between mostly solid dynamics and mostly liquid state dynamics. It is important to emphasize, however, that solid dynamics does not mean zero mobility.

A protein dissolved in another glassy component (i.e., sucrose) could behave as a two-phase system with regard to mobility. That is, the protein molecules themselves could undergo internal motion in a rigid matrix and have a pseudo glass transition or mobility transition, which is not strongly coupled with the glass transition of the sucrose matrix. Using Fourier transform infrared (FTIR) spectroscopy to study internal protein motion in carbonmonoxymyoglobin (MbCO) dissolved in aqueous glycerol, protein internal "glass transitions" were determined and compared to the glass transition temperatures of the systems as a whole determined by differential scanning calorimetry (DSC) (40). The protein glass transition temperatures were very close to the corresponding glass transition temperatures determined by DSC. For 65% glycerol and 75% glycerol, the DSC glass transition temperatures are -124°C and -98°C, respectively. The corresponding protein glass transition temperatures are -118°C and -95°C. Thus, at least in these systems, the solvent and the protein dynamics are strongly coupled, likely due to the hydrogen bonding interactions between the solvent and the protein surface (40). While it is perhaps somewhat unusual to refer to the mobility transition in the protein as a glass transition, it should also be noted that the glassy MbCO systems studied also show protein intramolecular relaxation process (i.e., transitions between protein substates) that are both nonexponential in time and non-Arrhenius in temperature dependence, a property characteristic of glasses (40).

Evidence for coupling between glassy matrix dynamics and protein dynamics is not restricted to low-temperature aqueous systems. Studies of the kinetics of ligand binding in MbCO (41) dissolved in *dry* glassy trehalose demonstrates that the glassy trehalose matrix suppresses the equilibrium between protein conformational substates on the timescale of the ligand binding reaction at least up to room temperature. While a protein glass transition temperature was not obtained, the data do demonstrate significant coupling between internal protein motions and the dynamics of the glassy matrix, trehalose.

Coupling between matrix dynamics and internal protein dynamics could have significant pharmaceutical stability implications. While limitations on translational diffusion would be expected to moderate bimolecular reactions regardless of the degree of coupling between protein internal dynamics and the matrix dynamics, degradation processes that depend only on motions within the protein molecule would not necessarily be quenched in the glassy state unless the protein internal dynamics was strongly coupled with the dynamics of the glassy system as a whole. Thus, one would expect optimal stability in those glassy systems that provide effective coupling of the protein dynamics with the dynamics of the glassy matrix.

Molecular Motion, Relaxation, and the Glass Transition

The Stokes–Einstein equation,

$$D = \frac{kT}{6\pi\eta a}, \tag{1}$$

predicts that the translational diffusion coefficient, D, is inversely proportional to the coefficient of viscosity, η, where k is the Boltzmann's constant and "a" is