GLASS TRANSITIONS AND FOLDING TRANSITIONS IN COMPLEX SYSTEMS

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Abstract We first consider the phenomenological relation between glass transitions in normal liquids and glass transitions in protein-like complex systems, taking into account the mesoscopic nature of proteins. We then show the phenomenological relation between the folding transition in proteins and the strong-to-fragile liquid transition in liquid systems with cooperative excitations. This process is presented alternatively as an extreme case in the hierarchy of excitation possibilities in complex liquids with bimodal densities of states.

1. Introduction

The objects of this contribution are two-fold. The first is to show how the effect of temperature on the development of relaxation processes in hydrated native proteins can be related to two processes familiar in the science of viscous liquids, namely the primary (α-) and secondary (β-) relaxation processes. The second is to show how the folding transition, which abruptly completes the slow accumulation of configurational excitations in the protein by abruptly changing its structure in a radical manner, is related to the sudden absorption of energy at first order, or sharp lambda-like, transitions between disordered states in much simpler systems. The two cases will then be united under the rubric of complex systems with bimodal distributions of configurational states.

2. Relaxational Transitions, and Mobility Onsets, in Liquids and Proteins

It is well known that biological function in proteins is lost at temperatures below about 220K [1,2] and that some sort of dynamical process appears to set in in normally hydrated proteins at about 180K [1-3]. The latter is frequently referred to as the glass transition although there is usually no clear jump in heat capacity like that encountered at the typical glass-to-liquid transition. In the latter it is almost always possible to compare the excitations produced in the amorphous phase by increase of temperature with those in a corresponding crystal state, usually with the finding that the two heat capacities remain very similar until the "glass transition" occurs - at which point the heat capacity usually increases by 50-100% [3,4]. In the case of proteins, the absence of a crystalline form for the heteropolymer makes such a comparison impossible*. However it is not necessary to have a crystalline reference state in order to see that there is a great difference between the behavior of the typical liquid undergoing its glass

*The fact that the folded protein molecules can organize themselves into crystalline packings, while very useful for structure determinations, is irrelevant. The relevant crystal would be one in which the individual heteropolymer units had repeat sequences which could stack in three dimensionally repeating units, consistent with the requirement of sufficient overlap.
transition and that of a protein passing the temperature of 180K. In the latter case very little of calorimetric significance occurs although there is a steady increase in the heat capacity as the temperature increases towards the temperature where denaturation quite suddenly takes over.

On the other hand, there are cases of simple glassformers such as toluene [5,6] in which a considerable difference in heat capacity between the crystal and the liquid builds up before the glass transition occurs. This pre-Tg build-up is very gradual, starting at a temperature some 35% below Tg. It is gradual because in these cases there is significant absorption of energy associated with the excitation of relaxational modes known as secondary, or beta-relaxations. The build-up is slow because the relaxation process is associated with an Arrhenius activation energy [7], rather than with the highly non-Arrhenius process characterizing the primary or alpha-relaxations which determine the glass transition [4,8]. This case is shown in Fig. 1 panel (a) where it may be compared with panel (b) the case of the hydrated protein cytochrome c in which the amount of crystallizable water has been reduced to a minimum [9].

A case in which there is a much more significant contribution to the total heat capacity build-up before the primary glass transition occurs is one in which there are clearly two types of interaction to account for. This is the case of the unsymmetrical alkyl ammonium salt hexylhexylammonium bromide [10]. Its behavior is illustrated in the third panel, panel (c) of Fig. 1. The onset of heat capacity at 180K is assumed to be associated with the onset of configurational freedom of the longer alky chains, while the main glass transition occurs when the coulomb interactions between cations and anions are overcome and viscous flow can commence.

