaviour as a continuum of a system composed of discrete molecules.

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

AN OVERVIEW OF LIQUID CRYSTALLINITY

For the purpose of description, the thermotropic liquid crystalline state may be caused by the possession of one of two phases, smectic or nematic, and give rise to three different major types of molecular arrangements: smectic, nematic or cholesteric the last one being regarded as a twisted nematic. In the smectic type elongate molecules are aligned along their long axis and their ends are in register on a plane perpendicular or inclined to the long axis of the molecules. In the nematic type, the former aspect, the alignment along the long axis is the only restriction. In the cholesteric variant successive sheets of molecules along the axis of alignment the molecules are arranged in a helicoidal fashion.

It may be pointed out with reference to Figure 1 that some other arrangements, especially subdivisions of the smectic class, have been described by Demus and Sackman.[2] Furthermore, the evidence for some of the models proposed is not conclusive. Recently two additional subdivisions of the nematic type have also been suggested in which molecules are in cybotactic groups, such that centers of molecules in each group are in a plane making an angle far removed from 90° in one case and close to 90° in another.[3]

The true liquid crystalline state which may occur normally in relatively small elongated molecules and of which a large number of examples are known, also occurs in case of some polypeptides;[4–8] in viruses; in sickel cell hemoglobin[9–10] and in *t*-RNA.[13]

The mesomorphic arrangements interposed between the crystalline and liquid state may be regarded as follows:

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

	Translations	*Rotations*
Crystals	Apart from vibrations, these do not occur.	Full rotations do not occur.
"Rotatorphase" solids (e.g., camphor, butylhalide)	Apart from vibrations, these do not occur	Rotations may occur.
Smectic structures	Center of gravity of molecular units can translate in one plane	Full rotation possible around one axis.
Nematic structures	Center of gravity of molecular units can translate in two planes	Full rotation possible around one axis.
Liquids	Center of gravity of molecular units can translate in three planes	Full rotations possible along three axis.

Amphiphiles like soap or phospholipids when placed in water and a combination of cholesterol, bile salt and lecithin in water, constitute the most frequent examples of lyotropic systems. These have been extensively studied from a structural point of view, using X-ray diffraction. The units of structures may be amphiphiles aggregated in the shape of plates, balls or tubes, in the latter case with polar groups all within or all without. These may be arranged in lamellar fashion or with hexagonal, cubic (body or face centered) symmetry. These units and their arrangements are shown in the following figures (Figures 2 and 3).

Polypeptides regarded as overall rods, when suspended in certain solvents also show lameller, hexagonal, close packed hexagonal forms as well as tetragonal and cholesteric arrangements.

A general classification of lyotropic liquid crystalline phases, an extended and modified version of that presented by Ekwall *et al*[20] and Brown *et al*,[21] is shown in the following table (Table I).

LIQUID CRYSTALLINITY IN BIOLOGICAL SYSTEMS

Table II lists various structures and living systems for which the term has been used. Unfortunately many of the systems were ill characterised, for example, the sperm. Also, the name was often used when the system merely

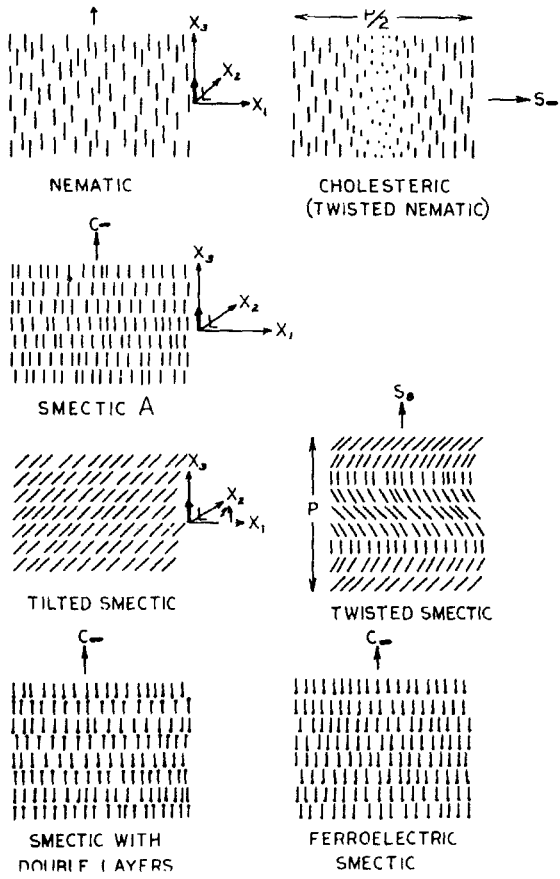

FIGURE 1 Structure of liquid crystalline phases, A. Saupe.[1] Reproduced by permission of Gordon and Breach, New York.

showed optical birefringence. Table II also lists efforts to assess significance of liquid crystallinity. However, suggestion that the state is essential for living processes has been made only occasionally (Bernal,[144] 1933; Mishra,[68] 1965).

As already stated the lyotropic mesophase as contrasted with the thermotropic is more liable to be involved in the living systems and it is important to recognise the units associated in the living systems. The above classification refers to the arrangements of associations of molecules of amphiphiles or polypeptides in a medium. This may also apply to the cholesterol-bile salt-lecithin-water system,[32] or to the state of certain cholesterol esters, for example, the cholesterol-oleate, -linoleate and -linolenate system in which the

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

solubility is modulated by lipoproteins. A cholesteric arrangement might also be present in case of *t*-RNA[11] or in gels of DNA[5]. In the liquid crystalline state TMV and other viruses are packed hexagonally. A modified tubular arrangement of globular units of HbS is proposed in a model of sickle cell

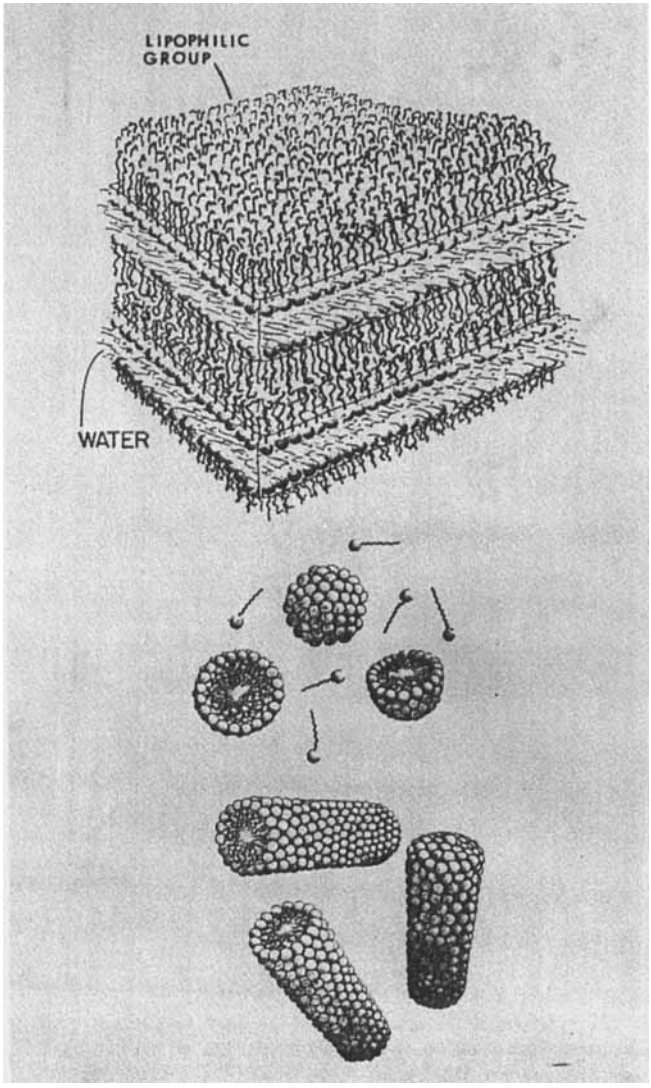

FIGURE 2 (Top) Schematic representation of the lamellar structure. (Bottom) Schematic representation of rod-like and spherical particles, Rosevear.[12] Reproduced by permission of the *Journal of the Society of Cosmetic Chemists.*

