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The Colloid Science of Lipids

New Paradigms for Self-Assembly in Science and Technology

Kåre Larsson Festschrift

Guest Editors:
B. Lindman and
B. W. Ninham (Lund)

Editors:
F. Kremer (Leipzig)
G. Lagaly (Kiel)

This volume includes a number of selected papers of the international conference "Colloidal Aspects of Lipids", held in June 1997 at Lund, Sweden.
In conjunction with the conference Professor Kåre Larsson, well-known and respected as a leading scientist in this field during the decades, was honored.

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PREFACE: THE WORK OF KÅRE LARSSON

Caption. Kåre Larsson on his 60th birthday
In honour of Kåre Larsson's contributions a meeting on the Colloid Science of Lipids was held on June 10, 1997 at the Medical Research Center of Lund University in Malmö. The Editors are grateful for the support of their organising committee Dr. Gunnar Sandberg, Professor Ann-Charlotte Eliasson, and Anita Sandberg of the Department of Food Technology. We are grateful too for the sponsorship of:
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Björn Lindman and Barry Ninham (editors).

CAPTION: Larsson's first original research as a 14 year old involved his formulation of an effective skin cream using lipids and attracted national press attention.

Kåre Larsson's first papers were published in 1960, three crystal structure reports on organosilicon compounds. It was probably of no importance, since no one asked for reprints, but he obtained his "licentiat" exam (equivalent to a modern Ph.D). He then moved from Uppsala University to Göteborg University with Einar Stenhagen, professor of medical chemistry and well-known in the lipid field. Kåre's work for his Doctor of Science degree concerned crystal structures of different fatty acid glycerides. At that time the molecular conformations of different polymorphic forms in the solid state of fats were unknown, and many groups were competing in the tricky work of growing good single crystals in order to solve the first structure. During the same month in 1963 two senior crystallographers in the US (Jensen and Mabis) reported the structure of the beta-form of tridecanoin at the same time that Larsson reported the structure of the beta-form of tridodecanoin. The structure determination was a milestone in fat research; the solid state behavior of fats could then be explained. After his Ph. D. (in 1964) he went to Vittorio Luzzati to learn low-angle X-ray methods in order to study glyceride-water phases. In papers published in 1966–67 he reported the structure determinations of all the aqueous phases of fatty acid monoglycerides with chain lengths C_6–C_{18}. For the cubic phases he proposed a reversed structure of water aggregates. He also filed a patent in 1965 where he described how to produce lipid crystal dispersions as gel-like formulations with up to 80 % water from onion-like lipid-water particles (later termed liposomes). This technology has been applied mainly in dermatology, and it is still used in topical treatment of psoriasis and skin infections. In a 1967 paper in Nature Larsson reported a single-crystal X-ray diffraction study of the free rotation of hydrocarbon chains in the solid state. From 1967–1971 he worked in the computing field and led the design of a complete system for the management of the entire health care system of Stockholm. To demonstrate the system, medical information on patients could be requested and transferred via transatlantic cable to and from New York, much like the internet today .... During his computing interlude he had an assistant to keep some lipid work going. He then returned to a research position and went into a number of different techniques to study lipid structure: surface balance, ESCA on LB films, and Raman spectroscopy. The Raman work using ordinary lipids mixed with perdeuterated lipids was very successful, and the results were applied to study lipid-protein phases. In 1975 Kåre became Professor of Food Technology at Lund University. The following list summarizes his most important contributions since 1975.

– *Fat crystallization* Molecular organization in the liquid state and the metastable phases alfa and beta prime were derived. Application work with industry involved a method to better control phase transition in margarines.

– *Emulsions of fats and oils* The significance of surface-active crystals of food emulsifiers in order to produce stable emulsions was demonstrated. The first edible microemulsion system was described.

– *Structure and functionality of polar lipids* Together with Sten Andersson and Stephen Hyde in 1984 the first complete description of the structure of the two glycerolmonooleate-water cubic phases was reported. It was based on infinite periodic minimal surfaces. The first lipid-protein-water phase diagram reported: lyzosyme/glycerolmonooleate/water. Colloidal cubic particles – cubosomes were first described.

– *Lipid oxidation* The relationship between oxidation reactions and physi-

cal state was examined, and a drastic improvement of the antioxidant effect could be achieved by an organized arrangement of ascorbic acid and tocoferol in a microemulsion.

– *Gastrointestinal lipid digestion and absorption* Association structures between bile acids and lipolysis products were studied; surface protective function of phospholipids from joint work with a group in surgery were reported.

