The Diagnosis of Concerted Organic Mechanisms

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1 Setting the Scene

Almost all discussions of mechanism involve the concept of concertedness. The relative sequence of bonding changes predicates the charge distribution in a reaction path and its revelation is therefore of the utmost importance to our understanding of mechanism. Despite intensive study it is surprising how little evidence is available which unambiguously excludes stepwise paths for the majority of reactions. The absence of evidence for intermediates (such as stereochemical integrity) while consistent with the postulate of a concerted mechanism does not exclude stepwise processes except in special cases which are the subject of this review.

A concerted mechanism has no intermediates and thus possesses only a single transition state.[1a] Although other definitions have been applied,[1b] the above is probably the most universally accepted, especially as it enables unambiguous diagnosis. A definition involving partial bond formation and fission[1b] presents an operational problem of distinguishing between hybridization changes and bond fission; moreover it tends to exclude those mechanisms where a bond change is almost or only partially complete in the transition state. A two-step consecutive process would give rise to an observation of partial bond formation and fission when neither step is rate limiting because both steps would then contribute to the rate. The preferred definition allows of concerted mechanisms where a particular bond change may not be very far advanced, and thus encompasses the concept of variable transition states.

The term 'synchronous' (see Figure 1) describes concerted mechanisms where the extents of bond fission and formation are equally advanced in the transition state. Concertedness refers to the major bonding changes in the reaction and does not include any initial or final steps (such as formation of encounter complexes) required to complete the overall process.

This review discusses contemporary work on some reactions hitherto regarded as not involving concerted mechanisms. The review emphasizes that out knowledge of whether or not a reaction proceeds *via* a concerted mechanism as opposed to a stepwise one is not firmly established in the majority of cases and it covers techniques developed over the past ten years for excluding stepwise or concerted mechanisms.[2] Since they are already covered at length in many general texts, reactions classically assumed to involve concerted mechanisms namely $E2$, S_N2, and cyclical rearrangements are not dealt with in depth.

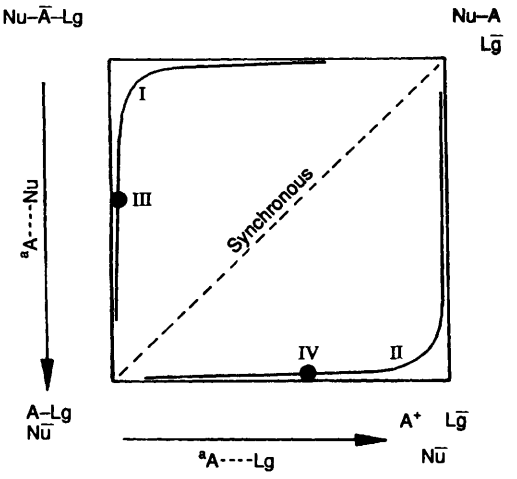
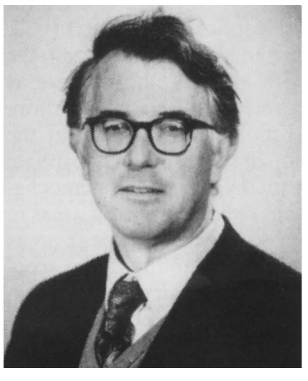


Figure 1 Reaction map for a general transfer reaction involving two major bond changes; the concerted path can take any route from reactants (A–Lg + Nu^-) to products (Nu–A + Lg^-). I and II refer to stepwise associative and stepwise dissociative mechanisms respectively. III and IV are transition states for enforced concerted mechanisms.

Interconversion between various molecular structures is a dynamic phenomenon. The mechanism for a particular interconversion describes the structures of intermediates (that is, discrete compounds) and the structures between the intermediates on the reaction path. The use of explicit 'Kekulé' structures has served very well to enable organic chemists to visualize mechanism graphically and also to enable predictions to be made. This method has the following shortcomings: (a) it does not display the solvent–solvent and solvent–solute interactions in a solution reaction; (b) it does not pay due regard to the fact that the reaction involves large collections of reacting molecules and that the Kekulé structure is only an average; (c) the application of Kekulé structures to the reaction path between reactants, products, and intermediates is not strictly valid as these are not of discrete compounds except at energy minima. Progress in elucidating reaction mechanisms was dramatically advanced when reactions were considered as interconversions of states (rather than of single molecules) and the use of the term transition STATE should continually emphasize this approach. The determination of transition-state structure does not easily follow from various kinetic parameters (which refer to collections of molecules), and a major challenge is to improve the techniques by which these parameters are translated into the Kekulé idiom.

Reactions in solution involve the collision of solvated molecules to form an arrangement which, becauses of inertia caused by solvent bulk, has a finite lifetime. During this period molecules enter the same solvent shell, the molecules then mix their electronic orbitals to give product and a similar process in reverse occurs to release the products to bulk solution. At all stages solvent is intimately involved with the reaction. The three-dimensional energy diagram (Figure 1) demonstrates the connection between concerted and stepwise mechanisms and refers to reaction within the solvent shell.

Andrew Williams obtained his D.Phil. under Gordon Lowe at Oxford in 1964 and spent a postdoctoral year with Myron Bender at Northwestern before being appointed lecturer at the University of Kent. He worked in Bill Jencks' laboratory at Brandeis during 1972–73 and was a senior Ciba-Geigy Fellow at Genoa in 1984; he was elected Professor of Organic Chemistry at Kent in 1987 and has served as Chairman of the Department. He is interested in the fundamental mechanisms of bio-organic reactions in solution, including enzyme- and polymer-catalysed reactions.



2 Bonding Indicators

There are numbers of techniques which attempt to reveal the extent of bonding in the transition state in solution reactions. Partial completion, in the transition state, of bond-breaking and forming steps is consistent with concertedness, but formation of an intermediate could involve changes in hybridization in a bond which only subsequently undergoes fission or formation. For example, it is well established that attack of hydroxide ion on esters involves a tetrahedral intermediate although the nature of the bond to the leaving group changes on formation of the intermediate. The observation of changes in bonding to entering and leaving groups would therefore not be diagnostic of concertedness unless there were some way of comparing these with expected hybridization changes.

