1. NMR was used to study the relationship between a Val → Glu mutation in the transmembrane domain of the neu cellular receptor and dimerization of this receptor. A normally functioning neu protein is a receptor tyrosine kinase for which ligand binding to the neu extracellular domain leads to protein dimerization and consequent ability of the intracellular domain to phosphorylate another protein. This neu mutation is correlated with an increased risk of breast cancer.

a. (20 points) A peptide corresponding to the neu transmembrane domain and $^{13}$C isotopically labeled the Cδ carbon in the Glu residue. The peptide was then incorporated into membranes. As shown in the attached NMR spectra and figure, there were $^{13}$C signals at 179 and 181 ppm and the relative intensity of the two signals depended on pH. The open circles and closed circles in the figure correspond to two different membrane compositions. In a few sentences, provide an assignment for the two peaks in the spectra and an explanation for the pH dependence.

b. (20 points) Explain what is anomalous about your explanation to part a. Provide a physicochemical explanation for the anomaly.

c. (20 points) Dimerization of neu receptors through association of their transmembrane domains activates the receptors and leads to increased cell division and sometimes cancer. Assume that the open circles in the figure correspond to the most physiologically relevant membrane composition. Using your results from a and b, provide a physicochemical model for how the Glu mutation in the neu transmembrane domain could lead to increased neu receptor dimerization.
low pH

intermediate pH

high pH

$^{13}$C Chemical Shift (ppm)

179 ppm relative intensity

pH