Abstract:
The aminolysis of carbonyl compounds is an essential functional group transformation that has proven to be highly relevant in organic and biological chemistry. Despite the vast use of this reaction, the details of the mechanistic pathway still being elucidated and the critical transition structures remain in debate. A long history of experimental studies\(^{1-11, 18-20}\) has been carried out in order to study the mechanism of aminolysis. Recently, computational studies\(^{12-17, 23-27}\) have been employed in an attempt to gain more detailed knowledge of the mechanism of aminolysis.

Computational studies have so far considered three possible mechanistic pathways (Figure 1) for the uncatalyzed aminolysis of esters and related compounds.\(^{14}\) The three mechanistic possibilities that have been considered computationally are: (1) a concerted mechanism where all bond forming and bond breaking events occur in a single step; (2) a stepwise addition/elimination pathway involving neutral intermediates; and (3) a stepwise pathway involving zwitterionic intermediates.

In 2000, Drueckhammer and co-workers studied computationally the aminolysis of oxoesters and thioesters.\(^{14}\) In this study they investigated the possibilities of the uncatalyzed and water-catalyzed aminolysis reaction via concerted and stepwise neutral pathway. Gas phase calculations were performed at the MP2/6-31+G* and MP2/6-31G** level of theory and solvent effects were studied using the SM3 solvation model. Based on his results, Drueckhammer concluded that the water-catalyzed stepwise mechanism was favored over the concerted pathway. In 2003 Schaefer and co-workers studied the aminolysis of methyl formate with ammonia using HF/6-31G* calculations in the gas phase along with a PCM solvent model for acetonitrile.\(^{15}\) Schaefer studied the concerted and stepwise neutral mechanism and proposed that the process could be catalyzed by a second amine molecule rather than by water. The role of the
second molecule of ammonia was to facilitate the proton transfer steps along the reaction coordinate. In contrast to these results, Ilieva & Morokuma reported in 2003 that the concerted mechanism was favored over the stepwise pathway in calculations on the aminolysis of 2-benzoxazolinone with methylamine using B3LYP/6-31G* calculations.  

Intriguingly, the results obtained by computational studies are not in agreement with what has been observed experimentally. A long history of studies have found that aminolysis is usually general base-catalyzed.\textsuperscript{1-11, 18-20} The details of this general base catalysis have been elucidated by a number of experiments.\textsuperscript{18-20} Jencks and Yang reported a particularly relevant experiment in 1988, were a stepwise zwitterionic mechanism was proposed to be involved on the aminolysis of methyl formate with aniline (Figure 2).\textsuperscript{20} The mechanism proposed by Jencks and Yang, involves the formation of a zwitterionic tetrahedral intermediate (T\textsuperscript{0}) after the nucleophilic addition of the amine, this is then followed by the encounter between the general base and T\textpm before the proton transfer takes place. Once the proton has been transferred, diffusion between the two species leads to the formation of intermediate T\textsuperscript{0}, which is in equilibrium with T\textsuperscript{0}, and finally these tetrahedral intermediates decompose to afford the products of the reaction.

\begin{center}
\begin{align*}
\text{H-N} & \quad \text{C=O} \quad K_T \quad \text{H-N} \quad \text{C=O} \quad \frac{k_a\text{[B]}}{k_a} \quad \text{B+H-N-C-O} \quad \frac{k_p}{k_p} \\
\text{BH}^+ \quad \text{H-N-C-O} \quad k_b \quad \text{N-C-O-H} \quad k_0 \quad \frac{k_2\text{[B]}}{k_2} \quad \text{products}
\end{align*}
\end{center}

**Figure 2.** Proposed trapping mechanism of aminolysis by Jencks.\textsuperscript{20}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig2}
\caption{(A) Bronsted plot for general base catalysis of the aminolysis of methyl formate by aniline at 25°C. (B) Solvent deuterium isotope effects for general base catalysis of the aminolysis of methyl formate by aniline.\textsuperscript{20}}
\end{figure}
In addition, evidence that suggests the aminolysis reaction to be general base-catalyzed with diffusion controlled proton transfer as part of the rate-determining step was presented on this study (Figure 3). The Bronsted plot shown in figure 3 (A) illustrates how the reaction rate is linearly dependent upon the pK$_a$ of the conjugate acid of the general base involved in the reaction. However, when the pK$_a$ of the conjugate acid of the general base used is above 5.3, the rate of proton transfer reaches a plateau that is consistent with encounter-limited or diffusion controlled proton transfer that unambiguously shows that an intermediate is involved in the reaction. Interestingly, around this same pK$_a$ value of 5.3, the reaction exhibits a large, $k_H/k_D = 5$, solvent deuterium isotope effect that supports the idea that a proton transfer from an initial zwitterionic intermediate is the rate-limiting step, this is consistent with the mechanism shown in figure 2.

Nonetheless, studies of isotope effects did not appear to support the mechanism proposed by Jencks. In 1997, Marlier and colleagues presented a heavy-atom and deuterium isotope effects on the hydrazinolysis of methyl formate (Figure 4). Marlier observed a primary normal $^{13}$C carbonyl isotope effect of 1.020 that suggested that the carbonyl carbon atom was undergoing a sigma bonding change in the rate-limiting step. This result along with the idea of the proton transfer also occurring on the rate-limiting step lead Marlier to conclude that a concerted nucleophilic attack and general base removal of a proton from the nucleophile was involved in the rate-limiting step of this reaction.

![Figure 4. Summary of the isotope effects on the hydrazinolysis of methyl formate.](image)

Singleton and Merrigan later found that the $^{13}$C isotope effect did not necessarily implied carbon-nitrogen bond formation in the rate-limiting step. The isotope effects were re-interpreted to be consistent with Jencks proposed mechanism.

In conclusion, a long history of experimental studies have supported the general base-catalyzed stepwise zwitterionic pathway as the plausible mechanism for the aminolysis of esters and related compounds. In spite of this, recent computational studies still consider the uncatalyzed concerted and stepwise neutral pathways as the only reasonable possibilities according to their studies. It is highly important to keep in mind that computational studies of polar reactions represent a challenge in the gas phase; however this does not imply that such possibilities should be ruled out.
References: