# Insights into controlling the rates of proton transfer

The transfer of a proton ($H^+$) between two sites (from an acid to a base) is a ubiquitous fundamental reaction which is involved in various key roles throughout chemistry and biology. Proton transfer reactions are invariably an important aspect of the action of natural and synthetic catalysts, but studying the transfer of a single proton in such systems is difficult because of the size of the catalysts and the complex multi-step (and sometimes multi-component) nature of these catalysts' reactions.

Studying proton transfer in relatively simple (small) compounds has revealed that the mechanism of all such reactions involves initial hydrogen-bonding of the acid (**A-H$^+$**) to the base (**B**) to form the precursor intermediate **A-H$^+$**…**B**, followed by movement of the proton from **A** to **B** and, finally, dissociation of **A** and **B-H$^+$** (Fig. 1, top line). Proton transfer reactions are usually very rapid with the slowest step being the diffusion together of the reactants **A-H$^+$** and **B**; a process which has a lifetime of *ca* 1 x $10^{-10}$ second. Consequently, observing the putative precursor intermediate is problematic. Recently, we have shown that in the protonation of certain nickel-sulfur compounds by weak acids not only is proton transfer slow but also the precursor intermediate is sufficiently long-lived to be detected (Fig. 1, bottom line).

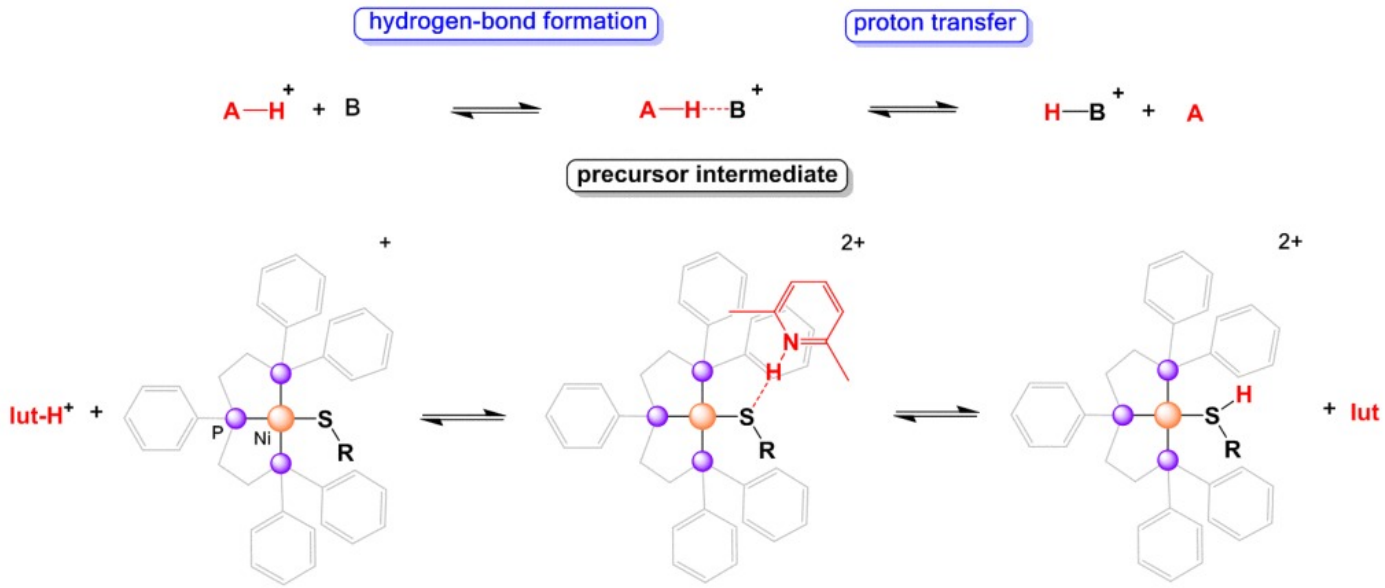


Fig. 1. TOP: Generic mechanism for the transfer of a proton from an acid A-H+ to base B. BOTTOM: Mechanism of proton transfer from acid = A-H+ = lut-H+ (structure shown in precursor intermediate in red) to base = B = sulfur in nickel complex

Because the proton is so small, the rates of proton transfer reactions are not usually sensitive to

the bulk of the reactants. However, the nickel-sulfur compounds we have synthesised and structurally characterised contain bulky substituents (shown in grey in Fig. 1, bottom) and these act as a barrier to the sterically-demanding acid (lut-$H^+$, shown in red in Fig. 1, bottom) approaching the sulfur, thus making protonation relatively slow and amenable to study on the millisecond timescale. Studying the time course of these reactions, and complementing the experimental results with theoretical calculations, yields unprecedented detail and unexpected features concerning the structure of the precursor intermediate and the subsequent movement of the proton on to sulfur.

Theoretical calculations indicate that the acid can penetrate into the cavity created by the bulky substituents to make a good lut-$H^+$…S hydrogen-bond which is conducive to subsequent proton transfer. However, the fit of the sterically-demanding acid in the cavity is constricted making protonation slow because the acid has difficulty negotiating its passage through the bulky substituents to get close to the sulfur.

Furthermore, it might be anticipated that the precursor intermediate is most stable when the lut$H^+$…S hydrogen-bonding is strongest. However, our results show that hydrogen-bonding is not the only (or indeed the principal) factor stabilizing the precursor intermediate. Rather it appears that an important factor stabilizing the precursor intermediate is the local environment created by the bulky substituents which encapsulate the hydrogen-bonded acid.

Understanding the factors which affect the rates of proton transfer, including stabilization of intermediates, is important in the design of new catalysts. Until now modulating the rates of proton transfer has been difficult to control, because the reaction is limited by the unchangeable rate of diffusion of the reactants. However, the results presented in this work suggest that designing elaborate scaffolds which generate extended cavities around reaction sites could be used to regulate the rates of proton transfer in a rational and predictable manner.

***Richard A Henderson***

## Publication

Mechanism of proton transfer to coordinated thiolates: encapsulation of acid stabilizes precursor intermediate.
Alwaaly A, Clegg W, Harrington RW, Petrou AL, Henderson RA.
*Dalton Trans. 2015 Jul 14*