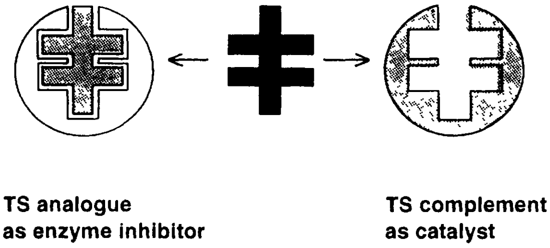
Interplay of Theory and Experiment in the Determination of Transition-state Structure

Ian H. Williams
School of Chemistry, University of Bath, Bath BA2 7AY, U.K.

1 Introduction

The transition state (TS) is of strategic importance within the field of chemical reactivity. Owing to its location in the region of the highest energy point on the most accessible route between reactants and products (Figure 1), it commands both the direction and the rate of chemical change. Questions of selectivity ('Which way is it to the observed product?') and efficiency ('How easy is it to get there?') may be answered by a knowledge of the structure and properties of the TS.

There are important practical reasons for investigating the nature of TS structure. Mechanisms-based approaches to drug design are directed towards the synthesis of TS analogues as inhibitory substrates for enzymes controlling key biochemical processes; this requires knowledge of the TS structure to be mimicked. The design of synthetic catalysts for specific chemical processes is aided by knowledge of the TS structure in order that its structural complement may be constructed; likewise, selection of catalytic antibodies requires a hapten adequately mimicking the TS for the reaction to be catalysed, which presupposes a knowledge of the TS structure and properties.



Scheme 1

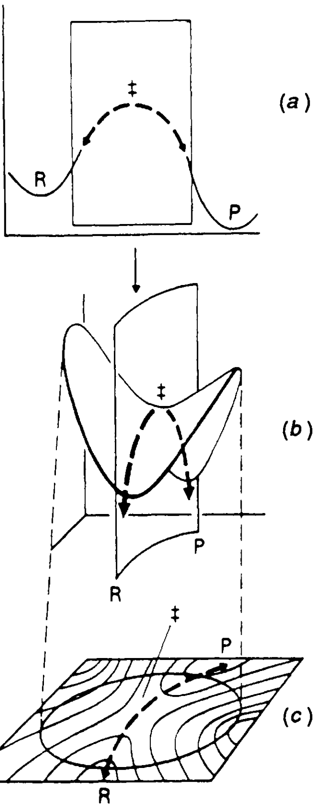


Figure 1 Saddle-shaped potential energy surface in the region of a transition state ‡. A vertical cut through the surface in (b) along the minimum energy path interconnecting reactants (R) and products (P) gives the potential energy profile (a). Horizontal cuts through the surface give the energy contours (c).

In a sense a TS is not a single physical entity in itself, but rather is a collection of species populating a range of energy levels encountered in the vicinity of a saddle point on the potential energy surface (PES) governing transformation of a chemical system from reactants to products. The actual saddle point is associated with a particular molecular entity with a definite structure. Commonly the term 'transition state' is used ambiguously to refer both to the quasi-thermodynamic *state* of the reacting system and to the molecular *structure* at the saddle point. This colloquial usage is perhaps not merely the result of muddled thinking but reflects a deeper ambiguity between different concepts of what is meant by the term 'transition state', deriving either from an experimental or from a theoretical viewpoint. In order to refer specifically to the molecular entity at the saddle point, it may be useful to speak of either the *activated complex* or the *transition structure* (see below).

By its very nature the TS is elusive to direct experimental study. Recently it has become possible, using sophisticated spectroscopic techniques, to study the structure and dynamics of molecular systems as they pass through the TS region between reactants and products for some simple gas-phase processes.[1] Zewail[2] has described laser experiments capable of probing the dynamics of elementary reactions on the femtosecond (10^{-15} s) timescale and Moore[3] has recently reported evidence for the energy levels of the TS for dissociation of ketene: these are indeed *direct* observations of TSs in the sense of activated complexes. However, the study of TSs for ordinary organic reactions in solution is still obliged to be *via indirect* methods

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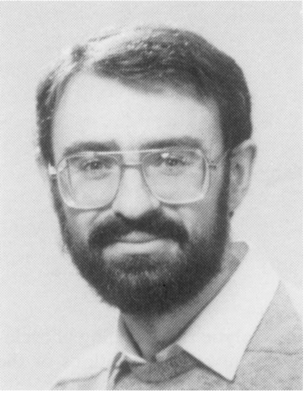
Ian Williams obtained his B.Sc. (1974) and Ph.D. (1978) degrees from the University of Sheffield under the supervision of James McKenna. Following postdoctoral research with Richard L. Schowen at the University of Kansas, he held a Royal Society Pickering Research Fellowship at the University of Cambridge (1980—1985) and a SERC Advanced Fellowship at the University of Bristol (1985—1989) in the Department of Theoretical Chemistry. He was appointed as Lecturer in Organic Chemistry at the University of Bath in 1989 and has been Reader in Physical Organic Chemistry since 1991. His research interests in theoretical organic chemistry range from atmospheric reactions to enzyme catalysis, but focus upon the role of the transition state in reactivity.

