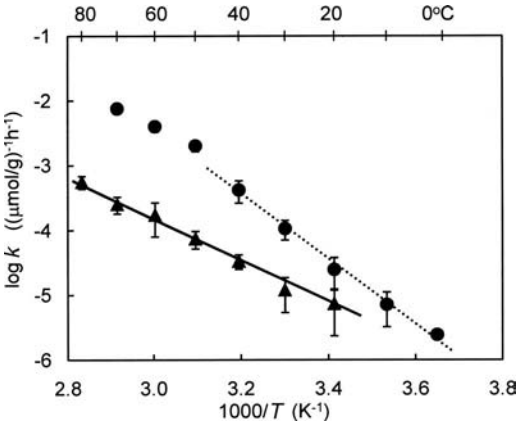

FIGURE 13 Temperature dependence of acetyl transfer between aspirin and sulfadiazine in freeze-dried formulations containing dextran at 12% (▲) and 60% RH (●).

is global mobility rapidly enhanced at temperatures above T_g, is also reflected by NMR relaxation times. Correlations between storage stability and structural relaxation as reflected by NMR relaxation times have been demonstrated for various freeze-dried formulations. Figure 13 shows the temperature dependence of the rate constant for acetyl transfer between aspirin and sulfadiazine in freeze-dried formulations containing dextran. Acetyl transfer is a bimolecular reaction in which the translational diffusion of reactant molecules becomes rate determining when molecular mobility is limited in the solid state (42). The rate constant of acetyl transfer (k_T) and the pseudo rate constant of hydrolysis ($k_{H,pseudo}$) that occurs in parallel with acetyl transfer in the presence of water are described by following equations.

$$\frac{d[SD]}{dt} = -k_T[SD][ASA] \tag{10}$$

$$\frac{d[ASA]}{dt} = -k_T[SD][ASA] - k_{H,pseudo}[ASA] \tag{11}$$

The temperature dependence of acetyl transfer at 60% RH exhibits a distinct break at approximately 40°C, although it is linear at 12% RH. The temperature of this distinct break observed at 60% RH is coincident with the T_{mc} as determined by the spin-spin relaxation measurements described in section "Molecular Mobility as Determined by NMR Relaxation Times." This indicates that the rate of acetyl transfer is affected by a change in the translational mobility of aspirin and sulfadiazine molecules at T_{mc}, resulting in a change in temperature dependence. The temperature dependence of acetyl transfer at 12% RH does not show any break because T_{mc} at 12% RH is higher than the highest temperature for the measurement. Compared with acetyl transfer, hydrolysis of aspirin occurring in parallel with acetyl transfer does not show such a distinct break at T_{mc}, even though hydrolysis is also a bimolecular reaction.

Similarly, no distinct break was observed in the temperature dependence of hydrolysis of cephalothin in freeze-dried formulations containing dextran, as shown in Figure 14. The hydrolysis rate of cephalothin increased with increasing humidity because the rate-limiting step involves water as a reactant. The