Eq. 1 $$\eta_I\{S\} = \frac{I - I_0}{I_0} 100$$

The Origin of the Nuclear Overhauser Effect

Description

An accurate definition of the Nuclear Overhauser Effect (NOE) is the change in intensity of one resonance when the spin transitions of a dipolarly coupled nucleus are somehow perturbed from their equilibrium populations. This perturbation is achieved by either saturating a resonance, i.e., equalising the spin population differences across the corresponding transitions (then it is called *steady-state* NOE), or inverting it by reversing the population differences across the transitions (transient NOE). Thus, the magnitude of the NOE observed for spin I when spin S is perturbed ($n_I S$) is expressed as the percentage of relative intensity change between the equilibrium intensity (I_0) and that in the presence of the NOE (I), so that

Eq. 1 $$\eta_I\{S\} = \frac{I - I_0}{I_0} 100$$

The intensity changes caused by NOE can be either positive ($I>I_0$) or negative (I_0) depending on the motional properties of the molecule and the signs of the magnetogyric ratios of the spins involved.

To facilitate the understanding of the origin of the NOE, we will consider a system only formed by two homonuclear spin-1/2 nuclei of ^1H (positive magnetogyric ratio), I and S, contained in a rigid molecule that tumbles isotropically in solution, i.e., it does not show any preferential axis about which to rotate. In this idealistic system both protons are not scalarly coupled ($J_{IS}=0$) but they are enough close in space as to share dipolar coupling, this is, magnetic interaction through space between two spins such that both of them are able to sense the presence of the other dipolar-coupled partner. Therefore, upon selective saturation of ^1H nucleus S, the spin populations of nucleus I will be also perturbed and the system will try to come back to the initial equilibrium situation. Although equilibrium recovery takes place by different relaxation mechanisms it is only the cross-relaxation pathways, characterized by the W_0 (zero-quantum) and W_2 (double-quantum) transition probabilities (or rates), those responsible for the NOE development (Fig. 1A). The rate at which S magnetization is transferred to I magnetization is proportional to the (W_2-W_0) term, known as *cross-relaxation* rate constant Ã•Æ?$_{IS}$.

It is important to note that the W_0 and W_2 cross-relaxation pathways always compete with one another, with the dominant mechanism dictating the sign of the observed NOE and being dependent on the re-orientational dynamics properties of the molecule (Fig. 1B). Thus, a small molecule performing a rapid tumbling in solution, which corresponds to a short correlation time Ã•â??$_c$, will generate fluctuating local magnetic fields of high frequency. On the other hand, a macromolecule, featuring slow tumbling rates (long Ã•â??$_c$) will give rise to low-frequency magnetic fields. These fluctuating local fields are the responsible for inducing cross-relaxation when their oscillation frequencies correspond to the W_0 and/or W_2 transitions. Furthermore, those of low-frequency are significantly more efficient than the high-frequency magnetic fields in activating the *cross-relaxation* pathways, due to the different spectral density functions that describe the fast, intermediate and slow motions (Fig. 1B). Therefore, for slow tumbling the lower energy W_0 process predominates such that a negative NOE (I_0) is efficiently developed (Fig. 1B and 2). On the contrary, W_2 (higher energy) is the dominant mechanism acting during cross-relaxation of fast tumbling molecules, so that a positive NOE (I_0) is observed (with lower intensity compared to negative NOE; see Fig. 2). For and intermediate tumbling rate (usually medium-size molecules), the NOE will be either positive or negative depending on the dominant *cross-relaxation* process. Also, it has to be noted that there are two limits of motion in terms of the magnitude of the NOE developed. Thus, the rapid tumbling of a small molecule in a low viscosity solvent will favour the W_2 process to a large extent, displaying high positive homonuclear NOEs. This is called *extreme narrowing limit*. In contrast, the slow molecular tumbling of large molecules in high viscosity solvents will stay in the *spin-diffusion limit,* characterised by an enormously favoured W_0 mechanism, and thus, highly negative homonuclear NOEs.

Apart from the *cross-relaxation* mechanisms, only responsible for the NOE growth, single quantum relaxation pathways (W_1) activate to re-establish the equilibrium population differences of the non-saturated nucleus (I in the simplified model) as soon as the NOE begins to develop, so acting against the NOE build-up. Thus, if W_1 relaxation happens to be rather more efficient than W_0 and W_2 pathways together, the macroscopic magnetization will probably come back to the equilibrium before a measurable NOE is developed and this will not be observed. The NOE therefore results from the balance between distinct competing relaxation pathways, with its sign depending on the W_2-W_0 difference and its magnitude on the three W_0, W_1 and W_2 rates (see Eq. 2, derived from the so-called Solomon equation).