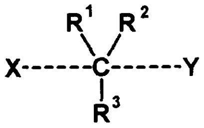


such as kinetic isotope effects (KIEs) and structure–reactivity correlations The interpretation of these kinetic data in terms of TS structure is, as yet, far from straightforward The purpose of this brief review is not only to sketch the outlines of the theoretical and empirical concepts of TS structure, and to signal some of the problems raised by each approach, but also to lay down a few pointers as to how computation and experiment may interact in a complementary way in the elucidation of TS structure

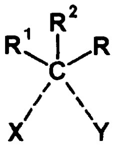
2 Early ideas

The essential notion that properties of the saddle point region of a PES hold the key to fundamental understanding of reaction kinetics is due to Eyring and Polanyi, who showed that the heat of activation for a simple triatomic reaction (*e g* $H + H_2$) could be identified with the height of the saddle point [4] The term 'transition state' was introduced by Polanyi and Evans[5] in papers which included discussion of the mechanism of displacement reactions $X^- + RY \rightarrow XR + Y^-$ At this stage it was clear that a reaction rate constant k could be regarded as the product of some generalized rate constant $k^{\ddagger}$ (roughly independent of temperature and the nature of the medium or the structure of the reactants) and a quantity $K^{\ddagger}$ with most of the properties of an equilibrium constant for formation of the TS from the reactants The significant step forward was made by Eyring, who proposed that $k^{\ddagger} = \boldsymbol{k}T/\boldsymbol{h}$ and that $K^{\ddagger}$ for the TS should be evaluated using partition functions lacking a factor for motion along the reaction coordinate [6]

Thus the TS was from the start an essentially theoretical concept, and the question of TS structure was a problem for quantum-mechanical theory Right from the outset the scope of the TS theory was greater than the ability of practitioners to produce reliable PESs and to characterize TS structures, the quantitative inadequacies of the methods available at that time were fully apparent to those involved in the development of the TS theory Nonetheless, the idea of a TS structure whose properties were responsible for (and in some way could be related to) the observed kinetic behaviour of organic reactions in solution was immediately appealing Ingold first referred to a TS in 1936,[7] and the next year his classic paper[8] on the mechanism of Walden inversion contained the following statement "inversion of configuration is presumed to be the rule for bimolecular substitutions (S_N2 and S_E2) primarily because the transition state (1), which leads to inversion, will have a smaller energy than that (2) which corresponds to retention "



(1)



(2)

The *idea* of the TS had captured the imagination of experimental chemists and was already proving to be a very useful means of explaining details of reaction mechanisms Indeed, it was not long before the issue of finding the mechanism for an organic reaction became essentially a matter of defining the TS (or TSs) occurring along the path between reactants and products

At the Faraday Society Discussion[9] on 'Reaction Kinetics' in 1937, Hinshelwood observed that there were two completely different approaches to the topic, mathematical and empirical, and Moelwyn-Hughes pointed out that the former approach (TS theory) was seriously limited by the fact that chemists were interested in systems for which partition functions were not available In response, Polanyi remarked that precise numerical agreement between theory and experiment was of less significance than the insight given into chemical reaction mechanisms, and Hammett commented that it was most important "to distinguish the very valuable qualitative and conceptual accomplishments of these new theories from the quantitative inadequacies which they may still possess "

3 Theoretical Approaches

The problem of determining TS structure by theoretical calculations divides into two parts first, how to construct a reliable PES to describe a particular chemical reaction, second, how to locate and characterize a saddle point on a multidimensional PES In regard to the former, suffice it to say here that the original semi-empirical valence-bond approach of Eyring and Polanyi[4] was superseded by developments occurring in several different directions *ab initio* wavefunctions of increasing sophistication, a totally empirical approach in the form of the bond-energy/bond-order (BEBO) method,[10] and semi-empirical molecular-orbital (MO) theories Early explorations of PESs employed either exhaustive point-by-point searches in multidimensional space – an approach doomed to futility – or else techniques based only upon energy minimization A breakthrough came with the publication by McIver and Komornicki[11] of a method for locating saddle points on surfaces by minimization of the gradient norm These authors not only reported a calculated TS structure for the electrocyclic ring-opening of cyclobutene to butadiene (Figure 2), but they also clearly stated the criteria which any proposed theoretical TS structure must satisfy it must be a stationary point on the PES, with zero gradient, its matrix of force constants must have one and only one negative eigenvalue, corresponding to the lack of a restoring force along the reaction coordinate, it must be the highest energy point on a continuous line connecting reactants and products, and it must be the lowest such point satisfying these conditions Milestones in the applications of *ab initio* MO theory were the development of analytical methods for evaluation of the first and second derivatives of the energy, a variety of efficient algorithms are now available for saddle-point searches, thus providing a range of powerful tools for studies of reactivity An excellent example of what may currently be achieved by means of theoretical approaches is provided by Houk's recent review of TS structures for hydrocarbon pericyclic reactions [12]

Although there is now[13] extremely good agreement between *ab initio* theory and experiment for the kinetics of the prototypical reaction $H + H_2$, it is still exceedingly difficult to calculate the barrier height for even $F + H_2$ to within 'chemical accuracy' ($\sim$ 4 kJ mol^{-1}) of the experimental value, and the TS structure for this particular reaction is quite sensitive to subtle refinements of the wavefunction [14] Of course, in the absence of structural data from experiment, it is difficult to judge whether a predicted TS structure is correct or not[1] Nonetheless, theoretical studies have now been carried out upon a great number of chemical reactions and in general it has been found that, as increasingly sophisticated (and expensive) methods are used, convergence of molecular geometry with respect to method is obtained con-