A process involving passage through a structure corresponding to a species which is still an intermediate but has negligible barrier to decomposition is defined as an enforced concerted mechanism.[3] An enforced concerted mechanism would result from change in the conditions in a stepwise process (I, Figure 2) decreasing the stability of an intermediate to the point where its barrier to decomposition (II, Figure 2) has a lifetime commensurate with a vibration period (*ca.* 10^{-13} seconds). The 'enforced concerted' mechanism is on the borderline between stepwise and regular concerted mechanisms (III, Figure 2) and possesses no energy well at the structure corresponding to that of an intermediate.

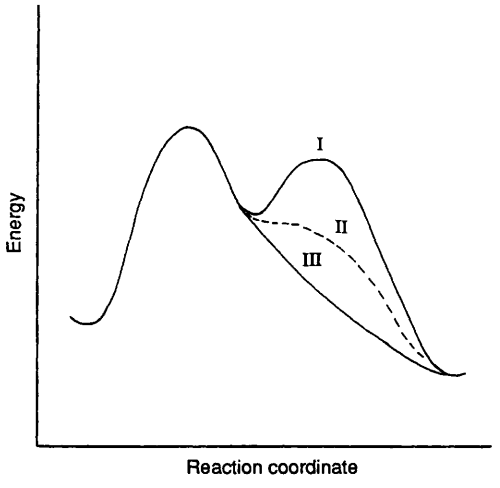


Figure 2 Two-dimensional energy diagram illustrating an enforced concerted mechanism (II) on the borderline between stepwise (I) and 'regular' concerted (I) paths.

3 Energy Considerations[2]

The energetic advantages of a concerted process are that (a) when the timing is substantially synchronous there is no large build up of charge in the transition state and (b) bond fission is aided by the energy released on bond formation. The energy of activation is usually less than the sum of the bond energies of the bonds undergoing major change. The disadvantage of a concerted process is that it generally requires more nuclear motion than do the individual steps of the corresponding stepwise process. Represention of reaction mechanisms by a series of curved arrows to simulate electron flow and to account for electron movement too easily degenerates into the description of a mechanism by a concerted process without attention being paid to its experimental demonstration.

4 Techniques for Excluding Mechanisms

4.1 General

Techniques for demonstrating intermediates and excluding concertedness are manifestly important in studies of timing of bond changes. We shall be discussing methods for detecting intermediates at concentrations too low for general instrumental techniques.

4.2 Stereochemistry

The discovery by Walden in the 19th century that change in configuration takes place during the course of aliphatic substitution reactions was followed in the first third of this century by a vigorous series of experiments which culminated in the formulation of the S_N2 concerted mechanism.[4] Despite its importance in formulating the concerted mechanism, the phenomenon of inversion has long been recognized as not being able to exclude stepwise mechanisms. Racemization or partial racemization is diagnostic of a symmetrical intermediate and therefore excludes a concerted mechanism.

The phenomenon of retention of configuration also diagnoses intermediates – for example many enzyme phosphotransfer reactions involve retention at the isotopomeric phosphorus atom by double inversion through the phospho–enzyme intermediate.[5] In summary:

(a) Retention is consistent with mechanisms which are adjacent concerted, stepwise ion-pair, or involve double inversion with an intermediate.
(b) Inversion is consistent with mechanisms which are concerted or involve an ion-pair reacting within the encounter complex faster than rotation.
(c) Racemization requires a mechanism involving an intermediate stable enough to rotate prior to reaction.

Techniques of analysis are the same as those used for studies of structure and need not be repeated at length. Chirality due to gross change measured by means such as rotation of the plane of polarized light, NMR experiments with chiral shift reagents or diastereoisomers, or by chiral chromatography require some form of Phillips–Kenyon or Walden cycle to identify the stereochemistry of the material. Isotopes have been employed increasingly since the late 1960s when isotopic chirality was introduced[6] for the study of mechanism in enzyme reactions. The advanced analytical procedures now available have enabled the widespread application of isotopic chirality as a mechanistic tool. The technique is particularly valuable in studies of bio-organic systems because gross structural change (such as methyl to hydrogen or ethyl *etc.*) employed to introduce chirality can serve to render a substrate completely inactive towards an enzyme or make it bind in an orientation different from that in the natural case. Isotopic change does not suffer from this problem but the tax to be paid for this increased flexibility is the requirement for advanced and expensive analytical techniques.

Recent advances in the study of phosphorus stereochemistry in reactions of [^{18}O,^{17}O,^{16}O]phosphate esters involve ^{31}P-NMR as the analytical method of choice.[5,7] This depends on the following two properties of oxygen isotopes bonded directly to phosphorus. The oxygen isotope ^{17}O broadens the ^{31}P resonance which is not therefore observed in the NMR spectrum; the oxygen isotope ^{18}O attached to the phosphorus causes a significant shift in the ^{31}P resonance to a field higher than with ^{16}O. The magnitude of the shift increases with P–O bond order and the position of the resonance therefore identifies whether the isotopic [^{18}O]oxygen is in a P–O or in a P=O bond. In a typical procedure the stereochemistry of phosphorus in phenyl [^{18}O, ^{17}O, ^{16}O]phosphate may be determined by transferring the phosphate to *S*-propan-1,2-diol with alkaline phosphatase as catalyst. The transfer occurs with retention of configuration. Cyclization of the phosphorylated diol (with inversion at the phosphorus) followed by methylation of the resulting phosphate ester gives *syn* and *anti* forms of the methyl ester. The stereochemical purity is obtained from a comparison of the peak areas in the ^{31}P NMR spectra. The accuracy with which the peak areas can be estimated (associated with the repeatability of the spectra) give confidence limits to the stereochemistry of the phosphate being analysed.