– *Structure of native starch and its gelatinization changes* The structure of the amylose lipid complex was determined and found to have profound effect on gelatinization and on enzymatic degradation; the molecular packing in starch granules has been related to that in quartz.

– *Cereal technology* Surface film determination of interfacial disulphide bridge formation between gluten protein molecules and various studies involving all components in wheat led to a complete description on the molecular/colloidal level of breadmaking, which was presented in a monograph written with Ann-Charlotte Eliasson in 1993; "Cereals in breadmaking".

– *Proteins at solid surfaces* Basic ellipsometry studies of adsorption of blood proteins and milk proteins at metal surfaces showed for the first time formation of protein bilayers; this was in collaboration with Per-Ingvar Brånemark involving his osseointegration of titanium implants.

– *Drug delivery* A series of patents have been developed based on lipid carriers for drug delivery, for example cubosomes. They have lead to commercial products, such as Elyzol dental gel against periodontal diseases.

Larsson's *main research interest at present* is the significance of periodic curvature along cell membranes and the dynamic properties of these wave shapes, lung surfactants, and the role of lipids generally in physiology.

Scientific Papers and Technological Contributions of Kåre Larsson

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Inventions which have lead to industrial products covered by patents world-wide.

1. Ointment base and dermatologic preparations. English patent 1174672 (1967) and follow-up patents.
   PETROGARD, an "invisible glove" for skin protection. Produced by Beiersdorf AG, Hamburg
   MICANOL, against psoriasis. Produced by Bioglan AB, Malmö
   MICACID, against impetigo. Produced by Bioglan AB, Malmö
   LHP (lipid-stabilized hydrogen peroxide), Antimicrobial formulation. Produced by Bioglan AB, Malmö
2. Cubic lipid-water phases for drug delivery. US patent 5151272 (1992), with S. Engström and B. Lindman.
   ELYZOL dental gel, against periodontal diseases such as paradontitis. Produced by Dumex AS, Copenhagen
3. Saliva substitute. German patent C44374/1 (1993). With R. Attström and P.-O. Glantz.
   SALINUM. Produced by Miwana AB, Gällivare, Sweden
4. Functional food products based on an oat flour formulation fermented by lactic acid bacteria able to colonize the gastrointestinal system. The initial invention together with S. Bengmark and S. Molin is now protected by a series of patents.
   PROVIVA, probiotic fruit drinks. In Scandinavia produced by Skånemejerier AB

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B.W. Ninham
B. Lindman

Conceptual locks and cubic phases

In "Eight Little Piggies", one of Stephen J. Gould's splendid collections of essays on the puzzle of evolution, he remarks: "I have long maintained that conceptual locks are a far more important barrier to progress in science than factual lacks". The statement is opposite to the work of Kåre Larsson that has to do with the importance of cubic phases in self-assembly.

To put what we have in mind into perspective, we remark that as long ago as 1836, in two reports to the British Association for Advancement of Science (in which he coined the term Mathematical Physics for what we now call Colloid and Surface Chemistry), the Rev. Challis of Trinity College laid out a program that has concerned us since. D'Arcy Thomson in his famous book on "Growth and Form" tells us that the early founders of the Cell theory of Biology and of Physiology then beginning made an urgent plea and recognized that progress in these sciences had to depend on understanding of the forces and problems of self-organization, which are the preoccupation of the physical chemist. Yet the fact remains that despite enormous progress in molecular biology, which uses the tools of physical chemistry and physics, the physical sciences have contributed nothing conceptually to modern biology during the last five decades. This fact poses a real dilemma and a challenge, because they ought to have contributed.

The reasons are only now becoming clear. To see how this situation came about, let us agree on the main goal: to understand function and structure. We would like to know how it is that molecular forces conspire with the geometry of molecules and the conformations available to macromolecules through the laws of statistical mechanics to give rise to the self-assembled equilibrium or dynamic steady states of matter that form cells and dictate biochemical reactivity. So posed, we can identify several places where such a program will have bogged down.

1. Theories of forces between surfaces did not include all important specific ion (Hofmeister) effects. The classical theories of colloid science are simply incorrect in the biological milieu. We do not know why and how to improve the situation. Words like hydrophobic, hydrophilic, and hydration are as ill-defined as the phlogiston theory of heat or that of the aether of last century. That is certainly a problem that we have reviewed elsewhere.