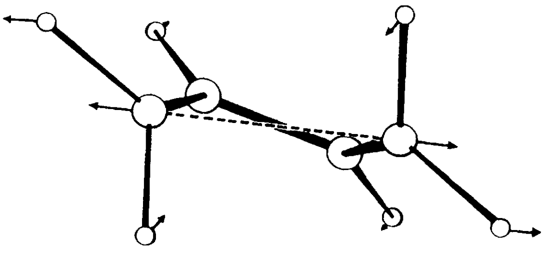


Figure 2 Calculated TS structure for electrolytic ring-opening of cyclobutene to butadiene, the arrows represent relative motions of the atoms in the reaction-coordinate vibrational mode

(Adapted with permission from ref 11 Copyright 1972 American Chemical Society) siderably more readily – even for a TS – than is convergence of the calculated barrier height

The molecular geometry corresponding to a saddle point on a PES is often referred to by computational chemists as a *transition structure* (*cf* reference 12) in order to distinguish it from the geometry corresponding to the maximum along the free-energy profile for an elementary step, which is the TS In many cases these two geometries may not be sensibly different A theoretical evaluation of an activation barrier must, however, take account of the contributions to $\Delta G^{\ddagger}$ from sources *other* than the potential-energy difference $\Delta\epsilon^{\ddagger}$ [15] these include differences in zero-point energy, thermal energy, the pressure–volume term, and entropy It is easy to compute these additional terms for a particular temperature and standard state, at least within the ideal-gas, rigid-rotor, harmonic-oscillator approximation,[16] provided that the second derivatives of the energy are obtained However, there are probably also many cases where the geometry at the maximum along the free-energy profile is significantly different from that at the saddle point in other words, *the TS structure is temperature dependent* Doubleday *et al* [17] have reported an example in the radical–radical disproportionation (equation 1) At the saddle point on the PES for this reaction,

$$\mathrm{H} + \mathrm{CH_3CH_2} \rightarrow \mathrm{H_2} + \mathrm{CH_2{=}CH_2} \qquad (1)$$

the C_2H_4 moiety resembles the ethyl radical (*i e* the *transition structure* is reactant-like) but at the maximum on the free-energy profile for high temperatures (> *ca* 900 K) this group more closely resembles ethene (*i e* the *TS structure* is product-like) Since the products are appreciably 'tighter' than the reactants, there is a decrease in entropy along the reaction coordinate, once the transition structure has been passed, the potential energy falls but the free energy may continue to rise to a maximum (Figure 3) In general, the TS structure shifts in the direction of lower entropy as the temperature is raised Improved agreement between calculated and observed reaction rate constants is obtained by using *variational* TS theory,[18] in which the reaction 'bottleneck' is associated not with the PES saddle point (as in conventional TS theory) but rather with the free-energy maximum along the reaction path It has been suggested that for reactions with low or flat barriers ($\Delta\epsilon^{\ddagger} <$ *ca* $5kT$) no claimed TS structure should be believed unless it has been obtained by a variational search [17]

4 Empirical Approaches

It may be coincidental that the very issue of *Chemical Reviews* which contained Eyring's seminal paper on TS theory[6] also contained an article by Hammett on rate-equilibrium relationships,[19] but the link between these two topics was recognized immediately the existence of linear free-energy relationships, implying the complete interchangeability of equilibrium and rate constants, was taken to be one of the simplest and strongest supports of TS theory On the basis of simple energy profiles it was noted, moreover, that the more thermodynamically favoured a member of a family of related reactions is, the faster it should proceed, and the earlier its TS should occur along the reaction coordinate, conversely, a thermodynamically unfavourable reaction would be slower and its TS would occur later (*cf* Hammond's postulate[20]) Leffler proposed that the slope of a linear correlation between log k and log K (*i e* of $\Delta G^{\ddagger}$ *vs* ΔG_{rxn}) could be identified as a parameter measuring the degree of resemblance of the TS to the products as compared with its resemblance to the reagents [21] Thus a slope $\beta \approx 0$ for a Brønsted correlation ($\Delta G^{\ddagger} = \beta\Delta G_{\mathrm{rxn}}$) would indicate a reactant-like TS in which essentially no proton transfer had occurred from the acid to the base, $\beta \approx 1$ would indicate a product-like TS in which proton transfer was essentially complete, and $\beta \approx 0\ 5$ would indicate a TS in which the proton was about half transferred In this way the value of the rate–equilibrium coefficient came to be interpreted as a qualitative measure of TS structure