Stereochemistry at carbon resulting from experiments with asymmetric isotopic labelling with deuterium may be analysed

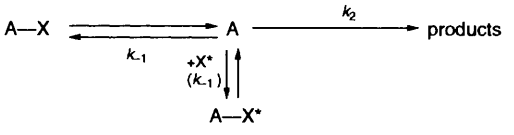
by optical rotation, but direct NMR analysis of the intact methyl group is the method of choice Diastereotopic protons in $-CH_2D$ in a suitable chiral molecule have an observable chemical shift difference [8] Normally the CH_3- group is degraded to CH_3COOH for chirality analysis

Analysis of chirality at sulfur as a result of transfer of the sulfuryl group may be carried out by employing infra red spectral analysis using a Fourier transform instrument [9a] The sulfuryl group is transferred to an optically active diol by heating in solution in carbon tetrachloride The sulfuryl diol is then deprotected and cyclized to yield a cyclic sulfate and the FTIR spectrum determined The shift in the S=O vibration (symmetric and antisymmetric stretching frequencies of the $>SO_2$ bond at 1400 and 1200 cm^{-1}) caused by isotopic substitution of oxygen in axial and equatorial positions forms the basis for the stereochemical analysis of the chirality of the sulfur

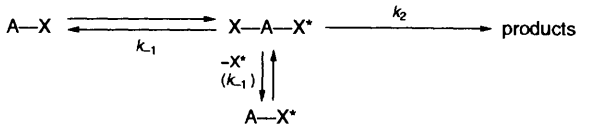
4.3 Positional Isotopic Exchange (PIX)

The system under investigation can often be designed so that return of intermediate to reactants would incur an exchange of isotopes (Scheme 1) The composition of the reactant is examined at increasing times for evidence of incorporation of the isotope The absence of positional isotope exchange in a system does not exclude a stepwise mechanism because return to exchanged reactant (k'_{-1}) could be slower than the forward rate constant (k_2) in the general scheme The presence of PIX could also result from intervention of solvent molecules to form a reactive intermediate (*e g* A–solvent) which then reacts with either X* or X

Dissociative Mechanism



Associative Mechanism



Scheme 1 General equations for positional isotope exchange in stepwise dissociative and associative reactions

5 Exclusion of Stepwise Mechanisms

5.1 Preliminaries

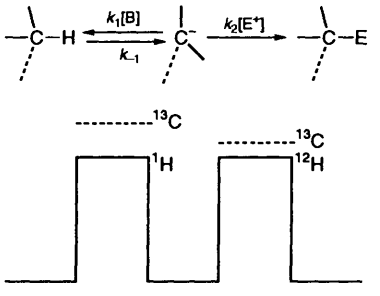
The observation of results arising from a change in rate limiting step which are thus indicative of a stepwise pathway is a classical method excluding a concerted process The absence of evidence *for* a change in rate determining step is not immediate evidence for a concerted mechanism (*excluding* a stepwise path) because the experiments could have been carried out under conditions where the change in rate limiting step would not be expected If it can be established that a change in rate determining step would be expected for a putative stepwise process then the absence of such a change is diagnostic for a concerted mechanism

5.2 Primary Kinetic Isotope Effects

The observation of a primary isotope effect indicates bond fission in the transition state of the rate limiting step, in order to demonstrate concertedness, primary isotope effects should be measured for all bonds undergoing a major bonding change Such a study is clearly not a minor undertaking and has only been achieved for a few systems, notably in elimination reactions of 2-arylethyl derivatives Heavy atom isotope effects as well as the hydrogen isotope effect must be studied and it is essential to know the expected primary isotope effects [9b] Even if a primary isotope effect is demonstrated for the two bonding changes, it is still necessary to show that these are not due to a 'balanced' stepwise process (*i e* where neither formation nor decomposition of the intermediate is rate limiting)

5.3 Double Isotope Fractionation Test[10]

One way of excluding a 'balanced' stepwise process is to study the effect of substitution of an isotope in one of the bonds on the isotope effect in the other bond undergoing a major change The influence of k_2 on the overall rate constant (Scheme 2) would be altered by variation in the partition ratio ($R = k_{-1}/k_2$) and if k_2 bears a second isotopic change (*i e* it is an isotopically sensitive step) the isotope effect on the overall rate constant should also be affected by the change in 'R' No change in isotope effects would be observed as a function of the change in isotope in the other bond if both the isotopically sensitive bonds are undergoing concerted change The principle is illustrated for a simple reaction when carbanion formation precedes bond formation between carbanion and electrophile in a stepwise process For this idealized case the possible observed isotope effects divide into four types (a) When the reaction is stepwise and k_1 is rate limiting the substitution of 2H for 1H will have no effect on the ^{13}C isotope effect (E^+ is, for example $-CHO$ and the carbon is isotopically substituted), which should be unity, (b) when k_2 and k_{-1} are of the same order the substitution of 2H for 1H will reduce k_{-1} and hence the partitioning ratio will increase and the effect of k_2 will decrease leading to a reduced ^{13}C isotope effect on the C–E bond, (c) a concerted process yields primary deuterium and ^{13}C isotope effects which are independent of isotopic substitution in the other bond, (d) when k_2 is rate limiting there will only be a secondary hydrogen isotope effect (equilibrium) and a primary isotope effect for the C–E bond



$k_{obs} = k_1 k_2[B][E^+]/(k_{-1} + k_2[E_+])$
when k_1 is rate limiting $k_{obs} = k_1[B]$
when k_2 is rate limiting $k_{obs} = (k_1 k_2/k_{-1})/[B][E^+]$

Scheme 2 Schematic view of free energies of activation for the two consecutive steps in a putative stepwise process, the energies of the reaction states are reduced to zero

The example can be applied to an associative reaction

$$A-B + D \longrightarrow D-A-B \longrightarrow A-D + B$$

but in practice this would require two heavy atom isotope effects which would not have the substantial effect on 'R' that hydrogen isotopes have

5.4 Polar Substituent Effects

The observation of Hammett or Brønsted relationships involving two intersecting straight lines is classic evidence for a stepwise mechanism Linearity of a free energy relationship is construed as evidence for a single rate limiting step within the

range of substituent parameters measured (such as sigma or pK_a) and a break in the plot would thus indicate the presence of at least two transition states Change in substituent leading to an increase in rate constant over that predicted indicates a change in rate limiting step (Figure 3)

