The Straight Story: Linear Relationships Amid Random Scatter

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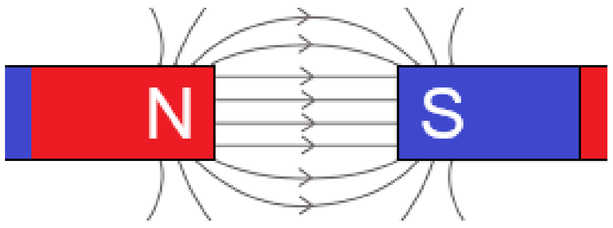
Abstract

Physical organic chemists love a straight line and we call these Linear Free Energy Relationships (LFERs); they allow us to graphically correlate a quantity that we have measured (*y* axis) against a parameter that depends on molecular structure (*x* axis). These relationships can be difficult to tease out, as was the case for the 32 molecules studied in this work. A complicating factor was that their reaction is enzyme catalysed, inviting use of Fischer's lock and key metaphor. Once the underlying trend was found, however, the result was elegant and satisfying, rather like scratching an itch.

Introduction

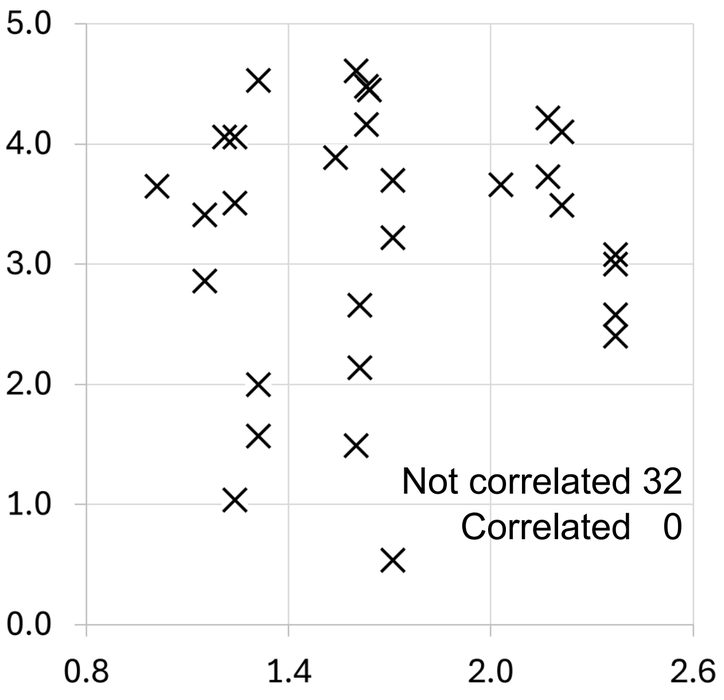
There are two types of itches; literal and metaphorical. While a quick back scratch might address a literal itch, perhaps as part of a reciprocal agreement, metaphorical itches can be more persistent.

When I was a PhD student, I had struggled to reconcile conventional wisdom with a set of historic data for the enzyme-catalysed reactions of 32 molecules.[1,2] There was little doubt about the veracity of these data; they were published in the prestigious Journal of the American Chemical Society. However, the rationale for the behaviour was incomplete and opposite to expectation; rather like saying that the strength of attraction between two electromagnets gets stronger as they are moved *further* apart.

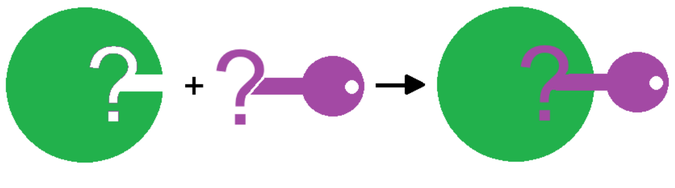


When I was appointed at LJMU, I had the opportunity to re-examine these data. My reasoning was that, based on precedent, it should be the size and shape of the molecules, not electromagnetic effects, that determined their behaviour. Surely then, a correlation of reaction rates against a parameter that measures the bulkiness of each molecule would yield a linear relationship? I began my plotting.

All the graphs on this poster have the same axes. The ***y* axis** shows the logarithm of the rate of the enzyme-catalysed reaction. The ***x* axis** is the Taft factor ($-E_s$),[3] a measure of the size and shape for the molecule whose reaction is being catalysed.

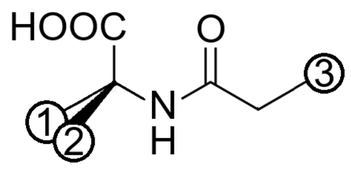


This graph shows apparently random data with no signs of correlation or linear trends. According to Fischer's metaphor,[1] enzymes evolve to fit specific molecules in the same way that only certain keys will fit into a particular lock. In this case, I had 32 keys but no clue as to what the lock looked like.