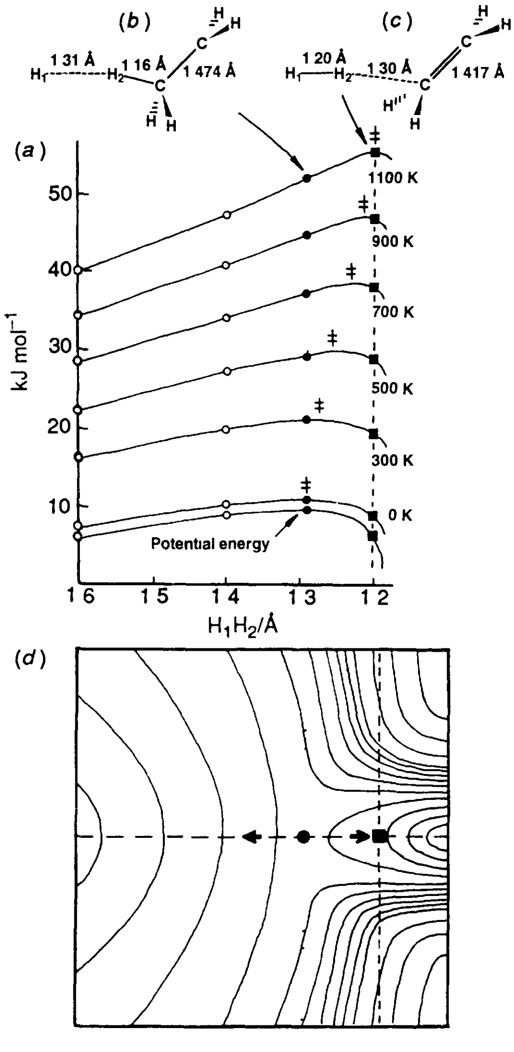


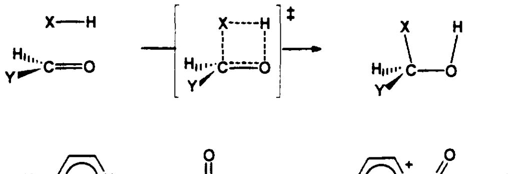
Figure 3 (a) Free energy curves (1M standard state) for the reaction in equation 1 at various temperatures, each curve is separately referenced to the free energy of reactants at the given temperature (b) Molecular structure at the saddle point [indicated by dotted line in (a)] (c) Molecular structure at $H_1H_2 = 1\ 2$ Å [indicated by dashed line in (a)] near to free-energy maximum for temperatures > 900 K (d) Schematic contour map showing free-energy bottleneck (■) between saddle point (●) and products at temperatures > 900 K (Adapted in part with permission from ref 17 Copyright 1985 American Chemical Society)

A problem with many structure–reactivity correlations – in which the effect of a substituent upon the rate of reaction is compared with its effect upon the equilibrium of either the same or some standard reaction – is that the substituent may not merely perturb the energetics of the PES for the reaction but may significantly alter the shape of the PES In this case, what was intended as a probe for TS structure may actually change the mechanism the act of observation affects the object in such a way as to render its original state inscrutable A KIE may be regarded as the most subtle form of substituent effect in that it arises by substitution only of neutrons which (within the Born–Oppenheimer approximation) do not affect the PES in any way the observed effect upon the rate arises solely from the difference in the non-potential-energy term $\Delta(G - \epsilon)^{\ddagger}$ due to the presence of a heavier isotope It is often attempted to relate the magnitude of primary hydrogen KIEs in a family of reactions to the extent of hydrogen transfer in the TS [22] Variation in TS structure from asymmetric and reactant-like, through symmetric, to asymmetric and product-like, is accompanied first by an increase and then by a decrease in the magnitude of the primary KIE as the transferring hydrogen isotope moves between the donor and acceptor.[23] Secondary hydrogen KIEs are also commonly employed as probes of TS structure; their magnitudes are often assumed to range approximately from unity for a very reactant-like TS to some extreme value – approaching the equilibrium isotope effect, which may be either less than or greater than unity – for a very product-like TS, and thus to provide a measure of progress along the reaction coordinate.[24]

5 Bridge-building Exercises

5.1 Rate–Equilibrium Correlations

The use of slopes derived from structure–reactivity correlations (particularly Brønsted β and Hammett ρ) as measures of TS structure has come under severe criticism in recent years, but has also been thoughtfully defended with appropriate cautionary notes.[26] It has long been recognized that there is a fundamental incompatibility within the body of ideas which have sprung from the fount of TS theory: if the slope of a linear rate-equilibrium relationship is interpreted as some index of TS structure, it must reflect some *constant* property of the TS for the entire family of reactions used to construct the correlation; however, the Leffler principle,[21] Hammond postulate,[20] and related notions[27] all suggest that changing the reaction energetics should cause *variation* in TS structure within this same family. Modern computational chemistry offers a means by which this paradox may be resolved. For a particular reaction of a series of substituted compounds, the energetics and geometries of reactants, TSs, and products may be obtained from calculated PESs. Rate–equilibrium relationships may be constructed from plots of calculated $\Delta G^{\ddagger}$ *vs.* $\Delta G^{\ddagger}_{\text{rxn}}$ (or $\Delta H^{\ddagger}$ *vs.* ΔH_{rxn}) values. The merit of this approach is that the TS structure, deduced *indirectly* from the slopes of these plots, may be compared with those determined *directly*. An initial attempt to realize this goal in an *ab initio* self-consistent field (SCF) theoretical study of addition of neutral protic nucleophiles to carbonyl compounds was unsuccessful for good reason.[28] The TS for addition with concerted proton transfer (equation 2) contains a four-membered ring, a structural feature not present in either the reactants or product: the TS is not structurally intermediate between reactants and products, and thus its properties are not modelled by any combination of their properties in the manner assumed by Leffler.[21]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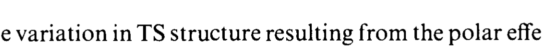
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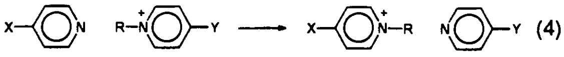
(X = CN, Cl, H, Me, NMe₂; IQ = isoquinoline)