2. Direct measurements of molecular forces between surfaces appeared to have confirmed the classical theory of lyophobic colloid stability and its extensions due to Verwey and Overbeek and Deryaguin and Landau. But as time has gone on practically *all* measurements interpreted in terms of these ideas invoke fitting parameters like effective charge of interacting surfaces. These vary from surface to surface and electrolyte to electrolyte in a bewildering manner. Even allowing such fitting parameters, theory still failed in many cases, and new forces have been called in. These are variously called hydration, secondary hydration, and that bugbear of the 1990s long range "hydrophobic" attraction.

These problems have arisen in part because of ignorance of the Gibb's adsorption isotherm, the two dimensional analogue of the second law of thermodynamics. This is unforgiveable and its resolution has to await the passing of the present generation.

They have also arisen because the ideal smooth surfaces of theory are usually not those of Nature. (Silica and aluminium hydroxide and protein surfaces and just about everything else are not mica). This is unfortunate, but makes life more interesting.

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3. Theories of colloid stability of solid particles that trace their origin to the ideas of Langmuir and Onsager are on more solid ground, but have little direct relevance to our problem. These theories used entropy to balance hard core repulsions. But when one has to deal with soft condensed matter like the flexible membranes of bilayers or the water–surfactant–oil interface and introduces yet another force due to fluctuations, the Helfrich fluctuation force, we are again moving on shifting sand. The interpretation of the microstructure and bending moduli in terms of indirect and apparently sophisticated methods like SAXS or SANS or light scattering is mostly nonsense. It is nonsense not just because the inverse scattering problem is not unique, but it is so because its interpretation invokes theoretical forces with curve fitting based on an incorrect theory. Just as for the direct force measurements in general.

4. The role of dissolved gas and other solutes in interactions, liquid structure, and in free radical production has been completely ignored. This is important if we are ever understand chemical reactivity, and this is an area virtually untouched. Dissolved gas at atmospheric pressure in water is about 2×10^{-3} molar and about ten times as much in oil. Dissolved gas may well be intimately coupled to the range of the mysterious long range "hydrophobic" interactions. The microstructure of water with dissolved gas and electrolyte, also depends on electrolyte type, and is a subject about which we do not know much about. Work on optical cavitation, sonoluminescence, and related phenomena are beginning to reveal the extraordinary complexity of water. This, the nature of water, is an essential key that remains to be unlocked.

These matters are of some concern. Taken together it would seem that the biologist, who has enough concerns of his own, is not to be bothered about the subtleties of modern extensions of simpler theories and has been right to ignore physical chemistry. We have made a beginning, but after much work and self congratulation and realize at last that we must begin again and have some awareness of what the conceptual locks that constrained us were.

The cubic and bicontinuous states of matter

However, there is yet another conceptual lock. Until recently theories of self assembly of surfactants, lipids, microemulsions, polymers and mixtures thereof were constrained by an intellectual mind set that limited thinking to a particular set of shapes. These are those provided by Euclidean geometry: points, spheres, cylinders, and planes. For example, for surfactants and phospholipids, we tended to think in terms of monomers, micelles, hexagonal phases, vesicles, lamellar and reverse phases. It turns out that hyperbolic geometries, everywhere bicontinuous, random, or regular with zero (cubic phases) or constant average curvature are the rule in Nature. The same holds for their two dimensional analogues, the mesh phases, which provide a richer framework in which to think of biomembranes and their action than the older Danielli–Davson model. This model relegates the lipids to an inconsequential nonspecific supporting role for the proteins and DNA.

The same holds for polymer and polymer–surfactant mixtures. These hyperbolic geometries also provide a broader framework in which to understand the structure and reactivity of inorganic materials. Such geometries, discovered by Gauss, Lobachevski, Riemann, and Weierstrass in the last century used to be thought of as a mathematical backwater and curiosity. But the structures described by these geometries turn out to be ubiquitous in Nature. For surfactants where local curvature is set by the balance of forces acting at an interface, these self-assembled structures emerge quite naturally as equilibrium phases when the global packing constraints imposed by mass conservation are also required.

For the lipid–polymer–protein mixtures that occur in biological cells we now know through the work of Larsson and his student Landh that there are structures, hitherto unrecognized, called "cubosomes" everywhere. These direct cell traffic and are involved in cell fusion. Their genesis is different to the surfactant mesophases. The dimensions of the connected channels that occur within them are macroscopic on the order of a thousand Ångstroms rather than the typical dimensions of about 20 Å connected with surfactant self-assembled structures. (Such structures emerge as a kind of three dimensional analogue of the Gibbs–Marangoni effect that occurs with double diffusion gradients at an interface. They form as steady state structures due to the need to generate energy flows outwards and reagent flows in).

