

STATISTIC OF THE ENTHALPY-ENTROPY RELATIONSHIP. II.*

THE GENERAL CASE

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The previously formulated mathematical model of the enthalpy-entropy relationship in a series of related reactions had been explicitly solved in the special case of corresponding temperatures only. In this paper the general case, characterized by an arbitrary set of temperatures and rate or equilibrium constants, and including variable weights, has been treated by an iterative procedure, using a computer; the same characteristics have been computed as previously defined. In practical examples a similar picture is usually obtained as in the mentioned special case: The residual sum of squares shows only one flat minimum, defining the isokinetic temperature β , and a sharp maximum. Exceptionally a different pattern can be obtained from a very irregular set of data. The isokinetic temperature can be defined unequivocally in any case but it has not always a physical meaning. Hence the most important result of the analysis is the decision, whether the isokinetic hypothesis can be rejected or not, the numerical value of β being of little significance.

The linear relationship between activation parameters in a series of related reactions, called the isokinetic relationship¹⁻⁴, is expressed by the equations:

$$E^* = e_0 + 2.303 R \beta \log A \quad \text{or} \quad \Delta H^* = h_0 + \beta \Delta S^*, \quad (1a, b)$$

using the Arrhenius parameters E^* and A , or the activation energy ΔH^* and activation entropy ΔS^* , respectively. The similar relation between reaction enthalpy ΔH^0 and standard reaction entropy ΔS^0 reads

$$\Delta H^0 = h_0 + \beta \Delta S^0. \quad (1c)$$

The proportionality constant β is called the isokinetic temperature, while the intercepts e_0 or h_0 have no distinct physical meaning. Similarly as in previous papers⁴⁻⁶ we shall not distinguish between the formulations (1a-c) and use the simple sym-

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bols ΔH and ΔS without superscript to denote either kinetic or thermodynamic quantities. Similarly the symbol k will refer either to the rate or equilibrium constant.

The general significance of the isokinetic relationship for any theory of reactivity is evident; only its validity allows one to discuss the reactivity in quantitative, temperature independent terms, as substituent effects, ring strain *etc.* For this reason this relationship has been extensively studied and the experimental support searched for¹⁻⁴. However, the experimental verification of the apparently simple equations ($la-c$) and the estimation of the coefficients involve difficult statistical problems, since the two variables have been simultaneously determined from the same set of experimental data and hence are mutually dependent^{5,6}. Particularly the simple plot of ΔH vs ΔS or the regression in these coordinates are fallacious and the result thus obtained need not accord with the original kinetic data, as we showed by a mathematical analysis and on numerous examples^{4,5}. For this reason new procedures have been searched for⁵⁻⁹, many of them being again statistically incorrect⁶.

We advanced subsequently two methods, which were statistically unobjectionable but limited in their applications. The original graphical method, based on the plot of $\log k$ at two temperatures against each other⁵, was applicable to measurements limited to two temperatures and is not suitable for a more elaborate mathematical treatment. However, it is always very useful for the first orientation⁶. The general mathematical model was formulated⁶ in the framework of the least-squares method in the coordinates $\log k$ vs T^{-1} . An explicit solution was achieved for the special case, when all the reactions were kinetically followed at the same set of temperatures and all the measurements have the same weight; the formulae were devised for calculation on a desk calculator⁶. This special case is rather frequent in practice, and in addition the formulae can be applied with a good approximation even when the assumptions are not strictly fulfilled, *e.g.* one measurement is lacking (Example 2). However, when these assumptions would fundamentally disagree with the actual pattern, the method is not applicable. Alternatively the use of a desk calculator may be found inconvenient and for a computer the explicit solution is of no advantage.

Hence we are dealing in this paper with the general solution of the problem by the iteration method using a computer. No explicit solution will be achieved and the mathematical analysis is not complete but confined even to such cases as may be encountered in practice.

THEORETICAL

The mathematical model used is essentially the same as previously⁶, except that different weights of individual measurements are also considered. It is based on the general representation of the isokinetic relationship in the coordinates $\log k$ vs T^{-1} (Fig. 1). Any reaction obeying the Arrhenius law is represented by a straight line. If in addition the isokinetic relationship is fulfilled, all the lines intersect in one point with the abscissa β^{-1} and ordinate $-e_0/2 \cdot 303 R\beta$.

