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The theoretical basis of the isoinversion principle

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The theoretical basis of the isoinversion principle is discussed in terms of the temperature dependence of absolute rate constants. This description gives an insight into the origin and physical meaning of the terms 'inversion temperature' and 'transition region'. The consequences of quantitative interpretation of non-linear Eyring plots are discussed.

Introduction

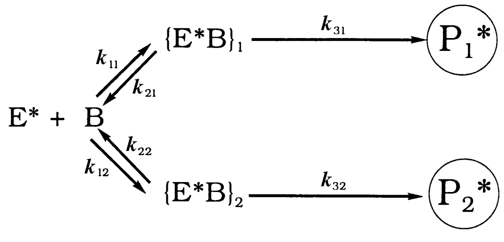
Selectivity and catalysis are highly important topics in synthetic organic chemistry. Whereas progress in the development of new stereo-, regio- and chemo-selective methods has already been made in many areas, there is still a need for new concepts, which enable us to understand the reaction mechanisms and also simplify the optimization of such processes.

The lead structure for synthetically useful catalysts is normally found by intuition. The optimization of the selectivities is performed by trial and error variation of the ligand structure and/or the reaction conditions. Rational design combines trial and error methods with molecular modelling of intermediates or transition states in the catalytic cycles. The catalytic cycles are very complex and it is in most cases not known whether the postulated intermediates are really relevant for the selectivity in the catalytic cycle.

Temperature dependent measurements on the basis of the Eyring theory allow the evaluation of reactions in terms of the activation enthalpies and entropies without the need of knowing the structure of transition states.

The isoinversion principle (IIP) is a deductive kinetic model, which has found widespread application by organic chemists since its introduction in 1989 by Scharf and co-workers.[1] Since then it has been used for both the optimization of selectivities and rationalization of reaction mechanisms in several stoichiometric and catalytic asymmetric reactions.[2–7] The isoinversion principle describes kinetically controlled reactions which show a temperature dependent change in the rate-determining step. In this paper we will focus on reactions which have a pre-equilibrium step, but the results given are also applicable to reactions undergoing a temperature dependent change in the mechanism.

The basic kinetic scheme is depicted in Scheme 1, which is not only applicable to stoichiometric reactions, but to catalytic reactions (Michaelis–Menten kinetics) as well.



Scheme 1 Basic kinetic scheme of the isoinversion principle

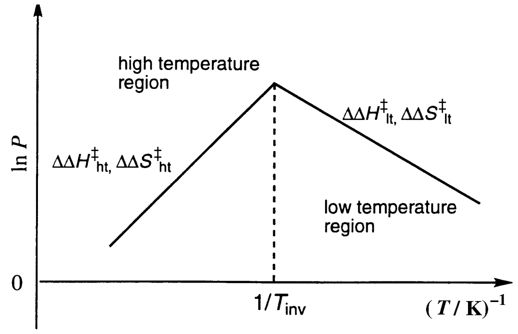


Fig. 1 Non-linear Eyring plots

At the 'first selection level' two diastereomeric intermediates $\{E^*B\}_1$ and $\{E^*B\}_2$ are formed from the prochiral starting material B and a chiral substrate E* (Scheme 1). At the 'second selection level' competition between conversion of the intermediates to the products (P_1^* and P_2^*) and then reversion to the starting materials (E* and B) can modify the initial selection event. By temperature variation the stereoselectivity can be either increased or decreased depending on constructive or destructive interaction of the two selection levels. Experimentally non-linear Eyring behaviour is observed in this case if a change in the rate-determining step occurs in the temperature window under investigation. Note that a linear plot does not necessarily imply that the reaction under investigation is proceeding on one 'selection level', since the deviation from linearity could be very small and, therefore, experimentally undetectable.

