

Mechanistic and Structural Investigations based on the Isokinetic Relationship

Wolfgang Linert

Institute of Inorganic Chemistry, Technical University Vienna, Getreidemarkt 9, A-1060 Vienna, Austria

1 Introduction

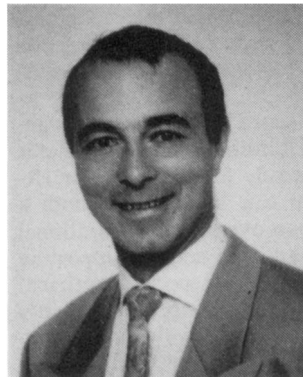
In 1989 a review article¹ concerning the Isokinetic Relationship (IKR) presented the history, method of performing statistical analyses of experimental data, theoretical basis, and interrelation of the IKR's with LFER's (linear free energy relationships). Since the appearance of that review several important developments have ensued. In addition to extending the amount of experimental evidence supporting the heat-bath theory of energy transference responsible for the origin of the IKR, more recent studies have made extensive use of IKR as a diagnostic tool in the field of mechanistic and structural investigations. The present Review concentrates on these applications of IKR.

The IKR, or its equivalent in thermodynamic terms, the isoequilibrium relationship (or IER) refers to a common point (or small area) of intersection of Arrhenius lines (*i.e.* $\ln k(\xi)$ versus $1/T$) or van't Hoff lines ($\ln K(\xi)$ versus $1/T$), for a series of reactions. The common point of intersection of Arrhenius lines or Van't Hoff lines (even when non-linear behaviour is observed) is expressed by (1) and defines a minimum of deviations between the different members of the reaction series.

$$\left. \frac{d \ln k(\xi, T)}{d(\xi)} \right|_{T_{\text{iso}}} = \left. \frac{d \ln k(\xi, T)}{d(1/T)} \right|_{\xi_{\text{iso}}} = 0 \quad (1)$$

Whether this can be accepted as a real IKR or rejected as an artefact for any given experimental case has to be decided upon by careful statistical analysis (suitable statistical procedures are found in reference 2 and, in a simplified form, in the Appendix). The parameter ξ identifies³ the individual members of the group; it might be a simple numbering (*i.e.*, an index i) but preferably it represents a continuous parameter having physical meaning. These parameters may be quite freely chosen but it must be one parameter only and it should yield a unique identification of the respective reaction within the series. If this is the case, the parameter (or several if interrelated) can be transformed to give

Wolfgang Linert graduated from the Technical University in Vienna both in Physics and in Chemistry, the latter under the supervision of V. Gutmann, and today leads the scientific working group for General and Theoretical Inorganic Chemistry at the Institute of Inorganic Chemistry at this University. His scientific interests concern solution and coordination chemistry and of course isokinetic relationships. The former was initiated by his Ph.D. supervisor. His work with solvatochromic compounds concerning Lewis acid-base indicators led to several scientific stays in Japan. Actual kinetic investigations are related to the metal-centre catalysed oxidation of biological important substrates. In 1993 he was awarded the Rudolf Wegscheider Prize of the Austrian Academy of Science and in 1994 the Sandoz Prize for Natural Sciences. He is a corresponding member of the Accademia Peloritana dei Pericolanti.



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a linear relationship with $\ln k$ or $\ln K$, *i.e.* behave as a generalized LFER.³ (Such a LFER must exist for a relationship such as (1) and there are methods of constructing one in the event that the commonly available LFER's are not applicable.) However, it is convenient and usually successful to use one of the generally accepted LFER parameters such as Hammett's substituent parameter; solvent parameters (*e.g.* donor or acceptor numbers); parameters characterizing catalysts (such as an applied temperature of tempering, or a percentage of an active component), all of which have been successfully applied. They might even be parameters of the reactions themselves, as shown for example in a study of the rate of conversion taking place in the thermal decomposition of solids.⁴ Thus it is always possible to find, or when necessary to construct, such a parameter. This implies that the reactions included in an IKR are similar, forming a 'series of reactions', where conditions for their similarities will be discussed below.

The term IKR (or IER) is employed exclusively in this review (and in previous papers) in preference to the often used 'compensation effect' (see below) in order to emphasize the necessity of employing a valid method of statistical analysis before accepting the effect as real. In fact a common point of intersection of Arrhenius (or van't Hoff) lines is mathematically equivalent to a linear relationship between activation energies and pre-exponential factors or between enthalpic and entropic terms. When expressed in the form of the latter linear relationship between ΔH° and ΔS° it is commonly referred to as a 'compensation effect'. However, this mathematical equivalence does not always hold from a statistical point of view² because experimental uncertainties of the derived parameters (for example E_a and $\ln A$ or $\Delta_r H^\circ$ and $\Delta_r S^\circ$) can all-too-often lead to an artificial linear dependence without a significant meaning. 'Mean values of mean values' cannot be used to investigate the existence of a relationship. (Derived parameters of a regression analysis, *i.e.* $\Delta_r H^\circ$ and $\Delta_r S^\circ$, are statistically dependent parameters which cannot be used for further regression analysis.)

This situation is best illustrated by an example: Figure 1 depicts an apparently good example of the 'compensation effect' which might be derived from a $\Delta_r H^\circ$ versus $\Delta_r S^\circ$ plot for the formation of cyclodextrin (CD) inclusion complexes. Although this certainly has the appearance of a linear dependence, replot-

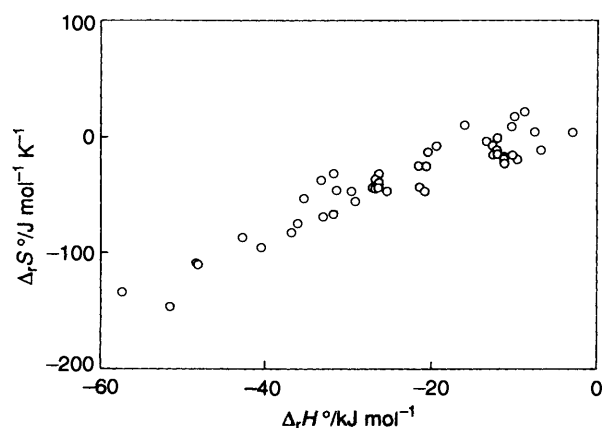


Figure 1 $\Delta_r S^\circ$ versus $\Delta_r H^\circ$ plot for the formation of CD-inclusion complexes.

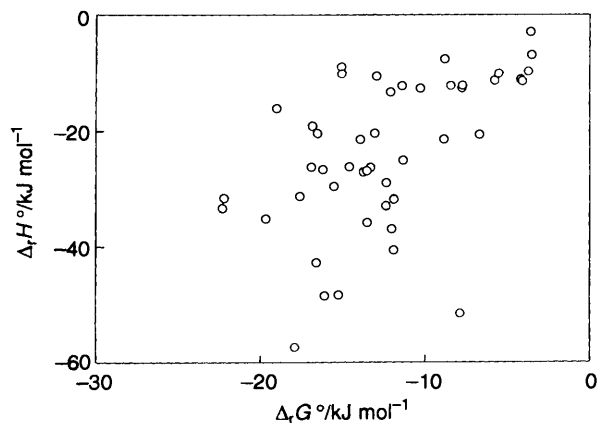


Figure 2 $\Delta_r H^\circ$ versus $\Delta_r G^\circ$ plot for the formation of CD-inclusion complexes. $\Delta_r G^\circ$ was taken at the harmonic mean of the experimental temperatures.^{5, 15}

ting the data in the statistically more meaningful⁵ form of $\Delta_r H^\circ$ versus $\Delta_r G^\circ$ (Figure 2) shows clearly that such a relationship does not exist (at least not in the simple form suggested by Figure 1). In fact a statistical analysis³ of the data shows that in this case a $\Delta_r H^\circ - \Delta_r S^\circ$ relationship, at least that which includes all the reactions simultaneously, has to be dismissed. Careful statistical evaluation shows, moreover, that the data fall into some six different IKR groups (see Section 2 below, and Figure 4).

