III. TECHNIQUES TO LOCATE A TRANSITION STATE

In addition to the location of minima, the calculation of transition states and reaction pathways is an interesting task for Quantum Chemistry (QC). The calculation of these properties can be an important complement to experimental data, since information about the transition state geometry, reaction pathways, and activation energies is often difficult to obtain. When interested in isomerization reactions and structural transitions, MM methods can be applied. When studying chemical reactions where bond breaking is involved, QM methods are required most times.

But there should be one warning from the beginning: the QC calculation of reaction rates from transition state theory is difficult, since due to the exponential factor a chemical accuracy $\leq$ 1kcal/mole is necessary to get meaningful rates. This requires high level calculations, which are often computationally too expensive, SE, HF or DFT methods are mostly not accurate enough. However, information about mechanisms and relative rates is much more easy to obtain.

Methods for locating transition states can be divided into so called local and global optimization methods. Local methods use local information only, i.e. the gradient at one point of the energy hypersurface. If we specify a point 'sufficiently' close to the transition state (TS), the Hessian will have one negative eigenvalue (see Chap.2, exercise 4.). We can the use the NR method to follow this eigenvalue until the TS is reached.

The negative eigenvalue exists only in a neighborhood of the TS. Consider as an example the function

$$f(x) = x^4 - x^2.$$

as shown in Fig. 22. The second derivative is

$$f''(x) = 12x^2 - 2.$$

That means, the second derivative is negative for $|x| \leq \sqrt{1/6}$.

Global optimization methods start from the knowledge of the product **and** reactant

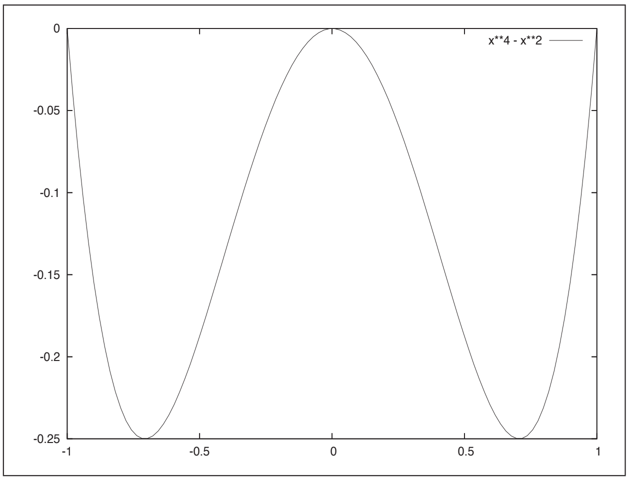

FIG. 22: f(x) = $x^4 - x^2$

structures and calculate the whole pathway connecting them, of course including the transition state. Pathways of interest are so called mimimum energy pathways, as shown in Fig. 23. In simple cases, they can be obtained by steepest descent optimization starting at the (first order) saddlepoint (TS), moving in both directions indicated by the negative eigenvalue. In more difficult cases, methods like CPR or NEB are used.

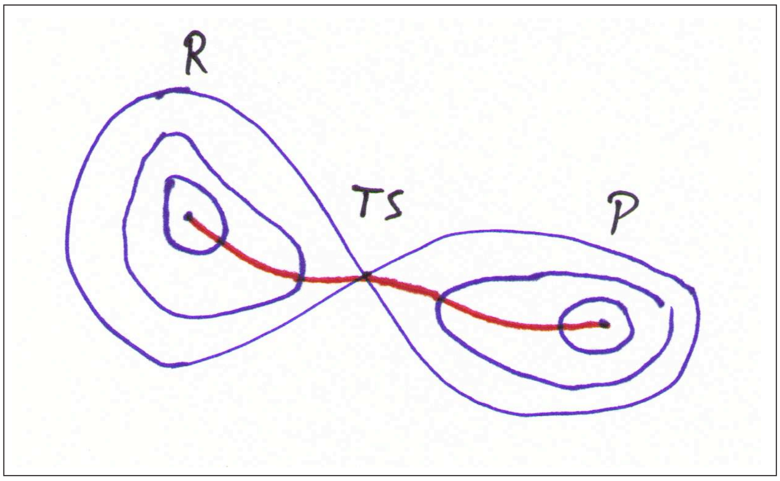

FIG. 23: The minimum energy path

A. Conjugate Peak Refinement: CPR

The CPR method developed by Fischer and Karplus in the early 90s (Chem. Phys. Lett. 194 (1992) 252) is not described in mathematical detail, but its principle is illustrated in

Fig. 24. The starting point of the method are the structures of product (P) and reactant

