Scatchard also used this approach to calculate the intermediate C_G in Equation 9.21. The r used in aforementioned equation is the radius of the intermediate and can be expressed as $r = r_A + r_B$ (Christiansen 1924). To react, this is the distance to which molecules A and B must approach. The Equation 9.26 demonstrates the relationship between rate of reaction and the dielectric constant of the medium.

In summary, an increase in the ϵ of the medium causes the increased reaction rate in the presence of ions with the same sign, and a decreased reaction rate when the ions have opposite signs. The rate of reaction between an ion and a neutral molecule will decrease as the dielectric constant of the solvent increases. The reader may want to consult further Reichardt's text for further theoretical discussions (Christian 2011).

Examples of Empirical Approaches

A typical first step in the development for a new molecule is to check the aqueous solubility and the pH of the drug molecule. It is very important that intrinsic solubility is also measured for molecules with ionizable groups. It appears that Garrett (1956) was the first one to report the effect of vehicle on the stability of drugs (vitamins) in a formulation. Even though, Garrett's focus was on stability studies and Arrhenius correlation to predict the rate constants at a lower (room) temperature for these formulations, the degradation of *d*-pantothenyl alcohol in two formulations provides an excellent example for the effect of vehicle on the rate constant.

Garrett's two formulation vehicles consisted mainly of 60% sugar and 19% alcohol (Preparation A) and 36% sugar and 2.35% alcohol (Preparation B). The slopes of Arrhenius plots as well as heats of activation for the *d*-pantothenyl alcohol in preparations A and B are same, but the plots are not superimposable indicating that the actual rates at a given temperature are different (Figure 9.1). Garrett's assumption of a similar mechanism of degradation in both

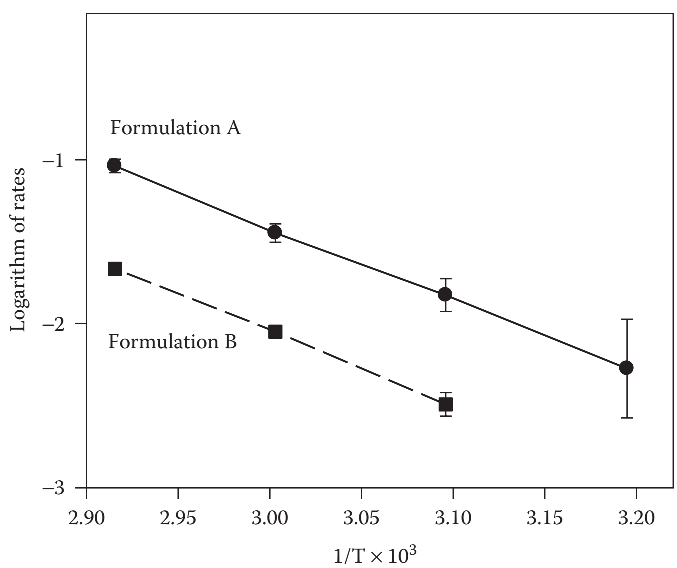

FIGURE 9.1 Arrhenius correlation for the first order rate constants for *d*-pantothenyl alcohol in Formulation A (60% sugar and 19% alcohol) and Formulation B (36% sugar and 2.35% alcohol). (Data replotted for Formulation A from *J. Am. Pharm. Assoc. Sci. Ed.*, 45, 470–473, 1956 (Table I) and for Formulation B, *J. Am. Pharm. Assoc. Sci. Ed.*, 45, 171–177, 1956 (Table II).)