

Page M I. The energetics of neighbouring group participation.

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The energy differences between intra- and intermolecular reactions can be enormous. This has inevitably given rise to pet names and phraseology. This review attempted to explain the observed rate and equilibrium differences by known and accepted concepts—strain, entropy, etc. [The SCI® indicates that this paper has been cited in over 145 publications.]

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From my early days as an undergraduate, and especially during my time as a graduate student with Brian Capon in Glasgow, I was interested in neighbouring group participation. I was particularly keen to understand the relationship, if any, between intramolecular reactions and enzyme catalysis.

In 1970 I went to Brandeis to learn from Bill Jencks, whose seminal book on catalysis and enzymology¹ had just been published. At that time it was a commonly held belief that holding two molecules together in close proximity would result in a maximum rate enhancement of 55. However, observed rate enhancements of intramolecular reactions over their intermolecular counterparts are enormous—up to 10¹⁵ or so. Consequently, it was felt obligatory to introduce a new term or concept to explain the large rate enhancement—propinquity, orbital steering, stereopopulation control, FARCE, etc.

Jencks and I felt that there must be a rational explanation for these rate enhancements. I started to think about the entropy differences between uni- and bimolecular reactions and was unfortunately forced to come to grips with statistical thermodynamics. This was a topic I had tackled as an undergraduate but had considered simply as one of the hurdles one had to jump to graduate—I did not believe that it was actually useful, but some of the most in-

tellectually rewarding days of my life were spent talking with Jencks about entropy and statistical thermodynamics. Probably because neither of us were "experts" in this field, we had no preconceived ideas and questioned every new equation and result. The steamroller of logic led us to the conclusion that there was a maximum rate difference of about 10⁸ between uni- and bimolecular reactions based simply on the differences in entropy changes between the two reactions. Jencks had just been elected a Fellow of the National Academy, so we decided to publish a *PNAS* article on our conclusions.² Our article was followed by many alternative explanations, and this generated a heated exchange in the literature.

On returning to England, I continued to be involved in this field. The variation in the rate enhancement of a series of intramolecular reactions could be accounted for by differences in strain energy, the entropy differences associated with the loss of internal rotation upon ring closure and "loose" transition states, where the entropy loss for the bimolecular reaction is smaller. These effects were considered quantitatively in my review. This was followed by correlations of rates with strain energies.³

One of the most exciting consequences of this work was the application of our thoughts to enzyme catalysis. We were forced to reappraise the importance of binding energy between the nonreacting parts of the substrate and enzyme in facilitating the enormous catalytic effect of enzymes.⁴⁻⁶

This paper has been cited many times, probably because of its timeliness. Many people around 1970 realised there was a problem with the prevailing explanations for the effectiveness of intramolecular reactions. What was needed was a theory that did not introduce new phenomena and that could be extended to enzyme catalysis. We were fortunate to provide that explanation, and it has been very satisfying to see the ideas so generally accepted.

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3. Page M I. Entropy, binding energy, and enzymic catalysis. *Angew. Chem. Int. Ed.* 16:449-59, 1977. (Cited 55 times.)
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5. Jencks W P. Binding energy, specificity, and enzymic catalysis: the Circe Effect. *Adv. Enzymol.* 43:219-410, 1975.
6. Page M I. *The chemistry of enzyme action*. Amsterdam: Elsevier, 1984. p. 1-54.