



Introduction to Symposium in Print on Tunnelling

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INTRODUCTION TO A SYMPOSIUM IN PRINT ON TUNNELLING

A revival of interest in tunnelling has followed the discovery of striking examples of tunnelling in enzyme-catalysed proton and hydrogen transfer reactions over the past fifteen years. That discovery has sparked original publications and a series of reviews, books and collections of articles as well as more popular news items in *Nature* or *Chemical and Engineering News*. The purpose of this 'symposium in print' is to invite principal participants in what have been wide-ranging experimental and theoretical studies to provide both an introduction to and overview of the present state of the field. Instructions to authors have included an injunction from Marie Françoise Ruasse, an associate editor of the journal and a principal proponent of the project: 'I hope that people will agree to contribute in a manner that is in no way similar to a full paper or even a review. What we need is their opinion, and the way in which they face the challenging story of tunnelling'.

The symposium comprises fifteen articles which take up this challenge and have been loosely grouped to highlight different aspects of the topic. A recurring theme is a contrast between the prevalence of tunnelling in recent studies of enzymatic reactions and the comparative rarity of examples for non-enzymatic reactions at ambient temperatures. The first four papers cover mainly non-enzymatic reactions. The paper by Watt examines an important element of experimental investigations, namely ensuring that evidence of tunnelling, especially large isotope effects and anomalous Arrhenius parameters, do not represent experimental artefacts. Watt surveys proton transfer reactions and notes that measurements of temperature dependences of isotope effects are confined to reactions of nitroalkanes with base. These reactions contrast with the classes of enzymatic reactions exhibiting pronounced tunnelling which generally involve transfer of a hydrogen atom. It is noteworthy that an enzyme-catalysed proton transfer from a nitroalkane shows no obvious evidence of tunnelling.

My own contribution attempts a qualitative and pictorial explanation of the relationship between tunnelling and zero point energy contributions to isotope effects based on the 'Westheimer-Melander' effect. Horsewill provides a clear analysis of the origin and temperature dependence of tunnelling for proton transfers within carboxylic acid dimers. NMR measurements over a wide temperature range provide a text book example of a transition from temperature independent isotope effects at low temperatures to control by activation energy at higher temperatures. Related measurements of tautomerisation or intramolecular hydrogen transfer are reviewed by Limbach and Richard and Barbara Schowen who emphasise a further feature of tunnelling, namely that a substantial part of the activation energy is associated with achieving a 'tunnelling-ready' configuration of a reaction complex from which transfer of the hydrogen can occur.

Klinman and Kohen take up the story of unusually large isotope effects in enzymatic reactions, most importantly but not only for oxygenase enzymes involving transfer of a hydrogen atom. Temperature independent isotope effects with k_H/k_D close to one hundred provide dramatic examples of tunnelling and have elicited a level of experimental checking that hardly leaves room for doubt as to their authenticity. As Klinman states these measurements seem to demand a new paradigm for analysis which the traditional tunnelling correction to a normally more important zero point energy effect cannot provide.

A favoured approach derives from the work of (the late) Sasha Kutznetsov with Dogonadze in the 1960s and later with Ulstrup. For a hydrogen atom transfer in the gas phase the 'slow' motion of heavy atoms of a reacting collision complex produces a structure within which these atoms come close enough for the faster process of hydrogen transfer to occur. This is the pre-tunnelling state referred to by Limbach. In solution the same close approach is achieved within the weak stretching vibration of a hydrogen bond. In addition, for ionic reactions, it is suggested that modulation of solvent interactions promotes a condition of resonance between stretching vibrational wave functions for the bonds to hydrogen in the reactant and product, which also favours tunnelling

A clear exposition of this model is provided by Siebrand and Smedarchina in an attempt to rationalise the large isotope effects (and their temperature dependences) measured by Klinman for the native soybean lipoxygenase enzyme and a series of mutants catalysing oxidation of linoleic acid. These authors represent heavy atom and hydrogen transfer modes by separate (harmonic) oscillators with the latter corresponding to a Franck-Condon term. Kiefer and Hynes offer an overview and discussion of their own contributions to this analysis focused on proton rather than hydrogen transfer and emphasize the importance of reactant and product solvation in non-enzymatic reactions. Kutznetsov and Ulstrup attempt to assess the scope for applications of the model to new areas including Grotthus-like transport of protons, reactions in the Marcus inverted region and the potential for STM monitored proton transfer of a 'single molecule'.

