A Reassessment of the Isoinversion Principle

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A maximum in a plot of ln P vs. $1/T$ does not necessarily imply that the values of $\Delta\Delta H^{\ddagger}$ for the two possible rate determining steps are of opposite sign.

In recent years, studies of chirality transfer have often involved plots of ln P against the inverse of the absolute temperature.[1] The quantity P is the ratio of the diastereoisomers produced in a given reaction and also the ratio of the experimental rate coefficients [$k_{a(obs)}$, $k_{b(obs)}$] for the production of these diastereoisomers. Such plots are normally linear and the slope of the line has then been used to calculate the difference in the enthalpies of activation ($\Delta\Delta H^{\ddagger}$) of the two reactions. Where the plot passes through a maximum[1b–d] (Fig. 1) the slopes of the two lines are considered to indicate the values of $\Delta\Delta H^{\ddagger}$ for two distinct rate determining steps and considerable attention[2,3] has been paid to the significance of the difference ($\delta\Delta\Delta H^{\ddagger}$) between these values of $\Delta\Delta H^{\ddagger}$. In related reactions, a plot of $\delta\Delta\Delta H^{\ddagger}$ against the corresponding entropy term ($\delta\Delta\Delta S^{\ddagger}$) has been found to be linear[1b,d,2,3] and this relationship has been termed the 'isoinversion principle'.[3]

However, on this interpretation, the experimental data indicate a curiously abrupt change in the rate determining step and this has led us to determine how ln P would be expected to vary with $1/T$ for possible values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in each stage of the overall reaction.

We have taken the reaction path shown in Scheme 1 as a representation of a thermal process with two potential rate determining steps† and in which both intermediates I_1 and I_2 exist as two diastereoisomers (labelled a and b). It then follows, assuming the concentration of the intermediate I_1 to be always small, that P is given by eqn. (1). The variation of each rate

$$P = \frac{k_{a(obs)}}{k_{b(obs)}} = \frac{k_{a1}k_{a3}(k_{b2} + k_{b3})}{(k_{a2} + k_{a3})k_{b1}k_{b3}} \tag{1}$$

coefficient with temperature has been calculated in the usual way[4] as shown for rate coefficient k_1, diastereoisomer a, in eqn. (2) where the symbols have their usual significance.[4] The

$$k_{a1} = \left(\frac{k_B T}{h}\right) e^{\frac{\Delta S_{a1}^{\ddagger}}{R}} e^{\frac{-\Delta H_{a1}^{\ddagger}}{RT}} \tag{2}$$

parameters used are listed in Table 1 and the resulting plots of ln P are shown in Fig. 2. The large negative entropy of activation for the first step accords with that for the Diels–Alder reaction[5] and the other parameters have been chosen to produce the desired change in the rate determining step with a clearly defined maximum and, incidently, to provide a half-life of ca. 15 min at 0 °C with reactant concentrations of 0.1 mol dm^{-3}.

Each plot can be roughly divided into three parts, as shown in Fig. 2. The limiting slopes in the two terminal regions are derived from the two possible rate determining steps but these
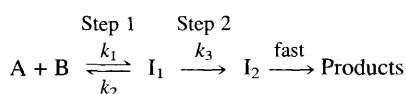
are separated by a wide transitional region in which much of the plot is also approximately linear. The values of the parameters in Table 1 are somewhat arbitrary but the above characteristics are reproduced when other values meeting the required criteria are used. The key point is that the difference in the enthalpy of activation between two reactions of a relatively high energy intermediate is insufficient to produce an abrupt change in the rate determining step when the temperature is varied. We suggest, therefore, that where clearly defined maxima in these experimental plots derive from a change in the rate determining step, then one slope is characteristic of a single rate determining stage and one slope derives from the transitional region. The points on the plot in Fig. 1 are, in fact, calculated using the maximum of curve A (Fig. 2).

The results in plots A, B and C show that the slope in the transitional region can retain the same sign when the slope in the following region is changed from positive through zero to
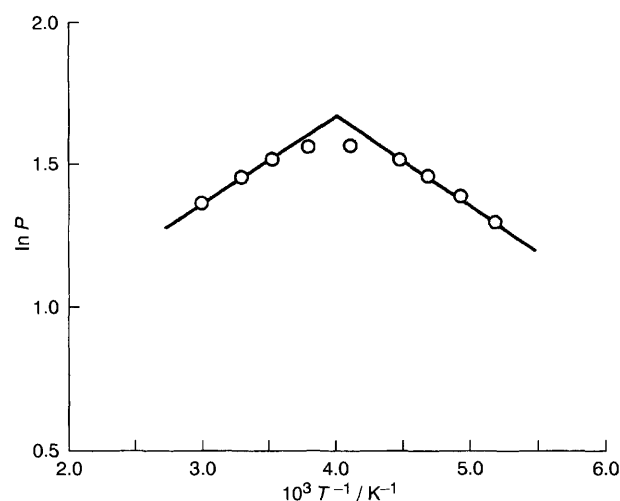