Eq. 2

$$\eta_I\{S\} = \frac{\gamma_S}{\gamma_I}\left(\frac{W_2 - W_0}{W_0 + 2W_1 + W_2}\right)$$

So, the ideal conditions for the NOE to be observed are inefficient W_1 processes and efficient W_0 or W_2 transitions.

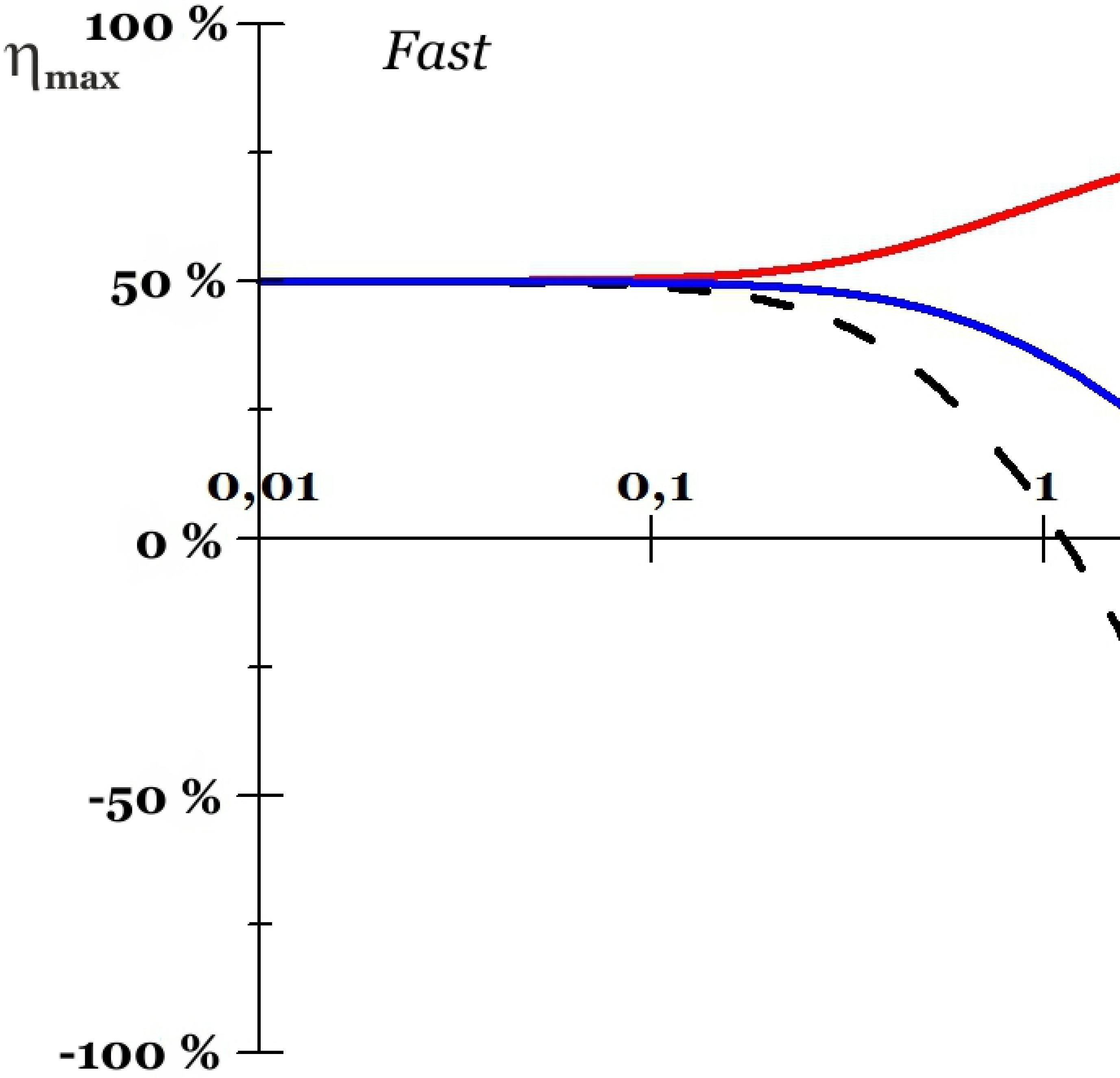

Figure 2. Variation of the maximum theoretical homonuclear steady-state enhancement (n max), for NOE (black dashed line), TROE (blue bold line) and ROE (red bold line) experiments, in a two-spin system as a function of molecular tumbling rates in logarithmic scale (defined by the dimensionless parameter Ã•â?°0Ã•â??c, with Ã•â?°0 being the spectrometer observation frequency and Ã•â??c the rotational correlation time). The region of fast motion is the extreme narrowing limit and that of slow motion is the spin-diffusion limit.

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