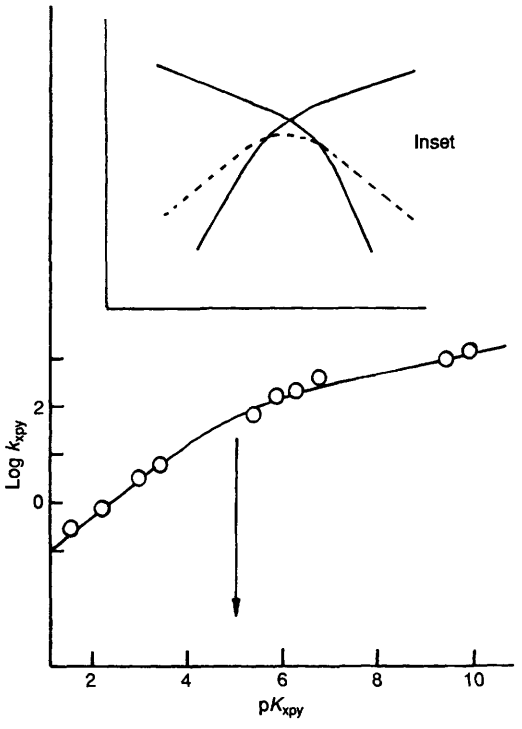


Figure 3 A non-linear Brønsted correlation indicating an intermediate in attack of pyridines on 2,4,6-trinitrophenyl acetate, the figure is plotted from data in E A Castro, F Ibanez, S Lagos, M Schick, and J G Santos, *J Org Chem*, 1992, **57**, 2691 The arrow indicates the pK_a of the pyridine where $k_{-1} = k_2$ The inset shows three types of non-linear free-energy plot demonstrating change in rate limiting step

It is difficult to predict unambiguously the position of the breakpoint in a two-step mechanism, except when the entering and leaving groups have similar structures Let us assume that a Brønsted dependence is under investigation for the putative stepwise mechanism involving nucleophilic (Nu) displacement of a leaving group (Lg) (equation 1a) Each step has its own Brønsted (or Hammett *etc*) equation (log $k_{nuc} = \beta_n\ pK_a + C_n$) and the measured rate constant will be governed by equation 1b

$$A{-}Lg + Nu \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Nu{-}A{-}Lg \xrightarrow{k_2} A{-}Nu + Lg \quad (1a)$$

$$k_{obs} = k_0\ 10^{\beta 1\ \Delta pK}/(1 + 10^{-\Delta\beta\ \Delta pK}) \quad (1b)$$

where k_0 is a constant, $\Delta pK = pK_{nuc} - pK_{lg}$ and $\Delta\beta = \beta_2 - \beta_{-1}$, βs refer to the exponents for Brønsted-type equations for the individual rate constants in the scheme Equation 1 predicts a free energy relationship with two straight lines intersecting (when the change in rate limiting step occurs) at $\Delta pK = 0$ (*i e* when $k_{-1} = k_2$) It is immediately obvious that nucleophile and leaving group are required to have similar structures otherwise the individual Brønsted relationships for k_{-1} and k_2 will not be the same, thus destroying the validity of the general equation and making it difficult to predict from simple considerations the value of pK_{nuc} or pK_{lg} when $k_{-1} = k_2$

Kinetic data can normally be measured extraordinarily accurately with little effort and yet Brønsted and Hammett plots all show varying degrees of scatter about a mean line The source of the scatter (when all obvious sources of error such as steric effects *etc* have been excluded) is ascribed to the small difference in energy induced by the substituent on the microscopic solvation in the standard reaction (usually an ionization) compared with the reaction under investigation The presence of such effects (called microscopic medium effects) means that the Brønsted or Hammett plots must possess sufficient data points to enable a reasonable statistical estimate to be made of slope, curvature *etc* The points must spread over a range of substituent parameters which substantially encompasses the pK or σ corresponding to the breakpoint The value of $\Delta\beta$ corresponds to the difference in effective charge on a reacting atom in the transition states corresponding to k_{-1} and k_2 in the putative stepwise path so that $\Delta\beta = 0$ (corresponding to a linear plot) indicates that the transition states have the same electronic charge (and by inference the same structure) and that there is no intermediate intervening between them Experimental techniques can never provide exact data and the fit gives an error on $\Delta\beta$ which is the extent to which we can be sure of the effective charge difference between the putative transition states In the examples to be shown where $\Delta\beta$ has a zero value, a typical error is ± 0 2 Taken as a percentage of the overall change in effective charge on the atom from reactant to product (β_{eq}) the error in $\Delta\beta$ gives an estimate of the maximal barrier height from putative intermediate to either forward or reverse transition states Thus an error of ± 0 2 with a typical β_{eq} of 1 8 (for carbonyl transfer between oxyanions) gives an overall uncertainty of 11% over the total change in effective charge Since the intermediate must lie somewhere between the two transition states on the effective charge scale, the change in effective charge from intermediate to one of the transition states must be less than 11%/2 of the overall change in effective charge It is considered unlikely that such a change would give rise to sufficient barrier to support a discrete intermediate Thus, even a slightly curved free energy relationship is consistent with concertedness, it is clearly of great interest to examine what ratio of $\Delta\beta/\beta_{eq}$ might be expected to be at the borderline between concerted and stepwise mechanisms, or indeed if there is a fixed ratio

5.5 Kinetics

Free energy relationships may be employed to calculate rate constants for putative reactions, comparison with the maximal rate constant (limited by the period for a bond vibration) may then be employed to decide if the reaction has a concerted mechanism within the range of substituent variation The decomposition of the carbanions of the aryl esters of phenylmethanesulfonic acid follows the Brønsted law $\log k = -2\ 0pK_a + 24$ and extrapolation to the pK_a (Figure 4) of 2,4-dinitrophenol indicates that the rate constant should be 10^{16} s^{-1}, which exceeds that for a reaction running at the vibration limit Thus for the 2,4-dinitrophenyl ester it is reasonable to assume that attack of hydroxide ion yields a carbanion which has no significant lifetime and that the mechanism is probably enforced concerted, in the region where the 'rate constants' are greater than 10^{13} s^{-1}

6 Systems under Contemporary Scrutiny

6.1 Displacement Reactions

6 1 1 Phosphorus Acyl (Phosphyl) Group Transfer

The most important biological phosphyl groups are the phosphoryl group O_3P-, the phosphodiester group $RO-PO_2-$, and the neutral phosphoryl group $(R-O)_2PO-$ Considerable mechanistic work has centred around the transfer of these and related groups which possess mechanisms conforming to those displayed in Figure 1 The metaphosphate ion (PO_3^-, analogous to a carbonyl acylium ion) formed by the dissociative pathway was for long postulated as an intermediate in phosphorylation reactions, but good evidence was not available although analogous metaphosphate species, (1)—(4), are intermediates in phosphyl transfer [11] The case for the metaphosphate intermediate is difficult to make because in aqueous solution the putative intermediate appears to be very reactive indeed