The variation in TS structure resulting from the polar effect of a remote substituent has been simulated theoretically, for the addition of a range of 4-substituted pyridines to *N*-methoxycarbonyl isoquinolinium (equation 3), by using the semi-empirical AM1 MO method.[29] Each nucleophile – and the nucleofuge – was satisfactorily mimicked by an ammonia molecule whose gas-phase basicity was modulated by a suitably located dipole to reproduce the experimental proton affinity, relative to ammonia, of a particular substituted pyridine. A plot of calculated $-\Delta H^{\ddagger}$ *vs.* $-\Delta H_{\text{rxn}}$ values revealed a very good linear correlation, despite being constructed from data for TSs of variable structure! The slope of this correlation might be interpreted as a measure of either the bond order B_{NC} of the making bond between the nucleophile and the acyl carbon, or of the developing charge q on the nucleophile (0 for reactants, + 1 for the tetrahedral adduct). Figure 4a shows how the normalized values (change between reactants and TS divided by change between reactants and adduct) of these important structural variables vary with ΔH_{rxn}: the more basic the nucleophile, the more reactant-like is the TS, in accord with the Hammond postulate. If a linear rate–equilibrium relationship is not, after all, incompatible with the Hammond postulate, its constant slope β cannot be interpreted simply as a measure of TS structure.


(4)

A similar theoretical approach has recently been taken[30] to simulate the elementary steps of proton transfer and methyl transfer between reactant and product encounter complexes. A curved Brønsted correlation is found for proton transfer (equation 4, R = H), the slope of which at any given point being similar in magnitude to the value of either the normalized bond order B_{NH} (for the making bond between the base and the transferring proton) or the normalized charge q on the basic moiety (Figure 4b). In contrast, a linear rate–equilibrium correlation is obtained for methyl transfer (equation 4, R = CH_3), the slope of which does not agree with the varying indices of TS structure B_{NC} and q (Figure 4c). These two reacting systems differ significantly in the magnitudes of their intrinsic barriers (the value of $\Delta H^{\ddagger}$ at $\Delta H_{\text{rxn}} = 0$): a very low value ($\sim$ 5 kJ mol^{-1}) for proton transfer – for which β does provide an approximate

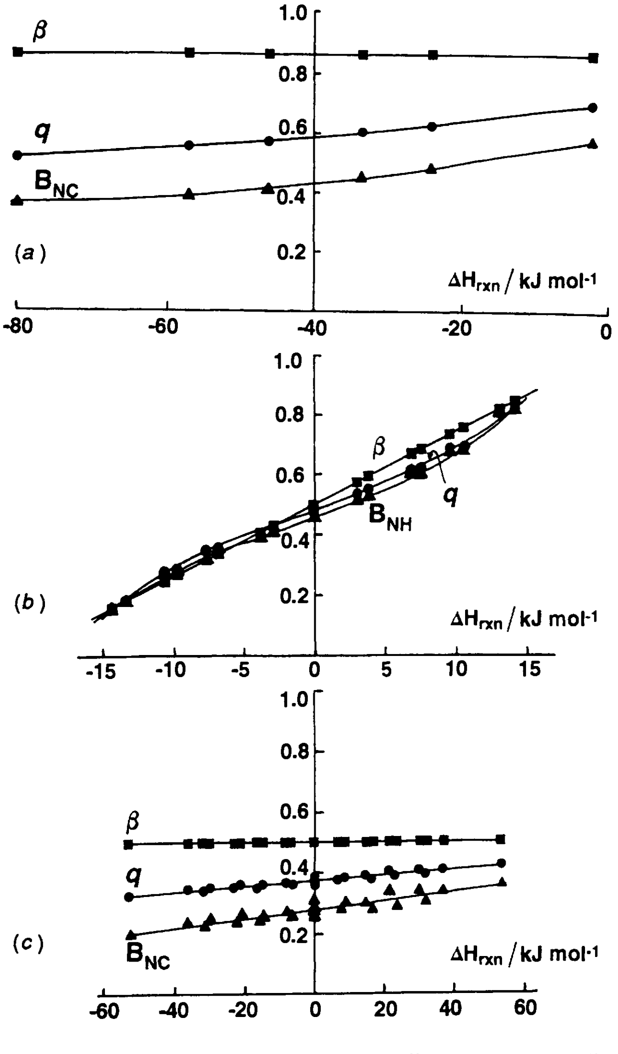
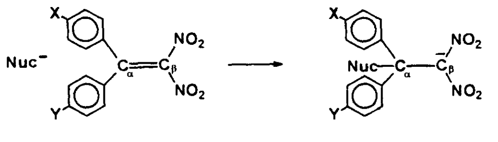


Figure 4 AM1 calculated rate–equilibrium coefficient β (■), normalized change in bond order for making bond to nucleophile or base (▲), and normalized change in charge on nucleophile or base (●) as a function of heat of reaction for (a) nucleophilic addition (equation 3) of substituted pyridines to methoxycarbonyl isoquinolinium, (b) proton transfer (equation 4, R = H) between substituted pyridines, and (c) methyl transfer (equation 4, R = CH_3) between substituted pyridines.

