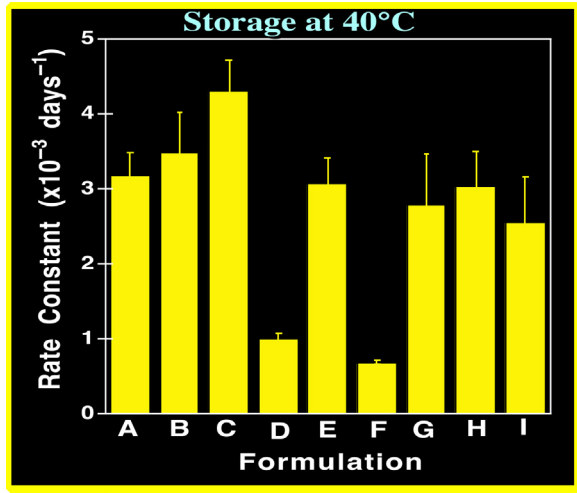

Figure 4.4 The pseudo first-order aggregation rate constant for an IgG1 mAb stored at 40 °C as a function of buffer species. A, no excipients; B, potassium phosphate, pH 7; C, sodium phosphate, pH 7; D, histidine, pH 7; E, sodium succinate, pH 6.5; F, histidine, pH 6; G, sodium succinate, pH 6; H, sodium succinate, pH 5.5; I, sodium succinate, pH 5.
Figure provided by Jim Andya or Jun Liu. 21st Interphex Japan, Tokyo, Japan 2008.

Ionic strength and tonicity modifiers

Ionic strength can impact the behavior of proteins resulting in salting in (increased solubility) or salting out (decreased solubility). The decrease in solubility with an increase in ionic strength is usually attributed to the colloidal stability of a protein. In this framework a protein at any given pH has a specific net charge. Thus the protein molecules repel each other and predominate over any attractive interactions. As the ionic strength is increased the net charge repulsion is decreased, resulting in potential attractive protein–protein interactions, resulting in decrease of solubility and increase in protein aggregation. It has been reported that the turbidity of an IgG_1 mAb solution increased with an increase in ionic strength of the formulation and that the T_m for unfolding as determined by DSC decreased with an increase in NaCl concentration (Wang, Hu, et al., 2009). It was also observed that the viscosity of these more turbid mAb solutions increased with an increase in ionic strength. In another example, an IgG_1 mAb showed increased turbidity with an increase in ionic strength, and appeared to correlate nicely with determination of the B22 and the DSC interaction parameter, k_D (discussed in greater detail in Chapter 9) (Figure 4.5), i.e., positive B22 and k_D at 15 mM NaCl where net interactions are repulsive, and negative B22 and k_D at 150 mM NaCl where net interactions are attractive.

The tonicity of a protein formulation is related to the osmotic pressure gradient across a semipermeable membrane. This pressure gradient is generated due to the concentration of solutes outside the membrane compartment versus inside the membrane compartment. The traditional discussion of tonicity as it relates to biological systems is usually assessed on the effect of the solution tonicity on red blood cells. When the concentration of solute is