thermal history, and perhaps most important, the degree of coupling of the protein motion to motion in the glass are important factors in determining protein mobility at a given value of $T_g - T$.

Stabilization by a thermodynamic mechanism requires that the rates of unfolding and refolding be fast on the timescale of the experiment, which for drying is on the order of hours. Thus, equilibrium is established quickly, and it is the position of the equilibrium (i.e., the ratio of "unfolded" to "native" species) that determines degradation rate and loss of activity. Assuming that drying is carried out close to the glass transition temperature (4), the structural relaxation time is on the order of minutes to tens of minutes (Fig. 7). Therefore, structural relaxation is moderately fast on the drying timescale. However, one can argue that the unfolding time is likely to be significantly greater than the structural relaxation time. Since unfolding involves rather large-scale motion, analogous to polymer chain diffusion, it is likely that coupling to structural relaxation will be strong. Recall that polymer chain diffusion appears to couple well with viscosity and the glass transition (Fig. 9). Further, since a large number of diffusional jumps would be required to complete the unfolding reaction, the total time required for unfolding would be much greater than the time for a single diffusional jump. Thus, one might expect that the unfolding time would consist of a large number of diffusional jump times, each of which is similar in duration to the structural relaxation time. We also note that crystallization of sucrose from an amorphous system near T_g, likely also a diffusion-controlled process, seems to require a reaction time significantly longer than the structural relaxation time. Onset of nucleation and crystallization requires about one day when carried out 10°C above the glass transition temperature of the system (81). The estimated structural relaxation time (Fig. 7) 10°C above the glass transition is $\approx 5 \times 10^{-6}$ days, so at least for sucrose crystallization, the ratio of the reaction time to the relaxation time is on the order of 10^5. Thus, we tentatively conclude that protein-unfolding times in stabilized glassy formulations near T_g are likely of the same order of magnitude as the drying time or longer. Given these considerations, the rates of unfolding and refolding do *not* appear to be fast on the drying timescale, and thermodynamic stabilization mechanisms do not appear plausible. However, uncertainty in the degree of coupling between the diffusional jump process and structural relaxation introduces considerable uncertainty in the above conclusion. Further, it is significant to note that the temperature denoted, $T_{g'}$, may be about 20°C higher than the true glass transition temperature (82). If this interpretation is correct, primary drying and early secondary drying are typically carried out well above the glass transition temperature. For a process carried out at a temperature 20°C above a glass transition temperature, the structural relaxation time is in the range of 10^{-8} to 10^{-5} days, depending on fragility, and one might argue that the rates of unfolding and refolding would be fast compared with the timescale of drying. Thermodynamic stabilization concepts would then become quite viable. However, as mentioned earlier, our data on rates of unfolding in viscous systems suggest unfolding rates can be on the timescale of months even 20°C above a glass transition temperature. To the extent this observation is general, one would not expect unfolding to occur during the usual drying process. However, since *instability* does occur during drying, either the *instability* does not depend on unfolding or the unfolding dynamics is not well coupled to the system mobility in these unstable systems.