measure of TS structure – and a rather high value (~ 152 J mol^{-1}) for methyl transfer – for which β does not measure TS structure

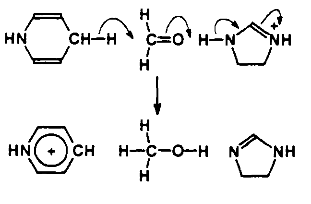
The sign and magnitude of the slope ρ of a Hammett correlation between log k and the substituent constant σ are used widely as a diagnostic tool for the determination of reaction mechanism in a completely empirical fashion, but a question arises whether ρ also provides a measure of charge development in the TS McLennan has argued that this may be the case provided that raw ρ values are corrected for variation in the efficiency of transmission of charge from a reacting centre in a molecule to a substituent group [31] According to this view, a small value of ρ for a Michael addition (equation 5), as determined by an aryl substituent at the α-carbon, would be interpreted as indicating an early TS with little charge development at C_α, a large value for ρ would, on the other hand, indicate a late TS with substantial charge development at C_α Hoz[32] has recently challenged this traditional interpretation, in the light of ^{13}C chemical shift correlations and a qualitative valence-bond curve-crossing analysis of the Michael addition process, by proposing that a large ρ signifies an early TS and *vice versa* He argues that an early TS for this reaction (equation 5) has diradical character (not present in either reactants or product) with an electron occupying a delocalized MO such that the C_α substituent readily senses the build up of electronic charge, in contrast, a late TS resembles the Michael adduct in which the negative charge at C_β is not readily transmitted to the substituent at C_α There is scope here for a careful theoretical study to examine these suggestions



(5)

It is of importance to know not only the nature of the TS structure itself, but also the manner in which TS structure changes in response to changes within the reacting system and its environment, *e g* substituent and solvent effects, changes in either acidity/basicity or nucleophilicity/electrophilicity of reacting moieties Physical organic chemists have developed empirical methods for rationalization of observed trends, as determined by experimental probes for TS structure including structure–reactivity correlations and kinetic isotope effects, and have adopted these methods for predictive purposes [27] Of particular popular use has been the empirical construct sometimes known as the Albery-More O'Ferrall–Jencks (AMJ) diagram [33] this is a two-dimensional 'map of alternative routes' with an implied third dimension of energy assumed to have the form of a saddle, thus representing the TS region of a PES for a reacting system A change in, say, the acidity of a catalytic proton-donor group causes changes in the relative energies of one or more corners or edges of the diagram, the consequences for TS structure are deduced by consideration of the resultant of effects parallel and perpendicular to the reaction coordinate

Figure 5a shows an AMJ diagram describing the hydride transfer and hydron transfer components of the concerted reduction of a carbonyl to an alcohol (equation 6), in which the hydride donor is dihydropyridine (HPyH) and the hydron donor is imidazolium cation (Im$^+$) It is of interest to enquire how the TS structure for this reaction varies as the base strength of the Im moiety is increased This change stabilizes HIm$^+$ and so lowers the energy of the whole left-hand side of the AMJ diagram The Hammond (parallel) effect of this change in exoergicity along the reaction coordinate is to shift the TS towards the top-right corner, and the anti-Hammond (perpendicular) effect is to shift the TS towards the top-left corner, since the energy of the unfavourable (HPy$^+$ CH$_3$O$^-$ HIm$^+$) intermediate is reduced The resultant of these component shifts leads to the prediction that increasing basicity of Im should cause a significant increase in the degree of hydride transfer in the TS with very little change in the degree of hydron transfer Systematic modification of the gas-phase basicity of the Im group does indeed cause the AM1-calculated TS structure (Figure 5b) to vary in this manner the transferring hydride moves from an early to a more central location between HPy and CH$_2$O whereas the position of the transferring hydron remains unaltered [34] This computational result serves to validate the use of AMJ diagrams as empirical tools for predictions of TS structural changes



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5.2 Kinetic Isotope Effects

Substitution of the transferring proton in the above reaction (equation 6) by a deuteron results in little change in the AM1 calculated value for the semi-classical primary kinetic isotope