This example shows that (i) reliance on $\Delta H - \Delta S$ plots can yield artifacts and (ii) series of apparently similar reactions fall into separate groups of IKR- or IER-series. The latter is particularly important and can be used to analyse detailed reaction mechanisms and/or structural changes of reactants and products within a generally related series. The present review explains and justifies this statement with the aid of several examples.

2 Theory

The theoretical description of an IKR requires that elementary reactions are observed.^{1, 6} The theory further assumes that the reactant molecules are distributed within a potential well into discrete energy levels, and that, provided there is an energy exchange with a 'heat bath' (comprising the molecular environment of the reactants), we will find a random walk of the reactants within the potential well. The transition probability $P(l)$ between the energy levels (denoted by l) depends upon the energy exchange between reactants and heat bath. If a chemical reaction is to take place, then a reaction barrier that constitutes a point of no return exists – which describes the energy of the activation barrier.⁷ This system can be expressed by balanced equations where for each energy level the change in the particle density is described by adding molecules jumping into the level and subtracting those that leave it, increasing the population elsewhere. Under the condition $E_a \gg kT$, which is fulfilled for common reactions, the discrete particle densities distributed to discrete levels can be approximated continuously, yielding a Langevin equation.^{6, 8–10} The resulting differential equation can be solved to obtain a steady-state flux of particles over the barrier, which in turn leads to a rate constant $k(\xi, T)$.

Although absolute rate constants are difficult to obtain from the integral equations¹⁰ without exact details about the potential barrier, it is possible to apply the IKR-condition given in (1) which yields⁶ conditions for the isokinetic temperature, T_{iso} , which mainly depends on the mechanism of energy exchange between heat-bath and reactants. This condition provides a method of using T_{iso} values to distinguish between various features of experimental results.

The effect of plotting Arrhenius lines (van't Hoff lines) for a series of reactions carried out at various temperatures leads to six general results, summarized pictorially in Figure 3.

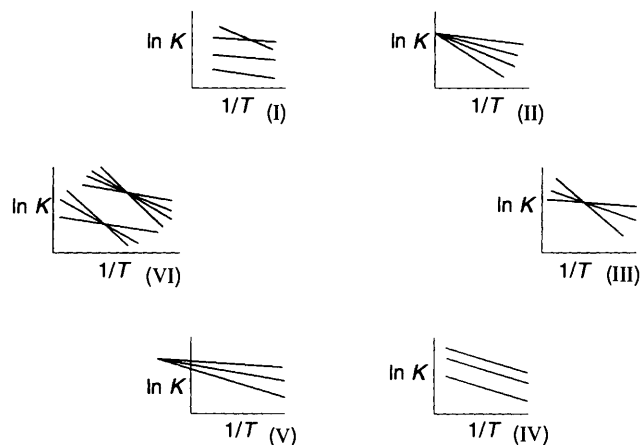


Figure 3 Different cases for the occurrence of IKR's (IER's). The numbers of the icons refer to the description of these cases given in the text.

(i) *Icon (I)* in Figure 3 shows the trivial case when no connection between the series of reactions can be inferred. In other words the reactions have no reaction profile in common.

(ii) *Icon (II)* illustrates an example where $1/T_{iso}$ approaches zero and an isoentropic reaction series is observed, i.e. only the activation energy varies. In the case of gas-phase reactions, including small particles or even a monatomic diluting gas the 'heat bath' stores energy in translational degrees of freedom. The corresponding translation-vibration energy exchange achieved by collision between reactant particles and others leads the transition properties $P(l)$ to be proportional to l resulting in an isoentropic reaction series where $T_{iso} \gg T_{exp}$, i.e. $1/T$ approaches zero. A clear example is quoted in the earlier Review¹ where, in the decomposition of diatomic molecules in the gas phase, fluorine does not form part of the isoentropic set of other halogens because of its reactivity towards the diluting gas, argon.

(iii) *Icon (III)* is most frequently observed for reactions occurring in the condensed phase. Here the energy in the heat-bath (i.e. the molecular surroundings of the reactants) is stored in vibrational, rather than translational, degrees of freedom. In this case the transition probabilities take on an exponential dependence upon the level of excitement and T_{iso} is related (2) to the vibrational spectrum of the heat bath.

$$T_{iso} = hv_{\text{heat bath}}/k_B \quad (2)$$

T_{iso} has a positive, finite value. This pattern refers to a *real compensation effect*, a fact which might be inconvenient for those who try to reduce the activation barrier by means of catalyst- or solvent-variation, because what one gains by a lower activation energy is (proportionally to T_{iso}) lost in the pre-exponential factor or the entropic part. This case is most frequently found for reactions series occurring in the condensed phase, where a vibrational-vibrational energy exchange between reactants and their direct molecular surroundings (i.e. solvent, catalyst) occurs. Large molecules (such as those making up many biologically active systems) might well act as their own heat bath.

Many examples have been collected^{1, 11} showing the validity of relationship (2). The IR-vibrational frequency that is directly related to T_{iso} and is usually found in the far IR-spectrum of the reacting system can be identified with a 'resonant condition', namely by an overlap of a vibrational frequency of both the reactant and the energy supporting system. In some sense, because the reacting species have a real chemical identity, selection rules have been implicitly invoked. Because most chemical reactions involve a change in polarity rather than in polarizability, IR-active vibrations – as opposed to Raman-active ones – are more likely to excite the

- reacting species. Additionally, this active frequency appears to be associated with bonds directly involved in the reactive site in the reactants
- (iv) *Icon (IV)* shows a series of parallel lines for an *isoenthalpic reaction series* where only the entropic contribution varies. This is the case when the resonance condition cannot be fulfilled, i.e. an active resonance frequency is either not available or forbidden by selection or symmetry conditions. This does not mean that the reaction does not run, it merely means that no compensation effect occurs, despite the reactions being related. This case is relatively frequent. An example is found below in the consideration of cyclodextrin inclusion complexes (Section 3.1, below)
- (v) *Icon (V)*. In a very few examples, T_{iso} has been shown to be finite but negative.¹¹ For example the ionization constants of substituted benzoic acids (the ionization of substituted benzoic acids is used to define the Hammett relationship¹²) are claimed to exhibit this effect.¹³ However, in this case $\ln K$ is not a linear function of T^{-1} . If the values of $\log K$ are corrected¹⁴ by allowing for the variation of $\Delta_r H^\circ$ with T ($\Delta_r C_p^\circ = \text{constant}$), then a linear dependence on $1/T$ is obtained. These corrected lines intersect to give a *positive* T_{iso}^1
- (vi) *Icon (VI)* includes more than one common point of intersection, and a discussion of this phenomenon forms the greater part of this review. There is one important condition, namely that the reaction profile must be essentially invariant within an IKR series. This condition means that any change in the *reaction mechanism* should be reflected in the IKR-plot by the corresponding Arrhenius line failing to meet the common point of intersection of the other members. [See for example the dissociation of fluorine in argon mentioned under icon (I)] Obviously a series of such divergent lines might themselves have another point of common intersection (see Icon III), and this enables us to postulate an alteration in reaction path or profile. Examples of this phenomenon are presented below

3 Experimental Examples

3.1 Cyclodextrin Inclusion Complexes

Cyclodextrins are large cyclic carbohydrates which are capable of binding many different species within their structure. The dependence on temperature of the equilibrium constants for a large number of cyclodextrin inclusion complexes have been measured and the experimental data have been analysed searching for significant common points of intersection of the respective van't Hoff lines.¹⁵ Five different groups of included molecules can be readily identified in this way (see Figure 4). These groups are not only separable on the basis of these IKR plots, but are also separable on the basis of their chemical properties. The groups are