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

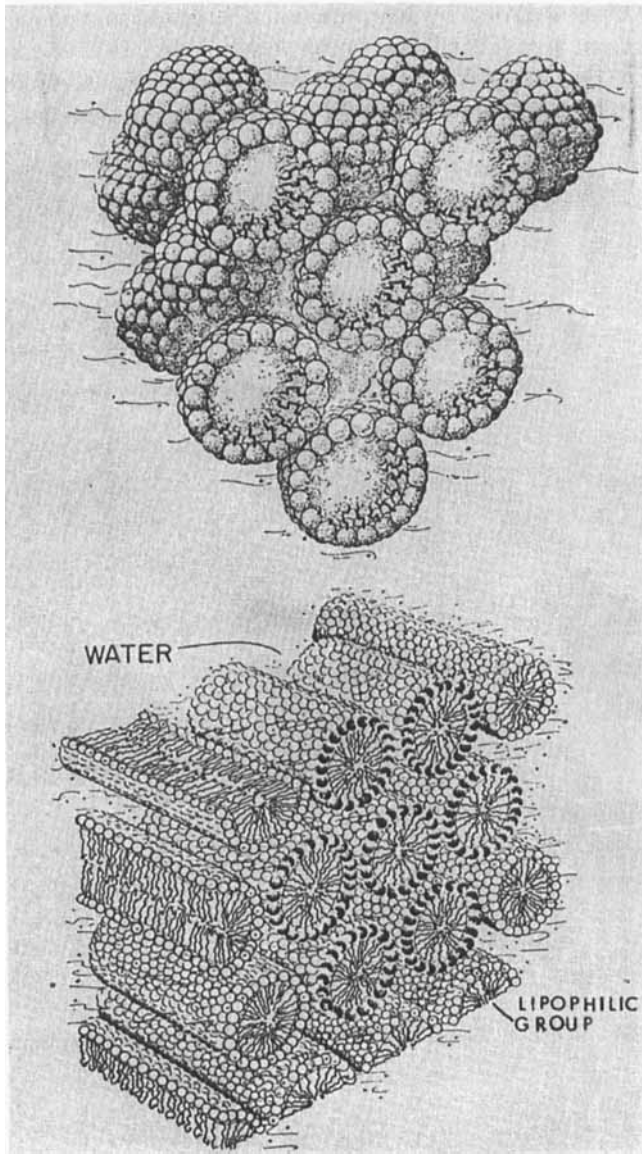

FIGURE 3 (Top) Schematic representation of the packing pattern of an isotropic phase. (Bottom) Schematic representation of the packing pattern of rod-like particles, Rosevear.[12] Reproduced by permission of the *Journal of the Society of Cosmetic Chemists*.

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

TABLE I

Different types of lyotropic liquid crystalline phases

Class	Description	Common Notation in Literature
	Structural arrangement displaying Bragg spacing ratio $1:\frac{1}{2}:\frac{1}{3}$ with one-dimensional symmetry (one-dimensional periodicity)	
L_{-1}	Lamellar packing with coherent double layers of molecules and ions separated by water. Neat phase type. In case of polypeptides extended β structures, hydrogen bonded to each other are held in stratified arrangement with solvent around.	Neat phase
L_{-2}	Lamellar packing with coherent single layers of molecules and ions separated by water. Single-layered lamellar type.	
L_{-3}	Lamellar packing with coherent double layers of molecules and ions separated by water. Mucous woven type.	
	Lyotropic liquid crystals with particle structure displaying Bragg spacing ratio $1:\frac{1}{2}:\frac{1}{3}:\frac{1}{4}$	
P_1	Rod-like particles with organic core surrounded by water. Rods with predominantly quadratic cross-section in tetragonal arrangement. Normal two-dimensional tetragonal type. In case of polypeptides similar form is called the ω-form. The helices constitute "solid" rodlets and those that have been observed are 4_{13} helices packed in a square lattice.	White phase
P_2	Rod-like particles with water core in organic environment. Rods with rectangular cross-section in an orthorhombic array. Normal two-dimensional rectangular type.	Rectangular phase
	Lyotropic liquid crystals displaying Bragg spacing ratio $1:\frac{1}{3}:\frac{1}{4}:\frac{1}{7}$ particle structure with molecules arranged in two-dimensional hexagonal symmetry.	
P_{H-1}	Rod-like particles with organic core in aqueous environment. Cylindrical to hexagonal cross-section in hexagonal array. Middle phase type; normal two-dimensional hexagonal type.	(1) Middle phase (2) Hexagonal phase–I
P_{H-2}	Rod-like particles with aqueous core in organic environment. Cylindrical to hexagonal cross-section in hexagonal array. Reversed two-dimensional type.	Hexagonal phase–II
P_{H-3}	Rod-like particles with complex structure in acqueous environment. Complex two-dimensional hexagonal type. (In case of polypeptides the complex phase is formed by more than one, for example, three rodlets, in place of each one. Solvent is reduced to a constant low amount.	Complex hexagonal phase
	Lyotropic liquid crystals displaying cubic symmetry. Isotropic lyotropic liquid crystals with spherical to dodecahedral particles arranged in face-centered cubic lattice.	
C_{f-1}	Particles with organic core in aqueous environment. Normal face-centered cubic type.	Cubic phase, C_{1-1}

table continues

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

TABLE I—*continued*

Class	Description	Common Notation in Literature
C_{f-2}	Particles with water core in organic environment. Reversed face-centered cubic type.	Cubic phase, C_{1-2}
C_{f-3}	Particles with complex structure. Complex face-centered cubic type.	
	Isotropic lyotropic liquid crystals with spherical particles packed in body-centered cubic lattice.	
C_{b-1}	Particles with organic core in aqueous environment. Normal body-centered cubic type	
C_{b-2}	Particles with complex structure. Complex body-centered cubic type.	
	Cholesteric lyotropic liquid crystals. X-ray diffractogram shows only one fairly diffuse reflection in the small angle region, the sharpness of which increases and the spacing decreases as concentration is raised.	
CH	Planar sheet of parallel rods, arranged hexagonally in the sheet, each sheet deriving from the next by a translation perpendicular to the plane and a very small systematic rotation in the plane.	

TABLE II

Molecules and structures from living systems claimed to exhibit liquid crystalline characteristics.

