Kinetic isotope effect models as a function of ring substituent for indole-3-carboxylic acids and indolin-2-ones.

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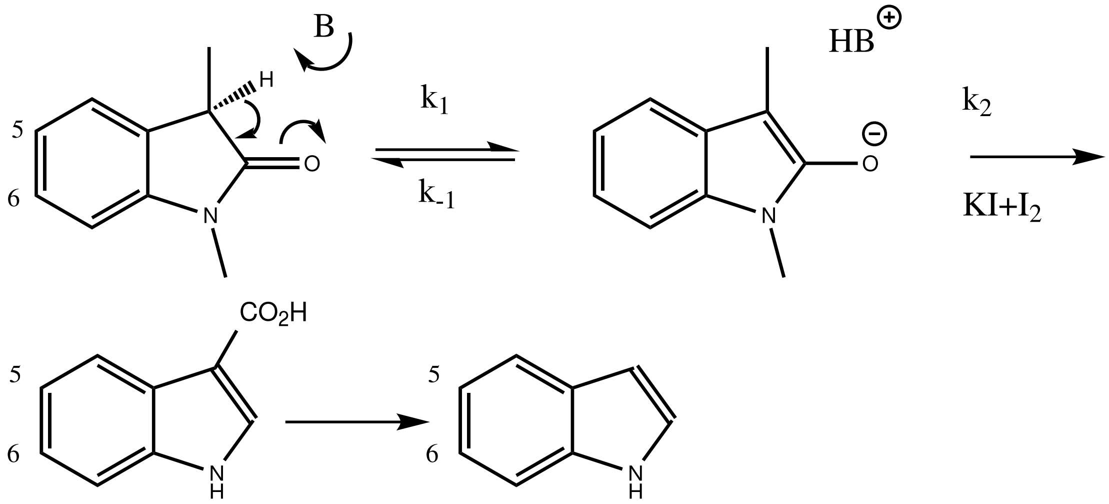
The original strategic objective of my PhD researches in 1972-74 was to explore how primary kinetic hydrogen isotope effects might be influenced by the underlying structures of the transition states involved. Earlier posts dealt with how one can construct quantum-chemical models of these transition states that fit the known properties of the reactions. Now, one can reverse the strategy by computing the expected variation with structure to see if anything interesting might emerge, and then if it does, open up the prospect of further exploration by experiment. Here I will use the base-catalysed enolisation of 1,3-dimethylindolin-2-ones and the decarboxylation of 3-indole carboxylates to explore this aspect.



The systems and results are shown in the table below, summarised by the points:

1,3-DIMETHYL-INDOLINONES:

1. The free energy barriers are very low, but show an overall increase when changing the substituent from nitro to amino, with the 6-position being more sensitive than the 5. However, the increase is not consistent.
2. The transition state mode changes regularly, the wavenumber more than doubling along the progression.

3. The basic structure of the proton transfer evolves smoothly, from being an early transition state with 6-nitro to being a late one with 6-amino.
4. The primary kinetic isotope effect shows less variation, but the trend is to increase as the transition state gets later, even beyond the point where the two bond lengths associated with the tranferring hydrogen are equal in length.
5. As Dan Singleton has pointed out on this blog, the observed KIE is a combination of effects based purely on the transition state structure and effects resulting from the *sharpness of the barrier* inducing **proton tunneling** and this is itself related to the magnitude of νi. The KIE ratios tabulated below derive purely from the former and do not take into account any such tunneling. We can see from the variation in νi that such tunnelling contributions are likely to vary substantially across this range of substituents. As a result, deconvoluting the KIE due to the symmetry of the proton transfer from the contribution due to tunnelling is going to be difficult.
6. There are other computational errors which might contribute, such as solvent reorganisations due to specific substituents, only partially taken into acount here. In effect the unsubstituted reaction geometry was used as the template for the others, followed of course by a re-optimisation which might not explore other more favourable orientations brought about by the substituents.

INDOLE-3-CARBOXYLIC ACIDS:

1. The free energy barriers are now much higher than the indolinones, but show a consistent decrease along the series from 6-nitro to 6-amino. This matches with the idea that the indole is a base and the basicity is increased by electron donation and decreased by electron withdrawal.
2. The transition state mode again changes regularly, increasing as the barrier decreases.
3. For 5-H, the computed free energy barrier matches that measured remarkably well.
4. The calculated KIE increase regularly along the series 6-nitro to 6-amino.
5. The calculated KIE for 5-H matches that measured very well, but that for the 5-chloro does not. One might safely conclude that the outlier is probably the experimental value. The KIE are not obtained by direct measurement of the rate of reaction, but inferred from solving the relatively complex rate equation with inclusion of some approximations and assumptions. Perhaps one of these approximations is not valid for this substituent, or possibly an experimental error has encroached. Were this work to ever be repeated, this entry should be prioritised.
6. The overall variation in KIE is in fact quite small, but if the KIE can be measured very accurately, then they should be useful for comparison with such calculations.
7. We cannot really conclude whether the magnitude of the KIE closely reflects the symmetry of the transition state. For all the examples below, the C-H bond is always shorter than the H-O bond. More extreme and probably multiple substituents on the ring (5,6-dinitro? 5,6-diamino?) might have to be used to probe a wider variation in transition state symmetry. For example, the maximum value for proton transfer from a hydronium ion was stated a long time ago to be around 3.6, [1] and it would be of interest to see if that value is attained when the proton transfer becomes fully symmetry.

1,3-dimethylindolin-2-ones[2]

Model	$\Delta G^{\ddagger}298$ ($\Delta H^{\ddagger}298$)	k^H/k^D (298K)	rC-H, rH-O	νi	DataDOIs
6-nitro	1.94	3.22	1.256, 1.417	611	[3],[4]
5-nitro	1.82	3.65	1.289, 1.364	895	[5],[6]
H	2.48	4.40	1.326, 1.316	1130	[7],[8]
5-amino	6.73	3.86	1.337, 1.304	1182	[9],[10]
6-amino	3.19	4.43	1.349, 1.291	1226	[11],[12]
Indole-3-carboxylic acids[13]					
6-nitro	25.1	2.72	1.279,1.391	706	[14],[15]

5-chloro	23.1	2.80 (2.23)	1.300,1.361 873	[16],[17]
5-H	22.1 (22.0)[a][18]	2.87 (2.72)[18]	1.304,1.354 921	[19],[20]
6-amino	20.5	3.04	1.308,1.348 950	[21],[22]

[a] The barrier is higher than previously reported because a significantly lower isomer of the ionised reactant was subsequently located. [21] Use of this new isomer also has a modest knock-on effect on the computed isotope effect for this system, bringing it into line with the other substituents and also with experiment.

Overall, this study of variation in kinetic isotope effects for proton transfer as induced by variation of ring substitution shows the viability of such computation. The total elapsed time since the start of this project is about three weeks, very much shorter than the original time taken to synthesize the molecules and measure their kinetics. Importantly, these were very much reactions occuring in aqueous solution, where solvation and general acid or general base catalysis occurred. Such reactions have long been thought to be very difficult to model in a non-dynamic discrete sense. The results obtained here tends towards optimism that such calculations may have a useful role to play in understanding such mechanisms.

I would like to express my enormous gratitude to my Ph.D. supervisor, Brian Challis, for starting me along this life-long exploration of reaction mechanisms. I hope the above gives him satisfaction that the endeavour back in 1972 has borne some more fruits.

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