In the experimental temperature range the Eyring plots generally consist of two apparently linear regions intersecting at the inversion point T_{inv}, which can either be a distinct extremum or a breaking point (Fig. 1). The region to the left of the inversion point is the high temperature region, the region to the right the low temperature region. According to the formalism of the IIP, the activation parameters $\Delta\Delta H_i^\ddagger$ and $\Delta\Delta S_i^\ddagger$ are determined from the slope and intercept of each of the two lines, respectively. A mathematical treatment of Scheme 1 has shown that this first-order approximation does not necessarily lead to the determination of the correct activation parameters because of a transition region in which none of the single steps in the mechanism is rate determining.[8,9]

Nevertheless a better solution for a quantitative treatment of temperature dependent measurements has not yet been advanced. We will discuss the non-linearity of relative rate plots

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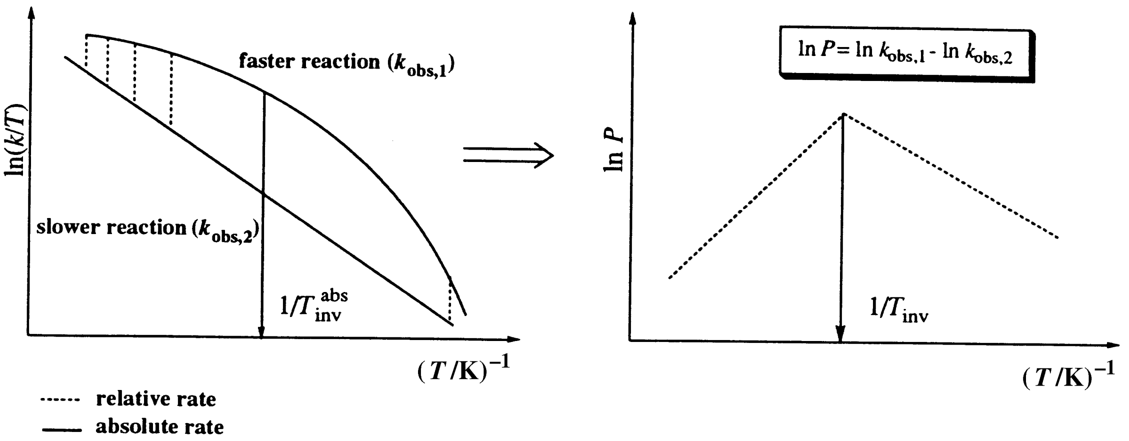

Fig. 2 Origin of non-linear relative rate Eyring plots based on the non-linearity of the corresponding absolute rate plots

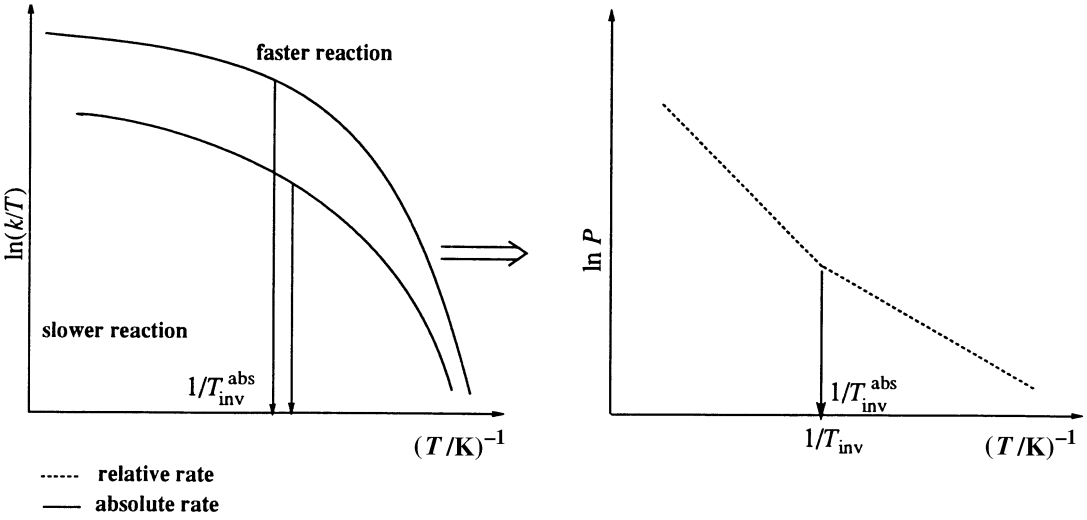

Fig. 3 Origin of non-linear relative rate Eyring plots based on the non-linearity of the corresponding absolute rate plots

in terms of the non-linearity of at least one of the corresponding Eyring plots for the absolute rates, a phenomenon which has been known and understood for a long time.[10]

