Menschutkin reaction involves the conversion of two neutral reagents (amine and haloalkane) into two charged products (cationic amine and halide anion). The reaction with primary amines as a nucleophile and chloride as a leaving group is very unfavorable in the gas phase and also faces a considerable activation barrier.

The reaction occurs in the solution and displays a large solvent effect. It would be interesting to test if modern QM/MM methodologies allow quantitative modeling of this reaction in different solutions. One of the first tasks in such QM/MM modeling is the determination of the geometry of the transition state in the solution. This task is considerably simplified if one has a good initial guess for the bond-making and bond-breaking distances in the transition state. Here the question arises: given the TS structure in the gas phase, how can one guess what a transition state in the solution looks like?

A qualitative insight into the effect of the solvent on the transition state structure can be gained from a simple analytical model in which the reactant and product potential energy wells are described by harmonic potentials. The Mathematica notebook below illustrates this approach.

We will start with the analysis of the gas phase reaction, then consider a solvent that interacts with the reactants and products equally well (e.g. apolar solvent such as cyclohexane for Menschutkin reactions) and finally look at the effect of a solvent that preferentially stabilizes the reaction products (e.g. a polar solvent, such as methanol for Menschutkin reaction)

Remove["Global`*"]
(* Define the potential, could be more complex that quadratic in principle *)
quadratic := a x^2 + b x + c

(* Reactant state is described by a quadratic potential (to model C-Cl stretching) *)
rgas = quadratic /. {a -> 1, b -> 0, c -> 1};

(* Product state is described by a quadratic potential (to model N-C stretching) *)
pgas = quadratic /. {a -> 1, b -> -2, c -> 2.5};

(* Plot the reactant state and product state potentials *)
Plot[{rgas, pgas}, {x, -2, 2}, PlotRange -> {{-2, 2}, {0, 3}},
PlotStyle -> {Black, Black, Blue, Blue}, Axes -> {True, True}]

(* Find stationary points; TS is at the intersection of the two potentials: *)
rmin = x /. Flatten[Solve[D[rgas == 0, x]]]
pmin = x /. Flatten[Solve[D[pgas == 0, x]]]
tspos = x /. Flatten[Solve[rgas == pgas, x]]; 
Print["Transition State in the Gas Phase is at x = ", tspos] 
0
1

Transition State in the Gas Phase is at x = 0.75

(* Calculate energies of states and energy differences *)
Print["Energy of the Reactant State at the gas phase minimum is ", rgas /. x -> rmin]
Print["Energy of the Product State at the gas phase minimum is ", pgas /. x -> pmin]
Print["Reaction Energy (Product-Reactant) is ", (pgas /. x -> pmin) - (rgas /. x -> rmin)]
Print["Activation Energy (TS-Reactant) is ", (rgas /. x -> tspos) - (rgas /. x -> rmin)]

Energy of the Reactant State at the gas phase minimum is 1
Energy of the Product State at the gas phase minimum is 1.5
Reaction Energy (Product-Reactant) is 0.5
Activation Energy (TS-Reactant) is 0.5625
- **Solvent Effect:** we first solvate the reactant state and the product state equally well

\[
\begin{align*}
\text{rsol} &= \text{rgas} - 0.4; \\
\text{psol} &= \text{pgas} - 0.4; \\
\text{Plot} &\left(\left\{\text{rgas}, \text{pgas}, \text{rsol}, \text{psol}\right\}, \{x, -2, 2\}, \text{PlotRange} \rightarrow \{-2, 2\}, \{0, 3\}, \text{PlotStyle} \rightarrow \text{Black, Black, Thick, Blue}, \{\text{Thick, Blue}\}, \text{Axes} \rightarrow \text{True, False}\right) \\
\text{tspos} &= x/. \text{Flatten}[\text{Solve}\left(\text{rsol} = \text{psol}, x\right)]; \\
\text{Print}["\text{Transition State in the Solution is at } x = \), tspos]; \\
\text{Print}["\text{Reaction Energy (Product-Reactant) is } \), (\text{psol} / . x \rightarrow \text{pmin}) - (\text{rsol} / . x \rightarrow \text{rmin})]; \\
\text{Print}["\text{Activation Energy (TS-Reactant) is } \), (\text{rsol} / . x \rightarrow \text{tspos}) - (\text{rsol} / . x \rightarrow \text{rmin})];
\end{align*}
\]

![Diagram showing solvation effects](Transition State in the Solution is at x = 0.75)

Reaction Energy (Product-Reactant) is 0.5

Activation Energy (TS-Reactant) is 0.5625
- **Solvent Effect:** we first solvate the reactant state and the product state equally well

\[
\begin{align*}
rsol &= rgas - 0.4; \\
psol &= pgas - 0.8; \\
\text{Plot}[\{rgas, pgas, rsol, psol\}, \{x, -2, 2\}, \text{PlotRange} \to \{\{-2, 2\}, \{0, 3\}\}, \\
\text{PlotStyle} \to \{\text{Black, Black, \{Thick, Blue\}}, \{\text{Thick, Blue}\}\}, \text{Axes} \to \{\text{True, False}\}]
\end{align*}
\]

\[tspos = x/. \text{Flatten}[\text{Solve}[rsol == psol, x]];\]
Print["Transition State in the Solution is at x = ", tspos]
Print["Reaction Energy (Product-Reactant) is ", (psol /. x \to pmin) - (rsol /. x \to rmin)]
Print["Activation Energy (TS-Reactant) is ", (rsol /. x \to tspos) - (rsol /. x \to rmin)]

- **Notice that when the solvent preferentially stabilizes the products, the transition state becomes more reactant like (i.e. the forming N-C bond will be longer and the breaking C-Cl bond will be shorter in the transition state for the Menschutlin reaction.**

Transition State in the Solution is at x = 0.55

Reaction Energy (Product-Reactant) is 0.1

Activation Energy (TS-Reactant) is 0.3025