The theory of the Nuclear Overhauser Effect (NOE) is far from trivial. Fortunately, for basic NOE studies, it is sufficient to know that the NOE depends on:

- \(1/r^6\) of the distance between the protons (well known fact!)
- the Larmor frequency \(\omega_0\) (400, 500 MHz etc.) which is proportional to the magnetic field
- the correlation time \(\tau_c\)

The correlation time \(\tau_c\) (*) itself is a function of

- the viscosity of the sample
- temperature of the sample
- the size of the dissolved molecules
The graph summarizes experimental (solid symbols) and calculated results (open symbols) based on measuring NOEs (not ROEs) of molecules of increasing molecular size but otherwise similar nature: from maltose (2 sugar units, m.w. ca. 340) to maltoheptose (7 sugar units, m.w. ca. 1150). Extrapolation to 10 units (m.w. ca. 1650) is also provided in the graph. **Every marked point (diamond, cross, square etc.) represents a situation where no NOEs are observed, even when the protons are in very close proximity.** The influence of temperature is evident from the left side scale, viscosity changes were not considered, i.e. taken as a more or less unchangeable feature of the sample (largely determined by the solvent).

**Example** Please note that to illustrate the behaviour of NOEs, the graph is interpreted as a *precise* tool when in fact is only an estimation but in this way it is easier to see what happens. Lets look at an NMR sample of maltohexaose (6 hexose units) with a m.w. of 990 measured at 300 K which is the default on all our spectrometers (27°C). At m.w. 990/300 K NOEs are almost zero at 500 MHz (the zero-NOE triangle is almost precisely located at m.w. 990/300 K). The NOEs are expected to be very small and positive (above the zero-NOE triangle). Measuring the same sample at 600 MHz and 300 K, the NOEs will become negative but stronger in absolute terms (m.w. 990/300 K is below the 600 MHz zero-NOE square at m.w. 990). Clearly, even better would be to move up to 800 MHz: stronger negative NOEs. On the other extreme at 300 MHz the NOEs should also be strong and positive. This is true in principle BUT there is a catch: the overall lower sensitivity of low field instruments makes it quite hard to measure NOEs. In comparison to e.g. GCOSY correlations, NOEs are much weaker and so lower field is not as good as one might think. Whether NOEs are positive or negative is not much of a concern but the fact that they can be zero or nearly zero is. Obviously, what has been said here can be applied to other combinations of m.w. and temperature.

**Conclusion:** **NOEs can be zero under certain circumstances** even when the distance between protons is short.

(*) The entire formula for $\tau_c$ is given by

$$\tau_c = \frac{4\pi\eta a^3}{3kT}$$

$\tau_c$: correlation time

$\omega_o$: Larmor frequency (e.g. 400, 600 MHz)

$\eta$: viscosity of the solution

$a$: radius of the spherical particles in solution

$k$: Boltzmann constant ($1.38 \times 10^{-23}$ JK$^{-1}$)

$T$: temperature in K