Lipids

Lecithin 22–26
Sphingomyelin 23, 27
Cephalin 23, 28
Phrenosin 29, 23
Kerasin 29, 23
Nervone 30
Cerebron 30
Various phospholipids and monoglycerides 25
Cholesterol esters: oleate, benzoate, propionate, stearate, palmitate, butyrate. Ammonium stearate and palmitate.
Lipids from erythrocytes 31
Lipids from beefheart mitochondria 26
Lipid-water model systems 16
Lecithin, cholesterol, bile salt, water as ternary system 31

Proteins and Polypeptides

"Muscle globulin," myosin 33–35
Histones 17, 36, 37
Sickle-cell hemoglobin 7, 10, 38
Hemoglobin 39

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

TABLE II—*continued*

Trypsin 40
Poly-γ-benzyl-L-glutamate 4, 5, 41, 13, 42
Poly-γ-methyl-L-glutamate 6
Poly-γ-ethyl-D-glutamate 6
Poly-β-benzyl-L-aspartate 6
Poly-α-L-glutamic acid 41
Poly-α-ecarbobenzoxy-L-lysine 41
Poly-α-sodium-L-glutamate 42
Poly-L-Lysine Hydrochloride 41

Proteins and lipids 26

Nucleic acids

DNA 6, 13, 43
t-RNA 11

Viruses

Tobacca mosaic virus 6, 44, 7, 8, 45
Cucumber virus 46

Various mixed systems

Myelin forms 46, 22, 47
Brain extract 24
"Neurokeratogenic colloid" 48
Nerves 30
Nerve myelin 24
Smooth muscle fibers 30
Muscles, tendon, nerves, viscera, bone 33–37
Adrenal extract 49–50
Ovaries 50
Structural aspects of colored beetles
cuticle 51, 52, 5, 53, 54
Living sperms—sepia officianalis 47–48
Red cell interior and red cell membrane 55
Atherosclerotic plaques 50, 56, 57, 58

General comments on liquid crystallinity in living systems and theories related to it

General implications 59, 60, 61, 62, 23, 63, 64, 65, 66, 67, 15
"Solubilising potential" of cholesterol esters, and lecithin as "common carrier" in red blood cells 59
Vision 19
"Mind"-brain interrelationship 68
Activity and growth of merismatic cells 69
Theory of anisotropy of tobacco mosaic virus suspensions 70, 71, 72
Relation of lipids to membrane function 16

hemoglobin. Ponder,[72] Rebuck[74] and Harris[9] had previously suggested a pararystalline state.

These observations thus extend the domain of liquid crystalline arrangements from small flat molecules to large molecules considered as rods, for example the helically coiled polypeptides and to globules like individual HbS molecules or to intermediate structures like *t*-RNA.

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

Theories for the Liquid Crystalline State

At this point one may consider the definition of the term "liquid crystalline' or "mesomorphic" and the forces that may induce it. This is not merely ar excercise in semasiology but is rather necessary to define the full scope of the field. A matter which deserves considerable attention is the question whether or not macromolecular structure comprised of repetitive units and internal symmetry is governed by the same principles and therefore, subject to anticipations resulting from liquid crystalline state. In other words, one would like to ask, if the secondary, tertiary and quaternary structures of macromolecules, in Linderstrom-Lang terminology, constitute a microscopic mesomorphism.

So far as the entire liquid crystalline state is concerned there is no generally accepted unified theory. Most work in the thermotropics series was done on the nematic state. A hypothesis to which contributions were made by three different groups of workers, Oseen,[74] Frank,[75] and Zocher,[76,77] the "distortion hypothesis," stated that the state was a continuum comprised of molecules aligned in parallel and a distorting force was met with by a restituting one. Recent treatments of the continuum idea are by Ericksen,[76] Leslie,[77] Coleman,[78] Wang,[79] and Peter and Peters.[80] Vorlander[81] and Bose[82] had earlier worked on the assumption that the molecules have a tendency to set in parallel. Ornstein and Zernike[83] argued that this does not imply that this structure stretches uniformly over the whole microscopic preparation and propounded the "swarm theory." In addition to these two theories recently a statistical theory has been proposed for the orientational melting. These are based on interaction between molecules possessing quadrupole–quadrupole type symmetry, and takes into account the orientational order parameter of Maier and Saupe.[84,85] These approaches were applicable to nematic state. Kobayashi,[86] extended the Maier and Saupe theory to take into account the translational and positional order parameter in order to help understand smectic phases. Continuum ideas have been proposed recently for cholesteric phase.[76,77,87] A review of most of the work in the area has been made recently.[88]

These theories need not be discussed in detail at this point, suffice to say that they do not provide a general approach to the various types of liquid crystalline phases and more specially to the transition within them. For example, cholesteryl pelargonate has a crystalline to smectic transition point at 78°C followed by smectic to cholesteric at 79°C and subsequently to liquid at 90.5°C. In case of ethyl-anisal-p-aminocinnamate two smectic transitions intervene between crystalline and nematic phase. Indeed recently compounds having eight transitions have been reported.[89] Similarly, a thermotropic compound may also exhibit lyotropic behaviour and indeed the type of liquid crystalline arrangement may be altered by the addition of

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

another compound. Friedel and Friedel[91] believed that the nematic structure could be transformed into stratified cholesteric structures by the addition of asymmetric molecules. Gaubert[92] showed that mixing cholesterol derivatives with different organic compounds gave different cholesteric states. Thus cholesterol with succinimide and tartaric acid gave optically positive crystals whereas with succinic, cinnamic or anisic acids optically negative crystals were obtained.

In the lyotropic system several attempts have been made to systematise the physical properties and phase equilibria in these systems, notably by Lawrence[93,94] McBain and Marsden,[95] Winsor,[96] Luzzati[97] and Ekwall *et al.*[20] Attempts at building a theory were made by Langmuir[69] and by Onsager.[71,98] Both of them attempted to resolve the problem of thixotropic or rheopectic sols like tobacco mosaic virus and bentonite particles which show coacervation at rather low concentration. This phase is characterised by spontaneous birefringence and may occur at concentration as low as 1 to 2%. Langmuir thought that Coulomb attraction between the micelles and the oppositely charged ions in the solution give an excess of attraction force which is balanced by the dispersive action of thermal agitation and another repulsive force. He ignored consideration of long range forces, as done by Kallman, Willstatter, Freundlich, DeBoer, Hamaker, Houwink and others.[69] Using Debye-Hückel theory he could roughly predict the conditions under which coacervation occurs. Onsager[70,98] argued that the phenomenon can be explained as a result of repulsive forces due to the observation that the mutual co-volume of two swarms of parallel rods (tobacco mosaic virus) or plates (bentonite sols) is roughly proportional to the sine of the angle between the orientation and larger than the volume of the particles by a factor which is proportional to the asymmetry. Onsager considered these sols as example of unipolar coacervates of molecules which were highly asymmetrical and contrary to bipolar or other complex coacervates the main force between them was repulsive. Isihara[71] developed the Onsager theory and showed the relation between critical concentration and various molecular shapes. That the stability of lyophobic colloids is the result of balance between attractive and repulsive forces is generally recognised.[99]

RECENT ANALYSIS OF THE MECHANISM OF LYOTROPIC MESOPHASE

Extensive data now exist for the lyotropic mesophase and the various alteration of associations are summarised in the following Figure 4, by Ekwell *et al.*[20]

Essentially similar documentation has been made by Winsor.[96] In the figure, on the top behaviour of molecules in lipophilic phase is described, at