Before further commentary on the relation between the behavior illustrated in panels (a-c) it is necessary to ask whether such comparisons are relevant when the protein system, whose behavior is being compared with that of isotropic liquid systems, is composed of so many quasi-independent microscopic entities. The answer is a provisional "yes", because the ability to exhibit a glass transition does not seem to be very dependent on the size of the system being observed. To demonstrate this, panel (d) shows the behavior of the toluene of panel (a) now observed in microemulsion form in which the toluene is dispersed in 5 nm droplets in a matrix of aqueous propylene glycol [11]. Such a droplet has mass on the order of 300000 Daltons, comparable with that of a very large protein. The position in temperature of the glass transition seems not to be affected by the huge reduction in sample size, although the sharpness of the glass transition is much reduced. The magnitude of the C_p jump adjusted for fraction of sample is barely affected. It is known, furthermore, that the glass transition can be seen in individual polystyrene molecules which have been formed by polymerization in microemulsion droplets [12]. Thus to manifest a glass transition, it seems that all that is necessary is for the system to have enough particles or rearrangeable subunits to exceed the dimensions of the quasi-independent domains of a macroscopic system within which all the characteristic configurations and modes of motion of the liquid can be represented [13], and these dimensions are considered to be very small, well within the dimension of an individual protein molecule (in fact small enough to be represented by the ~ 500 atom periodic boxes of MD computer simulations).

More serious is the heteropolymeric nature of the protein chain, but the effect of this can be tested by observing the behavior of the unfolded protein, which is generally found to be not very different from that of a homopolymer melt [4,9,14,15], see panel (e) Fig. 1. The major difference is between the behavior of the folded and unfolded protein [15].

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Figure 1. Thermal effects accompanying onset of motion in different types of systems obtained by differential scanning calorimetry, and adiabatic calorimetry: measurements of heat capacity. (a) excess over crystal of the heat capacity of glass and liquid toluene bulk samples by (a) adiabatic calorimetry [5] and (b) DSC [6]. (b) weak thermal effects during scanning through 180K in hydrated cytochrome c bulk sample [9] (c) strong secondary relaxation and weaker primary relaxation heat capacity jumps in dimethylhexylammonium bromide glass formed by liquid quench is compared with ordered phase formed by dehydration above Tg [10] (d) toluene 5 nm droplet microemulsion in propylene glycol + water matrix compared with bulk [11]. (e) comparison of DSC scans of denatured (keratin) and collagen with homopolymers of low water content. (f) comparison of heat capacity scans of the globular protein keratin before and after unfolding, at 0 and 10% wt % water.
This is shown in panel (a) of Fig. 1 where it is seen that the jump in heat capacity at the glass transition is much more pronounced in the denatured system. Note that in order to make this comparison free of the distortion of magnitudes due to the difference in unperturbed water content of native and denatured systems, it has been necessary, in the case of panel (a) to use a polymer of very low water content. When a more normal water content is present the glass transition in the folded protein case is even less evident calorimetrically, see panel (b) [9].

It is now time to emphasize the role of water and the additional structural heterogeneity which is implied for the folded protein case. The water is located predominantly on the outside of the protein, in the vicinity of hydrophilic residues [1,2]. These hydrated residues have considerable configurational freedom, though the motions which can be excited are rather local in character. That they are the motions which are excited in the process occurring at \( \sim 180 \text{K} \) is demonstrated by recent neutron scattering studies of Middendorf et al [16] on haemoglobin and collagen which show the \( Q \) range of the system in which irreversible processes are occurring in each temperature range. The results for deuterated collagen (a triple helix protein from skin and tendon which has little tertiary structure), are shown in Fig. 2 and demonstrate that the modes excited (losing elastic intensity) between 150 and 210K (above which all modes become overdamped on the time scale of this instrument) are in the \( Q \) range \( 1.1 - 1.3 \AA^{-1} \), implying relaxing entities of sizes \( 2\pi Q = 4.8 - 5.7 \AA \) are involved. These are the dimensions of the hydrated residues. Thus the processes occurring at \( \sim 180 \text{K} \) in the hydrated folded protein are like the sidechain motions responsible for the \( \beta \) relaxation in chain polymers - e.g. the methacrylates [17]. In this respect they have, as suggested in ref. 9, more in common with those occurring at \( \sim 60 \text{K} \) in toluene (Fig. 1a) than with those occurring at the normal segmental relaxation-controlled glass transition. However, unlike the simple glass the coupling between \( \alpha \) - and \( \beta \) - modes seems to be strong - see Fig. 3.