Results and discussion

The combination of a linear and a non-linear absolute rate Eyring plot gives a non-linear Eyring plot for the relative rates. Depending on the extent of curvature of the non-linear plot and whether the non-linear pathway is faster or slower than the linear one, curves with distinct maxima or minima can result (Fig. 2).

The general case, where both of the absolute rate plots are curved (Fig. 3) is considered next. The starting materials should react by a common mechanism, so that the curvatures in both plots are either both *concave up* or *concave down*. In this case, in the plots for the relative rates, not just maxima and minima can be realized, but also *concave up* or *concave down* curvatures.

Concave up plots in absolute rate studies indicate a change in the reaction mechanism, *concave down* plots show a reaction proceeding on a pathway with a pre-equilibrium (Fig. 4).[10]

Inversion temperature for absolute rates

The rate law applicable to Scheme 1 for each of the two reaction channels is given in eqn. (1), where k_{ij} are the rate constants for the elementary steps and k_{obs} is the observed overall rate constant.

$$\frac{d[P_i]}{dt} = k_{3i}[\{E^*B\}_i] = \frac{k_{1i}k_{3i}[B][E^*]}{(k_{2i} + k_{3i})} = k_{obs,i}[B][E^*] \quad (1)$$

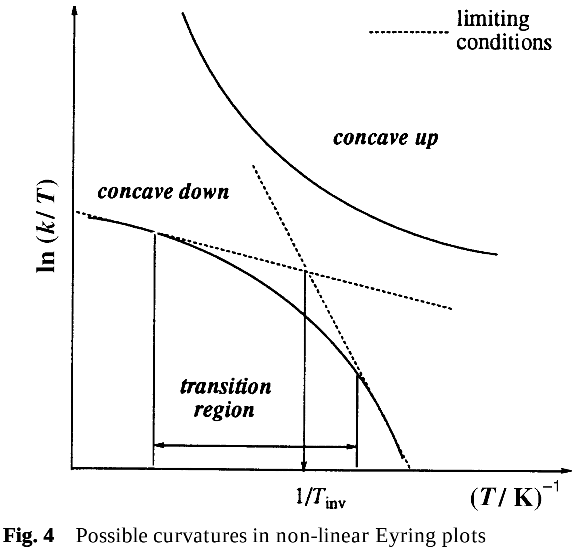

Fig. 4 Possible curvatures in non-linear Eyring plots

The two limiting conditions for this rate expression correspond to a change in the rate-determining step [eqn. (2)], which can be achieved by a variation in the reaction temperature.

$$\lim \frac{k_{2i}}{k_{3i}} = 0 \longrightarrow k_{obs,i} = k_{1i} \qquad (2a)$$

$$\lim \frac{k_{3i}}{k_{2i}} = 0 \longrightarrow k_{obs,i} = \frac{k_{1i}k_{3i}}{k_{2i}} \qquad (2b)$$

The activation parameters for the limiting cases are given in eqn. (3).