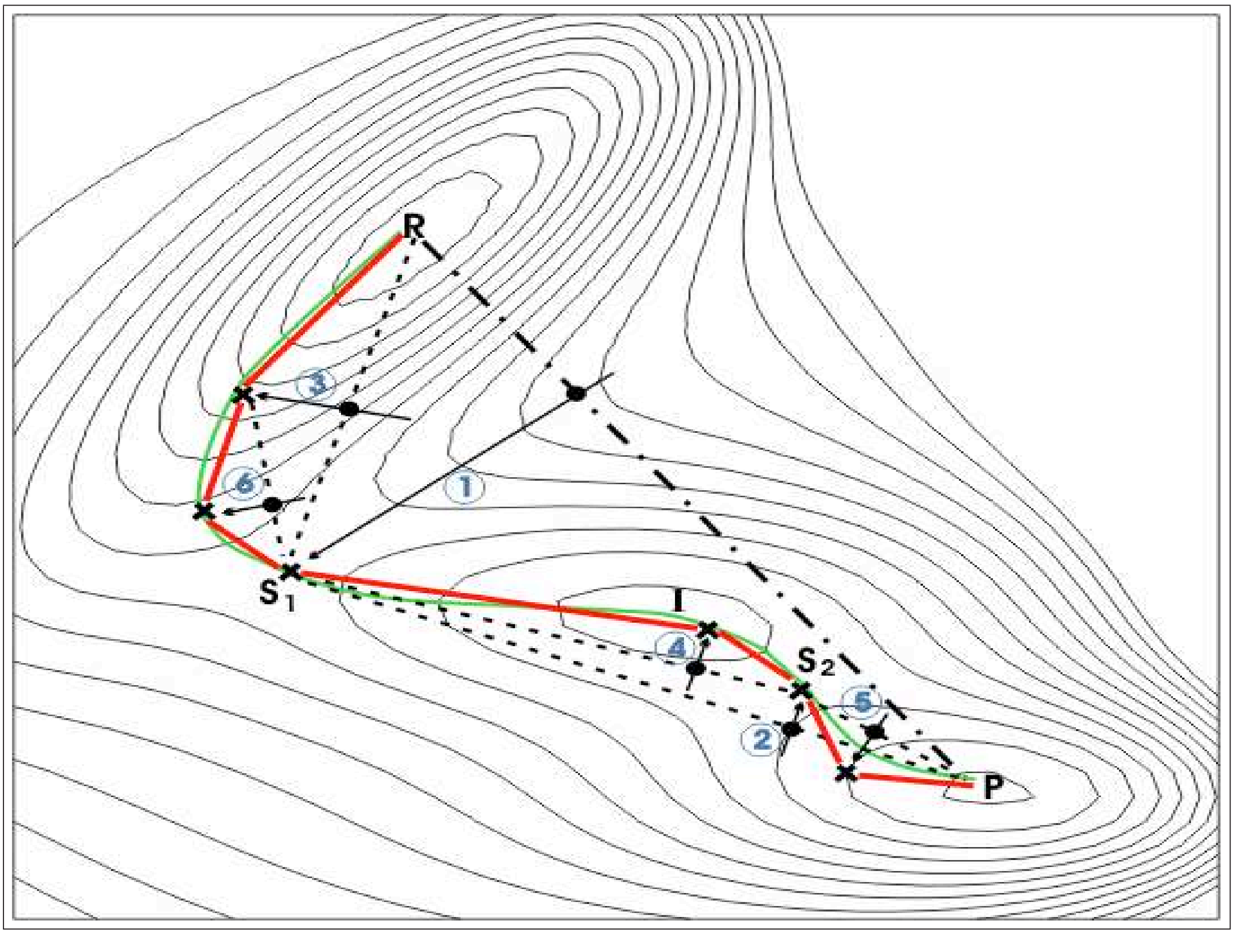

FIG. 24: Scheme of the CPR method from: http://spider.iwr.uni-heidelberg.de/fischer/research/cpr.html

(R) , which have to be well optimized using techniques described above. From these points, CPR works by performing these steps:

- Interpolate the geometries of P and R along the connecting line.
- Find the point with maximum (MAX) energy along this line.
- Optimize the the geometry starting from MAX **conjugate** to the direction $\overrightarrow{EP}$ to find the point E_1.
- Now interpolate between R and S_1 and S_1 and P and repeat the procedure.

A path of minimal energy (MEP: minimum energy path) will result from this procedure. Methods like CPR (NEB) are compuationally very costly, i.e. several 1000 to 10000 energy and gradient evaluations are necessary, therefore, it can be applied only for fast QM methods.