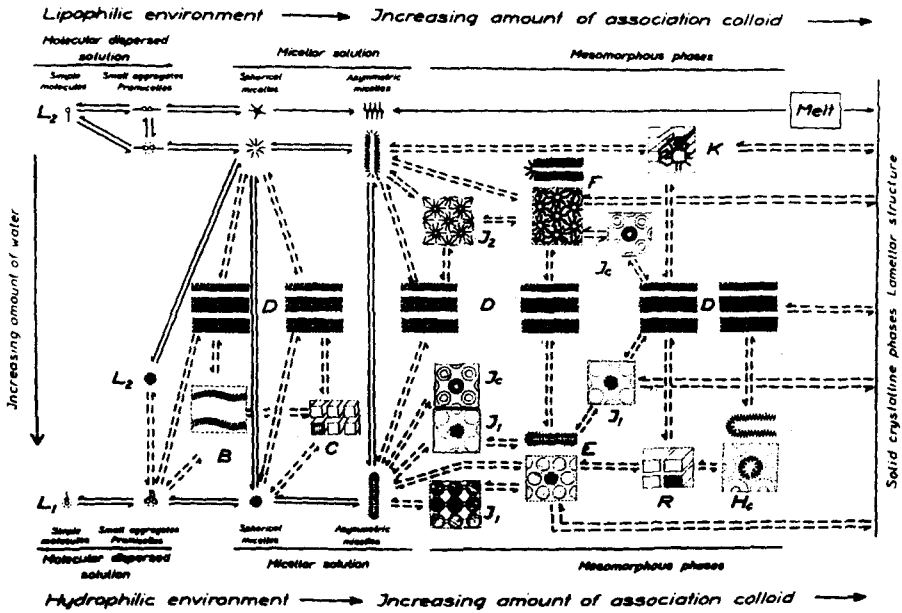

FIGURE 4 Lyotropic phase changes, Ekwall *et al.*[20] Reproduced with kind permission of Gordon and Breach, New York.

the bottom in aqueous medium. From left to right one notices the changes observed when solute concentration is raised. The structure of various associations is diagrammed in the figure. One notices that the horizontal mid-line shows the lamellar structure. Various modifications shown in Table II are possible both in predominantly lipophilic or in aqueous phases. The cholesteric structure of polypeptides is not shown. The lamellar structure in these macromolecules is also somewhat different and is formed by equidistant planar sheets, each containing polypeptide chain hydrogen bonded to each other in β conformation. The separation between the lamellae here depends on the structure of the residues and on the amount of the medium In polypeptide systems, association may show transitions from isotropic to cholesteric to hexagonal to complex hexagonal phase, the last one resulting with a fixed amount of solvent. In some polypeptides the tetragonal ω form with parallel or antiparallel packing of helix rods may be seen.

With the above summary of data it should be quite easy to see in perspective a mechanism of formation and transformations of the lyotropic mesophases, including their cholesteric phase. However, only a trend can be seen and a precise quantitative theory is impossible at the moment because of the absence of the following information:

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

a) precise conformational analysis of molecules and consequent evaluation of interatomic vectors between different molecules;

b) precise evaluation of molecular motion in a given solvent,

c) anisotropic polarisability of bonds and their precise ionisation potentials,

d) properties of solvent in microscopic domains of sizes comparable to the associated molecular species. The relevant properties are: dielectric constants, elasticity, viscosity and thermal motion near the suspended molecules. To these one must add the approximate nature of mathematical treatments available and the enormity of computational task.

At the outset attention may be drawn to the following facts:

1) The structures described are not too numerous, notwithstanding larger number of polar groups and apolar region of the molecules, indicating that variations in these structural parts are relatively less important in affecting the major patterns of association. It may appear that only some associations and relative dimensions are permitted. Indeed similar associations can result no matter whether system is a polymeric amphoplyte like a polypeptide, or a phospholipid. This is interesting in view of the fact that both high protein and high lipid membranes maintain similar electron microscopic structure.

2) In Figure 4 all molecules diagrammed are amphiphiles. In addition the polypeptides too may be regarded as polymeric amphiphiles, a regular arrangement of side-chain and dipole-chain exists not only in a backbone chain of poly α-amino acids but also in side-chain. Wada[100] investigated distribution of dipole characteristics in the polypeptide α helix and it seems that there is a regular distribution of dipole characteristics and affinity for polar and nonpolar environment. The tendency of side to side and head to tail association in these has been demonstrated.[100] The α helix can be considered as rods and may be effectively regarded as a string of dipoles.

3) The structures described vary with the amount of solvent.

4) Luzzati has pointed out some influence of the bulkiness of polar head group on the amphiphile cores. Those that have a large surface to volume ratio are favoured like the hexagonal phase compared to the lamellar ones.

In essence then the problem resolves into the question of arranging molecules which have some regions of greater affinity with themselves and other regions with greater affinity for the medium.

At this point one may state the three rules which seem to govern the association in lyotropic mesophases:

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

1) In the case of apolar molecules or those polar molecules where charge is effectively shielded charge fluctuation interaction dominates, specially in a molecule with large axial ratio. In such a case it can be shown that similar molecules will recognise and attract each other and be adlineated to permit maximum pair-wise dispersion interaction between various atoms. Between two types of molecules. A and B the arrangement AAABBBAAA is energetically preferable over ABABABA. Once these molecules aggregate many body interactions come into play and stabilize the system.

2) In the case of a set of polar molecules or amongst apolar molecules the arrangement would be such as to minimize abrupt changes of force fields.

3) The presence of another molecule, atom or ion in the liquid or other states will interfere with the charge fluctuation and other interactions and alter the interaction energy and induce another variety of association dependent upon rule 2. In the case of the medium properties of solvent and its amount may modulate association[101] and may dominate in this effect over the higher order perturbation of intermolecular interaction of suspended chemical species.

The arguments for the application of the above rules have been presented previously in relation to association in molecules in living systems.[102] It was shown at the same time that a large variety of associations could be generated depending upon constraints of rotation and translation imposed. It can be readily seen that in case of amphiphiles the polar ends would interact with polar solvents like water and tend to occupy a favourable thermodynamic position with respect to the solvent molecules and if the ends bear a similar net charge then they would be surrounded by a hydration shell of the polar solvent. However, large apolar segments will be attracted by London's charge fluctuation interactions. London showed that these were pairwise additive and in spite of some controversy[103] this still seems to be a probably correct view. This interaction between say, hydrocarbon chains in phospholipids can assume sufficient large values, up to 17 kcal/mole in 17 carbon side chains, to permit adlineation in spite of the polar end interactions dictating separation. This adlineation will increase with increasing chain length, and unsaturation leading to molecular geometry favourable for adlineation. Increase in concentration would also favour compaction due to increased probability of encounter and decrease in intermolecular distance. Above all it must be emphasized that in case of elongate and asymmetric molecules the magnitude of intermolecular interaction energy is a function of geometry and relative orientation of molecules. Thus associations of well defined and specific geometry result.

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

Calculations using Lifshitz method[104] indicate that charge fluctuation forces in macroscopic bodies are substantial; a membrane fragment of 1 micron width may attract another at comparable distance. Thus having arrived at an initial association long range order may arise. In the case of cubic clusters even ordering may be a consequence of long range potential function. So far as the clustering of atoms during crystal growth or homogeneous nucleation is concerned, study of interatomic potential functions provides the energy basis of various relationships. For example a 13 atom cubooctahedron, studied by computer under the optimization process, increased both the Lennard-Jones and Morse function energies in going to a distorted fcc structure, in reality a simple icosahedron.[105] As stated already in the molecular case too, the intermolecular conformational energy can be very high[102] and can well be of the same magnitude as intramolecular conformational energy which results for all the pairwise interactions of the nonbonded atom within a single macromolecule[105] and migration to such arrangements under varying distance-dependent potential values is feasible. The lengthwise association of helical polypeptices is known[100] and here too presence and amount of solvent may induce various arrangements by influencing the intermolecular potential functions. In several systems the solvent effect on molecular association has been investigated and good correlation between theory and experiment has been found as in case of *p*-benzoquinone-hydroquinone, stacking of thymines in thymine dimerization, or dimerization of actinomycin.[101]

Keating[87] developed an approximate theory for cholesteric state, which is perhaps more applicable to lyotropic cholesteric phase. According to him there are normal twist modes which are appreciably excited at the temperature at which mesophase exists. Because of anharmonicity in the forces opposing twist the time-average does not vanish and a macroscopic twist persists. The rigid helical polypeptides are asymetric rods and the presence of odd orders of anhormonicity necessary to give a non-zero average is likely. Keating's theory accounts for the cholesteric phase of cholesteryl nonanoate and decanoate.