Let us formulate the general problem as follows, its applicability to real systems will be considered in the next section. In the coordinates $x \equiv T^{-1}$ and $y \equiv \log k$ a family of l straight lines ($l \geq 3$) is given with slopes b_i ($i = 1, 2, \dots, l$) and with

a common point of intersection (x_0, y_0) . Hence the general equation of the i -th line reads

$$y - y_0 = b_i(x - x_0). \quad (2)$$

On the i -th line m_i points are situated ($m_i \geq 2$) with coordinates (x_{ij}, y'_{ij}) where $j = 1, 2, \dots, m_i$. Instead of true ordinates y'_{ij} only the values $y_{ij} = y'_{ij} + e_{ij}$ are available, where e_{ij} are random variables with zero average values and variances σ_{ij}^2 . The task is to estimate the parameters $x_0 (= \beta^{-1})$, $y_0 (= -e_0/2.303 R\beta)$, b_i and the average value of σ^2 from the set of values x_{ij} , y_{ij} only; it is supposed that relative values of σ_{ij}^2 are known or can be estimated. In the framework of the least squares method the basic condition has the form

$$\sum_{ij} w_{ij} [y_{ij} - y_0 - b_i(x_{ij} - x_0)]^2 = \min, \quad (3)$$

where the weights w_{ij} may be defined as

$$w_{ij} = (\sum_i m_i) / \sigma_{ij}^2 \sum_{ij} \sigma_{ij}^{-2}. \quad (4)$$

The estimates \hat{x}_0 , \hat{y}_0 and \hat{b}_i are then obtained by solving the system of normal equations

$$\begin{aligned} \sum_{ij} w_{ij} y_{ij} &= \hat{y}_0 \sum_i m_i - \hat{x}_0 \sum_{ij} w_{ij} \hat{b}_i + \sum_{ij} w_{ij} \hat{b}_i x_{ij}, \\ 0 &= \hat{y}_0 \sum_{ij} w_{ij} \hat{b}_i - \hat{x}_0 \sum_{ij} w_{ij} \hat{b}_i^2 - \sum_{ij} w_{ij} \hat{b}_i y_{ij} + \sum_{ij} w_{ij} \hat{b}_i^2 x_{ij} \\ \sum_j w_{ij} x_{ij} y_{ij} &= \hat{y}_0 \sum_j w_{ij} x_{ij} + \hat{x}_0 \sum_j w_{ij} y_{ij} - \hat{x}_0 \hat{y}_0 \sum_j w_{ij} + \hat{b}_i (\sum_j w_{ij} x_{ij}^2 - \\ &\quad - 2\hat{x}_0 \sum_j w_{ij} x_{ij} + \hat{x}_0^2 \sum_j w_{ij}). \end{aligned} \quad (5)$$

This non-linear set of $l + 2$ equations was solved explicitly in our previous communication⁶ in the simple case when $w_{ij} = 1$, $m_i = m$ and $x_{ij} = x_i$, i.e. when all the measurements have the same weight and all the reactions have been followed at the same set of temperatures. This pattern is further referred to as the "special case". Now a general numerical solution will be outlined, using similar symbols as previously⁶; it follows that all the formulae of this paper are transformed by the above three constraints into corresponding formulae of ref.⁶.

To achieve the solution let us first consider the simpler linear problem when the abscissa of the point of intersection is known, let us denote it by x . The task is to estimate its ordinate y , the slopes $b_{i,x}$, the residual sum of squares *etc.* The set (5) of normal equations is reduced by the second one and we get for \hat{y} and $\hat{b}_{i,x}$ the solution:

$$\hat{y} = \frac{\sum_{ij} w_{ij} y_{ij} - \sum_i [(\sum_j w_{ij} x_{ij} - x \sum_j w_{ij}) (\sum_j w_{ij} x_{ij} y_{ij} - x \sum_j w_{ij} y_{ij}) / X_i]}{\sum_i m_i - \sum_i [(\sum_j w_{ij} x_{ij} - x \sum_j w_{ij})^2 / X_i]}, \quad (6)$$

$$\hat{b}_{i,x} = (\sum_j w_{ij} x_{ij} y_{ij} - x \sum_j w_{ij} y_{ij} - y \sum_j w_{ij} x_{ij} + xy \sum_j w_{ij}) / X_i, \quad (7)$$

where the symbol X_i stands for

$$X_i = \sum_j w_{ij} x_{ij}^2 - 2x \sum_j w_{ij} x_{ij} + x^2 \sum_j w_{ij}. \quad (8)$$