B. Nudged Elastic Band: NEB

The NEB method starts like CPR from the optimized R and P structures and interpolates between them by constructing N copies (images), Fig. 25. The interpolation is illustrated for a simple proton transfer reaction in 26. The $\overrightarrow{x_i}$ denote the coordinates of all atoms in copy i, i=1,..N. We have the potential energy of the i-th system, $V(\overrightarrow{x_i})$. The basic idea is to optimize the energy of all N systems simultaneously, but to keep the N-2 non-minimum structures along the path, we put springs between them, i.e. we optimize the energy:

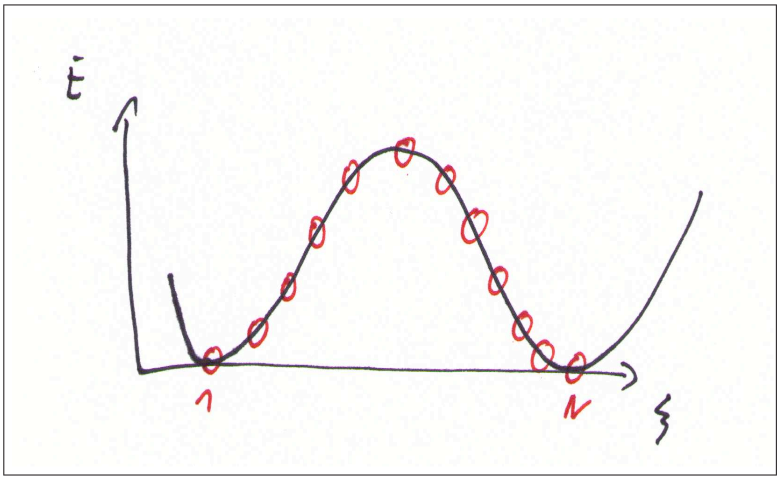

FIG. 25: Interpolation between R and P

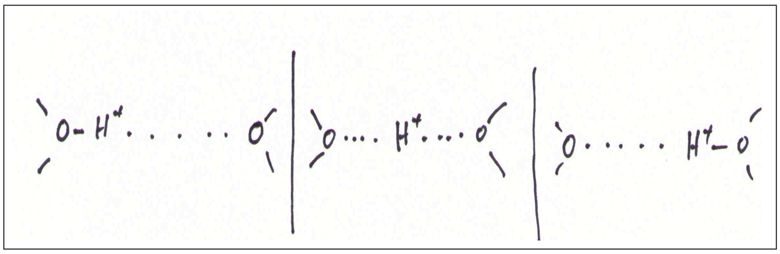

FIG. 26: R, TS and P images for a simple proton transfer reaction.

$$E = \sum_{i=1}^{N} V(\overrightarrow{x_i}) + \sum_{i=1}^{N-1} 0.5k(\overrightarrow{x_{i+1}} - \overrightarrow{x_i})^2,$$

a cartoon of the situation is given in Figs. 27 and 28. We can easily imagine, that the

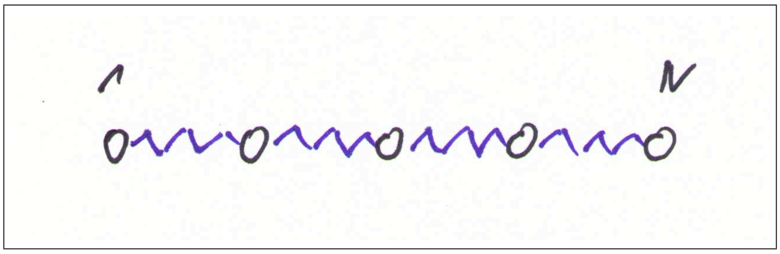

FIG. 27: Springs between the copies.

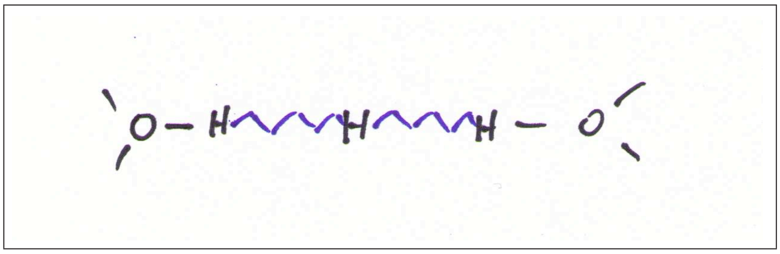

FIG. 28: NEB-springs between the R, TS and P images, where only the central H+ moves. The three images connected by the springs are different only in the H position.

springs with force constants k 'hold' the images even in regions with large forces, depending on the spring constant. Now, two problems arise:

- If the spring constants are too small, the images at steep potentials will slide down the potential energy hill, generated by $\sum_i V(\overrightarrow{x_i})$, and all images will be in the valley, none be at or close to the transition state.
- If the spring constants are too large, the images will move away from the MEP, the corners will be cut.