Part 1 Results

I subdivided the data by molecule structure:



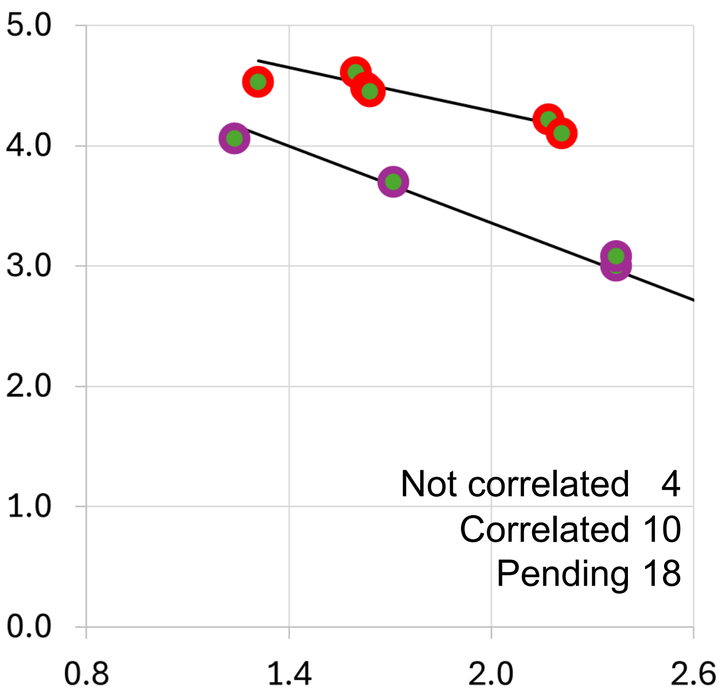
①, ② and ③ each represent substructures:

① is a hydrogen (H) or methyl (CH_3) group

② is a group with a Taft factor (*x* axis)

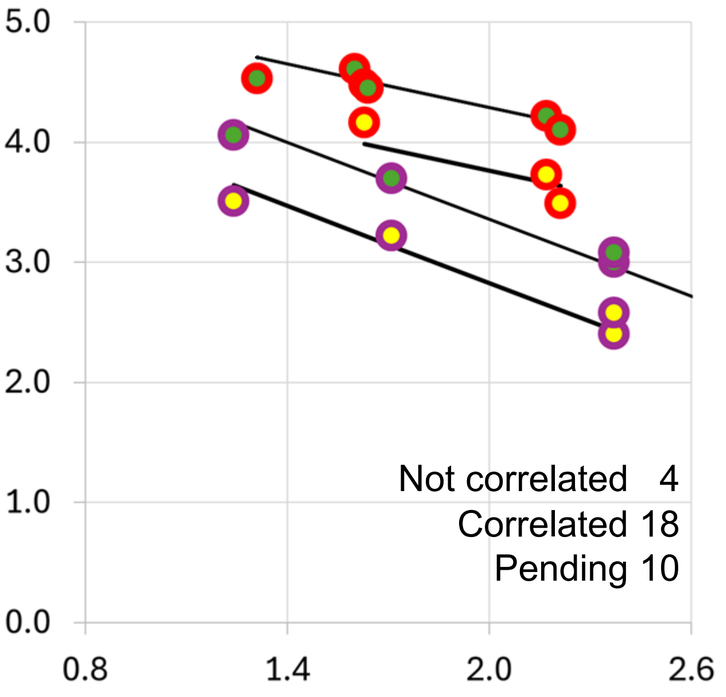
③ is a hydrogen (H) or chlorine (Cl) atom

Focus on ③ is chlorine ●



All the markers have a green fill to indicate ③ is chlorine. There are two distinct linear trends. The markers in red outline have a ② group that begins with $-CH_2CH<$ while the purple outline markers do not.

Add ③ is hydrogen ●



These markers use a yellow fill to represent ③ is hydrogen. We see the same two distinct linear trends that we saw before.

Part 1 Discussion

Downward slopes mean that the bulkier ② is, the slower the reaction rate; the larger a key is, the harder it is to fit and turn in a lock.

