Hydrophobicity is thought to underlie self-assembly in biological systems. However, the protein surface comprises hydrophobic and hydrophilic patches, and understanding the impact of such a chemical heterogeneity on protein self-assembly in water is of fundamental interest. Here, we report structural and thermodynamic investigations on the dimer formation of full-length amyloid-β proteins in water associated with Alzheimer’s disease. Spontaneous dimerization process—from the individual diffusive regime at large separations, through the approach stage in which two proteins come close to each other, to the structural adjustment stage toward compact dimer formation—was captured in full atomic detail via unguided, explicit-water molecular dynamics simulations. The integral-equation theory of liquids was then applied to simulated protein structures to analyze hydration thermodynamic properties and the water-mediated interaction between proteins. We demonstrate that hydrophilic residues play a key role in initiating the dimerization process. A long-range hydration force of enthalpic origin acting on the hydrophilic residues provides the major thermodynamic force that drives two proteins to approach from a large separation to a contact distance. After two proteins make atomic contacts, the nature of the water-mediated interaction switches from a long-range enthalpic attraction to a short-range entropic one. The latter acts both on the hydrophobic and hydrophilic residues. Along with the direct protein-protein interactions that lead to the formation of intermonomer hydrogen bonds and van der Waals contacts, the water-mediated attraction of entropic origin brings about structural adjustment of constituent monomer proteins toward the formation of a compact dimer structure.