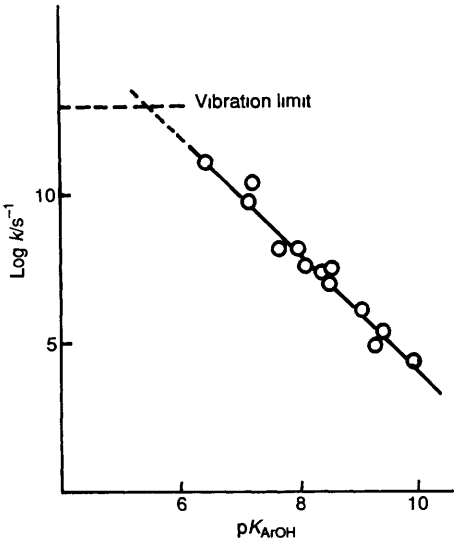
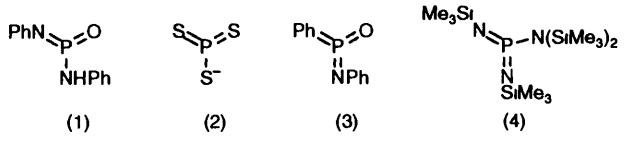


Figure 4 Brønsted dependence of the decompositon of $PhCH^-SO_2-O-Ar$ indicating a change to enforced concerted elimination at pK_a's for leaving groups lower than 5, the figure is plotted from data in M B Davy, K T Douglas, J S Loran, A Steltner, and A Williams, *J Am Chem Soc*, 1977, **99**, 1196



(1) (2) (3) (4)

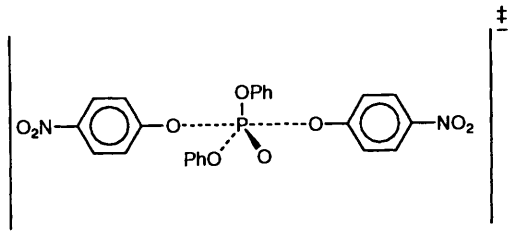
The stereochemistry of transfer of the PO_3^- group from Ar-O-PO_3^{2-} to an alcohol involves an inversion of configuration within the limits of the analytical data (about ± 2 5%) Inversion could arise from a dissociative path provided the intermediate reacted with the nucleophile in the cage in a 'pre-association' mechanism (equation 2) Reaction of substituted pyridines with pyridine-*N*-phosphonates[1a] gives *N*-phosphoryl-substituted pyridines The rate constants obey a Brønsted dependence, with no evidence for a break at the pK_a of the attacking pyridine corresponding to that of the leaving group, indicating that there is no change in rate limiting step required by a stepwise process The linearity excludes the pre-association mechanism where the metaphosphate ion would be formed in the solvent cage and react with nucleophile within the cage before the ion could escape (equation 2), the data also exclude a mechanism involving formation of a discrete metaphosphate ion intermediate

$$\text{isq-PO}_3 \underset{\text{step 1}}{\overset{+\text{xpy}}{\rightleftharpoons}} [\text{isq-PO}_3\ \text{xpy}] \underset{\text{step 2}}{\rightleftharpoons} [\text{isq xpy PO}_3] \underset{\text{step 3}}{\rightleftharpoons} [\text{isq xpy-PO}_3 \underset{\text{step 4}}{\overset{-\text{isq}}{\rightleftharpoons}} \text{xpy-PO}_3 \quad (2)$$

When fission of the N–P bond (step 2) is rate limiting (at $pK_{xpy} > pK_{isq}$) the Brønsted slope should approximate to zero because fission of the N–P bond should be independent of the substituent in the attacking pyridine

The observation of positional isotope exchange is in favour of a PO_3^- intermediate in the reaction of ADP in acetonitrile or acetonitrile–t-butyl alcohol solvents [13] This is due to the non-intervention of solvent which is sufficiently weak as a nucleophile to allow the existence of the PO_3^- intermediate

The linearity of the Brønsted plot for the attack of aryloxy-anions on the 4-nitrophenyl diphenylphosphate[14] is consistent with a concerted mechanism shown in structure (5)



(5)

6 1 2 Sulfur Acyl (Sulfuryl) Group Transfer

Sulfuryl group ($-SO_3^-$) transfer is closely analogous to the transfer of the phosphoryl group and for many years SO_3 (analogous to PO_3^-) was postulated as a very reactive intermediate The observation of a linear Brønsted dependence (Figure 5) for attack of substituted pyridines on isoquinoline-*N*-sulfonate (isq-SO_3) excludes SO_3 as an intermediate in this reaction

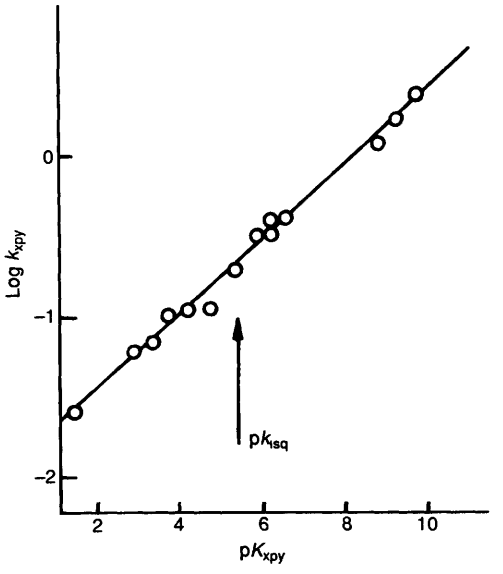
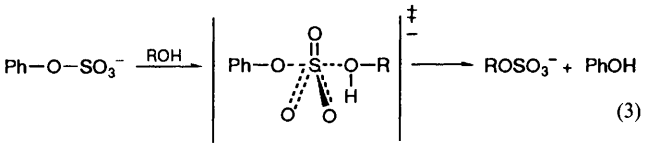


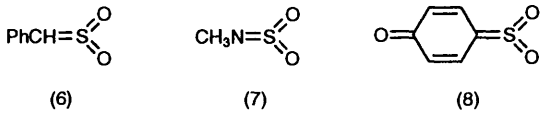
Figure 5 Brønsted dependence of the reaction of substituted pyridines (xpy) with isoquinoline-*N*-sulfonate (isq-SO_3) indicating a single transition step The figure is drawn from data in N Bourne, A Hopkins, and A Williams, *J Am Chem Soc*, 1985, **107**, 4327 The position of the breakpoint expected for a change in rate limiting step is indicated by the arrow