To get this clearer, lets consider the forces parallel and perpendicular to the NEB path as given by the sequence of images i=1,...N (Fig. 29). We can calculate the tangent vector on the path:

$$\overrightarrow{\tau_i}$$

The forces, which make the images slide down the hill are the contributions of $V(\overrightarrow{x_i})$ parallel to the NEB path:

$$\nabla V(\overrightarrow{x_i}) * \overrightarrow{\tau_i}.$$

Therefore, we project those out to get the contributions of the potential perpendicular to the NEB path:

$$[F_i^s]_\perp = [\nabla V(\overrightarrow{x_i})]_\perp = \nabla V(\overrightarrow{x_i}) - \nabla V(\overrightarrow{x_i}) * \overrightarrow{\tau_i}. \tag{III.1}$$

The forces leading to the corner cutting come from the contributions of the springs perpendicular to the NEB path $[F_i^s]_\perp$, therefore, we consider only those parallel to the path:

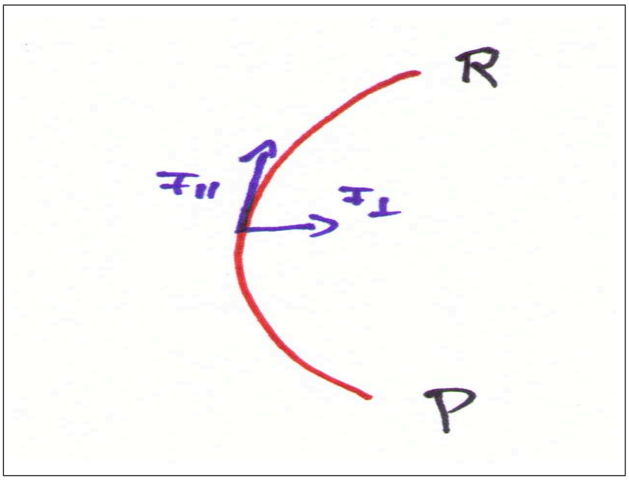

FIG. 29: Forces parallel and perpendicular to the NEB path.

$$[F_i^s]_{||} = [\nabla V(\overrightarrow{x_i})]_{||} = [k(\overrightarrow{x_{i+1}} - \overrightarrow{x_i}) - k(\overrightarrow{x_i} - \overrightarrow{x_{i-1}})]\, \overrightarrow{\tau_i} \tag{III.2}$$

If we now optimize the whole system only using the forces from the equations III.1 and III.2, we will find images evenly spaced along the NEB path, perfectly following the MEP. Practically, we construct all the images, calculate the tangents τ_i and remove the forces of the MM force field which are parallel to the tangents. Then we add the forces due to the springs, again projected. We will move the atoms then due to the resultant forces.

We can use a SD optimizer then, CG and NR do not work due to the following reason: When deriving the CG and NR methods, we always made use of the fact, that the forces (gradients) are the gradients of the energy function, since we used the Hessian of the energy. In NEB, this is no longer the case, therefore we can not use these optimizers and have to stick to the very inefficient SD method.

CPR and NEB are powerful tools, when the reaction considered is dominated by the potential energy, protein dynamics and entropy do not play a significant role. If the protein fluctuates a lot, the reaction can be different for different protein conformations. An example is shown in Fig. 30, where the barrier and reaction energy varies over several kcal/mole. Clearly, the protein undergoes important structural fluctuations during its dynamics, meeting various local minima. For many proteins, the notion of a single global minimum does not make sense any more. To describe a reaction, we have to average over all the reaction energies for the various minima. Doing this, we leave the potential energy surface and consider the free energy surface. For that, we have to describe the molecular dynamics of the protein.

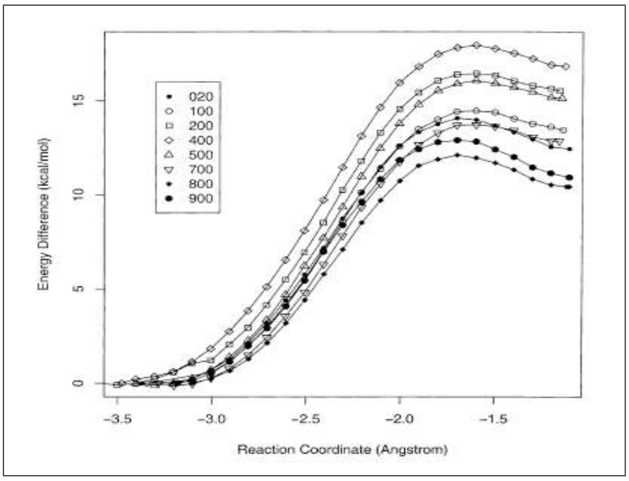

FIG. 30: Energy profiles (acylation reaction) for various protein conformations: from Zhang et al. JPCB 107 (2003) 4459.