The residual sum of squares S_x , *i.e.* still related to a given x , is given by

$$S_x = \sum_{ij} w_{ij} y_{ij}^2 - y \sum_{ij} w_{ij} y_{ij} - \sum_i [(\sum_j w_{ij} x_{ij} y_{ij} - x \sum_j w_{ij} y_{ij}) (\sum_j w_{ij} x_{ij} y_{ij} - x \sum_j w_{ij} y_{ij} - y \sum_j w_{ij} x_{ij} + xy \sum_j w_{ij}) / X_i], \quad (9)$$

and has $f = \sum_i m_i - l - 1$ degrees of freedom.

This calculation can now be repeated for various values of x ; one obtains y and S_x as functions of x and one can find the minimum value of S_x (denoted S_0) by successive approximations. The value of x at this minimum (x_0) represents the estimate of the isokinetic temperature ($x_0 = \beta^{-1}$), the corresponding values y_0 , b_i and S_0 are obtained by substituting x_0 for x into the equations (6) – (9); S_0 has $f = \sum_i m_i - l - 2$ degrees of freedom.

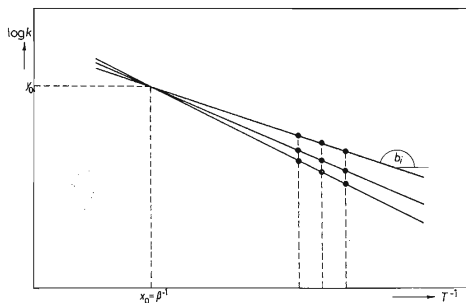


FIG. 1.

Representation of the Isokinetic Relationship in the Coordinates $\log k$ vs T^{-1}

The values of slopes b_i can be compared to the slopes $b_{i,0}$ of the regression lines computed without the constraint of a common point of intersection. These are given according to common formulae of linear regression*

$$b_{i,0} = \frac{(\sum_j w_{ij})(\sum_j w_{it} x_{ij} y_{ij}) - (\sum_j w_{ij} x_{ij})(\sum_j w_{ij} y_{ij})}{(\sum_j w_{ij})(\sum_j w_{ij} x_{ij}^2) - (\sum_j w_{ij} x_{ij})^2} \quad (10)$$

Similarly S_0 differs from the sum of squares S_{00} , related to these unconstrained regression lines, which is given by*

$$S_{00} = \sum_{ij} w_{ij} y_{ij}^2 - \sum_j \frac{(\sum_j w_{ij} y_{ij})^2}{\sum_j w_{ij}} - \sum_i \frac{[(\sum_j w_{ij})(\sum_j w_{ij} x_{ij} y_{ij}) - (\sum_j w_{ij} x_{ij})(\sum_j w_{ij} y_{ij})]^2}{(\sum_j w_{ij})^2 (\sum_j w_{ij} x_{ij}^2) - (\sum_j w_{ij})(\sum_j w_{ij} x_{ij})^2} \quad (11)$$

with $f = \sum_i m_i - 2l$ degrees of freedom. Of course S_0 is larger or at least equal to S_{00} , the equality can occur in the particular (unrealistic) case when all the unconstrained regression lines intersect in one point (it would also be fulfilled for $l = 2$).

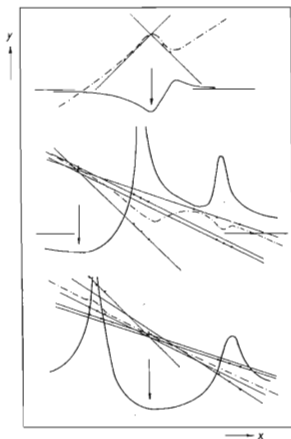


FIG. 2

Some Artificial Examples of the Isokinetic Relationship with Very Different Temperature Values of Individual Reactions

Shown are the set of points and unconstrained regression lines, s_x (—) and y (---) as functions of x and the optimum point of intersection (+).