Retention of configuration at sulfur in the product of hydroxyl attack on phenyl sulfate[15] is consistent with either a concerted mechanism (equation 3) or a mechanism involving formation of sulfur trioxide in a cage which reacts with nucleophile faster than rotation can occur Analogues of sulfur trioxide have been demonstrated as intermediates [(6)—(8)] and some have even been isolated



(3)

It should be noted that although 'sulfur trioxide' may be purchased, it is not as a monomer, it is so reactive that in the condensed phase it exists only in a polymeric form Stabilized sulfur trioxide liquid has an amount of stabilizer (usually



(6) (7) (8)

dioxane) present which bonds with the sulfur The monomer only exists in the dilute gas phase

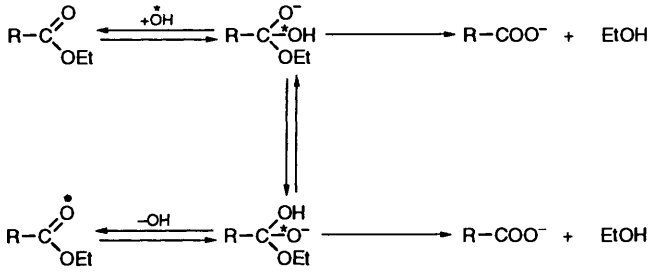
Displacement reactions of oxyanions with aryl sulfonate esters have been shown[1a] to involve a concerted mechanism

6 1 3 Carbonyl Group Transfer

Mechanisms available for transfer of the carbonyl group (RCO–) bear a strong relationship with other group transfers such as alkyl substitution (Figure 1 where 'A' is the RCO-group)

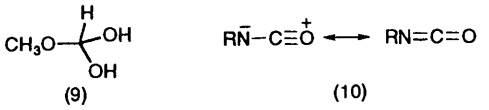
In direct opposition to the general opinion of the previous 20 or 30 years that carbonyl group transfer reactions always involve the intervention of tetrahedral intermediates, the most dramatic conclusion of the recent results is that some acyl group transfer reactions can involve a concerted mechanism

Incorporation of ^{18}O into the carbonyl oxygen of the ester during alkaline hydrolysis in ^{18}O-enriched water[16] indicates the existence of a tetrahedral intermediate (Scheme 3) and that the proton transfer step is faster than decomposition of the tetrahedral intermediate The detection of 'tetrahedral' intermediates is difficult in general because of their great propensity to decompose to product or reactant, and many laboratories have searched for stable examples Observable but *reactive* tetrahedral intermediates, such as (9), have been thoroughly investigated [17]

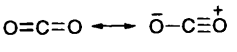


Scheme 3 Positional isotope exchange for ester hydrolysis

The acylium ion (RCO^+) has long been accepted as an intermediate in the gas phase, although it is likely to be very reactive in nucleophilic solvents The expression of the acylium ion in solution reactions depends on the provision of factors stabilizing it and on good leaving groups Some examples of stabilized acylium ions occurring as intermediates in various dissociative mechanisms are illustrated in structures (10)—(12)


(9)

(10)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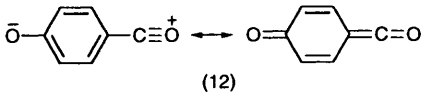

(12)

The existence of both extremes of timing in acyl group transfer (Figure 1) begs the question of the existence of a concerted mechanism on the border between the extremes The concerted mechanism for ester hydrolysis was formally expressed by Dewar in 1949[1a] but it was overshadowed by Myron Bender's seminal paper on the tetrahedral intermediate [16] There was no compelling evidence against a stepwise process until it was reported[1a] that the reaction of substituted pyridines (xpy) with the *N*-methoxycarbonylisoquinolinium ion (isq-COOMe) to yield *N*-methoxycarbonylpyridinium ions had a linear Brønsted correlation over a range of pK_a values greater than and less than that of isoquinoline A stepwise process would require a change in rate limiting step to occur at the pK_a of isoquinoline and give rise to a breakpoint at that place Similar evidence indicates that transfer of the acetyl group between phenolate ions is concerted (Figure 6) [1a]

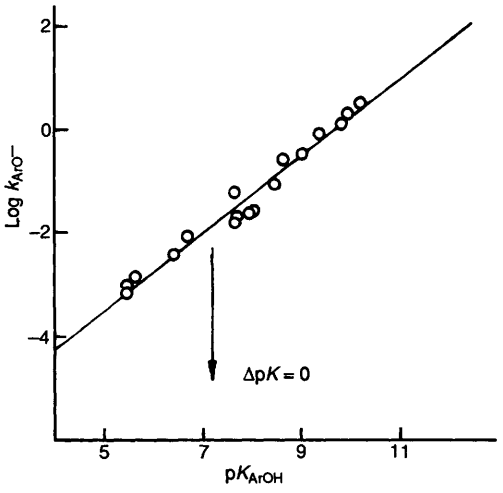
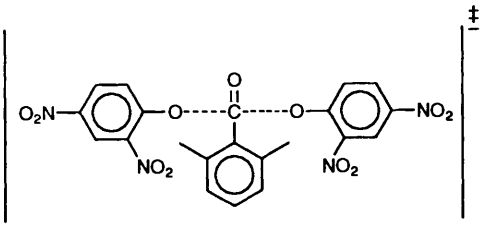
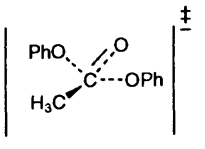


Figure 6 Brønsted dependence of the reaction of substituted phenolate anions with 4-nitrophenyl acetate The figure is drawn from data in S A Ba-Saif, A K Luthra, and A Williams, *J Am Chem Soc*, 1987, **109**, 6362 The arrow shows the breakpoint for the putative stepwise process

The value of $\Delta\beta$ of zero (see equation 1) indicates that there is no charge difference between the nitrogen on the substituted pyridine for both transition states of the putative stepwise process Reaction of substituted phenolate ions on 4-nitrophenylacetate has likewise been shown to involve a concerted pathway [1a]