Klinman's case that the new enzymatic results defy explanation by 'traditional' methods does not go uncontested. Truhlar argues that modern (variational) transition state treatments using semiempirical potential energy surfaces provide a basis for calculations incorporating effective tunnelling protocols which allow reproduction of the large magnitudes of isotope effects, if not as yet their temperature independence. Truhlar prefaces this assessment with a review of methods for including tunnelling pathways removed from the classical minimum energy path for reaction.

Warshel and Kamerlin also make the case for the effectiveness of simulations of rate constants and isotope effects based on realistic potential energy surfaces including the empirical valence bond (EVB) surface tested in Warshel's research group. In the spirit of a symposium they highlight points of discussion or disagreement within the field, and the paper will be helpful to those seeking to make their own assessment of these issues. Thus a counterintuitive suggestion is that the often proposed compression of heavy atoms between which hydrogen transfer occurs within an enzyme substrate complex may not be conducive to tunnelling. Williams joins Warshel and Kammerlin in arguing that comparisons of calculated isotope effects for comparable enzymatic and non-enzymatic reactions offer little evidence of enhanced tunnelling in the case of enzymes. The computational evidence is important partly because few unambiguous experimental comparisons of enzymatic and non-enzymatic reactions have been possible. However, strong advocates of a catalytic role for tunnelling remain.

Part of the interest of tunnelling is its implications for the nature of enzymatic catalysis itself. Schwartz and co-workers provide a stimulating discussion of the application of molecular dynamics to conformational changes preceding the covalent bond-making and bond-breaking step of a catalysed reaction. Their mechanisms for facilitating the covalent reaction offer a radical alternative to Warshel's view that 'preorganisation' of the enzyme disposes it for stabilisation of a substantially ionic transition state. Truhlar

also reminds us that emphasis on promotion of a 'tunnelling-ready' state should not obscure competing or overriding demands on enzymes to lower the activation energies or meet wider requirements of 'evolutionary systems biology'.

Two further papers report on-going experimental studies of isotope effects. Kohen's (earlier) contribution emphasised a role for tunnelling in secondary as well as a primary isotope effects. Scrutton reports measurements of the pressure dependence of a secondary isotope effect, which, together with a computational analysis, offer an introduction to the extensive work of his research group. Formosinho reports measurements for a non-enzymatic hydrogen transfer which uniquely involves reaction of acetophenone in a photoexcited state. He analyses the experimental results using his own widely applied interacting-state model (ISM) for calculating activation energies, isotope effects and the contribution of tunnelling to the reactions.

Together the papers of this symposium offer a wide perspective on tunnelling and its context in hydrogen transfer reactions with and without enzymatic catalysis. They are certainly not bland. As in all serious scientific discussions there are disagreements: including as to whether tunnelling contributes to catalysis in enzymes or if new experimental results can be interpreted within existing theoretical frameworks. The role of protein dynamics in both tunnelling and catalysis continues to attract controversy. A symposium does not aim to achieve a complete balance of viewpoints. Where an argument is deemed to demand a further response, the 'review commentary' feature of this journal offers one mechanism for achieving it. There is also confusion over concepts and nomenclature. Thus a tunnelling-ready or pre-tunnelling configuration might be regarded as the 'tunnelling equivalent' of a transition state and is not to be confused with the conformation which precedes it. Nor is the area free of relatively complex mathematical formalism. Nevertheless, the papers are impressive in their attempts to express clearly their different points of view. In so doing they go far towards exploring not only isotope effects and tunnelling but our current understanding of enzymes and indeed of fundamental aspects of catalysis and reactivity in general.

Finally we note with regret the death of Sasha Kutznetsov during the planning period of this symposium. He had agreed to join Jens Ulstrup in contributing an article, and his name has been retained as an author on that paper. His contributions to a new approach to tunnelling in the latter part of the last century were highly influential. It seems a small but appropriate memorial that his name should be included among authors whose work he had known and influenced.

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