Awareness of the existence and the consequences of such states especially the cubic phases of self assembly adopted by phospholipids and lipid–protein mixtures, is in large measure due to the pioneering insistence of Larsson that these structures were indeed bicontinuous cubic phases and the consequences thereof important. Others have contributed, especially Andersson, Hyde, Fontell and Luzzatti who found them first in phospholipids.

In two dimensions the analogue of the 3-D cubic phases are the newly discovered and controversial mesh phases. Phospholipids self-assemble, it seems, into a whole rich diversity of bilayer membrane phases that contain catenoidal holes designed to accommodate the proteins. Just like the bulk cubic phases they can transform from one form to another with extravagant ease. Such structures and their implications for problems like conduction

of the nervous impulse were postulated by Larsson a long time ago. The proteins and lipids are coupled together, and the lipids have a much more vital role than simply to serve as a passive sea in which the proteins do their work. The "vesicles" that transport calcium and acetylcholine across the synaptic junction are cubic phases. Long surfactants at the alveola surface are in equilibrium with a cubic phase which is intimately and essentially coupled to the business of oxygen and carbon dioxide transport without which we cannot live. The omega-3 lipids so abundant in the brain may well be there because they may form bicontinuous cubic phases at the nerve membrane surface which act as the necessary reservoirs for calcium.

At the present time we have only just begun to dimly perceive that something is afoot. There is movement in the world of physical chemistry, and its relation and relevance to biology is about to change. It will do so in large measure because of the opening of the conceptual lock associated with our restriction in imagination to Euclidean geometries. This may well be more important than other limitations of present theories in physical chemistry. There is emerging a new language of shape. This represents a paradigm shift of great moment that deserves awareness and proper recognition.

It is for these reasons that we honor Kåre Larsson and his contributions in this commemorative volume.

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Secondary nucleation in triglyceride crystallization

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Abstract From published results on nucleation and crystallization of emulsified fats, on crystal size observed in the emulsion droplets, and on permeabilities as a function of the fraction of solid in the same fats in bulk, it is concluded that copious secondary nucleation can occur, explaining the high number and small size of the crystals often observed. The effect is very large for milk fat (a mixture of many triglycerides), somewhat less for a typical margarine fat, much less for a fairly simple triglyceride blend, and absent for a paraffin blend.

A hypothetical explanation is given, which implies that clusters of partially oriented molecules diffuse away from a crystal face that grows via kinetic roughening; some of these clusters may give rise to nuclei. Kinetic roughening needs a high supersaturation. A further condition would be that crystal growth is small enough for the diffusing clusters to have a reasonable life time. This hypothesis can qualitatively explain the results discussed, but would need further testing.

Key words Triglyceride crystallization – crystal size – secondary nucleation

Introduction

In several applications of "plastic fats", i.e. mixtures of triglycerides that are partly crystalline and partly liquid, the size of the crystals is an important variable. It greatly affects (i) mechanical (rheological) properties, (ii) "oiling off" and (iii) for emulsified fats, stability against partial coalescence. Something similar holds for paraffin mixtures and comparable substances. There is little understanding of the factors governing fat crystal size.

The general idea is that crystal size is governed by the rates of crystal nucleation and crystal growth, which both increase with supersaturation or supercooling, but in a very different manner. Three types of crystal nucleation are generally distinguished [1]:

Homogeneous. This happens in a pure liquid. Generally, considerable supercooling is needed for homogeneous nucleation to occur at an appreciable rate.

Heterogeneous. This happens at a foreign surface (F), be it of a particle or of the vessel wall. It greatly depends on (i) the three interfacial free energies involved: L–C, L–F and C–F (L = liquid and C = crystal phase) and (ii) the shape of the foreign surface. Very small foreign particles may suffice to induce heterogeneous nucleation, and such particles are called "catalytic impurities". The number of impurities that can be catalytic generally increases with supercooling. In most practical situations, where supercooling is not very great, nucleation is predominantly heterogeneous.

Secondary. Here nucleation occurs near (not at) the surface of an already existing crystal of the solute. It is

a somewhat mysterious phenomenon. It has especially been studied in (situations mimicking) industrial crystallizers, involving considerable agitation. It can, however, also happen under quiescent conditions.