$$\lim \frac{k_{2i}}{k_{3i}} = 0 \longrightarrow \Delta H^{\ddagger}_{\mathbf{lt},i} = \Delta H^{\ddagger}_{\mathbf{l}i};\ \Delta S^{\ddagger}_{\mathbf{lt},i} = \Delta S^{\ddagger}_{\mathbf{l}i} \qquad (3a)$$

$$\lim \frac{k_{3i}}{k_{2i}} = 0 \longrightarrow \Delta H^{\ddagger}_{\mathbf{ht},i} = \Delta H^{\ddagger}_{\mathbf{1}i} + \Delta H^{\ddagger}_{\mathbf{3}i} - \Delta H^{\ddagger}_{\mathbf{2}i};$$

$$\Delta S^{\ddagger}_{\mathbf{ht},i} = \Delta S^{\ddagger}_{\mathbf{1}i} + \Delta S^{\ddagger}_{\mathbf{3}i} - \Delta S^{\ddagger}_{\mathbf{2}i} \qquad (3b)$$

Combining $\Delta H^{\ddagger}_{\mathbf{2}i}$ and $\Delta H^{\ddagger}_{\mathbf{3}i}$ leads to eqn (4).

$$\lim \frac{k_{3i}}{k_{2i}} = 0 \longrightarrow \Delta H^{\ddagger}_{\mathbf{ht},i} = \Delta H^{\ddagger}_{\mathbf{1}i} - \delta\Delta H^{\ddagger}_{i};$$

$$\Delta S^{\ddagger}_{\mathbf{ht},i} = \Delta S^{\ddagger}_{\mathbf{1}i} - \delta\Delta S^{\ddagger}_{i} \qquad (4)$$

The two lines corresponding to the equations which describe the limiting conditions computed by Ridd[8,9] intersect at a single point [eqn. (5)] in an Eyring plot, whose abscissa value is the

$$T^{\mathbf{abs}}_{inv,i} = \frac{\Delta H^{\ddagger}_{\mathbf{3}i} - \Delta H^{\ddagger}_{\mathbf{2}i}}{\Delta S^{\ddagger}_{\mathbf{3}i} - \Delta S^{\ddagger}_{\mathbf{2}i}} = \frac{\delta\Delta H^{\ddagger}_{i}}{\delta\Delta S^{\ddagger}_{i}} \qquad (5)$$

inversion temperature for the absolute rates, where $\Delta G^{\ddagger}$ (first selection level) = $\Delta G^{\ddagger}$ (second selection level).

At the inversion point the influence of the two selection levels just cancels so a change in the dominance of one step over the other occurs by going from one of the limiting conditions to the other.[8,9]

The value of the inversion temperature is independent of the activation parameters of the first selection level (represented by the activation parameters $\Delta H^{\ddagger}_{\mathbf{1}i}$ and $\Delta S^{\ddagger}_{\mathbf{1}i}$). The first selection level still has an influence on the amount of curvature in the so called 'transition region' (*vide infra*). The analogous method by Scharf and co-workers[3] applied to relative rate plots does not necessarily give the correct inversion point,[9,10] but here no problems arise since the absolute rate plots generally are monotonic. Two limiting conditions also apply to eqn. (5) in the cases where either the numerator or the denominator approach zero. This leads to $T^{\mathbf{abs}}_{\mathbf{inv},i} = 0$ and infinity, respectively. The rate-determining step does not change, which corresponds to a reaction proceeding on just one selection level. Negative inversion temperatures, which obviously have no simple physical meaning are rationalized this way as well.

The transition region

Usually neither limiting condition is achieved in the direct vicinity of the inversion point. This led to the proposal of the 'transition region' where neither of the two rate-limiting steps of the two selection levels is rate determining.[8,9] The width of the transition region can be calculated in the following way: for a change in the rate-determining step the ratio k_{2i}/k_{3i} must pass unity. To fulfill the limiting conditions we assume that k_{2i}/k_{3i} changes from n to $1/n$ [eqn. (6)].

$$\frac{k_{2i}}{k_{3i}} = \frac{n}{1} : \ln n = -\frac{\delta\Delta H^{\ddagger}_{i}}{RT_{\mathbf{lim\ 1},i}} + \frac{\delta\Delta S^{\ddagger}_{i}}{R} \qquad (6a)$$

$$\frac{k_{2i}}{k_{3i}} = \frac{n}{1} : -\ln n = -\frac{\delta\Delta H^{\ddagger}_{i}}{RT_{\mathbf{lim\ 2},i}} + \frac{\delta\Delta S^{\ddagger}_{i}}{R} \qquad (6b)$$

Choosing a typical inversion temperature, *e.g.* 250 K, allows computation of the width of the transition region as a function of the activation parameters (Table 1), where n is a measure of the confidence level for the fit between the plot and its linear approximation.

