^{19}F in amorphous flufenamic acid dispersed with PVP (drug-PVP, 7:3). The T_1 of ^{19}F shows a minimum at approximately 110°C as well as a maximum at approximately −10°C, as shown in Figure 12A. The temperature dependence can be described by assuming that the ^{19}F atom has two Arrhenius-type motions with an equivalent contribution to the process of T_1 but with different activation energies of 50 and 5 kJ/mol, as shown by the solid line in Figure 12A. The motion with greater activation energy may be attributed to β-relaxation and the other one to the rotation of the trifluoromethyl group, which is faster than β-relaxation.

The $T_{1\rho}$ of ^{19}F in flufenamic acid shows a minimum at approximately 60°C, as shown in Figure 12B. The temperature coefficient of $T_{1\rho}$ is about 50 kJ/mol at temperatures below 60°C, suggesting that $T_{1\rho}$ is determined by β-relaxation in this temperature range. In contrast, a greater temperature coefficient of $T_{1\rho}$ is observed at temperatures above 60°C, suggesting that $T_{1\rho}$ is determined by a larger-scale motion than β-relaxation. Thus, motion reflected by the T_1 and $T_{1\rho}$ of ^{19}F varies with temperature.

RELATIONSHIP BETWEEN STORAGE STABILITY AND MOLECULAR MOBILITY AS DETERMINED BY NMR RELAXATION TIMES

The storage stability of pharmaceuticals in the solid state is largely affected by molecular mobility. Changes in the molecular mobility of amorphous pharmaceuticals at T_g bring about changes in the temperature dependence of chemical and physical degradation rates. Coupling between chemical degradation and molecular mobility has been reported for several drugs of small molecular weight in freeze-dried formulation (1–5); hydrolysis of aspirin in freeze-dried hydroxypropyl-β-cyclodextrin/aspirin complex (1), hydrolysis of peptides in freeze-dried formulations containing cross-linked sucrose polymer (3), and deamidation of peptide in freeze-dried formulations containing poly(vinylpyrrolidone) (4,5). In addition to chemical instability, physical instability of pharmaceuticals, such as crystallization of amorphous compounds, is related to molecular mobility (36–40). Crystallization of freeze-dried sucrose is inhibited in the presence of PVP at a level as low as 10% due to the decreased molecular mobility of sucrose as indicated by the decreased enthalpy relaxation of the mixtures relative to sucrose alone (41).

Coupling between degradation and molecular mobility has also been reported for degradation of protein pharmaceuticals (6–15). An excellent correlation has been demonstrated between T_g and chemical degradation of freeze-dried antibody-vinca conjugate (8).

This section discusses the relationship between the storage stability of freeze-dried formulations and the molecular mobility as determined by NMR relaxation times, described in the previous section. Focus is placed on the degradation of small molecular weight drugs via bimolecular reaction and protein aggregation in the freeze-dried formulations.

Correlations Between Storage Stability and Structural Relaxation as Reflected by NMR Relaxation Times

NMR relaxation times are useful to determine fast dynamics of freeze-dried formulations, whereas structural relaxation of freeze-dried formulations, which