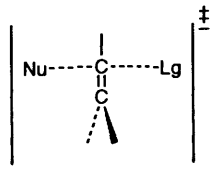
Thermodynamic arguments indicate that the adduct from methyl acetate and hydroxide ion decomposes with a half life of about 10^{-7} seconds [18] The adduct between phenolate ions has a predicted half-life too short for the species to exist, and the reaction thus becomes concerted Oxyanions with pK_a greater than about 11 were shown to give tetrahedral adducts which had sufficient stability to exist The transition state of the concerted mechanism probably has square planar stereochemistry (13) for weakly basic nucleophiles and leaving groups, the transition state would possess a tetrahedral shape (14) for more basic nucleophiles and leaving groups


(13)

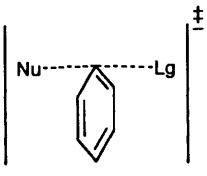

(14)

6.2 Substitution at Aromatic and Olefinic Carbon

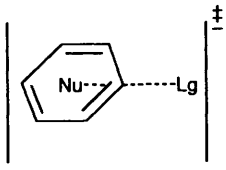
Concerted mechanisms for nucleophilic vinyl and aromatic substitution have been considered from time to time Various spatial models have been considered, (15) to (18), and in some cases the concerted mechanism has been discarded[19] because concerted displacements were thought to require 'in-line' bond formation and fission



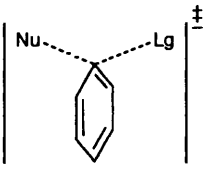
(15)



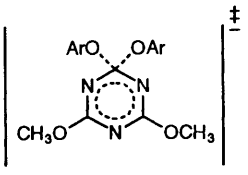
(16)



(17)

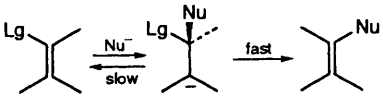


(18)



(19)

Such restrictions disappear when it is considered that the stereochemistry of the concerted acyl group transfer need not have square planar geometry (except when the entering and leaving bonds are weak) Observations of stereochemical retention were believed to indicate concertedness, but these results are now thought to be due to a barrier to rotation of the central bond in a carbanion intermediate significant compared with that for expulsion of the leaving group (equation 4) [20]



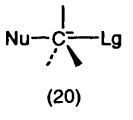
(4)

The observation of generally stable Meisenheimer addition complexes has dominated the field of mechanism in nucleophilic aromatic substitution and requires that they must be positively excluded if a concerted mechanism is to be believed Many nucleophilic substitutions at the aromatic centre involve groups which activate the reaction by withdrawing electrons, in particular, the nitro-group is a favourite activating species The nitro-group can stabilize Meisenheimer adducts by strongly localizing the negative charge on its oxygens, so that it would probably be futile to look for concertedness in substitution in nitro-activated aromatic species

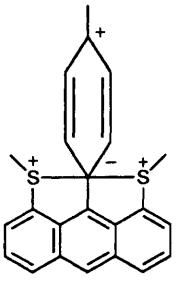
The nucleophilic attack of phenolate ions on 4-nitrophenoxytriazine ethers has been shown to have a single transition state (19) The second-order rate constant for the displacement has a linear Brønsted relationship over a large range of pK_a values on either side of that (pK_a of the leaving 4-nitrophenol) where a change in rate limiting step is predicted for the stepwise process [21]

6.3 Substitution at Saturated Carbon

Undoubtedly the most important reaction as an architype/paradigm for mechanism is the nucleophilic aliphatic substitution reaction The work of Hughes and Ingold[4] culminated in the description of the classic transition state It was discovered during the investigations of the reaction mechanism of nucleophilic substitution that a carbenium ion mechanism could also occur Carbenium ion intermediates which are also so reactive that they cannot exist outside the reaction complex have been demonstrated in substitution reactions The inversion of configuration at the central carbon atom can sometimes amount to 100%, simply because the carbenium ion intermediate reacts within the complex before it can rotate Although the relative timing involving addition of nucleophile prior to departure of leaving group has not been demonstrated (corresponding to the top left corner of the reaction map in Figure 1), there seems no reason why a pentacoordinate intermediate (20) should not exist under favourable conditions Species such as (21)[22] and other, less obvious, analogues, (22) and (23), are well known



(20)



(21)

(22) (23)

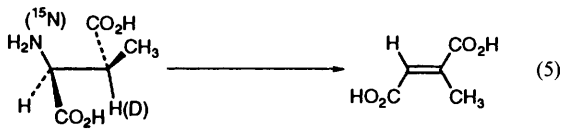
Positional isotope exchange has also been employed extensively in studies of ion-pair intermediates in nucleophilic aliphatic substitution and in electron-deficient rearrangements The ethanolysis of norbornyl brosylate can be followed readily by ^{17}O-NMR[23] and suffers positional isotopic exchange Although the S_N2 mechanism was thought at one time to be firmly established, new ideas concerning reactivity of caged intermediates[4] cast substantial doubt on many of the conclusions based on stereochemistry It would now appear that the aliphatic substitution mechanism is presumed to involve reactive carbenium ions unless proved otherwise The concerted aliphatic mechanism should still be considered as possible, especially as there are analogues of the pentacoordinate intermediate which suggest a continuum of mechanism from S_N1 through S_N2 to stepwise associative Recent work has shown that concerted mechanisms hold in substitution at other saturated centres such as at silicon,[24a] and more positive evidence is appearing for the concerted process in aliphatic substitution For example, some carbenium ions may be estimated to have lifetime less than the vibration limit in the presence of azide ions [24b]

6.4 Elimination Reactions

Historically, the first well-documented evidence for a concerted mechanism appears to be for base-catalysed elimination reactions, the transition state of the reaction is familiar to all The evidence for this has been discussed in depth and we refer readers to Bordwell's critical discussion [25] An interesting modern example is the mechanism of the aspartate deaminase reaction, which has been studied by the double isotope fractionation method The equality of the ^{15}N isotope effect for both ^{1}H and ^{2}H substituents (1 0246 ± 0 0013) indicates that the reaction of (2*S*,3*S*)-3-methylaspartic acid has a concerted mechanism (equation 5) [26]

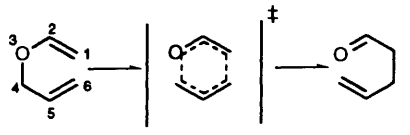
6.5 Cyclical Reactions

The evidence for the concertedness of certain rearrangements which form the basis of the data correlated by the famous



(5)

Woodward–Hoffman rules is summarized by Rhoads.[27] Evidence unambiguously excluding stepwise mechanisms for these reactions is rare; the major stepwise competitor for these reactions involves radicals. Probably the most useful tool in studies of concertedness in these reactions is the isotope effect. A modern example centres on the Claisen-type rearrangement (equation 6) where the primary isotope effects have been measured for ^{14}C-2, ^{14}C-4, ^{14}C-6, and ^{18}O, as well as for secondary deuterium isotope effects (where the C–H bonds are not broken).[28] Comparison with a matrix of calculated effects for various extents of bonding indicates the best fit of the observed isotope effects to be C-4–C-6 at 10—30% formed, and C-4–O to be 50—70% broken, in the rate limiting step (Figure 7).