![Figure 2. Scattered neutron intensity \( S_{\text{neut}}(Q,T) \) as function of the difference between incident and scattered neutron wave vector (momentum transfer) \( Q = (4\pi/\lambda)\sin(\theta) \), where \( \theta = 1/2(\text{scattering angle}) \) and \( \lambda = \text{the neutron wavelength} \) and temperature showing the \( Q \) values of structural elements whose relaxation times become shorter than the experiment time scale at each \( T \). Note that the \( Q \) values which drop out at the lowest temperatures, \( -170 \text{K} \), are those characteristic of distances typical of side chain structures.](image)

As the latter authors showed (and also, with more clarity, Hofer at al [18]), the folded protein above 180K has a continuum of configurational processes that are being excited all the way up to the onset of denaturation i.e. there is no definable alpha glass transition in the folded protein case. In other words, at any temperature above 180K, there is an enormous spread of relaxation processes, some with time scales much shorter than the 200s typical of the glass transition onset in ordinary glassforming liquids and some with time scales much longer. The latter are, of course, ergodic at the temperature in question. This places the folded protein in a class of system unlike any single liquid, so it is an oversimplification to describe the folded protein as a strong liquid like \( \text{SiO}_2 \) (or like water near its glass transition) [19]. On the other hand, then, the folding transition and the strong/fragile transition in water [19] seem to have features in common [4], as will be discussed in more detail in the next section.

The behavior of glassforming binary solutions in which the protein molecules act as one component - one for which the molecular size is much greater than that of the other component - may be studied as a separate phenomenon. Then the behavior will be seen in a different light. A solution of large rigid molecules in a matrix of smaller molecules should behave like a system of hard spheres in a dispersed phase and, while not much specific information is available on such systems, a fragile liquid character might be expected. This will be more clear after the next section on proteins as a member of the complex liquid hierarchy has been covered.

![Figure 3. Depiction of the temperature dependence both of the most probable relaxation time and of the relaxation spectrum (loss vs. 1/T) for the frequency \( f = 1/(2\pi\tau) \) in the \( \alpha \)- and \( \beta \)-relaxation regimes, for a typical fragile liquid (solid line). Log \( \tau \) corresponding to each constant frequency is marked on each plot. The distribution narrows to a single value, giving a Lorentzian spectrum, at very high \( T \). Compared with this is the behavior of the folded protein indicated by the dashed line for the frequency \( 10^3 \text{Hz} \), which would normally give a loss peak with characteristic \( \tau = 200 \text{ns} \). For proteins however, we see no loss peak, but rather a rapid onset at \( \sim 180 \text{K} \) and then continuing high loss up to the temperature \( T_g \) where denaturation occurs, and the spectrum narrows greatly. Evidence for this view see the mechanical loss data at constant frequency 10 Hz by Morozov et al, ref. 2(c).](image)

The best way to sum up this section on the hydrated protein molecule as a self-contained complex system may be to represent the effect of temperature on the relaxation kinetics on a hybrid plot which depicts also both relaxation time and relaxation width (i.e. spread of
relaxation times) for a typical liquid. This is shown in Fig. 3. Note the much greater and more temperature-dependent width for the secondary relaxations. In the case of the protein, the relaxation must be thought of as continuous with the β relaxation and two together have a combined width which remains broad at all temperatures [20], as depicted by the dashed lines in Fig. 3. On denaturing, however, there would presumably be a major narrowing of the relaxation spectrum with loss of the longer times components though we do not know of any data to the point. We elaborate on this picture in the following sections dealing first with the case of the "simple" glass-forming liquid.

