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The Elusive Enamine Intermediate in Proline-Catalyzed Aldol Reactions: NMR Detection, Formation Pathway, and Stabilization Trends

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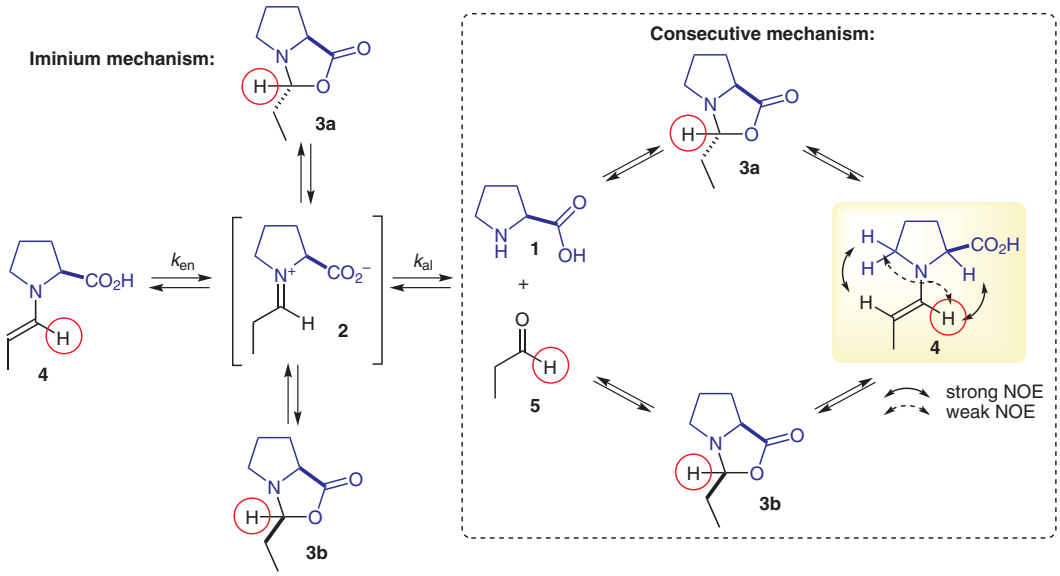
NMR Detection of the Enamine Intermediate in Proline-Catalyzed Aldol Reactions



Significance: An enamine intermediate in proline-catalyzed aldol reactions was indentified in situ by NMR studies on self-aldolization of aldehydes in DMSO. Only *E*-configured s-*trans*-enamines were detected in accordance with the generally accepted mechanism of enamine catalysis. The enamines were found to form *directly* from oxazolidinones (e.g., **3**), and not via central iminium or iminium-like intermediates (e.g., **2**) as evidenced by NMR exchange spectroscopy (EXSY). These results indicate a possible role of oxazolidinones in the catalytic cycle, beyond their involvement in 'parasitic equilibria'.

Comment: In enamine catalysis iminium species (e.g., **2**) are generally proposed as intermediates in the interconversion between aldehydes, enamines, and oxazolidinones. In the current paper, the iminium intermediate **2** was not detected by NMR spectroscopy, probably due to its low concentration. However, the absence of EXSY cross-peak (for the proton circled red in the Scheme) between aldehyde **5** and enamine **4** suggested that enamine **4** might not be formed via the iminium intermediate **2**, but directly from oxazolidinones **3**. A concerted E2 mechanism was recently proposed by Seebach (*Helv. Chim. Acta* **2007**, *90*, 425). As the unobserved **4**/**5** EXSY cross-peak might simply be below detection limit, more conclusive evidence was offered by the observation that the relative rate k_{al}/k_{en} (calculated from the volumes of EXSY cross-peaks of **5** and **4** with **3a** or **3b**) was highly dependant on the oxazolidinone from which the aldehyde and enamine originate. This excludes a common intermediate (e.g., **2**) and supports the consecutive mechanism.

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Organo- and Biocatalysis

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