Homogeneous and heterogeneous nucleation are thus variants of primary nucleation, which occurs in the absence of the crystalline phase. Nucleation rate theory for crystallization is at present in a stage of some onfusion, but classification into the three types just given still holds.

Various studies on triglyceride crystallization, for the greater part involving milk fat, have led the author to the conclusion that copious secondary nucleation can occur, also in the absence of agitation. In this manner, very small crystals could be formed. There would be considerable variation in secondary nucleation rate among various fats. The evidence discussed here is, however, of a circumstantial nature. This article does not include any new data, but it does give some new considerations.

Experimental evidence

Studies of nucleation and its rate are generally performed in emulsified material. This has been done with reasonably pure triglycerides [2], simple mixtures of triglycerides [3] and milk fat [4], which is a mixture of at least 10^5 different triglycerides. The results of these studies were consistent and point to homogeneous nucleation occurring at a supercooling of about 20 K below the final melting point of α-crystals in the mixture. Hence, under most conditions nucleation would be heterogeneous. For milk fat (melting range about 230–310 K, final melting of α-crystals about 295 K [5]), extensive studies were done, varying emulsion droplet size, temperature and methods of determining the crystalline proportion. Consistent results for the number concentration of catalytic impurities N_{cat} were obtained (surface nucleation at the droplet boundary could be excluded). These results are summarized in Fig. 1. It is seen that $\log N_{cat}$ decreases linearly with increasing temperature, which is commonly observed for heterogeneous nucleation.

On the other hand, partly crystalline droplets of various fats were viewed under the light microscope, using polarized light with crossed nicols [6–8]. The droplets were typically some μm in diameter and the temperature was mostly 20 °C; here, only those studies where no precooling to a lower temperature was applied will be considered. Several types of droplets could be observed, and those relevant for the present case can be classified as follows:

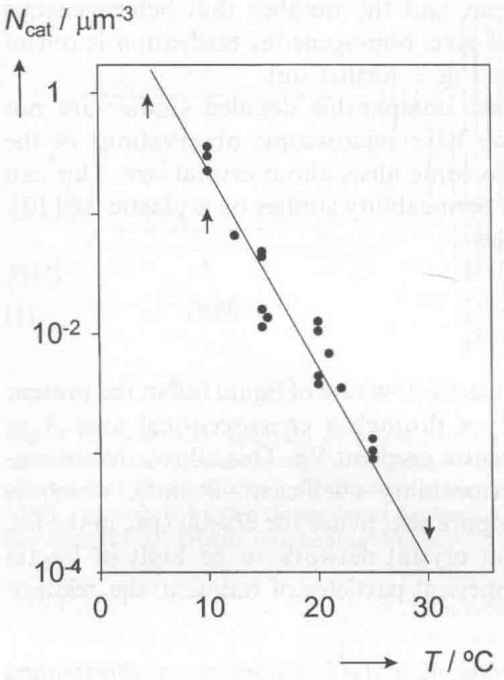

Fig. 1 Number concentration of catalytic impurities N_{cat} for heterogeneous nucleation in milk fat at various temperatures. Arrows indicate minimum or maximum values. From results in [4]

Type O. No crystals are observed. However, in most droplets, part of the fat was solid, since all methods for determining the solid fraction, and also X-ray diffraction studies, showed so. Moreover, small crystals could vaguely be seen by phase contrast microscopy. It must be concluded that the crystals are too small or too thin to be observed by polarized light microscopy.

Type N. Some needle-like crystals appear to be present, but they are more likely long platelets. Typically, 20 crystals can be observed and they have random orientation throughout the droplet. The droplet most likely contains "invisible", i.e. smaller, crystals also.

Type C. Here, the droplet contains one, or sometimes two crystals of elongated shape, length comparable to droplet diameter.

We will first consider milk fat, which almost exclusively shows Type O droplets. Figure 1 shows that at the relevant conditions, N_{cat} would be of the order of one per 100 μm^3, which is also about the size of the droplets examined under the microscope. Hence, there should be zero, one, or occasionally two, crystals in a droplet. However, a typical droplet would contain about 25% solid fat. Electron micrographs show, at comparable conditions, crystals that are typically $0.7 \times 0.15 \times 0.05$ μm in size [9], i.e. making up 0.005 μm^3. For a drop of 100 μm^3, this would result in a number of $100 \times 0.25/0.005 = 5000$ crystals. In other words, there is enormous discrepancy between the number