It is worth noting that in the lyotropic system the liquid crystallinity is induced by changing the mount of solvent and/or nature of solvent. The former fact demands that one must examine number-dependent influences on the intermolecular forces. Kestner and Sinanoglu[106] proposed a theory of effective intermolecular pair potentials in non polar media; a more comprehensive treatment was later proposed.[101] An important feature of the theory is that the three body interaction includes terms that reduce the intermolecular interaction. The total interaction is a sum of several two-body pair terms, along with three body and higher effects. In the current context the ratio of the total third order energy to the second-order energy between the molecules is

given by these workers as

$$\frac{\xi_3}{E_2} = -\frac{\delta c(\delta a + \delta b + \delta c)}{(\delta a + \delta c)(\delta b + \delta c)} \alpha_\omega K_{\text{cont}}$$

in case the solvent is treated as a continuum; and

$$\frac{\xi_3}{E_2} = -\frac{\delta c(\delta a + \delta b + \delta c)}{(\delta a + \delta c)(\delta b + \delta c)} \cdot \frac{\alpha_c}{R_0^3} \cdot K_{\text{lattice}}$$

if the solvent is limited in amount and is situated in a discrete shell around the molecules immersed.

Using a different approach Axilrod[107] got a ratio of -1.96 (α/R_0^3). In these δa, δb, δc refer to mean excitation energies of molecules a, b, c, respectively and $\alpha\omega$, polarisability per unit volume of the solvent. R_0 is the nearest neighbour distance and K_{cont} and K_{lattice} are constants pertaining to continuum or lattice models of solvents.

Sinanoglu's method gives the value of the constant in the Axilrod ratio as -1.94. Fourth and fifth order effects were calculated by Bade using Drude formula as

$$\frac{E_4}{E_3} \text{ is } -4.2\frac{\alpha}{R_0^3}$$

$$\frac{E_5}{E_6} \text{ is } -0.9\frac{\alpha}{R_0^3}$$

Kestner and Sinanoglu estimate that dispersion forces may be reduced within a DNA base pair on the average by 28%. If ΔS for the entropy of helix formation in water, is taken as approximately -23 eu per mole of base pair,[108] the dispersion force will reduce the "melting temperature," Tm, of poly-GC by kcal/ΔS or 30°K. On such grounds authors examine the stacking of base pairs and photodimerization (see 101). The exact magnitude of the effect will be subject to much refinement, taking into account the anisotropy and inhomogeniety, and size and shape of the molecules, however, the relative importance of these with reference to the additive attractive forces is such as to permit one to consider that molecular separation introduced by the medium will cause progressive reduction in the affinity of molecules to associate and lead to progressive variation in the intermolecular vectors and systematic change in geometry. A proper theory must await developing a reliable method for proper distribution function of amphiphile molecules in a medium, refined data on polarisability, solvent-corrected intramolecular conformation,[105] inclusion of molecular motion, vibration and stretching, calculation of second, third, fourth and fifth order interactions by one method, and a three dimensional map of intermolecular energy distribution. Effects of

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

the variation of pH, ionicity, temperature which need to be investigated are under study.[108–115]

Thus a variety of associations are possible by changing the geometry and magnitude of intermolecular interaction energy by the use of medium. It should be recognized that the medium may be any dissimilar molecule and need not be in any particular state like the liquid, gaseous, or solid state in order to be effective. Since the basis is electron correlation in the entire assembly incoming electromagnetic field, and momentum and mass transfer will also bring about the changes in association.

EXTENSION OF THE CONCEPT OF LYOTROPIC MESOMORPHISM TO MACROMOLECULAR CONFORMATIONS

Given these operating rules one is tempted to consider if Linderstrom-Lang's secondary, tertiary and quaternary structures are also not examples of lyotropic liquid crystallinity in microscopic domains. All these are influenced by the type and the nature of solvent or presence of specific molecules. Influence of angles on the helix parameter is well known and evidence of anisotropy is provided by various studies, for example, by optical rotatory dispersion, and the structures once formed are stable enough not to be nonexistant.

Having given the specified atoms and the spin-paired bonds, and special situation like the position of disulfide bonds[116] or the imino acid like proline or other amino acid types like aspartic and glutamic acid and histidine conformation is determined by non-bonded repulsions, dipole–dipole interactions and hydrophobic forces[117] and variety of interaction with the solvent, including both the nature of species involved in it and its bulk properties. Attempts have been made to calculate different parts of this interactions by a variety of methods[116–122] all assuming some constraints provided by nature of covalent bonds involved. The balance of attractive and repulsive forces then determine the conformation. In essence, then one may conclude that the mechanisms of conformational moulding have substantial similarity to those responsible for the association of individual molecules, or macromolecules or even larger particles.

By itself this may appear to be a trivial conclusion to arrive at. However, it introduces concepts which are not hitherto particularly developed in living systems and which provide a physical basis to several phenomena. Also, at the same time, it suggests new methods to investigate them.

THE CONCEPTS STRESSED BY THE ABOVE CONCLUSION

1) The structurisation of living systems composed of specific molecules and functional groups manifests also properties of a continuum wherein a

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

substantial amount of electron correlation exists. These volumes may be bounded by other structures like for instance a cell membrane, presenting functional discontinuity due to widely differing macroscopic properties.

2) Associations or conformations deduced from study of molecules in solid state, or computed under certain conditions, reflect, within the uncertainty of the methods used, only an instantaneous picture of the structure concerned. The actual state would be a mixture of a variety of conformations undergoing fluctuations due to fields of molecules and ions and transfer of momentum in the system. These fluctuations may define a variety of potential surfaces and may in themselves define specific situations.

3) Co-operative effects and energy transfer in general should exist because of the nature of the continuum. Co-operative effects are attributed to a conformation at one site affecting another by a direct structure transfer of constraints through the molecules. The continuum concept provides for direct effect. It should be emphasized these considerations do not exclude specific interactions and modifications of molecular species by the formation of covalent bonds and their individual specific consequences, even in the matter of control of events, but rather these suggest the dynamic aspects of the variation in the environment and these may be critically important in some situations.

CONSEQUENCES OF THE CONCEPT

We shall now examine the relevance of these concepts to several biologic phenomena.