Fig. 1 The type of maximum observed in plots of ln P vs. $1/T$ and attributed to the linear plots deriving from two rate determining steps

Step 1   Step 2

$$A + B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} I_1 \xrightarrow{k_3} I_2 \xrightarrow{fast} Products$$

Scheme 1

Table 1 Parameters $\Delta S^{\ddagger}/J$ deg^{-1} mol^{-1} and $\Delta H^{\ddagger}/kJ$ mol^{-1} used for the plots in Fig. 2

Parameter	Isomer	Plot			
		A	B	C	D
$\Delta S_1^{\ddagger}$	a	−100	−100	−100	−75
	b	−100	−100	−100	−107
$\Delta H_1^{\ddagger}$	a	47	48	48	47.5
	b	48	48	47	45
$\Delta S_2^{\ddagger}$	a	60	60	60	85
	b	60	60	60	55
$\Delta H_2^{\ddagger}$	a	38	38	38	38
	b	38	38	38	38
$\Delta S_3^{\ddagger}$	a	0	0	0	0
	b	0	0	0	0
$\Delta H_3^{\ddagger}$	a	24	24	24	25.5
	b	27	27	27	28

negative. Thus, a maximum in the plot does not require a reversal in the sign of $\Delta\Delta H^{\ddagger}$ between the two rate determining steps. The slope in the transitional region is determined mainly by the difference in the overall (enthalpic + entropic) discrimination between the steps.

In the plots A, B and C, the slope giving a true value of $\Delta\Delta H^{\ddagger}$ is positive, but plot D shows that this is not necessarily so when both enthalpic and entropic discrimination is present. Thus, a random selection of one of the two slopes at a maximum gives a 50% probability of obtaining a true value of $\Delta\Delta H^{\ddagger}$. A related
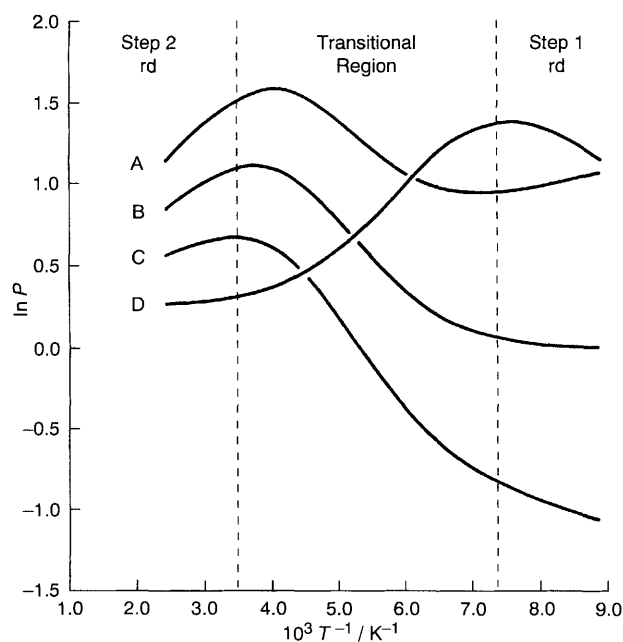
uncertainty arises when only a linear plot is observed, but the probability of obtaining a true value of $\Delta\Delta H^{\ddagger}$ is then less easy to quantify.

On the above model, the quantities previously defined as $\delta\Delta\Delta H^{\ddagger}$ and $\delta\Delta\Delta S^{\ddagger}$ have no simple physical significance, but the model can accommodate the observed linear relation[2,3] between them. When the value of $\Delta H^{\ddagger}_{3a}$ for plot A is increased from 24 to 26 kJ mol^{-1} in steps of 0.25 kJ (thereby reducing the enthalpic discrimination between the diastereoisomers from 3 to 1 kJ mol^{-1}) the resulting plot of '$\delta\Delta\Delta H^{\ddagger}$' against '$\delta\Delta\Delta S^{\ddagger}$' is linear with a correlation coefficient >0.999. We hope to consider this in more detail in a later publication.

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Fig. 2 Theoretical plots of ln P vs. $1/T$ corresponding to the parameters in Table 1

Footnote

† In choosing this reaction path (Scheme 1), we had in mind the two stage mechanism for the osmium tetroxide asymmetric hydroxylation[1c,6] but the argument is, of course, more general.

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