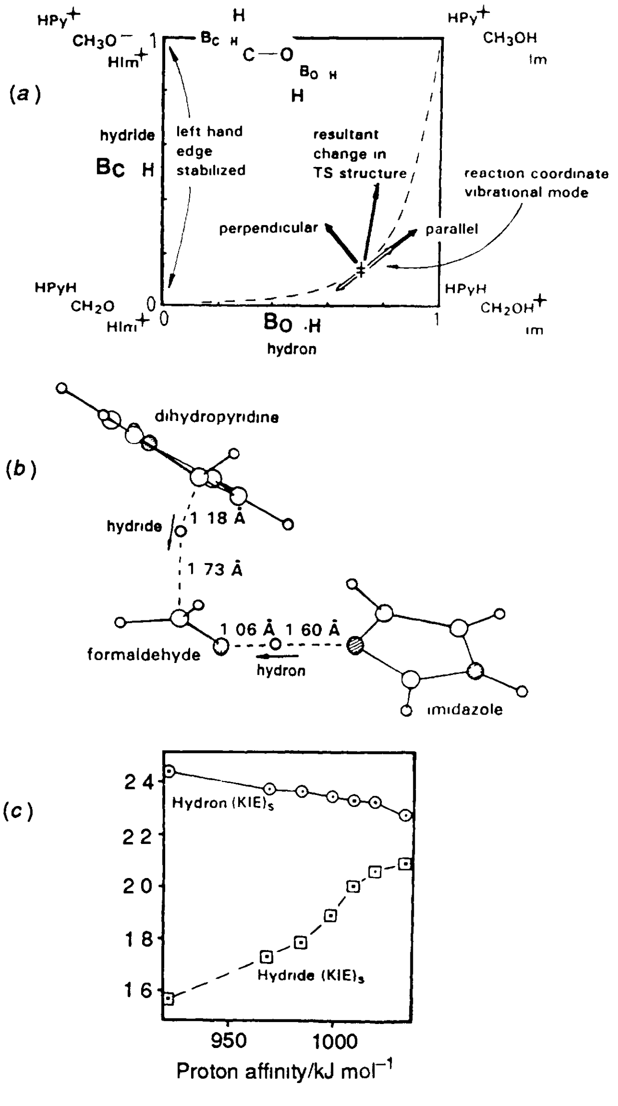


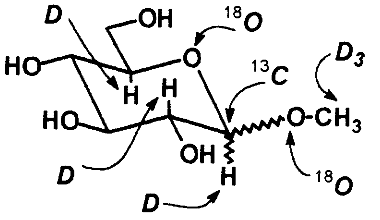
Figure 5 (a) Albery – More O'Ferrall – Jencks diagram for concerted reduction of carbonyl to alcohol (equation 6), showing location of TS and predicted change in structure in response to increase in basicity of imidazole (b) AM1 calculated TS structure for reaction (equation 6) (c) AM1 calculated semi-classical primary deuterium kinetic isotope effects for hydron transfer and hydride transfer in this reaction as a function of imidazole base strength Points on the left of the diagram correspond to unsubstituted imidazole

effect k_H/k_D ['hydron (KIE)$_s$'] as the proton affinity of Im is raised, consistent with little or no structural change in this component of the reaction; however, substitution of the transferring protide by deuteride results in a steady increase in the calculated value for k_H/k_D ['hydride (KIE)$_s$'] with increasing basicity, in accord with a structural change from an asymmetric to a more nearly symmetric TS for the hydride transfer component (Figure 5c).[34] A recent experimental study of general-acid-catalysis of the reduction of *p*-benzoquinone by an NADH analogue suggests a single TS for concerted hydride and hydron transfer, and also shows some evidence that the magnitude of the substrate (hydride) kinetic isotope effect increases with pK_a within a family of related catalysts.[35]

Schowen has pioneered a method for obtaining semi-quantitative, relative structural information about a series of TSs by a combination of experimental kinetic isotope effect measurements with theoretical modelling of isotope effects based upon the BEBO approach. The initial application[36] was to methyl transfer from sulfur to oxygen, and the TS structures were characterized in terms of Pauling bond orders B_{CO} and B_{CS} for the making and breaking bonds; all other structural features of the TSs were related to these two parameters by means of various assumptions. For a particular isotope effect (*e.g.* $k(\text{CH}_3)/k(\text{CD}_3)$), the predicted effects as a function of B_{CO} and B_{CS} form a surface which may be projected as a contour map of constant isotope effects upon which may then be traced a figure representing the experimental isotope effect, together with its estimated error (Figure 6a). To the extent that the calculational procedure is reliable, such a figure contains the space of TS structures 'allowed' by the experimental measurement. Superimposition of similar maps constructed for other isotope effects (*e.g.* $k(^{12}\text{CH}_3)/k(^{13}\text{CH}_3)$, Figure 6b) then leads to a reduced space of 'allowed' TS structures simultaneously consistent with all the experimental isotope effects (Figure 6c). Comparison of the 'allowed' structures for enzymic and non-enzymic methyl transfers led Schowen and co-workers to conclude that the making and breaking CO and CS bonds are shorter in the TS for the former than for the latter, and to suggest that the methyl transferase enzyme exerts compression upon the TS in order to achieve catalysis.[36] Independent theoretical support for this hypothesis was obtained from *ab initio* SCF calculations upon mechanically compressed and uncompressed TSs for methyl transfer.[37]

Murray has recently used the isotopic mapping method to characterize the TS for general-base-catalysed addition of alcohols to acetaldehyde,[38] here the maps were constructed as functions of bond orders B_{CO} and B_{OH} for the making bonds between the nucleophile and the carbonyl group, and between the catalyst and hydroxylic proton respectively. It was concluded that a reaction coordinate with essentially equal contributions of proton and heavy-atom motion was most consistent with the experimental solvent deuterium kinetic isotope effects for additions of different alcohols.

The use of KIEs as probes of TS structure is most convincing when multiple isotopic substitutions are performed, as in Sinnott's studies of acid-catalysed hydrolysis of methyl α- and β-glucopyranosides (3) where seven different KIEs were measured.[39] There may be several possible TS structures (modelled using, say, the BEBO approach) which are consistent with experimental KIEs for substitution at only one or two positions, but agreement with multiple KIEs provides a much more stringent test for any proposed TS structure. In Sinnott's work, theory was used to assist experimental interpretation in another way, by providing estimates for equilibrium isotope effects which were not easily accessible to experiment. Thus *ab initio* SCF MO equilibrium isotope effects calculated for models of glucosyl cation formation were used to calibrate the experimental KIEs in order to determine the degree of oxocarbonium ion character in the TS.