* See ref.¹⁰ for all common statistical formulae.

Usually S_0 is significantly larger than S_{00} and by comparing the corresponding standard deviations s_0 and s_{00} to each other and to the estimated experimental error (δ), one can draw conclusions as to the validity of the Arrhenius and isokinetic laws. If s_{00} is not significantly higher than δ , the Arrhenius law is valid within the limits of experimental error. If s_0 is not significantly higher than s_{00} , the isokinetic hypothesis (including the point of intersection at the infinite distance) cannot be rejected. Quite rigorously the F-test* can be used for comparisons of s_{00} , s_x and δ but not s_0 since the problem is not linear. However, even a semiquantitative comparison can be useful as in the examples of the previous paper⁶. Finally, the confidence interval of x_0 can be estimated from the graph of s_x (or S_x) vs x , taking an essentially arbitrary limit for s_x , based on comparison with δ or with s_0 .

The final task of the mathematical analysis would be to establish under which conditions the problem has a solution, particularly whether the function $S_x = f(x)$ has always a minimum, when it has more than one minimum *etc.* However, having in mind the practical purpose of this paper, we shall not deal with the extreme and/or degenerate cases. Thus, as in the previous communication⁶, the analysis will remain incomplete from the mathematical point of view, but satisfactory from the practical one.

The dependence of S_x on x is a rational function, generally of the degree $(4l - 1)$, and is represented by the ratio of two polynomials of the degree $(4l - 2)$, see equation (9). It is continuous, single valued, finite and non-negative in the whole range of x , and has a horizontal asymptote at the value S_∞ .

$$S_\infty = \frac{\sum_{ij} w_{ij} y_{ij}^2}{\sum_{ij} w_{ij}} - \frac{\left(\sum_{ij} w_{ij} y_{ij} \right)^2}{\left(\sum_{ij} w_{ij} x_{ij}^2 - \frac{\left[\sum_{ij} w_{ij} x_{ij} \right]^2}{\sum_{ij} w_{ij}} \right)} \quad (12)$$

In general the function S_x can possess several maxima and minima as it is signaled in Fig. 2 on some artificial (unrealistic) examples. In practical, "reasonable" examples, *i.e.* when the set of x -values is not very different for individual straight lines, the function has often one minimum and one maximum only and its shape resembles the curve of the third degree derived⁶ for the special case (see further Fig. 4). In real examples there is little danger that a local minimum is found instead of the absolute one, especially when the calculations are controlled by the graphical representation, which is strongly recommended.

The function $y = f(x)$ is, according to equation (6), also continuous and single-valued in the whole range of x , and finite for finite values of x . In general, it is a rational fraction with a polynomial of the degree $(2l - 1)$ in the numerator and of the degree $(2l - 2)$ in the denominator. It has one asymptote with the slope

$$b_\infty = \frac{\sum_{ij} w_{ij} x_{ij} y_{ij} - \frac{\left[\sum_{ij} w_{ij} x_{ij} \right] \left[\sum_{ij} w_{ij} y_{ij} \right]}{\sum_{ij} w_{ij}}}{\sum_{ij} w_{ij} x_{ij}^2 - \frac{\left[\sum_{ij} w_{ij} x_{ij} \right]^2}{\sum_{ij} w_{ij}}} \quad (13)$$

The quantities b_∞ and S_∞ together represent the solution of a particular problem to draw parallel lines through a given set of points by the method of least squares. They are computed relatively easily so they can be useful to check the whole calculation. In addition according to S_∞ one can test the hypothesis that the reaction series is isoenthalpic. In general, the function

$y = f(x)$ can have maxima and minima as shown in Fig. 2 on some artificial examples. In "reasonable" examples, occurring at practice most frequently, the function is close to its asymptote (Fig. 4) and in the "special case" is reduced to a straight line (Fig. 3).