- (1) *Organic solvents*, which show almost parallel van't Hoff lines (Figure 4a) suggesting isoenthalpic behaviour. Molecular mechanics (MM) calculations support^{16,17} this and show that the displacement of water molecules from the CD-cavity, and hence the related entropic changes are the driving force for complex formation in this case
- (2) *Substituted benzoic acids* are the guest molecules belonging to this group ($T_{\text{iso}} = 396\text{K}$) (Figure 4b). MM-calculations indicate that the carboxy group attached to the aromatic ring structure points into the CD-cavity.¹⁶ Both experiment and MM-calculations show that orientation leads to significant enthalpy changes. The complex formation might be considered as being entropy driven
- (3) *Aliphatic carboxylic acids* ($T_{\text{iso}} = 450\text{K}$) (Figure 4c). The variation of the entropic part within this group is significantly smaller than those of group (ii). This trend may be ascribed to the linear structure of the guest molecules and this is reflected in MM-calculations.¹⁶ Furthermore polar interactions, mainly determined by H-bonds, appear to play a significant role

- (4) *Molecules built around a large hydrophilic group* ($T_{\text{iso}} = 472\text{K}$) (Figure 4d). Most of these molecules contain aliphatic organic rings. The hydrophilic part of the molecule determines the mode of interaction with the cyclodextrin
- (5) *Ionic compounds*. The isokinetic temperature of this group ($T_{\text{iso}} = 230\text{K}$) is below the experimental temperature range (Figure 4e) so that enthalpy changes compensate entropy changes to a great extent leading to the effect that the selectivity of this reaction is increased with increasing temperature (which in some ways contradicts the common reactivity-selectivity rule based on chemical intuition). The interaction mechanism involved in this group is attributable to Coulombic interactions and this conclusion is reflected in the MM calculations.¹⁶
- (6) *Derivatives of the well-known methylorange indicator* might well define a sixth group. There are not, however, enough examples to analyse this group in detail (Figure 4f). This group would seem to be made up of species where only small H-bond contributions between guest molecule and CD occur and where hydrophobic interactions are predominant. Therefore, beside the size of these molecules, their main interactions may be compared with those of group (i) with, however, the hydrophilic groups pointing *out* of the cavity

3.2 The Isomerization of Triphenylformazanes

Figure 5 summarizes the reactions which occur when a series of substituted formazanes, whose general formula is depicted, are dissolved in toluene and then photolysed.¹⁸ The product of photolysis, I, then reacts *via* two steps, A and B, both of which can be followed spectrophotometrically

Isomerizations of this type can potentially proceed *via* two pathways, namely rotation or inversion, and on the basis of linear $\Delta^2 H^\circ$ versus $\Delta^2 S^\circ$ plots obtained¹⁸ it was argued that both processes, A and B, followed the same single reaction mechanism. However, an examination of the IKR's obtained from the data (Table 1) shows that reaction series A results in two IKR's (Figures 6) and reaction series B produces three distinct IKR groups. This shows clearly that reaction series A follows *both* paths depicted in Figure 5, and depends on the substituents R, R', X, and Y present

It is not quite clear why compound (5) should lie in the rotational group for reaction A but in the inversion group for reaction B, but this is no doubt related to the point of rotation concerned. Similarly, the failure of (11) to conform to the expected inversion mechanism for group A is not at all clear

The fact that the inversion mechanism for group B divides into *two* T_{iso} groups could probably be connected to the fact illustrated in Figure 5 that inversion is possible through either of two N-atoms (dictated, perhaps, by the position of the proton) but what affects this is not immediately obvious. Figure 5 for these reactions thus suggests that for compounds substituted in the Y position six reaction paths and hence six distinct IKR-groups are to be expected for reaction B. However, data to confirm or to deny this prediction are not at present to hand – note that this implies also that compound (2) only accidentally conforms to the rotational groups in Table 1 for both series of reactions

3.3 Reversed-phase Liquid Chromatographic Separation of Alkaloids

A detailed investigation of the retention behaviour of a series of closely related alkaloids when separated by reversed-phase liquid chromatography has been carried out.¹⁹ Addition of salts (Na^+ , K^+ , NH_4^+ , and NBU_4^+ , combined with anions such as ethanoate⁻, Br^- , SCN^- , and I^-) eliminates peak tailing in a reversed phase liquid chromatography experiment and deactivates the stationary phase.²⁰ Potassium iodide is especially successful in aiding the separation of this group of closely related alkaloids (See Table 2) and when the surface of the stationary phase was deactivated with KI two groups of van't Hoff plots are found, namely those of tertiary alkaloids with low basicity and