(6)

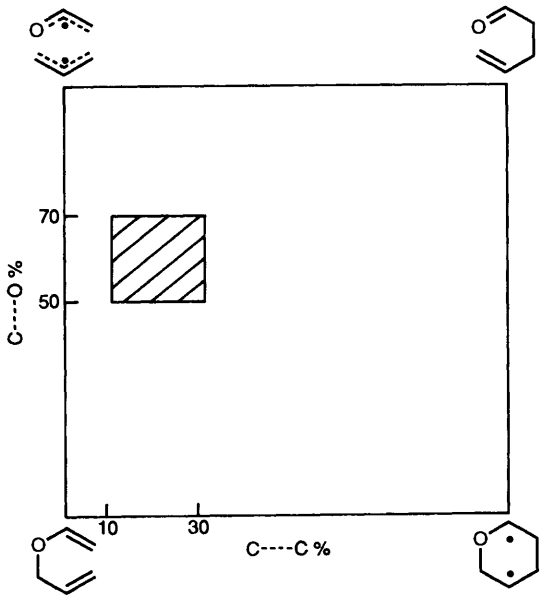


Figure 7 Reaction map for the Claisen-type rearrangement of allyl vinyl ether. The shaded portion indicates the area of uncertainty for the transition 'structure' derived from multiple kinetic isotope effects. The top left and bottom right corners represent dissociative and associative stepwise paths respectively.

While there is excellent evidence that there are no free radical or diradical intermediates, future work would be to exclude the intervention of radical pairs within an encounter complex in a balanced stepwise process.

7 Envoi

It is generally assumed that, due to their lack of inertia, solvation changes and changes in other forms of weak bonding will be coupled with major bonding changes. It is possible to conceive of a solvation or hydrogen bond change which cannot keep up with a very fast major bonding change occurring within an encounter complex. Indeed, there are a number of experimental observations which are consistent with bonding changes being uncoupled from solvation changes,[3,29] and this region of study will surely come under scrutiny as the effect of solvents on reactions becomes better understood.

8 References

1 (*a*) A. Williams, *Acc. Chem. Res.*, 1989, **22**, 387. (*b*) J. P. Lowe, *J. Chem. Educ.*, 1974, **51**, 785.
2 F. G. Bordwell, *Acc. Chem. Res.*, 1970, **3**, 281.
3 W. P. Jencks, *Chem. Soc. Rev.*, 1981, **10**, 354.
4 D. J. McLennan, *Acc. Chem. Res.*, 1978, **9**, 281.
5 G. Lowe, *Acc. Chem. Res.*, 1983, **16**, 244.
6 J. W. Cornforth, *Quart. Rev. Chem. Soc.*, 1969, **23**, 125.
7 P. A. Frey, *Tetrahedron*, 1982, **38**, 1541.
8 F. A. L. Anet and M. Kopelewich, *J. Am. Chem. Soc.*, 1989, **111**, 3429.
9 (*a*) G. Lowe, *Phil. Trans. R. Soc. (London)*, 1991, **332(B)**, 141. (*b*) W. H. Saunders, *Acc. Chem. Res.*, 1976, **8**, 19.
10 J. G. Belasco, W. J. Albery, and J. R. Knowles, *J. Am. Chem. Soc.*, 1983, **105**, 2475.
11 A. Williams and K. T. Douglas, *Chem. Rev.*, 1975, **75**, 627.
12 S. L. Buchwald, J. M. Friedman, and J. R. Knowles, *J. Am. Chem. Soc.*, 1984, **106**, 4911.
13 P. M. Cullis and D. Nicholls, *J. Chem. Soc., Chem. Commun.* 1987, 783.
14 S. A. Ba-Saif, M. A. Waring, and A. Williams, *J. Am. Chem. Soc.*, 1990, **112**, 8115.
15 C. L. L. Chai, W. A. Loughlin, and G. Lowe, *Biochem. J.*, 1992, **287**, 805.
16 M. L. Bender, *Chem. Rev.*, 1960, **60**, 53.
17 (*a*) B. Capon, A. K. Ghosh, and D. Mc. L. A. Grieve, *Acc. Chem. Res.*, 1981, **14**, 306. (*b*) R. A. McClelland and L. J. Santry, *Acc. Chem. Res.*, 1983, **16**, 394.
18 J. P. Guthrie, *J. Am. Chem. Soc.*, 1991, **113**, 3941.
19 J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **51**, 273.
20 Z. Rappoport, *Acc. Chem. Res.*, 1992, **25**, 474.
21 A. H. M. Renfrew, J. A. Taylor, J. M. J. Whitmore, and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1703.
22 J. C. Martin, *Science*, 1983, **221**, 509.
23 S. Chang and W. J. LeNoble, *J. Am. Chem. Soc.*, 1983, **105**, 3708.
24 (*a*) Y. Xu and P. E. Dietze, *J. Am. Chem. Soc.*, 1993, **115**, 10722. (*b*) J. P. Richard and W. P. Jencks, *J. Am. Chem. Soc.*, 1984, **106**, 1383.
25 F. G. Bordwell, *Acc. Chem. Res.*, 1972, **5**, 374.
26 N. P Botting, A. A. Jackson, and D. Gani, *J. Chem. Soc., Chem. Commun.*, 1989, 1583.
27 S. J. Rhoads, in 'Molecular Rearrangements', Vol. 1, ed. P. B. DeMayo, Interscience, New York, 1963, p.655.
28 L. Kupczyk-Subotkowska, W. H. Saunders, H. J. Shine, and W. Subotkowska, *J. Am. Chem. Soc.*, 1993, **115**, 5957.
29 T. E. Casamassina and W. P. Huskey, *J. Am. Chem. Soc.*, 1993, **115**, 14.