of XNAs is their ability to form regular Watson–Crick base pairs, as seen in DNA, and prominent examples include peptide nucleic acid (PNA), 2′-substituted nucleic acids and locked nucleic acid (LNA) (Figure 6.9). In PNA, the deoxyribose-phosphate backbone of DNA is replaced with *N*-(2-aminoethyl)-glycine units which confer several advantages over regular DNA: The backbone is linked by peptide bonds, and can be easily synthesized, and the stability of PNA is significantly increased compared to DNA. In LNA, the ribose moiety has been locked into the bioactive 3′-endo conformation via an extra carbon–oxygen bond connecting the 2′-oxygen and 4′-carbon. This locked conformation enhances base pairing affinities and backbone pre-organization, as well as increases the stability. Finally, replacement of the 2′-hydroxy on ribose with substituents such as 2′-fluoro

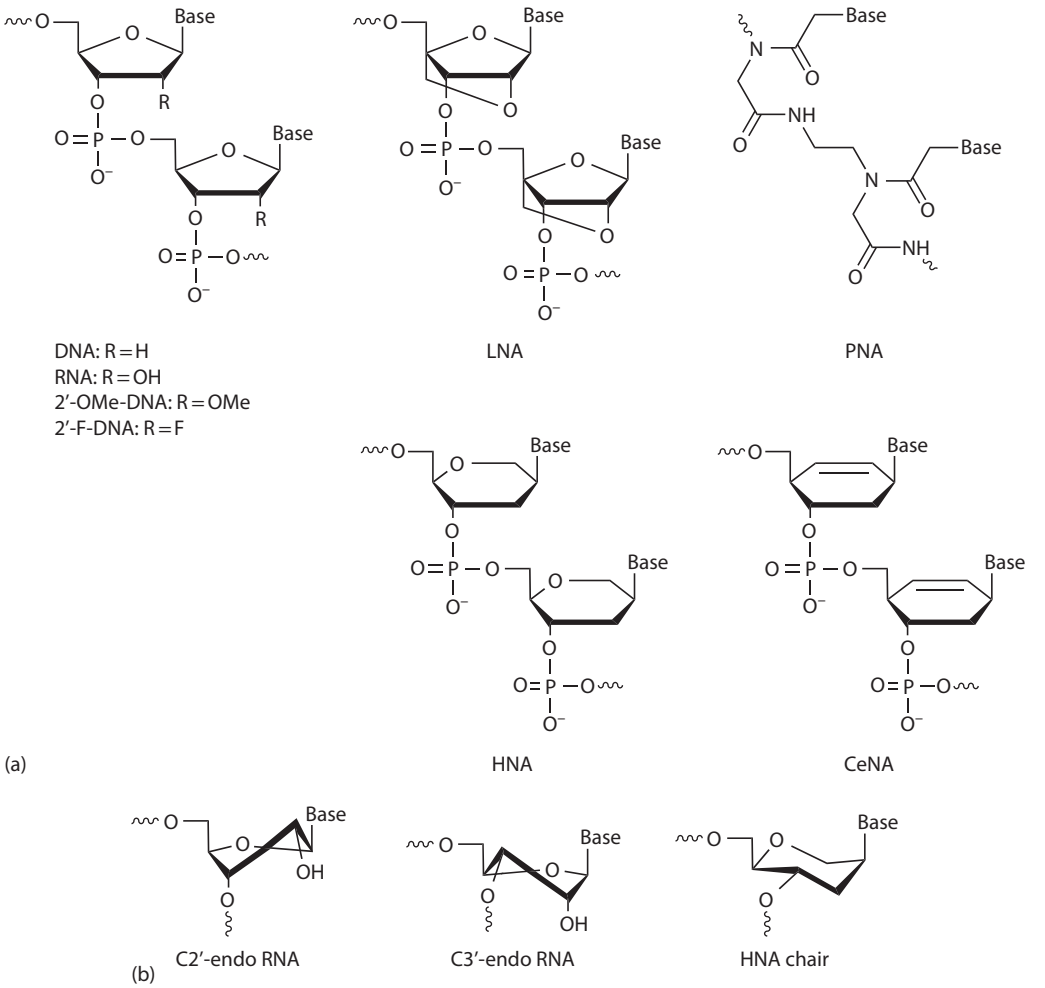

FIGURE 6.9 Examples on backbone-modified nucleic acid analogs. (a) Substitution of DNA/RNA on the 2′ position with a fluoro or methoxy group results in 2′-F-DNA and 2′-MeO-DNA, respectively. In locked nucleic acid (LNA), the ribose moiety of RNA is modified with an extra bridge connecting the 2′ oxygen and 4′ carbon. In peptide nucleic acid (PNA), the deoxyribose-phosphate backbone of DNA is replaced with *N*-(2-aminoethyl)-glycine units. In hexitol nucleic acids (HNA) and cyclohexene nucleic acids (CeNA), the sugar moiety is altered to anhydrohexitol and cyclohexenyl, respectively. (b) The electronegative 2′-hydroxy substituent of RNA influences the conformation of the sugar moiety so that RNA is predominantly found in the bioactive C3′-endo conformation. The anhydrohexitol chair conformation found in HNA resembles the C3′ endo conformation of ribose.