Unveiling the Mechanism of Direct Amide Formation

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The amide bond is ubiquitous. Its formation is the most frequently used chemical transformation in medicinal chemistry. It is commonly taught in undergraduate chemistry that you cannot prepare an amide directly from a carboxylic acid and amine without pre-activation (*e.g.* via acid chloride or by addition of carbodiimides/catalysts) due to the formation of unreactive salt pairs. However, previous reports have shown that certain combinations of substrates can react in the absence of additives.[1] Despite the potential for this direct coupling to afford amides through a cheaper, cleaner, atomically efficient route, mechanistic studies into this additive-free reaction remain extremely limited.

This work employs *in-situ* ^{19}F-NMR spectroscopy to continuously monitor and analyse the kinetics of additive-free direct amide formation, and all without the need for water removal. The change in chemical shift and diffusion behaviour in NMR titrations reveal information about speciation, from which equilibrium constants (K_1, K_2) can be determined for each substrate pair. These findings provide evidence for the importance of the homoconjugate intermediate for enhanced reactivity. Isotopic effects (^{13}C, ^{15}N, ^{18}O) and computational studies provide additional mechanistic insight and show this to be a more complex reaction than first appears, with multiple equilibria contributing to the overall reaction rate.

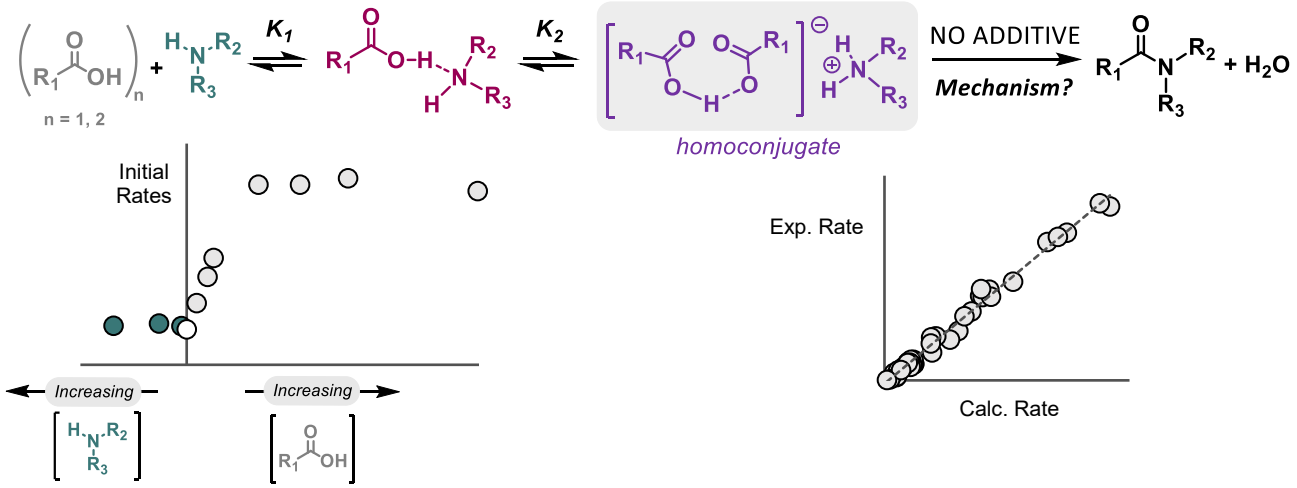

Figure 1. Evidence for the homoconjugate contributing to the rate of direct amide formation in a model that fits very well with all experimental data.

1 H. Charville, D. A. Jackson, G. Hodges, A. Whiting, M. R. Wilson, *Chem. Comm.*, **2012,** *48,* 666.