Allosteric effects

The jigsaw puzzle model explaining the substrate specificity of enzymes has been questioned on kinetic grounds and Koshland[123] suggests the active site of an enzyme is flexible and the substrate induces a conformation change in the active site, leading to appropriate alignment of reacting groups. Monod *et al*[124] proposed a theory of allosteric effects, indirect interactions between distinct specific binding sites. They visualized allosteric proteins as oligomers of some protomers, which possess two states with different affinities to a ligand. The conformation of each protomer is constrained by its association with other protomers. When the protein goes from one state to another its molecular symmetry, including the symmetry of conformation constraints upon each protomer is preserved. On this basis Monod *et al* explained the data on allosteric effects. Atkinson *et al*[125] however postulated a progressive change in the ligand site interactions in the system. Koshland *et al*[126] have recently shown that no unique mechanisms can be considered and variety of models can fit the data. Perhaps it is better to recognise that the Michaelis-Menton equation relating as it does

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

velocity of enzyme reaction to the amounts of enzyme substrate complex at the time subsumes an interaction amongst the number of various enzyme substrate complex units. The equation of Monod *et al*[124] reduces to Michaelis-Henri, if affinity of both states of the enzyme units toward the ligand in the same and the allosteric constant is very small i.e., the equilibrium is strongly toward one conformation of enzyme. Perhaps cooperative effects due to coupling between units, effecting apparent activity is an essential feature in all enzyme action. There is however in the presence of medium with gegenious and general smoothing of charge distribution, no powerful physical basis to account for these phenomena. Electron correlation and London forces provide a plausible basis.

As required by the theory of reactions in solid state the topotaxy and asymmetry of biochemical events again suggest that the reactions do not take place by random encounter but that the sequence is polarised in space.

Conformational changes by association

In this regard it is interesting to note that macromolecular structure may be altered, as optically determined by compaction of units and as shown by Lerman.[145] This again emphasizes the coupling of various macromolecular units. Essential involvement of reversible conformational change in physiological processes is being increasingly recognized. This, in addition to hemoglobin[124,127] and allosteric enzymes, coenzymes may also manifest essential change during activity as found by Adam *et al*,[128] and Sarma and Kaplan[129] in case of NAD, and β-lactoglobulin and bovine plasma albumin under the influence of anaesthetics[130] Antigen-antibody union has been often cited as an example of such a change. Luzzati *et al*[19] have suggested that the photo-induced isomerisation of retinine (Wald), could lead to a phase transition and thereby to transduction to an electric signal. Recently visual pigments having two stable states, which contribute antagonistically to the receptor potential have been demonstrated.[130] Density variation in the membrane as a result of drugs[131] and changes in birefringence during activity[132,133] or electric oscillation in lipid bilayers[134] indicate conformational variation. In the haem–haem interaction transition to the quaternary deoxy structure changes ferrous subunits to a constrained state of high spin.[135] Associated increase of bond length and consequent low oxygen affinity can be best explained if the system has strong electron correlation. Indeed oscillatory phenomena in general as in case of spontaneous rhythmicity of a cardiac pacemaker may indicate rhythmic conformational variation. Such oscillations have also been suggested in mitochondrial electron transport. This subject has been reviewed by Green and Harris.[135] Antibiotic mediated transport as of potassium by valinomycin may be due to rhythmic alteration in conformation.[136]

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

Need of a physical state with associated molecules

Evidence that the physical state of phospholipids governs the action of phospholipases has been reviewed by Dawson.[137] It is also known that deposits of cholesteryl oleate or other cholesterol esters in liquid crystalline state in atherometous plaques[57] or gallstones depend upon association of various molecules.

Photovoltaic effect and photoconduction in biomolecular lipid layers as shown by Tien also indicate an associated and coupled system,[138] as do charge mosaic membranes,[139] as well as piezoelectric properties of dry and wet bone (Bassett and Bach[140]).

Rhythmic variation of conformation

Rhythmic increase in crystallinity or crystallization is well recognised in physical systems.[141] Shnol[142] reported synchronous fluctuations in the enzyme activity of actin, myosin and actomyosin. Rhythmic contraction in flagella, cilia, mitochondial membranes, smooth muscle all indicate rhythmic and spontaneous variation in conformation, if the contraction is related to the activity of contractile proteins.

Role of fluctuations

Conformational or associational fluctuation may be responsible for large distance energy transfer in, as well as generators of forms, since superposition of various fluctuations may cause newer association and generate macroscopic form. This may also be a basic mechanism of control of cellular process. Based on network thermodynamics it can be shown, by implication, after the work of Oster *et al*[143] that absence of reciprocal elements in a biochemical reaction may lead to oscillation and amplification, which may otherwise need negative resistance or parametric amplification.

It may indeed be noted that liquid crystalline matter which does not readily fluctuate in its phases in the living body may well belong to pathology, for example, gallstones or deposit in atherosclerotic plaques in the blood vessels.

These concepts suggest the need to investigate not merely the molecular structures but whole ranges of associational units and superposition of various conformations of such units. A proper solvent-corrected conformational analysis followed by study of association and its modulation by other molecules or fields is much in order.

In summary, the above discussion shows that the forces that give rise to lyotropic liquid crystallinity are operative in biological system involving amphiphiles. These forces also cause similar phenomena in polypeptides or

large units like viruses and possibly other structures. The conformation of macromolecules can be considered to be related to these problems. These considerations introduce the concept of continuum in the sense of extensive electron correlation which can form the fundamental basis for cooperative phenomena, allosteric effects, fluctuation of conformation and associations, control and communication and energy transfer in living systems, preserving at the same time sufficient structural stability. Some aspects of specificity are generated.

The existence of large data and the association of biologic molecules and their conformation will in the reverse throw considerable light on the lyotropic liquid crystallinity in general.

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

References

1. A. Saupe, *Liquid Crystal*, **2**, Part I, G. H. Brown (ed.). Gordon and Breach, N.Y., p. 59 (1969).
2. D. Demus and H. Sackmann, *Ztschr. Naturfosch.*, **23**, 76 (1968).
3. A. DeVries, *Mol. Cryst. Liq. Cryst.*, **10**, 31 (1970).
4. A. Elliott and E. J. Ambrose, *Disc. Faraday Soc.*, **9**, 246 (1950).
5. C. Robinson, *Tetradhedron*, **13**, 219 (1961).
6. F. C. Bowden and N. W. Pirie, *Proc. Roy. Soc., London*, **123**, 274 (1931).
7. J. D. Bernal and I. Fankuchen, *Nature*, **139**, 923 (1937).
8. J. D. Bernal and I. Fankuchen, *J. General Physiology*, **23**, 111 (1941).
9. J. W. Harris, *Proc. Soc. Exper. Biol.*, **75**, 197 (1950).
10. M. Murayama, *J. Cell Physiol.*, **67**, 21 (1966).
11. M. Spencer, W. Fuller, M. H. F. Wilkins, and G. L. Brown, *Nature*, **194**, 1014 (1962).
12. F. B. Rosevear, *J. Soc. Cosmetic. Chem.*, **19**, 581 (1968).
13. V. Luzzati, M. Cesari, G. Spach, F. Masson, and J. M. Vincent, *J. Mol. Biol.*, **3**, 566 (1961).
14. V. Luzzatti, T. Gulik-Krzywicki, E. Rivas, F. Reis-Husson, and R. P. Rand, *J. Gen. Physiol.*, **51**, 375 (1968).
15. V. Luzzati, T. Gulik-Krzywicki, A. Tardieu, E. Rivas, and F. Reis-Husson, in *Molecular Basis of Membrane Function*, Tosteson (ed.). Prentice-Hall, Englewood Cliffs, 79 (1969).
16. V. Luzzati, T. Gulik-Krzywicki, and A. Tardieu, *Nature*, **48**, 1031 (1968).
17. V. Luzzati and A. Nicolaieff, *Mol. Biol.*, **1**, 127 (1959).
18. V. Luzzati, A. Nicolaieff, and F. Masson, *J. Mol. Biol.*, **3**, 185 (1961).
19. V. Luzzati, F. Reis-Husson, E. Rivas, and T. Gulik-Krzywicki, 137, *Ann. N.Y. Acad. Sci.*, **409** (1966).
20. P. Ekwall, Mandell, and K. Fontell, *Liquid Crystals*, **2**, G. H. Brown (ed.). Gordon and Breach, New York, 325 (1969).
21. G. H. Brown and R. K. Mishra, *Agricultural and Food Chemistry*, **19**, 645 (1971).
22. O. Lehmann, *Ber. Beut. Physik, Ges.*, **6**, 321 (1908).
23. F. Rinne, *Trans. Faraday Soc.*, **29**, 1016 (1933).
24. F. O. Schmitt, R. S. Bear, and K. J. Palmer, *J. Cell and Comp. Physiol.*, **18**, 31 (1941).
25. A. Steiger, *Mikrokosmos*, **35**, 54 (1941).
26. T. Gulik-Krzywicki, E. Rivas, and V. Luzzati, *J. Mol. Biol.*, **27**, 303 (1967).
27. F. Reis-Husson, *J. Mol. Biol.*, **25**, 363 (1967).
28. D. G. Dervichian, *Trans. Faraday Soc.*, **423**, 180 (1946).
29. O. Rosenheim, *Biochem. J.*, **8**, 110 (1914).
30. R. P. Rand and V. Luzzati, *Biophys. J.*, **8**, 125 (1968).
31. D. M. Small, M. Bourges, and D. G. Dervichian, *Nature*, **211**, 816 (1966).
32. D. M. Small and M. Bourges, *Mol. Cryst.*, **1**, 541 (1966).

