Solvent Effects on Transition States:

Analytical Model for Menschutkin reaction

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- 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.

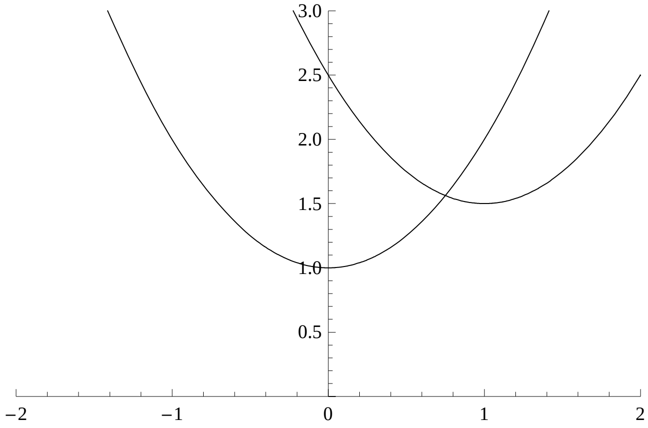
  The reaction occurs in the solution and displays a large solvent effect. It would be interesting to test if modern QM/MM methodologies allow quantitative modeling of this reaction in different solutions. One of the first tasks in such QM/MM modeling is the determination of the geometry of the transition 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]
```

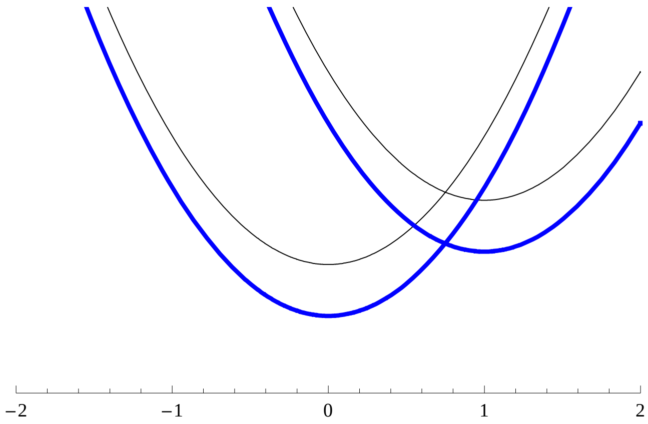
```
0

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 stae equally well**

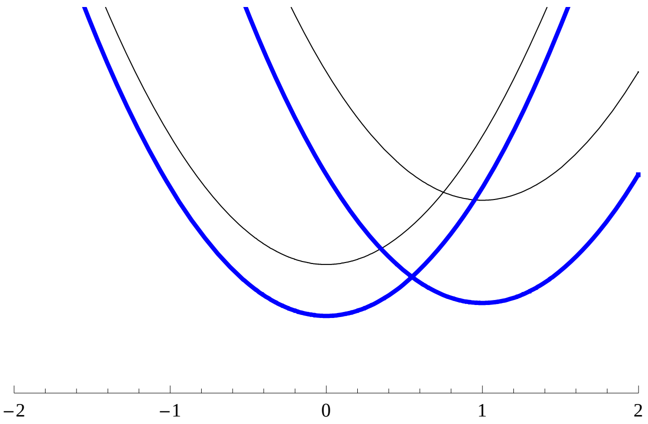
```
rsol = rgas - 0.4;
psol = pgas - 0.4;
Plot[{rgas, pgas, rsol,  psol}, {x, -2, 2}, PlotRange → {{-2, 2}, {0, 3}},
 PlotStyle → {Black, Black, {Thick, Blue}, {Thick, Blue}}, Axes → {True, False}]

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



```
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 stae equally well**

```
rsol = rgas - 0.4;
psol = pgas - 0.8;
Plot[{rgas, pgas, rsol,  psol}, {x, -2, 2}, PlotRange → {{-2, 2}, {0, 3}},
 PlotStyle → {Black, Black, {Thick, Blue}, {Thick, Blue}}, Axes → {True, False}]

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



```
Transition State in the Solution is at x = 0.55

Reaction Energy (Product-Reactant) is 0.1

Activation Energy (TS-Reactant) is 0.3025
```

- **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 beaking C-Cl bond will be shorter in the transition state for the Menschutlin reaction.**