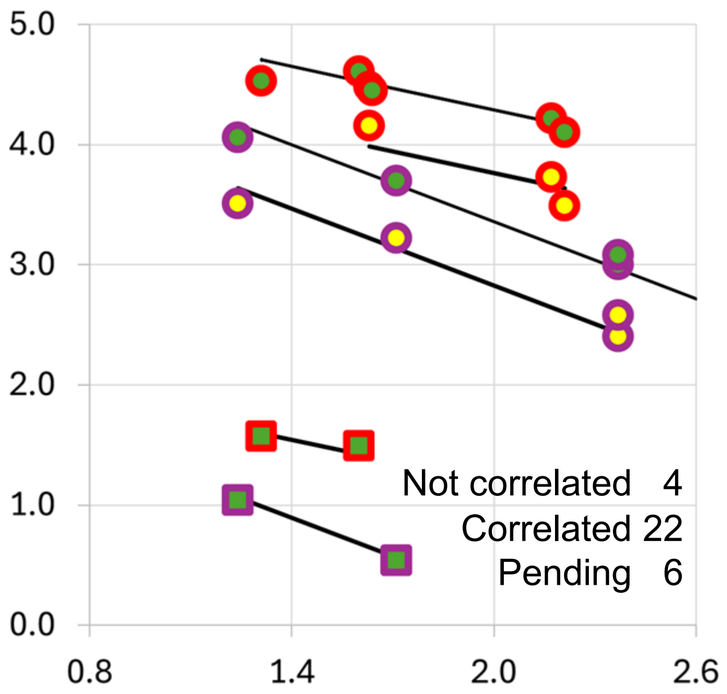
When ② is $-CH_2CH<$, reaction is faster and shows less reliance on the size of ②; this is a Yale lock and these are the Yale keys.

Reaction is faster if ③ is chlorine, a typical electromagnetic effect: chlorine is like a magnet that attracts the key to the lock.

Part 2 Results

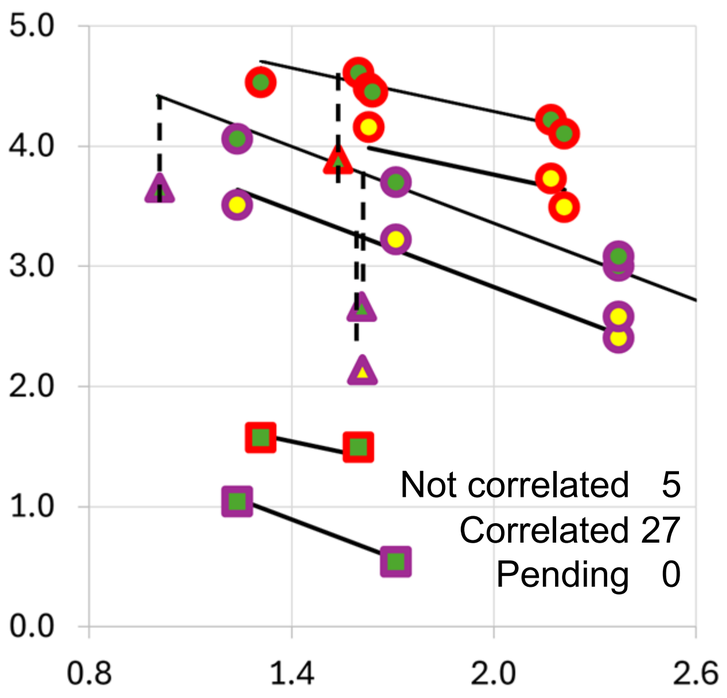
Eighteen molecules correlated so far…

Add ① is methyl □



Square markers for molecules with ① is methyl show the same split trend as before.

Add ② has six carbon atoms or more △



Dash lines' lengths are 0.93 units and they link to triangle markers where ② is massive.

Part 2 Discussion

Changing group ① from hydrogen to methyl causes rate to drop 1000 times (3 log units). This is because natural molecules only have ① as hydrogen. Having ① as methyl is artificial; like copying an original key and finding that the replica does not work as well.

When group ② is massive (more than six carbon atoms), the molecule struggles to fit in the enzyme and rate drops by 0.93 log units. This is a bit like trying to squeeze a key covered in mud into a lock: it works, eventually, but just not as smoothly.

Conclusion

The behaviour of 27 out of the 32 molecules in this system is entirely in accord with generally-accepted theories. Rates can be predicted using an LFER and this analysis provides new insights.[3] Sometimes, the key to a story is buried within the scatter.

References

1 S. C. J. Fu and S. M. Birnbaum, *J. Am. Chem. Soc.*, 1953, **75(4)**, 918-920.
2 C. G. Baker, S. C. J. Fu, S. M. Birnbaum, H. A. Sober and J. P. Greenstein, *J. Am. Chem. Soc.*, 1952, **74(18)**, 4701-4702.
3 P. Denton, 2000, *Bioorganic Chemistry*, **28(4)**, 205-213.