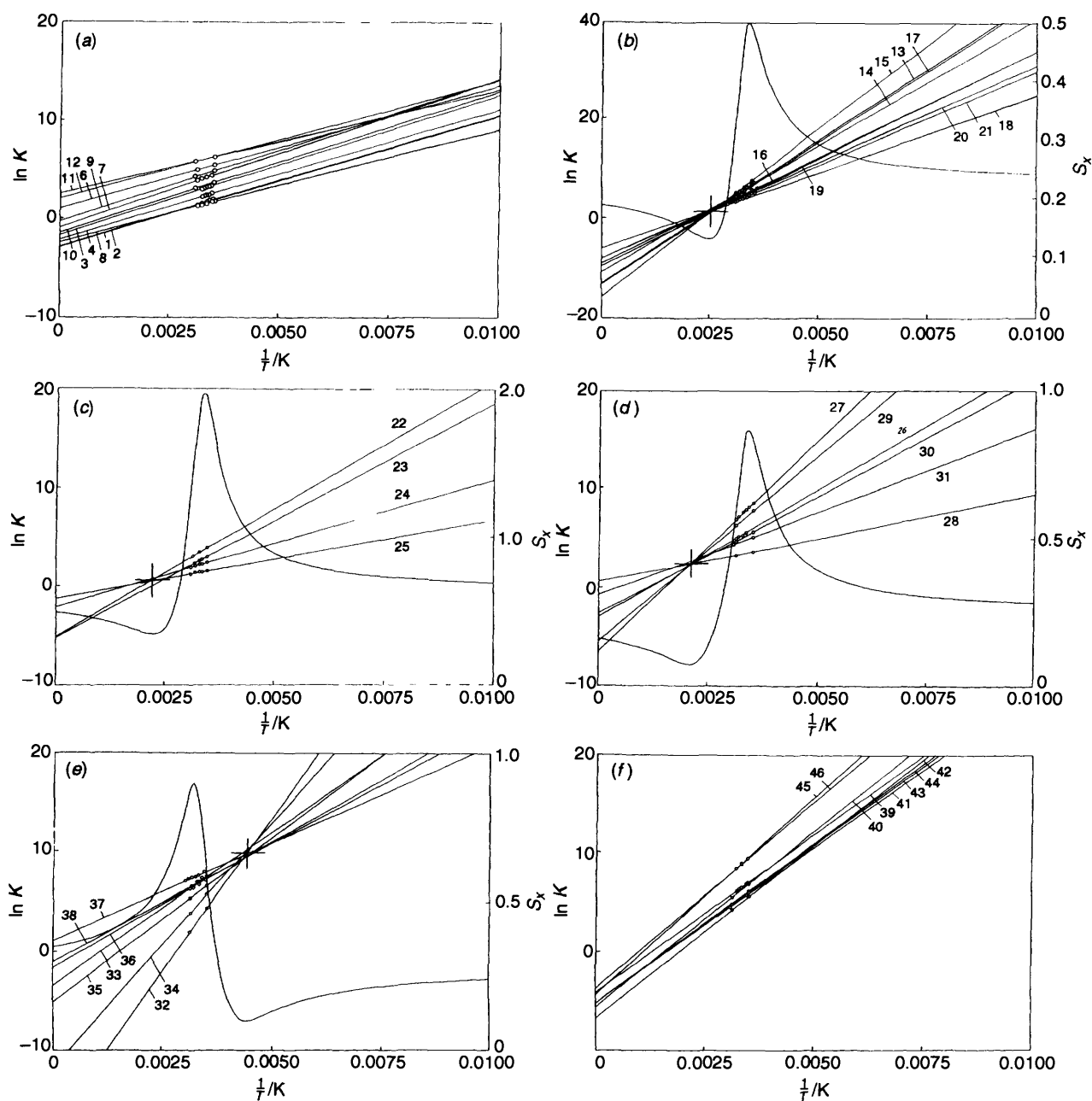


Figure 4 Van't Hoff plots of the formation of inclusion complexes of substances with α -cyclodextrine. (a) IKR-group 1 ($T_{iso} = \pm \infty$, *i.e.* isenthalpic): 1 = isopropanol; 2 = acetonitrile; 3 = propanol; 4 = 2-butanone; 5 = ethanol; 6 = pyridine; 7 = cyclohexanol; 8 = dioxane, 9 = 1-butanol; 10 = 2,2-dimethylpropanol; 11 = 2,2-dimethylpropanol (with β -CD); 12 = cyclohexanol (with β -CD). (b) IKR-group 2 ($T_{iso} = 396$ K): 13 = 4-aminobenzoic acid; 14 = benzoic acid; 15 = 4-hydroxybenzoic acid; 16 = 4-nitrobenzoic acid; 17 = *m*-hydroxybenzoic acid; 18 = *m*-cyanophenol; 19 = *m*-nitrobenzoic acid; 20 = *m*-nitrophenol; 21 = benzoic acid (β -CD). Curved lines in this graph and in other IKR-plots below refer to residual sums S_0 varied along the x (*i.e.* $1/T$) axes (S_0). (c) IKR-group 3 ($T_{iso} = 450$ K): 22 = propionic acid; 23 = trimethylacetic acid; 24 = acetic acid; 25 = formic acid. (d) IKR-group 4 ($T_{iso} = 471$ K): 26 = adamantane-1-ylamine; 27 = L-

tryptophan; 29 = hydrocinamic acid; 30 = L-malic acid; 31 = adamantanecarboxylic acid. (e) IKR-group 5 ($T_{iso} = 230$ K): 32 = anilinium perchlorate; 33 = sodium perchlorate; 34 = 4-(4-oxidophenylazo)naphthalene-1-sulfonate; 35 = adamantanecarboxylate (with β -CD); 36 = 4-(3,5-diisopropyl-4-hydroxy-phenylazo)benzene-sulfonate; 37 = 4-(3,5-diisopropyl-4-oxido-phenylazo)-benzene-sulfonate; 38 = 4-iodoanilinium ion. (f) IKR-group 6 ($T_{iso} = \pm \infty$, *i.e.* isenthalpic): 40 = methylorange; 41 = 4-(4-dimethylamino-phenylazo)naphthalene-1-sulfonate; 42 = 4-(4-hydroxy-3-methyl-phenylazo)naphthalene-1-sulfonate; 43 = 4-(4-hydroxy-phenylazo)naphthalene-1-sulfonate; 44 = 4-(3-ethyl-4-hydroxy-phenylazo)naphthalene-1-sulfonate; 45 = 4-(4-nitrophenylazo)-naphthalene-1-sulfonate; 46 = 4-(4-oxido-3-propylphenylazo)-benzene-sulfonate.

those of strong basic tertiary and quaternary alkaloids. The different behaviour is interpreted in terms of different retention mechanisms depending on the basicity of the eluates. Those of low basicity [namely (1), (2), (3), and (4) in Table 2 and Figure 7a] exhibit isenthalpic behaviour. These alkaloids are present as neutral species in the mobile phase, and show only slight donor or acceptor properties, and therefore their separation is

due to their differing solvophobic interactions with the long-chain alkyl ligates of the bonded phase.²¹ The remaining alkaloids are all separable on the basis of their varying basicities and exhibit a T_{iso} above the experimental temperature range (Table 2 and Figure 7b) which illustrates the experimental fact that selectivity decreases with increase of temperature (*i.e.* exhibits usual retention behaviour).

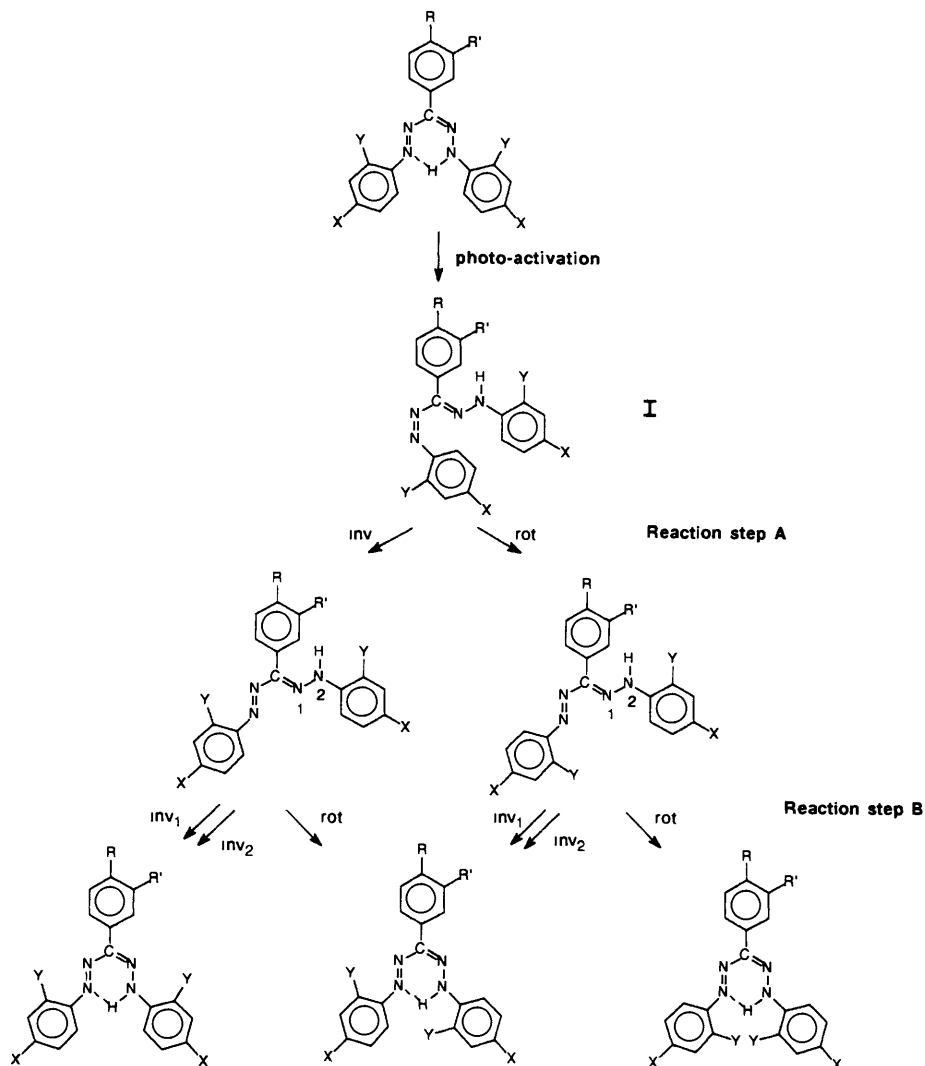


Figure 5 Reactions which can occur following photolysis of a series of substituted formazanes. *Note:* For reaction step B, two possible inversions can occur at either N-(1) or at N-(2) (leading to the same product in each case) and depending possibly on the position of the

proton. This possibility would explain the existence of two distinct IKR's for the inversion mechanism observed for reaction step B (see text and Table 1).