(3)

6 Theory as an Aid to Experimental Interpretation

Theory and experiment are sometimes viewed as opposites, and computational chemistry is sometimes portrayed as an alternative to experiment. Although it is necessary to perform definitive calculations upon benchmark systems to demonstrate the accuracy of theoretical methods, this competitive mode of operation should perhaps be regarded as the exception rather than the rule.

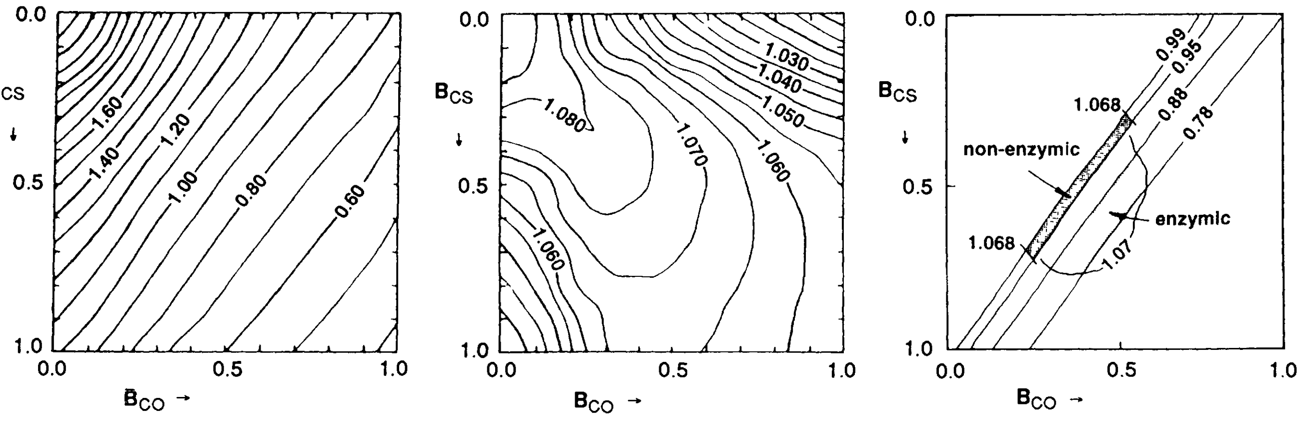


Figure 6 (a) Map of kinetic isotope effects $k(\text{CH}_3)/k(\text{CD}_3)$ for methyl transfer between sulfur and oxygen calculated using BEBO approach as a function of bond orders B_{CO} and B_{CS} to nucleophile and leaving group. (b) Similar map of calculated kinetic isotope effects $k(^{12}\text{CH}_3)/k\text{CH}_3)$. (c) Superposition of (a) and (b) showing spaces of 'allowed' TS structures for non-enzymic (dark shading) and enzymic (light shading) methyl transfer; the limits of these spaces are set by the experimental kinetic isotope effects for reaction of methoxide with a methyl sulfonium salt ($k(\text{CH}_3/k(\text{CD}_3) = 0.97 \pm 0.02$, $k(^{12}\text{CH}_3/k(^{13}\text{CH}_3) \pm 1.080 = 0.012$) and reaction of 3,4-dihydroxyacetophenone with *S*-adenosylmethionine catalysed by catechol *O*-methyl transferase [$k(\text{CH}_3)/k(\text{CD}_3) = 0.83 \pm 0.05$, $k(^{12}\text{CH}_3)/k(^{13}\text{CH}_3) \pm 1.09 \pm 0.02$]. (Adapted with permission from ref. 36. Copyright 1982 American Chemical Society.)

Besides the enormous value of theory for generating insight into chemical phenomena, not least in the area of reactivity, there is a vital role for theory as a tool complementary with experiment a co-operative mode in which the aim is not so much to provide an answer in place of performing an experiment, but rather to provide a sound framework within which experimental results may be interpreted reliably and new experiments suggested The TS remains an elusive entity for most chemical reactions of interest in condensed media While there is considerable progress in theoretical techniques for describing solvated systems and enzymic reactions, these methods alone are unlikely to solve all the problems However, theory and experiment working together offer an exceedingly powerful combination

7 New Horizons

Computational molecular modelling has developed over the past fifteen years or so into a powerful tool for the study of chemical behaviour, complementary with experimental methods Most of the activity in this area may be characterized as exploration of valley bottoms on energy surfaces governing chemical equilibria for example, molecular modelling in the pharmaceuticals industry has mainly focused on determination of conformation and binding properties of drug molecules with receptors In contrast, questions of reactivity – the making and breaking of chemical bonds – require study of the mountain passes on these energy surfaces Two adjacent energy minima on a surface are separated by just one saddle point, but a little thought shows that a surface containing multiple minima is likely to possess at least as many saddle points a rectangular egg-carton containing six holes, for example, has seven saddle points separating adjacent pairs of minima To the extent that molecular modelling has hitherto tended to concentrate upon equilibrium properties of molecules in valley bottoms, it has neglected a good half of chemistry, *i e* the top half, where all the mountain passes are to be found! The current importance of such issues as stereospecific synthesis and catalysis, where rational design requires the use of computational modelling to assist experimental endeavour, makes it imperative to turn the spotlight upon modelling of transition states Many exciting developments are in prospect upon this horizon

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