3. Excitations and Dynamics in Simple Glassforming Liquids: the Gibbs-Goldstein Picture

In order to show how the protein folding transition constitutes an extreme case in a hierarchy of systems in which intramolecular two-state processes are superimposed on a background of lower energy lower entropy configurational excitations, we need to first consider what constitutes the normal behavior of a non-crystallizing liquid. While there is by no means any generally agreed upon theory of the glass transition, a broad brush phenomenological picture of the physics of glassformers is emerging after a turbulent period in which many workers felt the important part of the problem had been solved by mode coupling theory [21]. In broad brush, it now seems, rather, that mode coupling theory (MCT) in the form developed by Götze and co-workers, has succeeded in bridging the gap between a description of the simple liquid domain and the "glassy dynamics" or "landscape"-dominated regime of glassformer behavior.

In the latter, thermodynamics and dynamics are controlled by the physics of exploration of the complex N + 1 dimensional energy hypersurface, characteristic of each system [8,22,23] and directly determined by the intermolecular potential. The accessible minima on the landscape determine the configurational part of the thermodynamic properties, in particular the entropy in excess of the crystal at any given temperature. MCT describes in detail how the system enters and gets trapped in any single minimum of this hypersurface [24] but leaves unanswered the question of how to enumerate the approximately \( \exp(N) \) minima characteristic of each \( N \) particle system, their relationship in the energy coordinate, or (in particular) the manner in which the system explores them in the process of defining a condition of equilibrium at any given temperature. In this sense, MCT brings us to the edge of the "real" glassy state problem [25].

Many attempts have been made to address the glassy state problem using molecular dynamics studies of the simple hard sphere and Lennard-Jones systems. While such systems can indeed be trapped in amorphous states by sufficiently rapid compressions and/or cooling, they do not provide good models for addressing key questions, because their hypersurface topologies funnel the system directly to the crystalline state, i.e. there are temperatures at which the probability of moving into a crystalline minimum on the hypersurface becomes much greater, even on the short computer simulation time scales, than relaxation into a lower energy amorphous state minimum. In other words, the barrier to nucleation disappears. For "good" glassy systems, which include some Lennard-Jones mixtures [26,27] this barrier remains high at all temperatures, so the system is funnelled towards the deepest amorphous state minimum on the entire surface. However it can never reach it in finite time because the time scale for exploration of the surface, hence for obtaining equilibrium states, lengthens as the number of accessible minima diminishes.

These ideas are captured in the Adam-Gibbs description of viscous liquid relaxation [28] which builds on the evidence provided by the Kauffmann analysis of supercooling liquid entropies (vis-à-vis crystal entropies [29]) that there exists for many liquids a statistically small number of minima at energies lower than any others, i.e. an amorphous packing ground state, and these are separated by large barriers from any crystalline state. For these, there exists a non-zero K temperature (at least by extrapolation of observable behavior) at which the entropy of the equilibrated supercooled liquid would have an entropy comparable to that of any crystalline polymorph. Kauffman's analysis suggested that the temperature, \( T_g \), at which the equilibrated liquid would reach this state could be quite close to the melting point in some liquids (which we now call "fragile" liquids) but below 0 K in others (which we now call "strong" [25]). \( T_g \), as a finite temperature, can be demystified by reference to the simple two state model "excitation profiles" [25] which show a fairly abrupt but continuous "onset" of excitations near the temperature \( T_g \) determined by the elementary excitation energy. Such models imply a bimodal type of "configuration" states for simple glassformers. We will see below how, in more complex systems, this can be strongly modified, and the configuration density of states can become more complex.

