Within an α helix, each carbonyl oxygen (residue \( n \)) of the polypeptide backbone is hydrogen-bonded to the backbone amide hydrogen of the fourth residue further toward the C-terminus (residue \( n + 4 \)). (The three amino groups at one end of the helix and the three carbonyl groups at the other end lack hydrogen-bonding partners within the helix.) Each hydrogen bond closes a loop containing 13 atoms—the carbonyl oxygen, 11 backbone atoms, and the amide hydrogen. Thus, an α helix can also be called a 3.6\(_1\) helix based on its pitch and hydrogen-bonded loop size. The hydrogen bonds that stabilize the helix are nearly parallel to the long axis of the helix.

The \( \varphi \) and \( \psi \) angles of each residue in an α helix are similar. They cluster around a stable region of the Ramachandran plot centered at a \( \varphi \) value of \(-57^\circ\) and a \( \psi \) value of \(-47^\circ\) (Figure 4.9). The similarity of these values is what gives the α helix a regular, repeating structure. The intramolecular hydrogen bonds between residues \( n \) and \( n + 4 \) tend to “lock in” rotation around the \( \mathrm{N}^-\mathrm{Ca} \) and \( \mathrm{Ca}^-\mathrm{C} \) bonds restricting the \( \varphi \) and \( \psi \) angles to a relatively narrow range.

A single intrahelical hydrogen bond would not provide appreciable structural stability but the cumulative effect of many hydrogen bonds within an α helix stabilizes this conformation. Hydrogen bonds between amino acid residues are especially stable in the hydrophobic interior of a protein where water molecules do not enter and therefore cannot compete for hydrogen bonding. In an α helix, all the carbonyl groups point toward the C-terminus. The entire helix is a dipole with a positive N-terminus and a negative C-terminus since each peptide group is polar and all the hydrogen bonds point in the same direction.

The side chains of the amino acids in an α helix point outward from the cylinder of the helix and they are not involved in the hydrogen bonds that stabilize the α helix (Figure 4.11). However, the identity of the side chains affects the stability in other ways. Because of this, some amino acid residues are found in α-helical conformations more often than others. For example, alanine has a small, uncharged side chain and fits well into the α-helical conformation. Alanine residues are prevalent in the α helices of all classes of proteins. In contrast, tyrosine and asparagine with their bulky side chains are less common in α helices. Glycine, whose side chain is a single hydrogen atom, destabilizes α-helical structures since rotation around its α-carbon is so unconstrained. For this reason, many α helices begin or end with glycine residues.

Proline is the least common residue in an α helix because its rigid cyclic side chain disrupts the right-handed helical conformation by occupying space that a neighboring residue of the helix would otherwise occupy. In addition, because it lacks a hydrogen atom on its amide nitrogen, proline cannot fully participate in intrahelical hydrogen bonding. For these reasons, proline residues are found more often at the ends of α helices than in the interior.

Proteins vary in their α-helical content. In some proteins most of the residues are in α helices, whereas other proteins contain very little α-helical structure. The average content of α helix in the proteins that have been examined is 26%. The length of a helix in a protein can range from about 4 or 5 residues to more than 40—the average is about 12.

Many α helices have hydrophilic amino acids on one face of the helix cylinder and hydrophobic amino acids on the opposite face. The amphipathic nature of the helix is easy to see when the amino acid sequence is drawn as a spiral called a helical wheel. The α helix shown in Figure 4.11 can be drawn as a helical wheel representing the helix viewed along its axis. Because there are 3.6 residues per turn of the helix, the residues are plotted every 100° along the spiral (Figure 4.12). Note that the helix is a right-handed screw and it is terminated by a glycine residue at the C-terminal end. The hydrophilic residues (asparagine, glutamate, aspartate, and arginine) tend to cluster on one side of the helical wheel.

Amphipathic helices are often located on the surface of a protein with the hydrophilic side chains facing outward (toward the aqueous solvent) and the hydrophobic side chains facing inward (toward the hydrophobic interior). For example, the helix shown in Figures 4.11 and 4.12 is on the surface of the water-soluble liver enzyme alcohol dehydrogenase with the side chains of the first, fifth, and eighth residues (asparagine, glutamate, aspartate, and arginine) tend to cluster on one side of the helical wheel.

**Figure 4.11** View of a right-handed α helix. The blue ribbon indicates the shape of the polypeptide backbone. All the side chains, shown as ball-and-stick models, project outward from the helix axis. This example is from residues Ile-355 (bottom) to Gly-365 (top) of horse liver alcohol dehydrogenase. Some hydrogen atoms are not shown. (PDB 1ADF).

**Figure 4.12** A right-handed α helix. This helix was created by Julian Voss-Andreae. It stands outside Linus Pauling’s childhood home in Portland, Oregon, United States.
C. Hemoglobin Is an Allosteric Protein

The binding and release of oxygen by hemoglobin are regulated by allosteric interactions (from the Greek *allo*, “other”). In this respect, hemoglobin—a carrier protein, not an enzyme—resembles certain regulatory enzymes (Section 5.9). Allosteric interactions occur when a specific small molecule, called an allosteric modulator, or allosteric effector, binds to a protein (usually an enzyme) and modulates its activity. The allosteric modulator binds reversibly at a site separate from the functional binding site of the protein. An effector molecule may be an activator or an inhibitor. A protein whose activity is modulated by allosteric effectors is called an allosteric protein.

Allosteric modulation is accomplished by small but significant changes in the conformations of allosteric proteins. It involves cooperativity of binding that is regulated by binding of the allosteric effector to a distinct site that doesn’t overlap the normal binding site of a substrate, product, or transported molecule such as oxygen. An allosteric protein is in an equilibrium in which its active shape (R state) and its inactive shape (T state) are rapidly interconverting. A substrate, which obviously binds at the active site (to heme in hemoglobin), binds most avidly when the protein is in the R state. An allosteric inhibitor, which binds at an allosteric or regulatory site, binds most avidly to the T state. The binding of an allosteric inhibitor to its own site causes the allosteric protein to change rapidly from the R state to the T state. The binding of a substrate to the active site (or an allosteric activator to the allosteric site) causes the reverse change.

The change in conformation of an allosteric protein caused by binding or release of an effector extends from the allosteric site to the functional binding site (the active site). The activity level of an allosteric protein depends on the relative proportions of molecules in the R and T forms and these, in turn, depend on the relative concentrations of the substrates and modulators that bind to each form.

The molecule 2,3-*bisphospho-D-glycerate* (2,3BPG) is an allosteric effector of mammalian hemoglobin. The presence of 2,3BPG in erythrocytes raises the $P_{50}$ for binding of oxygen to adult hemoglobin to about 26 torr—much higher than the $P_{50}$ for oxygen binding to purified hemoglobin in aqueous solution (about 12 torr). In other words, 2,3BPG in erythrocytes substantially lowers the affinity of deoxyhemoglobin for oxygen. The concentrations of 2,3BPG and hemoglobin within erythrocytes are nearly equal (about 4.7 mM).