Table 1 Triphenylformazanes with different substituents yielding different IKR's groups in both reaction steps A and B given in Figure 4f

Compound	Substituents				Reaction A	Reaction B
	R	R'	X	Y		
1	H	H	CH ₃	H	_____	_____
2	H	H	H	CH ₃	$T_{iso} > T_{exp}$	Rotational
3	H	NO ₂	H	H	Rotational	Mechanism
4	NO ₂	H	H	H	_____	_____
5	CN	H	H	H	$T_{iso} < T_{exp}$	Inversion
6	OCH ₃	H	H	H	_____	_____
7	CH ₃	H	H	H	$T_{iso} \approx T_{exp}$	Mechanism
8	H	H	H	H	Inversion	_____
9	Cl	H	H	H	Mechanism	$T_{iso} < T_{exp}$
10	Br	H	H	H	_____	Inversion
11	H	H	Cl	H	_____	Mechanism

3.4 Distribution Between Phases

Closely related to the above example of chromatographic separations is that of distribution between phases. When the temperature-dependent partition coefficients for the distribution between water and di-n-butyl ether of a series of 12 isomeric and homologous pyridylalkamides (12) are analysed for an IKR they divide into two groups.²² One group is not able, on steric grounds, to ring-close in the ether solution whereas the other is able to: this pattern is summarized in Figure 8 and readily explains the existence of two distinct IER's for this system.

3.5 Solvatochromic and Thermochromic Compounds

The next two examples deal with solvatochromic and thermochromic compounds.²³ The latter have been investigated from the point of view of their ability to act as Lewis acid-base indicators. Mixed ligand Cu^(II) and Ni^(II) complexes that include in their square planar configuration (13) a β -diketonate [e.g. acetylacetonate (*acac*)] and a diamine [e.g. tetramethylethylenediamine (*tmen*)] coordinate to two Lewis-base molecules forming an octahedron. This reaction leads to continuous colour change dependent upon the Lewis basicity of the ligand. In the case of copper complexes this colour change is based on the strong Jahn-Teller effect exhibited by copper(II) whereas in the Ni^{II} system discrete changes between a diamagnetic, square planar, red species, and a paramagnetic, octahedral, blue species occur.

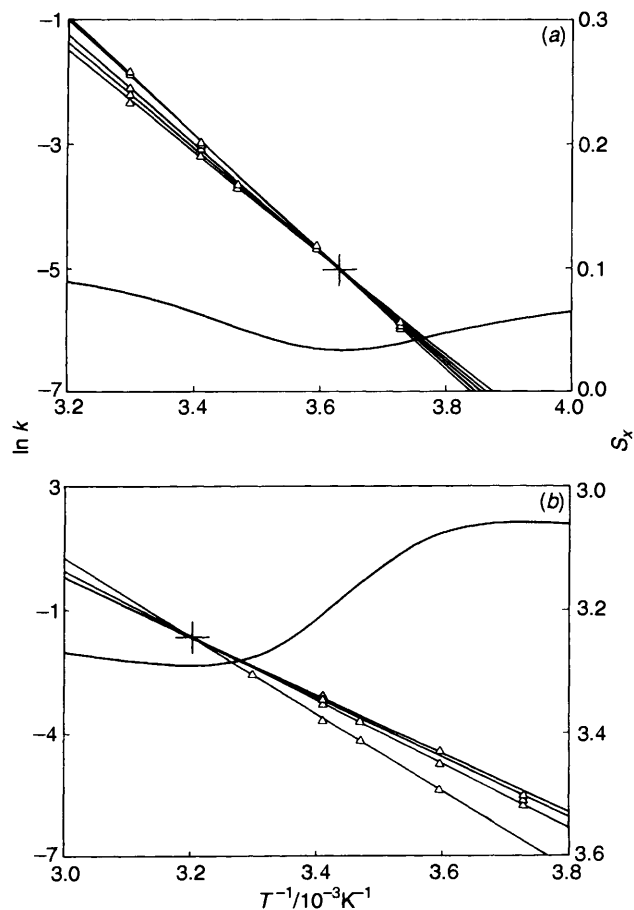
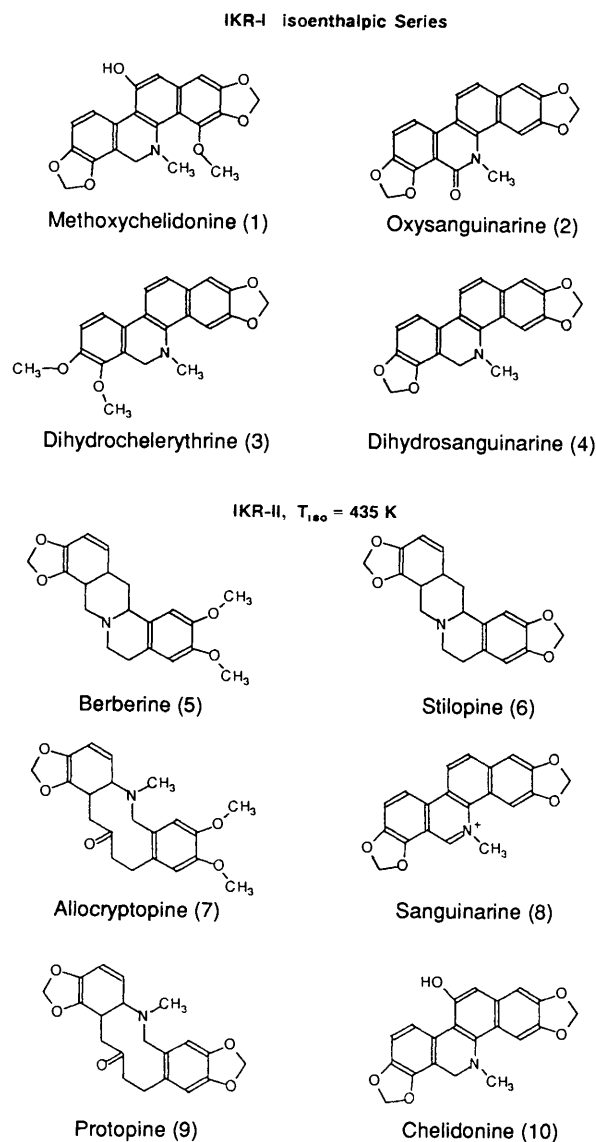


Figure 6 Arrhenius plot for the thermal isomerization of triphenylformazans in toluene. (a) Process A, compounds 1–5. Process B, compounds 6–10 (see Table 1). (b) Process B, compounds 6–10 (see Table 1).

The equilibrium constants of the nickel system have been measured while varying substituents positioned at the diketone and the diamine, the coordinating ligand itself, and the temperature, and this has allowed for a detailed IKR analysis. The van't Hoff plots for the nickel system (Figure 9) show that two common points of intersection occur. This pattern is found for both the equilibrium constant K_1 describing the formation of a five-coordinated intermediate and for K_2 describing the formation of the octahedral species, as well as for the polarographic reduction potentials measured at various temperatures. One common point of intersection includes always the same, strong donor solvents, the other involves weakly coordinating solvents. When, however, the fluorinated complex (14) is examined, only one common point of intersection is exhibited (Figure 10). This result can be interpreted on the basis of the scheme outlined in Figure 11. An increase in donor strength leads to increasing distortion while at first essentially maintaining the initially square planar arrangement of the *bis*-chelate species (bond angle variation rule,²⁴ Figure 12). Eventually an increase in donor strength leads to a change of geometry, to a trigonal bipyramidal arrangement of donor atoms about the metal ion. Thus K_1 implies the formation of *either* a square pyramidal *or* a trigonal bipyramidal species; K_2 then refers to the formation of the final *trans*- or *cis*-complex respectively. The solvents interacting with the fluorinated complexes all behave as 'strong' bases towards the Ni-centre as a result of the electron-withdrawing behaviour of the fluorines.