The Adam-Gibbs equation for viscous liquid relaxation asserts that the time scale for equilibration after some perturbation is related to the excess entropy of liquid over crystal, according to

\[
\tau = \tau_0 \exp \left[ C d \mu/TS_C \right]
\]

where \( \tau_0 \) is a quasi-static vibration time, \( 10^{-14} \text{ s} \), \( C \) is a constant, \( \mu \) is a free energy barrier per particle to cooperative rearrangements, and \( S_C \) is the excess (configurational) entropy. Evaluating \( S_C \) as the entropy generated above \( T_g \) leads to the well-known Vogel-Fulcher-Tammann (VFT) equation as an identity or a good approximation depending on how the excess heat capacity, \( C_p \), vs. \( T \) relation is approximated [30]. Although the VFT equation is itself only a rough description of the behavior of supercooling liquids over the 16 orders of magnitude of relaxation times which can now be measured [31], a fitting of data to that equation under the constraint that \( \tau_0 \) have the physical (phonon) value \( 10^{-14} \text{ s} \) yields an agreement between the VFT relaxation time dependence temperature \( T_g \) and the thermodynamically determined \( T_g \) within a variance of \( 2\% \) for 50 liquids with \( T_g \) ranging from 500 to 1000 K [32].

Thus, in broad brush, the Adam-Gibbs approach within the landscape paradigm, which is summarized pictorially in Fig. 4, provides a good basic understanding of some key features of the behavior of glassforming liquids and polymers in their ergodic states above \( T_g \). Furthermore, by setting \( S_C \) in Eq. (1) at a value fixed by cooling rate or annealing time, the Adam-Gibbs equation goes far towards a description of behavior in the non-ergodic regime below \( T_g \) [32]. The viscosity of polymers above \( T_g \) can be incorporated in this picture by inclusion of a molecular weight-dependent pre-exponent in Eq. 1.

There are important refinements to this picture, such as (i) the onset of cooperativity (and microheterogeneity [30, 34]) where the α-relaxation splits off from the "slow" β relaxation (as highlighted by the β-\( T_g \) scaled Arrhenius plot of Fujimoto and Ojima [7]) and (ii) the resolution of problems with the VFT equation which is obtained by the "landscape scaled" Arrhenius plot of Rössler and Novikov [35], which we cannot discuss here. Rather our aim is to look beyond this basic model to examine and systematize cases in which there occurs some more or less gross departure from the smoothly evolving picture we have so far invoked. While the cases we will cite are few in number, they include some extremely important phenomena, for example, protein folding. Indeed the value of looking at the broad picture is that it allows the folding transition to be removed from the unique state it is usually accorded, and placed in context as an extreme (mesoscopic) example of a molecular liquid phenomenon which hopefully will lend itself to systematic study.
4. Second Tier Two-State Excitations. Slow Degrees of Freedom in Glassforming Liquids

The departures from the smooth behavior of the basic model which we describe above vary from the trivial microscopic case of molecules with cis-trans isomerization to the profound in which the second state is in fact macroscopic and represents a second liquid phase of the substance—one which may in some cases itself be supercooled to the glassy state. Each instance has its own calorimetric signature. This varies from a simple Schottky anomaly riding on top of an otherwise normal background for the gauche-trans isomer case, to a sharp, almost first-order-like, spike in the case of protein denaturation. Finally, in the case of the liquid-liquid transition, there is an outright latent heat of transition but this interesting case can be rationalized simply in terms of the basic two-state model of the glass transition in which the excitations are strongly cooperative [25].

The range of phenomena encompassed in our discussion is summarized in Fig. 5.

We describe each case only in summary. Details are given in cited articles. We should note at the outset that each complexity has not only its own calorimetric signature, but also its own time scale, so that ergodicity with respect to the two-state degree of freedom is usually lost at temperatures well above \( T_g \) for the liquid as a whole. A question of interest then is the extent to which this freezing in of the slow degrees of freedom can affect the main glass transition for the liquid. We divide the possible cases into intramolecular microscopic, intermolecular microscopic, mesoscopic, and macroscopic.