This transition region can be rather broad and, even in the case of very high reaction entropy differences, it is in the order of the experimentally accessible temperature range. So the experimentally determined Eyring plots are generally not made up of the lines corresponding to two different rate-determining steps, but will contain influences of the transition region.

Table 1 Dependence of transition region widths and limits on activation parameters

$\delta\Delta H^{\ddagger}$/ kJ mol^{-1}	$\delta\Delta S^{\ddagger}$/ J mol^{-1} K^{-1}	$T_{\mathbf{lim},1}$/ K[a]	$T_{\mathbf{lim},2}$/ K[a]	$\Delta T_{\mathbf{trans}}$/ K[b]
5	20	150	755	606
10	40	187	376	188
15	60	204	322	117
20	80	214	300	86
25	100	220	289	68
30	120	225	281	56

[a] $T_{\mathbf{lim},1}$, $T_{\mathbf{lim},2}$; lower and upper limit of the transition region. [b] ΔT_{trans}; width of the transition region, $n = 5$.

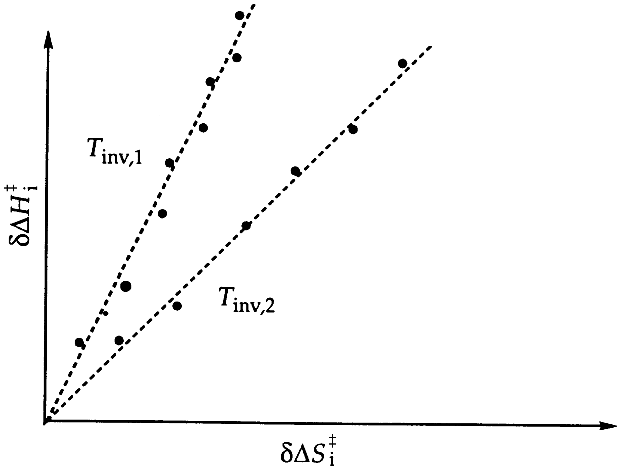

Fig. 5 Isoinversion relationship for the absolute rates

Inversion temperature for relative rates

If the inversion temperatures of the absolute rates are identical for two corresponding reaction paths, the inversion temperature for the relative rates is equal to those for the absolute rates. Also, if only one of the absolute rate plots shows a break, the isoinversion temperature equals its inversion temperature.

In the case of unequal inversion temperatures for the absolute rates, the inversion temperature for the relative rates has to be somewhere in between those for the absolute rates. It can be formally computed according to eqn. (7).

$$\int_{T_{\mathbf{inv,1}}}^{T^{\mathbf{rel}}_{\mathbf{inv}}} \Delta G^{\ddagger}_{\mathbf{1}}\, \mathrm{d}\left(\frac{1}{T}\right) = \int_{T^{\mathbf{rel}}_{\mathbf{inv}}}^{T_{\mathbf{inv,2}}} \Delta G^{\ddagger}_{\mathbf{2}}\, \mathrm{d}\left(\frac{1}{T}\right) \qquad (7)$$

The influence of the activation parameters of the two reaction pathways compensate for each other, if the change in $\Delta G^{\ddagger}_{i}$ for each pathway i with respect to the reciprocal temperature is identical. The physical meaning of the inversion temperature $T^{\mathbf{rel}}_{\mathbf{inv}}$ still remains dubious in this case. Therefore the compensation in the absolute rates for each of the reaction pathways is more important. We predict correlations for each path itself if $\delta\Delta H^{\ddagger}_{i}$ *vs.* $\delta\Delta S^{\ddagger}_{i}$ is plotted, showing the compensation phenomenon in the absolute rates rather than the relative rates (Fig. 5).