33. A. L. Muralt and J. T. von Edsall, *J. Biol. Chem.*, **89**, 315 (1920).
34. A. L. Muralt and J. T. von Edsall, *J. Biol. Chem.*, **89**, 350 (1930).
35. A. L. Muralt and J. T. von Edsall, *Trans. Faraday Soc.*, **26**, 837 (1930).
36. R. K. Mishra, G. H. Brown, and W. H. Falor, *Proc. Canad. Fed. Soc. Expr. Biol. Abstr.*, 254 (1970).
37. R. K. Mishra, A. DeVries, G. H. Brown, and W. H. Falor, *Mol. Cryst. Liq. Cryst.*, **20**, 191 (1973).
38. M. Murayama, *Clinical Chemistry*, **13** (1967).
39. M. F. Perutz, A. M. Liquori, and S. Eirich, *Nature*, **167**, 929 (1951).
40. C. M. Fronchi and De E. Robertis, *Proc. Soc. Exp. Biol.*, **76**, 515 (1951).
41. P. Saludjian and V. Luzzati, *Poly-amino acids*, G. D. Fasman (ed.), Marcel Dekker, Inc., N.Y., 157 (1967).
42. J. M. Squire and A. Elliott, *J. Mol. Biol.*, **65**, 291 (1972).
43. C. F. Jordan, L. S. Lerman, and J. H. Venable Jr., *Nature New Biology*, **236**, 67 (1972).
44. R. Virchow, *Virchow's Arch. Pathol. Anat. u. Physiol.*, **6**, 562 (1854).
45. M. A. Lauffer and W. M. Stanley, *J. Biol. Chem.*, **123**, 507 (1938).
46. F. C. Bowden and N. W. Pirie, *Nature*, **139**, 546 (1937).
47. W. J. Schmidt, *Naturwiss*, **16**, 900 (1928).
48. F. Rinne, *Nature*, **126**, 279 (1930).
49. F. W. Dempsy, *Rec. Proc. Horm. Res.*, **3**, 127 (1948) and V. Diamare, *Rend. Accad. Sci. (Napoli)*, **33**, 132 (1927).
50. G. T. Stewart, *Nature*, **183**, 873 (1959).
51. A. A. Michelson, *Phil. Mag.*, **21**, 554 (1911).
52. P. Gaubert, *Compte Rend.*, **179**, 1148 (1924).
53. A. C. Neville and S. Caveney, *Biol. Rev.*, **44**, 531 (1969).
54. A. Pace, Jr., *Science*, **176**, 678 (1972).
55. L. Dintenfass, *Liquid Crystals*, **2**, G. H. Brown (ed.), 403, Gordon and Breach, N.Y. (1969).
56. G. T. Stewart, *J. Path. Bart.*, **81**, 385 (1961).
57. R. K. Mishra, G. H. Brown, and W. H. Falor, *Proc. Canad. Fed. Soc. Expr. Biol. Abstr.*, 253 (1970).
58. P. D. Land and Wm. Insull, Jr., *J. Clin. Invest*, **49**, 1479 (1970).
59. J. G. Adami and L. Aschoff, *Proc. Roy. Soc. London*, **B78**, 359 (1906).
60. O. Lehmann, *Flussige Kristalle und die Theorien des Lebens*, Engelmann, Leipzig (1906).
61. H. Zocher and V. Birstein, *Z. Physik. Chem.*, **A142**, 177 (1929).
62. J. D. Bernal, *Disc. Faraday Soc.*, **25**, 7 (1958).
63. G. Wald, *Sci. American*, **191**, 45 (1954).
64. G. H. Brown and W. G. Shaw, *Chemical Rev.*, **57**, 1049 (1957).
65. J. Fergason and G. H. Brown, *J. Amer. Oil Chemists Soc.*, **45**, 120 (1966).
66. G. T. Stewart, *Molecular Crystals*, **1**, 563 (1966).
67. G. T. Stewart, *Liquid Crystals*, **2**, I, 75, G. H. Brown (ed.), Gordon and Breach, N.Y., 75 (1969).
68. R. K. Mishra, *I. J. Psychiatry*, **7**, 190 (1965).
69. W. H. Chambers, *Proc. Sci. Exper. Biol. Med.*, **23**, 134 (1925).
70. I. Langmuir, *J. Chem. Phys.*, **6**, 873 (1938).
71. L. Onsager, *Phys. Rev.*, **62**, 558 (1942).
72. A. Isihara, *J. Chem. Phys.*, **19**, 1142 (1951).
73. E. Ponder, *Hemolysis and Related Phenomena*, Grune and Stratton, N.Y., 145 (1946).
74. J. W. Rebuck, R. M. Sturrock, and E. A. Monaghan, *Fed. Proc.*, **9**, 340 (1950).
75. C. W. Oseen, *Trans. Faraday Soc.*, **29**, 883 (1933).
76. F. C. Frank, *Faraday Soc. Disc.*, **25**, 19 (1958).
77. J. L. Ericksen, *Liquid Crystal*, G. H. Brown (ed.), Gordon and Breach, N.Y., 473 (1969) and H. Zocher, *Physik Z.*, **28**, 790 (1927).
78. F. M. Leslie, *Arch. Rat'l Mech. Anal.*, **28**, 265 (1968) and H. Zocher, *Trans. Faraday Soc.*, **29**, 945 (1933).
79. B. D. Coleman, *Arch. Ratl. Mech. Anal.*, **20**, 41 (1965).
80. C. C. Wang, *Arch. Ratl. Mech. Anal.*, **20**, 1 (1965).