4.1. Microscopic complexity

(i) Intramolecular cases

We cite two examples of this phenomenon though both are reported for the plastic crystal equivalent of the supercooled liquid state. They are add-on two-state capacities due to (1) a gauche-trans isomerism, in the case of \( \text{Cl}_3\text{F}_{12} \) [36], and (2) a boat-chair inversion in the case of isocyanocyclohexane [37], both of which become arrested well above \( T_g \). Both are very small effects that would be lost among the noise except in measurements of the high quality of the cited studies. They also cannot be distinguished when they occur in the glassforming liquid (as opposed to the plastic crystal state) [38]. Both cases conform to the Schottky two-state heat capacity formula so well that the energy difference between the two states extracted from the
data fit proves to be in quantitative agreement with the values obtained from alternative established methods [36]. It is not established yet whether such phenomena can be seen in the liquid, as opposed to the plastic crystal state. Annealing effects on the behavior of CP at the point where the two-state equilibrium becomes arrested are interesting: at the normal glass transition, annealing below $T_g$ results in the jump in $C_p$ during cooling being postponed to a higher temperature, and then overshooting as the enthalpy deficit is quickly made up. In the two-state case, the enthalpy deficit from annealing below the $T_g$ is made up by an earlier onset of the excess heat capacity, and the overshoot is minimal [see open circles in Fig. 5(a)].

A much larger heat capacity jump in the liquid state, but one which exhibits the same annealing behavior, is observed in the case of the sugar fructose [38]. This may be studied in the melt of the pure sugar where detailed studies are prejudiced by slow decomposition, or in aqueous solutions in which the phenomenon appears at a lower temperature [see Fig. 5(b)]. It is assigned to a two-state equilibrium between furanose and pyranose ring forms of the sugar. A similar phenomenon is seen with galactose, and the large excess CP relative to the simple Schottky value of Eq. 1 at $T \neq 0$ is assigned to a substantial entropy increase on isomerization. This stronger anomaly shows qualitatively the same annealing behavior as observed in the Fig. 5(a) case. However, in this case, there seems to be some influence on the primary glass transition because $T_g$ is found to be a few degrees higher when measured for a glass in which more of the high temperature conformer is present (due to fast cooling through the upper "transition") [38].

The anomalous annealing behavior in the two-state processes indicates that the time scale for the two-state equilibration is determined by the background viscosity rather than by the position of the two-state equilibrium itself, i.e. an Adam-Gibbs-like formula for the relaxation time is not appropriate.

(ii) Intermolecular cases

Intermolecular two-state complexities are not as clearly established as the above, but seem to be present in cases where hydrogen bonds, which are all intact in the liquid near $T_g$, commence to break in the supercooled liquid. The clearest case to date is the molecule cresol [39] in which the heat capacity jump at $T_g$ is smaller than for other molecules of the substituted benzene family, but which displays a rapid buildup in heat capacity as $T > T_g$. The increase corresponding to a two-state add-on due to hydrogen bond breaking [see Fig. 5(c)]. A number of additional cases of this type await quantitative study and should be very interesting with respect to their relaxation time temperature dependence. The extra degrees of freedom should couple to the viscosity, so it might be expected that the entropy generation accompanying the excitation of the new degree of freedom will generate changes in the relaxation time temperature dependence that cannot be accounted for by simple three parameter equations like the VF equation. Indeed, the gross departures from VF behavior documented for salol [31], and to a lesser extent several other cases are well rationalized by assuming the presence of a two-state exchange within the liquid [40]. Although this is not obvious from the heat capacity behavior, such an exchange could be the source of departure from the hyperbolic temperature dependence of $C_p$ observed for simple molecules of lower temperature $T_g$.

