



# I've started so I'll finish. Kinetic isotope effect models for a general acid as a catalyst in the protidecarboxylation of indoles.

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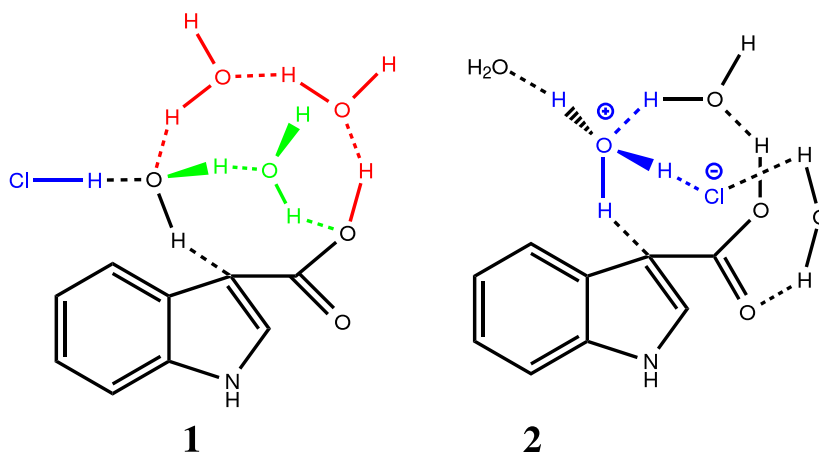
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Earlier I explored models for the heteroaromatic electrophilic protidecarboxylation of an 3-substituted indole, focusing on the role of water as the proton transfer and delivery agent. Next, came [models](#) for both water and the general **base** catalysed ionization of indolinones. Here I explore general **acid** catalysis by evaluating the properties of two possible models for decarboxylation of 3-indole carboxylic acid, one involving proton transfer (PT) from neutral water in the presence of covalent un-ionized HCl (**1**) and one with PT from a protonated water resulting from ionised HCl (**2**).



The original study[1] noted that the rate of decarboxylation fitted well to the kinetic expression:  $\text{rate} = \frac{a + b[\text{L3O}^+]}{1 + c[\text{L3O}^+]}$  [indole], where L can be H or D. Experimentally,  $[\text{L3O}^+]$  is controlled by adding a strong general acid such as HCl, which when the [appropriate](#) number of water molecules are added[2] fully ionizes to  $\text{H3O}^+.\text{OH}^-$ . Now for B3LYP+D3/Def2-TZVPD/SCRF=water calculations:

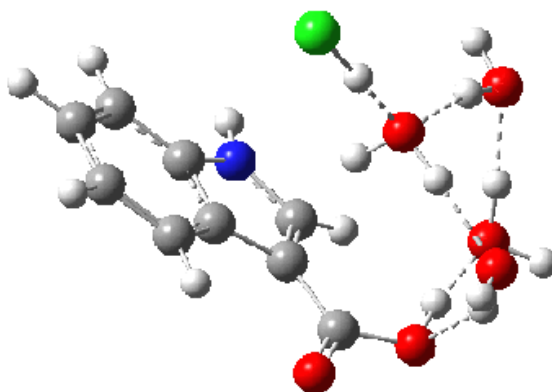
- Model **1** takes the pure water model and adds HCl (blue above) *via* hydrogen bonding to the H<sub>2</sub>O that is transferring the proton to the indole ring. Three water molecules are hydrogen bonding to the carboxylate oxygens to create a bicyclic network in which a ring of either 8 or 10 atoms can act as the proton relay structure. The question now arises whether the proton relay takes the longer (red) route or the slightly shorter green route.
- Isomeric model **2** uses H<sub>3</sub>O<sup>+</sup> for proton transfer, with an adjacent Cl<sup>-</sup> to complete the ion-pair.

**Model**  $\Delta G^\ddagger$  298 (0.044M) **Data** DOIs  $k^H/k_D$  [3]  
1 27.4 [4], [5], [6], [7] 5.69

2 16.8<sup>‡</sup> (14.8)<sup>†</sup> [5], [8], [9] 2.45

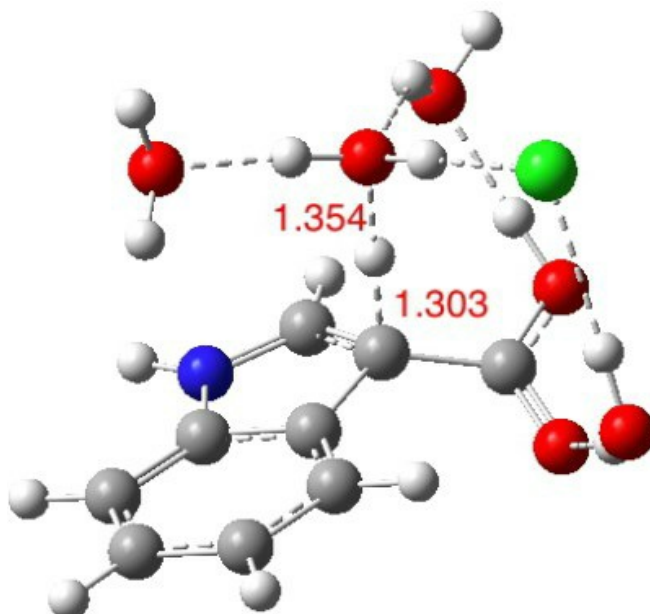
<sup>‡</sup> Reactant as a non-ionised covalent HCl. <sup>†</sup> reactant as an isomeric ionized  $H_3O^+ \cdot Cl^-$  being 2.0 kcal/mol higher in energy within this solvation model. **Note** added in proof. A significantly lower form of the reactant has subsequently been located which increases the free energy barrier to 22.1 kcal (vis 22.0 actually measured!). Discussion of this can be seen in the [associated post here](#).

1. An IRC for Model 1 shows that the proton relay takes the red path, whereas without the HCl the green path is followed.



The transition state free energy however is ..

2. 10.6<sup>‡</sup> or 12.6<sup>†</sup> kcal/mol **higher** than model 2 (click on the image below to load a 3D model). The general acid catalysed model is therefore preferred. The difference in free energy between the two models corresponds to a rate acceleration of  $>10^6$ , which is indeed similar to that observed [1].



The clincher comes with calculation[3] of the kinetic isotope effects (KIE). For general acid catalysis, they were measured as  $k^H/k^D \sim 2.5$ . [1]

- For model 1, using an un-ionised reactant and un-ionised transition state, the calculated KIE is 5.69 (very similar to that calculated for the water catalysed reaction, 5.66) but not a good fit to experiment.
- For model 2, using the same un-ionised reactant but an ionised transition state, KIE = 2.04, a much better fit.
- For model 2, using ionised reactant AND transition state, KIE = 2.45, an even better fit to experiment.

So we now have a model for the general acid catalysed decarboxylation of a 3-indole carboxylate which agrees with both the kinetic behaviours and the isotope effects measured for this reaction. Since the barrier is a relatively large one, proton tunnelling may play a lesser role in this interpretation, and the stage is set to use this model to e.g. explore how isotope effects are indeed influenced by tuning the reactivity using ring substituents, the original purpose of my researches all those years ago. Perhaps the catch phrase *I've started so I'll start* is now more apposite.

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