To confirm this suggestion on the actual system presents some difficulty since, independent of N- or O-coordinating donor solvents, the next neighbour atoms of both the *cis*- and the *trans*-species are identical. Therefore any changes in the observed *d-d*

Table 2 Alkaloids extracted from a *Chelidonium majus L* divided into two IKR-groups based on their chromatographic separation behaviour



transition spectra are very small and do not enable distinction between the species to be made. NMR experiments are also not possible owing to the paramagnetic behaviour of the complexes. However, the *cis*- and *trans*-species should be distinguishable by their metal–ligand vibrational spectra and in fact the symmetric L–Ni–L stretching vibration should not be IR-active in the *trans*-species whereas in the case of the *cis*-species it should be observable. The respective IR-spectra which would seem to confirm the *cis-trans* assignments made on the basis of an examination of the IKR's. This isomerism has, however, been conclusively established by X-ray diffraction for a series of related compounds, e.g. a dinuclear complex²⁵ (15) formed with a tetraketonate where in one half of the molecule no solvent has been coordinated, illustrating the *trans* case (*i.e.* the square planar case for very weak interaction). The other half of the molecule has two oxygen donor molecules coordinated to the Ni-coordination centre and this has given rise to the predicted *cis*-arrangement. Similar observations are reported for five-coordinated Ni-systems²⁶ as well as for the solvatochromic VO(acac)₂ system.²⁷

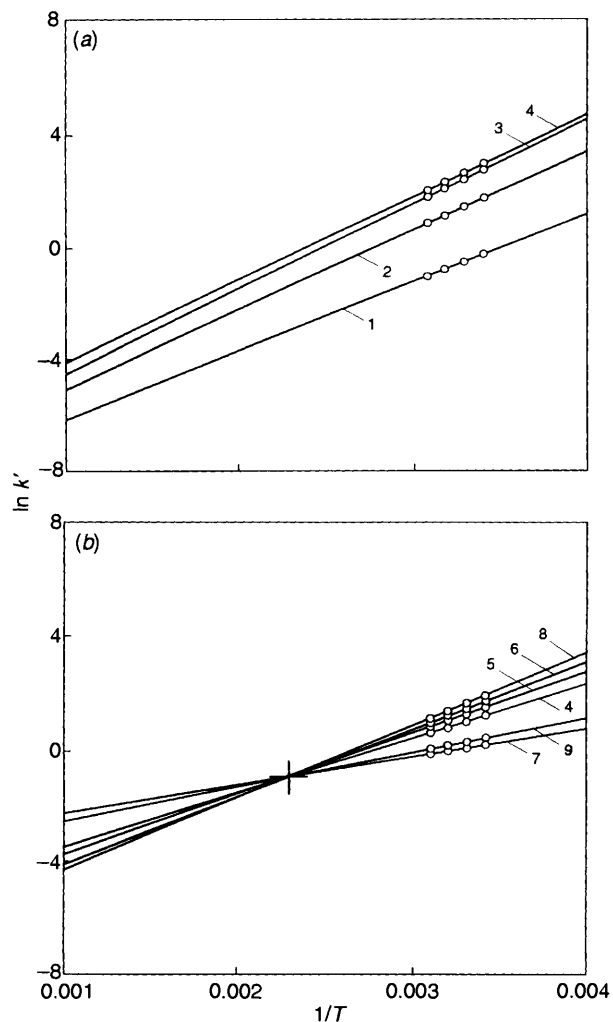


Figure 7 Van't Hoff plots of logarithms of the capacity factors of the alkaloids belonging to (a) isoenthalpic IKR-group I (listed in Table 2) versus $1/T$, (b) IKR group II (listed in Table 2).

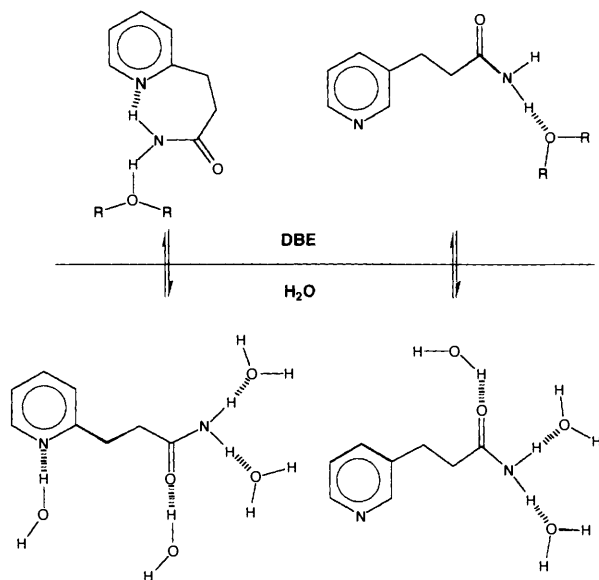


Figure 8 Hypothetical mechanism for the transfer of pyridylalkanamides between DBE and water. Only polar (H-bond) solute-solvent interactions are shown (*i.e.* van der Waals interactions are not depicted). 4-pyridylalkanamides are not shown but behave analogously (see Table 3).

Table 3 Division of pyridylalkylamides into different IKR-groups, based on the temperature-dependence of partition coefficients measured for water/dibutylether. The numbers refer to the number of CH_2 -groups in the carbon chain

IKR-I	IKR-II
<i>o</i> -; 1	<i>m</i> -; 1
<i>o</i> -; 2	<i>m</i> -; 2
<i>o</i> -; 3	
<i>o</i> -; 4	
<i>m</i> -; 3	
<i>m</i> -; 4	
	<i>p</i> -; 1
	<i>p</i> -; 2
	<i>p</i> -; 3
	<i>p</i> -; 4

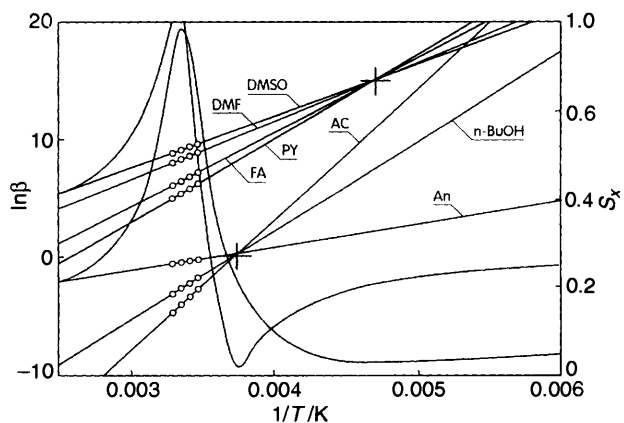


Figure 9 Van't Hoff plots for overall information constants ($\beta = K_1 K_2$) of solvates of nickel(II) complexes of general formula (13).