4.3. Macroscopic complexity

As the molecular weight of glassforming substances increases, the glass transition temperature increases, though the proportionality is not simple and depends on the degree of aromaticity, intramolecular, H-bonding, etc. As seen in chain polymers, there is also a tendency to level off at high molecular weight. Proteins are large molecules, basically chain heteropolymers with intramolecular hydrogen bonding which are capable of folding into stereochemically specific, low energy structures in which they perform life functions. In the dry unfolded states, they exhibit glass transitions in the vicinity of 100-200°C depending on size and structure. However, they can exhibit two-state ("all or nothing") transitions between folded and unfolded states [41]. In aqueous solutions of appropriate composition and concentration, the folding is reversible, but in the dry state, only the unfolding can be observed. In solutions, the phenomenon is essentially a two-state equilibrium superimposed on the background, analogous to that in the fructose solution described above but much sharper due to the higher $T_g$. In the dry state, it is better viewed as the consequence of a huge collection of mesoscopic glassy samples, each undergoing a polyamorphic transition [42], as would be an apt description of a microemulsion of 5 nm droplets of water near 23 K (described in the next section). Thus the protein unfolding transition, the calorimetric consequences of which are shown in Fig. 5(d), occupies a metastable position between microscopic two-state add-ons to normal glassforming liquid behavior, and macroscopic two-state phenomena involving actual change of thermodynamic phase.

It will be very interesting to identify molecular systems which fall in between the unfolding protein and the furanose-pyranose ring exchange in fructose and galactose. One very recent example exists, and we believe there must be a variety of others waiting to be identified. The recent example is the two-state equilibrium in the isolated polypeptide hairpin turn synthesized and characterized by Munoz et al. [43]. According to the Fig. 4 sequence, its unfolding should be spread over a wider temperature range than the more complex cytochrome $c$ unfolding. Still, an individual hairpin is apparently either a hairpin or a chain, a two species equilibrium.

It would be exciting if a system could be identified in which, like the fructose case, the liquid consisted only of molecules which could exist in either of two states, but in which the complexity approached that of the hairpin system. In any case it seems clear that such cases could be described in reasonable approximation as liquid systems with bimodal densities of configural states each mode of which could have its own fragility, depending on the excitation entropy parameter for the mode [25(b)].

4.3. Macroscopic complexity

Here we make only a brief reference to the final case of two-state complexity which, if we restrict attention to isotropic substances, is illustrated by a small group of substances currently under study. If we admit anisotropy, then the field is enormous - the field of liquid crystals. Restricting attention to isotropic cases, we refer to the emerging phenomenology of supercooled water [44-48] and liquid silicon [49-52] in which first order liquid-liquid phase transitions are observed or implied under cooling/heating conditions fast enough to exclude crystallization. Then a weak first order transition, with small changes in coordination number and density, intervenes to avoid a spinodal collapse of the initial phase (similar to liquid crystal behavior near a mesophase transition). A case in which the process can be observed directly because of slower crystallization kinetics is that of Al$_2$O$_3$-Y$_2$O$_3$ liquids [53]. In those cases, the $T_g$ of the two-state process is so large that the temperature interval over which the change of state occurs is reduced to a point, and the process becomes a macroscopic phase transition at temperature $T_g = AHAS$. The relation the protein folding transition can be seen by considering a system of nanoscopic droplets of water molecules (e.g. in microemulsions). In such a system, fluctuations intrinsic to small systems would spread out the temperature interval over which all droplets would change phase, so that the phase transition would look like the protein-unfolding transition of Fig. 5(d).
5. Concluding Remarks

Recognition of a systematic relation between various phenomena which may complicate the simple viscous liquid/glass transition scenario should hasten the recognition and quantification of other examples of this interesting and important phenomenology. It is around the mesoscopic case that there must enter a crossover from simple activated state kinetics to nucleation and growth kinetics in the transition from high energy to low energy states. The elucidation of this phenomenology is a key requirement for the solution of the protein folding problem, and is of general interest to the complex liquid problem as well.

6. Acknowledgments

This work was supported by the National Science Foundation under Grant No. DMR9108028-002. We are indebted to Doster Middendorf and coworkers for sharing their findings on collagen dynamics (SodaQ17) with us in advance of publication, and providing us with Figure 2.

References