Curve shapes as a function of different inversion temperatures and transition widths

Since it is plausible but by no means proven that the inversion temperatures for both reaction channels of a stereo- or chemoselective reaction are identical or at least very similar, it is useful to discuss the shape of the resulting Eyring plots in terms of the

Table 2 Activation parameters, inversion temperatures and transition regions for Figs. 6–8

	$\Delta S_{11}^{\ddagger}$/ J mol^{-1} K^{-1}	$\Delta S_{12}^{\ddagger}$/ J mol^{-1} K^{-1}	$\Delta H_{11}^{\ddagger}$/ kJ mol^{-1}	$\Delta H_{12}^{\ddagger}$/ kJ mol^{-1}	$\delta\Delta S_1^{\ddagger}$/ J mol^{-1} K^{-1}	$\delta\Delta S_2^{\ddagger}$/ J mol^{-1} K^{-1}	$\delta\Delta H_1^{\ddagger}$/ kJ mol^{-1}	$\delta\Delta H_2^{\ddagger}$/ kJ mol^{-1}	$T_{\mathrm{inv},1}$/ K	$T_{\mathrm{inv},2}$/ K	$T_{\mathrm{lim1},1}$/ K	$T_{\mathrm{lim2},1}$/ K	$T_{\mathrm{lim1},2}$/ K	$T_{\mathrm{lim2},2}$/ K
A	−90	−90	36	43	40	60	10	15	250	250	187	376	204	322
B	−85	−70	36	43	40	60	10	12	250	200	187	376	164	257
C	−90	−90	43	43	60	40	15	4.8	250	120	204	322	90	180

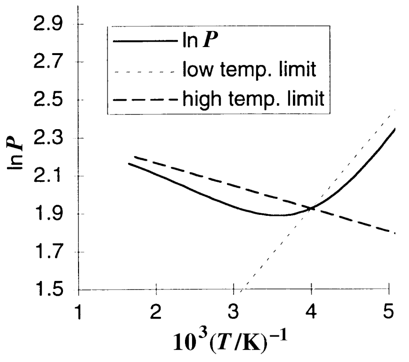

Fig. 6 Example A

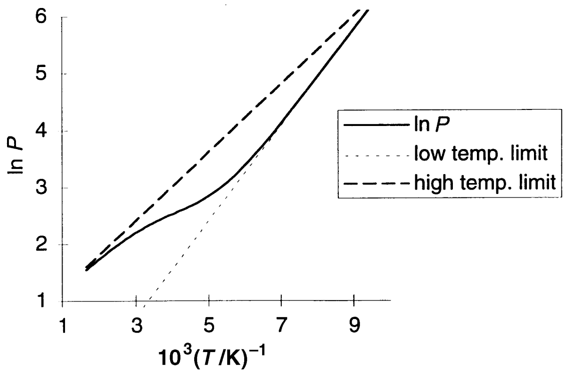

Fig. 7 Example B

inversion temperature and the transition region widths (see Fig. 7).

Example A shows identical inversion temperatures for both reaction channels, but different transition region widths. Unequal inversion temperatures with overlapping transition region widths (example B) are an intermediate case leading to example C where neither inversion temperature is in the transition region of the other reaction channel. The lines corresponding to the limiting conditions are given by the straight lines in each of the plots Figs. 6–8. The activation parameters, inversion temperatures and transition regions for Figs. 6–8 are given in Table 2. In Fig. 8, the low temperature limit corresponds to the abscissa.

For example A the inversion point for the relative rates is at the same temperature as the inversion temperature for the absolute rates. Furthermore, the transition region will be as large as the larger one in the two absolute rate plots (Fig. 6). The inversion point can be determined correctly from this plot also by the first-order approximation mentioned above (the inversion point is at the intersection point of the lines for the two limiting conditions), but quantitative estimates of the activation parameters are still problematic due to the deviations of the linear and the non-linear fits shown in Fig. 4.

