Designing molecular spacers for multivalent ligands by modeling and simulation methods

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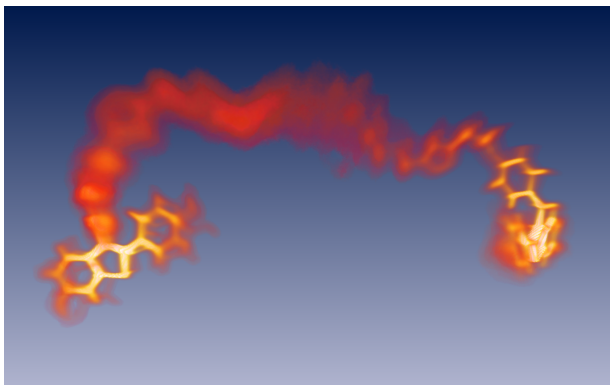

Multivalency is the chemical interaction of a ligand system that is equipped with several identical binding sites on a multimeric receptor system. It plays a decisive role in the self-organization of matter, as well as in recognition processes and signal transduction in biological systems. Multivalent ligands, when presented at a defined distance and direction on a selected scaffold, can cause a disproportionaly high increase of the binding constants with a corresponding multivalent receptor, and thus completely shift the equilibrium in favor of the ligand-receptor complex. A determining factor in multivalent binding processes is the molecular spacer (sometimes also denoted as linker) used to bridge the separate ligands. A molecular spacer not only has to cover the correct distance between receptor binding sites, but should also allow for convenient binding of the attached ligands without introducing additional energy barriers. Furthermore, the inevitable loss of spacer entropy at ligand binding has to be minimized in order to improve binding constants. We are going to introduce our computational studies on the design of molecular spacers, talk about the design paradigms we have found, and give different biological example systems where multivalent binding is applicable.

[1] A. Bujotzek, M. Shan, R. Haag, M. Weber, *J. Comput. Aided Mol. Des.*, **2011**, *25(3)*, 253-262.