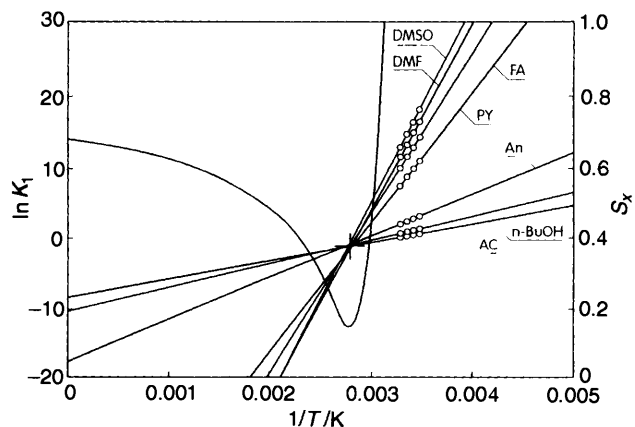


Figure 10 Van't Hoff plots for the formation constants (K_1) of solvates of $\text{Ni}(\text{tmen})(\text{tfac})^+$ (14).

3.6 An Examination of Solvent Parameters

An application of IKR-like relationships sheds light²⁸ on the correlations between solvent parameters describing Lewis acidities (or acceptor properties) of solvents in terms of (i) the acceptor number, AN, of Gutmann²⁹ and (ii) Reichardt's³⁰ solvent polarity scale, namely the E_t parameter. Figure 13 illustrates the interactions which give rise to these two scales, namely (i) the chemical shift of ^{31}P in triethylphosphine oxide and (ii) the shift in the visible absorption band of a betaine when

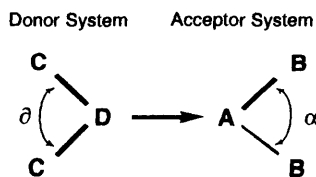


Figure 11 Diagram illustrating the effect on the bond angles of a donor and acceptor system. As the intermolecular interaction increases the intramolecular angles of the donor component (δ) are increased and the intramolecular angles of the acceptor component (α) are decreased.

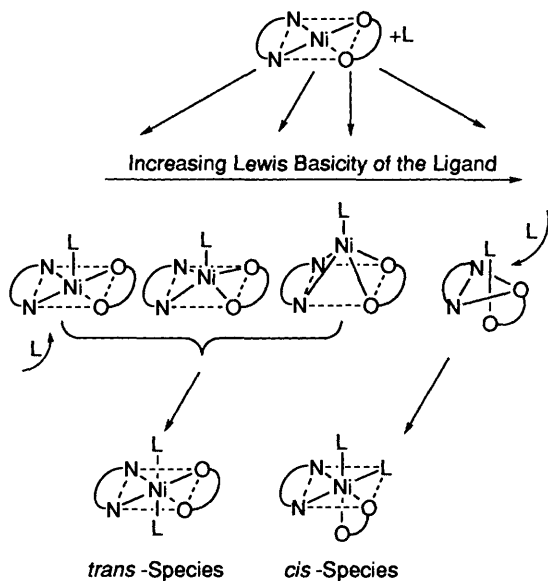
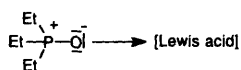


Figure 12 The effects of donor strength (Lewis basicity) on the mode of entry of coordinated solvent molecules (L).

AN: Chemical shift of the ^{31}P NMR-signal in Et_3PO solutions



$E_T(30)$: Solvatochromic shift of an absorption maximum of betaine solutions. Betaine II contains the Bu^t substitute given in parentheses

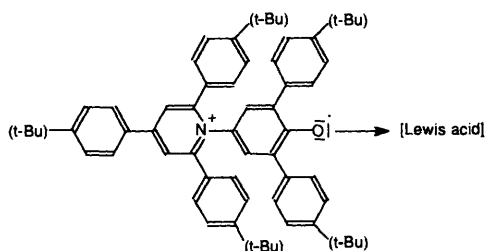


Figure 13 Interactions used to define Gutmann's acceptor number (AN) and Reichardt's $E_T(30)$ parameters. To extend the range of solvents available, two betaine dyes were used in this work.

each species reacts with a Lewis acid (*i.e.* an acceptor solvent). Many attempts have been made^{29,31} to correlate or to reconcile these two scales but it was not until the thermochromism of the betaine dye was used in an IKR investigation²⁸ that the position became clear.

Table 4 shows how the various solvents divide into separate groups based on their differing isokinetic behaviour. Figure 14

Table 4 Division of various solvents into isokinetic groups based on their solvatochromism and thermochromism with betaines

Group 1 = Alkanes			
Cyclohexane, decaline, $n\text{-C}_7\text{H}_{16}$, $n\text{-C}_{10}\text{H}_{22}$			
Betaine	II	$T_{\text{iso}}/\text{K} = 800 \text{ K}$	$\nu_{\text{iso}} = 556 \text{ cm}^{-1}$
Group 2 = Solvents with poor acceptor properties			
Ac, An, DMSO, DMF, DMA, EtOAc, NMF, Py, NM			
Betaine	I	$T_{\text{iso}}/\text{K} = 83 \text{ K}$	$\nu_{\text{iso}} = 58 \text{ cm}^{-1}$
Betaine	II	$T_{\text{iso}}/\text{K} = 90 \text{ K}$	$\nu_{\text{iso}} = 63 \text{ cm}^{-1}$
Group 3 = Aromatics			
PhH, PhMe, $p\text{-PhMe}_2$, PhC ₆ H ₅ , Ph ₂ O, (dioxane)			
Betaine	I	$T_{\text{iso}}/\text{K} = 749 \text{ K}$	$\nu_{\text{iso}} = 521 \text{ cm}^{-1}$
Betaine	II	$T_{\text{iso}}/\text{K} = 670 \text{ K}$	$\nu_{\text{iso}} = 466 \text{ cm}^{-1}$
Group 4 = Amines			
Fa, Et ₂ NH, en			
Betaine	I	$T_{\text{iso}}/\text{K} = 118 \text{ K}$	$\nu_{\text{iso}} = 82.6 \text{ cm}^{-1}$
Group 5 = Alcohols			
Glycol, MeOH, EtOH, $n\text{-PrOH}$, $n\text{-BuOH}$, $i\text{-AmOH}$			
Betaine	I	$T_{\text{iso}}/\text{K} = 130 \text{ K}$	$\nu_{\text{iso}} = 90 \text{ cm}^{-1}$
Betaine	II	$T_{\text{iso}}/\text{K} = 164 \text{ K}$	$\nu_{\text{iso}} = 114 \text{ cm}^{-1}$

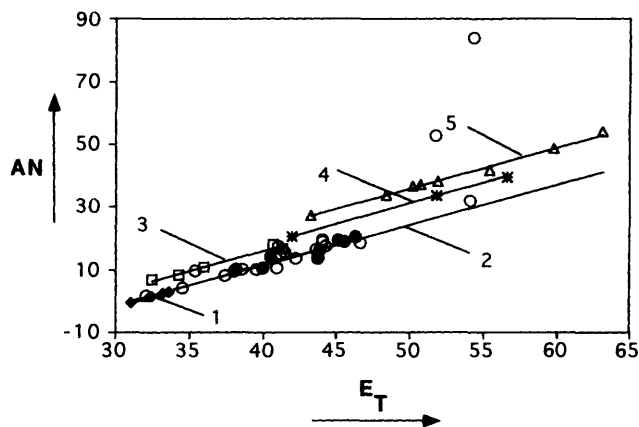


Figure 14 Linear relationships between AN and E_T for different IKR (solvent) groups.

shows clearly that the AN's for each group can then be separately and accurately correlated linearly with Reichardt's E_T value. These correlation lines form an exactly parallel set, and thus a measure of their deviation from the alkanes (with no acceptor properties) can be obtained from the amount by which the intercepts differ from that for the alkanes. This information is presented as a plot of these differences against acceptor number of the solvent in Figure 15. The deviation from the base-line (*i.e.* that of the alkanes) varies fairly smoothly with AN. This, of course, strongly supports the widely held belief that, strictly speaking, a single solvent parameter is insufficient to define a unique solvent scale! The converse of the effect noted here was observed in a recent study²⁸ of the donor properties of anions, when it was found that the effective donor numbers depended strongly on the acceptor numbers of the solvents.