Example B shows different inversion points for the two competing pathways, but overlapping transition regions. Fig. 7 shows two inflection points, which correspond to the inversion temperatures for the absolute rates (since the other reaction path is also still in the transition region they are not yet identical with these).

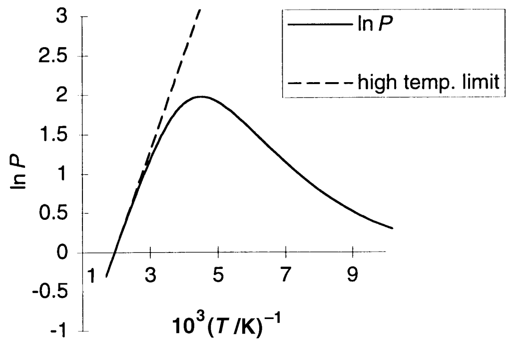

Fig. 8 Example C

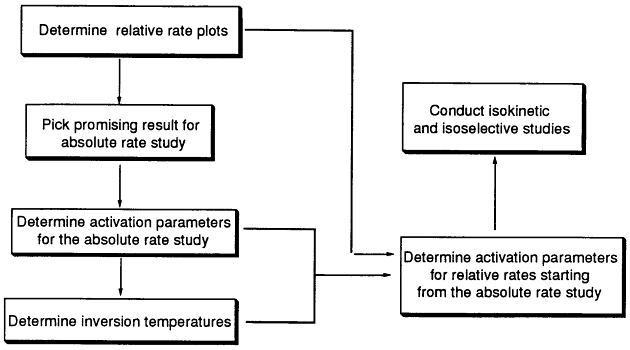

Fig. 9 Proposed strategy for the evaluation of non-linear Eyring behaviour

A second maximum or inflection point will also be realized if the inversion temperature for the second reaction path shifts out of the transition region of the first (example C). In this case these two points in the relative rate plot will be identical to the inversion points of the absolute rate plots. Although a common inversion point for the relative rates formally could still be determined, it is obviously meaningless since the two reaction paths change the rate-determining step independently of each other.

Conclusions

The isoinversion principle focuses on the quantitative evaluation of non-linear Eyring behaviour. Ridd has already pointed out general problems with this process, which stimulated our work in this area. We have considered the non-linear relative rate plots in terms of their absolute rate behaviour.

The important features of the interpretation of relative rate plots are the ‘transition region width’ and the ‘inversion temperatures’ of the corresponding absolute rate plots. Since the temperature window normally is too narrow to reach the limiting conditions of the rate law, a relative rate study must be supported by an absolute rate study for the quantitative determination of the activation parameters. Otherwise, fatal misinterpretations could arise, *e.g.* in the extrapolation to isoselective points that lie outside the experimentally accessible temperature range.

We found that inversion points for relative rates are physically significant only if the inversion temperatures for the absolute rates are identical. If the inversion points for the absolute rates differ, a 'formal' isoinversion temperature can still be defined, but it has no physical meaning.

In the limit of non-overlapping transition regions, not only one but two extrema or inflection points can occur in the relative rate Eyring plot. They refer to the inversion points for each of the two pathways of the absolute rate plots.

Nevertheless, precious information still can be obtained from the experimental plots. For the optimization of selectivities, the maximum in the plot still contains the most useful information since it represents the point with the maximum available selectivity. For the purpose of mechanistic interpretations, the basic experiments should be conducted such that absolute and relative rate studies are combined. These studies give activation parameters and information on the inversion points for the absolute rates. For the evaluation of relative rate studies we propose the procedure shown in Fig. 9. First, a number of relative rate studies should be conducted to find examples with pronounced curvatures. Then the absolute rates for these examples are determined. The activation parameter and the inversion temperatures are then evaluated. Using these data, the other relative rate plots can be fitted. The application of our theoretical efforts to experimental kinetic data will be presented in a forthcoming paper.

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