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

81. S. Peter and H. Peters, *Z. Phys. Chem.*, **3**, 103 (1955).
82. D. Vorlander, *Ber. Deut. Chem. Ges.*, **40**, 1970 (1907).
83. E. Bose, *Physik Z.*, **32**, 230 (1909).
84. L. S. Ornstein and F. Zernike, *Physik Z.*, **19**, 134 (1918).
85. W. Maier and A. Saupe, *Z. Naturforsch*, **13a**, 564 (1958).
86. W. Maier and A. Saupe, *Z. Naturforsch*, **15a**, 287 (1960).
87. K. Kobayashi, *Mol. Cryst. Liq. Cryst.*, **13**, 137 (1971).
88. P. N. Keating, *Liquid Crystals*, **2**, G. H. Brown (ed.), Gordon and Breach, N.Y., 279 (1969).
89. G. H. Brown, J. W. Doane, and V. D. Neff, *Critical Revs. in Solid State Sciences*, **1**, 303, Chemical Rubber Publ. (1972).
90. S. L. Arora, T. R. Taylor, J. L. Fergason, and A. Saupe, *J.A.C.S.*, **91**, 3671 (1969).
91. G. Friedel, and E. Friedel, *Z. Krist.*, **79**, 1 (1931).
92. P. Gaubert, *Compte rend.*, **156**, 149 (1913).
93. A. S. C. Lawrence, *Trans. Faraday Soc.*, **29**, 1008 (1933).
94. A. S. C. Lawrence, *Liquid Crystals*, **2**, Part 1, 1–57 (1969).
95. J. W. McBain and S. S. Marsden, Jr., *Acta. Cryst. L.*, 270 (1948).
96. P. A. Winsor, *Chem. Rev.*, **68**, 1 (1968).
97. V. Luzzati, H. Mustacchi, A. Skoulios, and F. Reiss Husson, *Acta. Cryst.*, **13**, 660 (1960).
98. L. Onsager, *Ann N.Y., Acad. Sci.*, **51**, 627 (1949).
99. E. J. W. Verwey and J. Th. G. Overbeek, *Theory of the Stability of the Lyophobic Collaids*, Elsevier Publ. Co. Inc., N.Y. (1948).
100. A. Wada, *J. Polymer Sc.*, **45**, 145 (1960).
101. O. Sinanoglu, in *Molecular, Associations in Biology*, B. A. Pullman (ed.), Academic Press, N.Y., 427 (1966).
102. R. K. Mishra, *Liquid Crystals*, G. H. Brown (ed.), Gordon and Breach, N.Y., Part II, 443 (1969).
103. R. J. Zwanzig, *Chem. Phys.*, **39**, 2251 (1963).
104. YeM. Lifshitz, *J. Exper. Theor. Phys.*, **29**, 94 (1955).
105. A. J. Hopfinger, *Biopolymers*, **10**, 1299 (1971).
106. N. R. Kestner and O. Sinanoglu, *J. Chem. Phys.*, **38**, 1730 (1963).
107. B. M. Axilrod, *J. Chem. Phys.*, **19**, 719 (1951).
108. H. DeVoe and I. Tinoco, *J. Mol. Biol.*, **4**, 500 (1962).
109. R. Hosemann, *Kreutz Naturuiss*, **53**, 298 (1966).
110. N. Norman in *Selected Topical Structural Chemistry*, Oslo, 195 (1967).
111. R. Gordon, R. Bender, and G. T. Herman, *J. Therm. Biol.*, **29**, 471 (1970).
112. G. N. Ramachandron and A. V. Laxmnnarayanan, *Proc. N.A.Sc.*, USA 68, 2236 (1971).
113. R. Hoffman, *J. Chem. Phys.*, **39**, 1397 (1963).
114. J. A. Pople and G. A. Segal, *J. Chem. Phys.*, **44**, 3298 (1966).
115. P. Claverie and R. Rein, *Int. J. Quant. Chem.*, 2837 (1968).
116. A. Guzzo, *Biophys. J.*, **5**, 809 (1965).
117. W. Kauzmann, *Adv. Protein Chem.*, **14**, 1 (1959).
118. D. A. Brant and P. J. Flory, *J. Amer. Chem. Soc.*, **87**, 2791 (1965).
119. P. E. DeSantis, A. M. Giglig, and A. R. Liquori, *Ramonth Nuova Cimento*, **26**, 616 (1962).
120. R. A. Scott and H. A. Scheraga, *J. Chem. Phys.*, **44**, 3054 (1966).
121. A. Kitagoradski, *Tetrahedron*, **14**, 230 (1961).
122. A. Kitagoradski, *Acta. Cryst.*, **18**, 585 (1965).
123. D. E. Koshland, *Science*, **142**, 1533 (1963).
124. J. Monod and F. Jacob, *Cold. Spr. Harb. Symp. Quant. Biol.*, **26**, 389 (1961).
125. D. E. Atkinson, J. A. Hathaway, and E. C. Smith, *J. Biol. Chem.*, **240**, 2682 (1965).
126. D. Koshland, in *The Enzymes Vol. I*, Chap. 7, Acad. Press (1959), *Proc. Natl. Acad. Sc., USA*, **44**, 18 (1958), *J. Theoretical Biol.*, **2**, 75 (1962).
127. A. RossiFanelli, E. Antonini, and A. Caputo, *J. Biol. Chem.*, **236**, 391 (1961).
128. J. Adams, A. McPherson, Jr., M. G. Rossman, R. W. Schewitz, and A. J. Wonacott, *et al.*, *J. Mol. Biol.*, **51**, 31 (1970).

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013

129. R. H. Sarma and N. O. Kaplan, *Biochemistry*, **9**, 539 (1970). A. Saupe, in *Liquid Crystals*, **2**, G. H. Brown (ed.), Part I, Gordon and Breach, N.Y., p. 59 (1969).
130. P. Hillman, S. Hochstein, and B. Minke, *Science*, **175**, 1486 (1972). Weber, *Biochemistry*, **11**, 864 (1972).
131. R. K. Mishra, D. N. S. Rao, R. S. Khare, M. Sajid, V. K. Jain, K. Anand, and Y. N. Malhotra, *Sc. Cult.*, **34**, 139 (1968).
132. J. M. Tobias, *Cold Spr. Harb. Symp. Quant. Biol.*, **17**, 15 (1952).
133. D. K. Hill and R. D. Keyness, *J. Physiol.*, **108**, 278 (1949).
134. P. Mueller and P. O. Rudin, *Nature*, **213**, 603 (1967).
135. M. F. Perutz, *Nature*, **237**, 495 (1972).
136. T. Funck, F. Eggers, and E. Gvell, *First European Biophy. Con.* (1971), E. Brode and A. Licker Springer-Lederer (eds.), Wiener Med. Akad., Vienna (1971).
137. R. M. C. Dawson, in *Essays in Biochemical*, P. N. Campbell and G. D. Grenville (eds.), 69, Academic Press, N.Y. (1966).
138. D. E. Green and R. A. Harris, in *Physical Principles of Biological Membranes*, F. Snell, J. Wolken, G. Iverson, and J. Lam (eds.), Gordon and Breach, N.Y., 315 (1970).
139. J. N. Weinstein and S. R. Caplan, *Science*, **169**, 296 (1970).
140. C. A. Bassett and R. O. Becker, *Science*, **137**, 1063 (1962).
141. H. Brumberger, *Nature*, **227**, 490 (1970).
142. S. E. Shnol, *Molecular Biophysics*, *Nauka*, 56 (1965).
143. G. Oster, A. Perelson, and A. Katchalsky, *Nature*, **234**, 393 (1971).
144. J. D. Bernal, *Disc Faraday Soc.*, **29**, 1082 (1933).
145. S. Lerman, *Proc. Natl. Acad. Sc. U.S.A.*, **68**, 1886 (1971).

Downloaded by [Tomsk State University of Control Systems and Radio] at 07:01 23 February 2013