3.7 Enzymes, Proteins, and Heat Baths

The 'active site' of most enzymes is surrounded by large protein molecules. One of the roles of these proteins is to provide stereospecific sites, but this still leaves open the questions as to how such extremely high rates of reaction are attained and how the protein is involved in the energy transfer process. We would like to suggest that the way in which the energy is transferred to the active site of an enzyme is closely related to the manner in which a solvent surrounding a reacting pair of molecules is involved in this reaction.

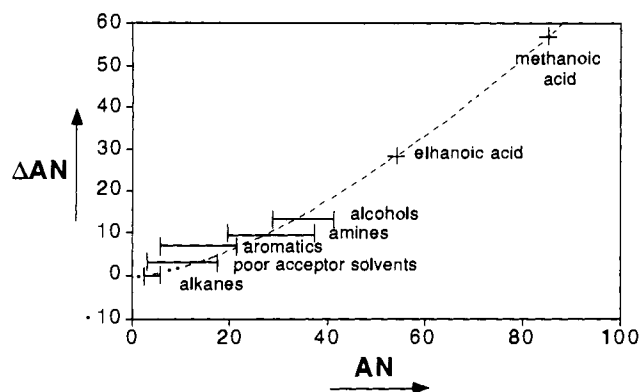


Figure 15 Dependence on the acceptor number AN of the displacement of AN versus E_T lines from that of the alkanes.

The investigation of the temperature-dependence of many series of related reactions shows, with few exceptions, isokinetic behaviour. This means that a common point of intersection of straight lines in the Arrhenius ($\ln k$ vs. $1/T$) or van't Hoff ($\ln K$ vs. $1/T$) plane is observed for such a series of closely related (homologous) reactions. Interpretation of these isokinetic phenomena¹ establishes that an important role of the solvent (or heterogeneous catalyst) is to transfer energy to reactants situated in energy states below the activation barrier (mainly from the ground state) enabling them to overcome the barrier. This effect must be present in any reaction and can only be explained¹ by assuming a quasi resonant energy exchange between reactants and the molecular surroundings, e.g. the solvent. No specific structure in the surroundings is implied except that it provides energy by acting as a thermodynamic heat-bath. The frequency demanded by the theoretical relationship is related to the Boltzmann energy of T_{iso} and as such must appear within a vibrational absorption band evident in the system.

It seems reasonable, therefore, to suggest that enzyme molecules (or other biologically active molecules) make use of the (often large) protein molecule surrounding the active site as a thermodynamic heat-bath with which to facilitate energy transfer. This prediction would imply that the protein takes the place of a solvent as far as the provision of this resonant energy is concerned and is thus open to testing by making a study of enzyme kinetics with a view to investigating the possible existence of an IKR together with its associated absorption band in the far IR-spectrum of the system.

4 Conclusions

The isokinetic relationship has developed rapidly over the past few years, growing from a scientific curiosity into a powerful tool for investigating kinetics and equilibria phenomena within related series of reactions. The existence of an IKR has now been firmly established and explained on a theoretical basis and, furthermore, unlike the $\Delta_r H^\circ / \Delta_r S^\circ$ compensation relationship, it has been proved to be extremely sensitive to changes in reaction pathway. The investigation of reaction series in terms of the IKR or IER is now readily available because of the development of simple, but reliable, statistical procedures. It is hoped that the examples presented in this Review will act as a spur to others, especially those who already collect temperature-dependent data for the interpretation of enthalpic and entropic contributions to their reactions, to adopt this technique to their investigations.

5 Appendix: Simplified Statistical IKR-Analysis

It is crucial to use an appropriate statistical analysis based on rate or equilibrium constants measured at different tempera-

tures when trying to show the existence of an IKR (IER) within a series of reactions.^{1,2} An exact method for this has been published earlier and computer programs are available. However, the following simplified method can be used instead (without serious loss in accuracy) when determining T_{iso} and $\ln k_{iso}$ ($\ln K_{iso}$). Statistically, the simplified method yields a positive IKR-proof at slightly higher significance, i.e. any IKR found by this method also holds when the original method is applied. The procedure can be performed with most scientific pocket calculators or with PC's equipped with simple regression (least square fit) statistics. It is of advantage first to plot the Arrhenius (or van't Hoff) lines and visualise whether or not there is the probability of a point of intersection or small area of intersection. If necessary, single lines or groups of reactions which do not meet such a point and which might be related to a different reaction mechanism should be excluded. Calculate linear regressions for each of the lines involved in one group separately and sum up their residual sum of squares of deviations (if necessary this might be obtained from mean deviations or variance data – this depends upon the program used). This is the residual sum of squares of the unconstrained lines S_{00} . Add to each of the lines a 'new measurement point', namely the coordinates of the (estimated) point of intersection. This might be pre-evaluated graphically, or by solving the obtained least square lines for their common point of intersection, i.e. setting them equal (here the method is simplified to the original approach). Calculate again a residual sum of squares of all points from their least squares straight line, including however the assumed ($\ln k_{iso}$; T_{iso}) point. With this a residual sum of squares of the constrained lines S_x is approximated. As in the original approach one might vary the ($\ln k_{iso}$; T_{iso}) until a minimum in S_0 ($= \min S_x$) is obtained. However, if an IKR exists, the point of intersection found as described above is accurate enough.

With S_{00} and S_0 an almost F -distributed value (the F -test is relatively insensitive to non-linear distribution) can be calculated from equation 3:

$$F = \frac{(S_0 - S_{00})}{f_1} \frac{f_2}{S_{00}} \quad (3)$$

where f_1 equals the numbers of straight lines minus 1 and f_2 equals the number of all measurement points minus twice the number of straight lines.

Should this value be smaller than the respective F -table value for f_1 and f_2 the existence of an IKR cannot be rejected at the respective significance level, i.e. an IKR might exist. In the case that $1/F$ is larger than the respective table value for f_2, f_1 the hypothesis that 'there exists no IKR for this series' can be rejected on the respective significance level. In other words the IKR has to be accepted as existing (at this significance level). Although these concepts might sound complicated, they are, in fact, quite straightforward and it is necessary to understand their meaning: often an IKR (or other statistical hypothesis) is taken as being proved in cases such as the former which implies that acceptance becomes more and more easy the higher the significance level – a result which is hardly logical!

The method described seems to be simple enough to avoid further artefacts in this field. Other methods exist, but many of them should be treated with care.

For example, most of them do not even set correct statistical hypotheses and one easily falls into the trap described above. Care is also necessary when parallel lines occur. The case of a very long extrapolation to obtain IKR-points can strongly suggest an isenthalpic reaction series, a special case which exists. This can be statistically proven separately.² Very large T_{iso} values might refer to isentropic reaction series ($1/T_{iso} = 0$), another special case. It might be that negative T_{iso} values are found, but in this case they should be treated with caution (we obviously cannot measure at such a temperature). Note in this respect also the comment concerning the Hammett relationship made above (see Section 2, Icon V). However, another possible mechanism by which a negative T_{iso} might occur has been made¹

in which it is postulated that this could arise in the case of reaction mechanisms in which a pre-equilibrium (precursor formation) exists and where enthalpic and entropic contributions might vary in just the opposite direction to that of the actual rate-determining step when going from one member of the reaction series to another. In this case T_{iso} is obviously not simply related via equation 2 to a vibrational frequency of the solvent, catalyst, or large reactant molecule (this is only possible for elementary steps). However, for distinction of reaction mechanisms as described in this paper a negative T_{iso} can be used without invoking substantiating theory, i.e. the negative isokinetic temperature is treated as an *ad hoc* unifying device. More work is required to attempt a substantiation of this effect, and, if so justified, to look for a theoretical explanation.

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