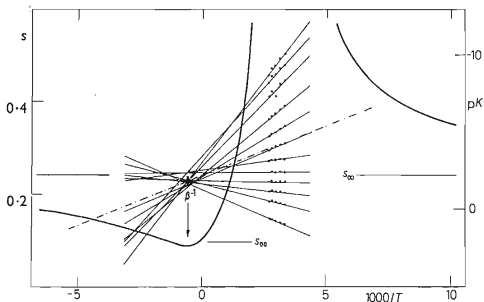


FIG. 3

Isoequilibrium Relationship for the Protonation of Nitroanilines¹⁴

Shown are s_x (—) and y (---) as functions of x , unconstrained regression lines, s_{00} , s_{∞} , δ , the isokinetic point (+).

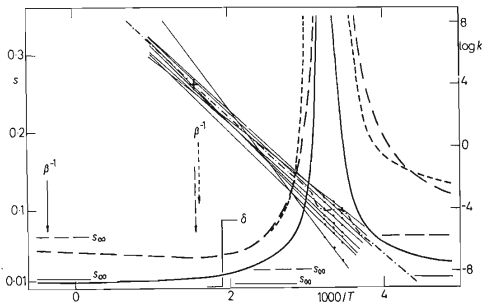


FIG. 4

Isokinetic Relationship for the Proton Transfer from Nitromethane to Anions of Various Aliphatic Acids⁹

— Solution using different weights, --- with equal weights, - - - approximate solution; limits of experimental errors shown by δ .

Similarly as the value of S_∞ (or s_∞) serves to test the isenthalpic hypothesis, one can also test the isentropic hypothesis using the value $S_x(s_x)$ from equation (9) for $x = 0$. Let us denote these values $S_S(s_S)$. When the isentropic hypothesis is accepted, one can calculate the pertinent slopes $b_{i,S}$ according to equation (7) with $x = 0$.

APPLICATION

Before applying the developed formulae to a real example, it is necessary to consider the preassumptions inherent in their derivation. Some of them were discussed previously⁶ in connection with the "special case", other are released in this general case.

1) The validity of the Arrhenius law in the range of experimental temperatures remains the basic precondition. In structural chemistry this law is mostly fulfilled, due to limited accuracy and limited temperature range accessible in solution kinetics. The validity is tested on the basis of the s_{00} value. Some remarks concerning the isokinetic relationship when the dependence of $\log k$ on T^{-1} is not linear, see⁴.

2) As shown previously⁶, temperature may be always considered as an exact quantity, free of error.

3) When the isokinetic relationship holds, the values e_{ij} may be identified with experimental errors. If their distribution is normal, the least squares method is fully justified, however, its application need not be confined to this case. The normal distribution of $\log k$ is a more natural assumption than a normal distribution of k , and it is usually preferred^{11,12}. Our model allows us to give each rate (equilibrium) constant a different weight, according to the accuracy of the pertinent experiment, as recommended especially by McBride and Villars¹³. However, according to our previous discussion⁶, it would be dangerous to give individual reactions different weights without very good reasons. In our opinion in most applications of the equations (5)–(13) the values of w_{ij} should depend only on j , i.e. the accuracy dependent only on temperature; in many applications the simplification $w_{ij} = 1$ will be most reasonable.

4) The computational procedure in this paper has been devised for a small computer, as shown in the Appendix, and is of advantage only in connection with this technique. Hence the accuracy of data and their number should be considered, whether they are worth this elaborate treatment. A preliminary graphic test⁵ by plotting $\log k_{2j}$ against $\log k_{1j}$ may be useful to decide whether the reaction series is homogenous or whether it should be divided into parts, or some reactions eliminated *etc.* In some cases it may be possible to transform the general case into the "special case" by completing 1–2 lacking data by extrapolation or interpolation, then a desk calculator is used for computation⁶. The results may differ only insignificantly from the exact treatment (Example 2).

The following examples were computed using the program outlined in the Appendix and show a complete treatment of a given reaction series and some typical results which may be obtained. They are arranged starting with the "special case" and typical normal examples up to less regular ones.

Example 1. Basic dissociation constants of twelve nitro- and polynitroanilines were measured¹⁴ in sulfuric acid, each at the temperatures 25, 40, 60, 80 and 90°C. Hence it is the "special case" which can be treated also using the explicit solution⁶. We used these data to test our computer program and we reproduce the results to show a regular case for comparison. There is an additional ground, that it is one of the best examples hitherto known of an exactly fulfilled isokinetic relationship.

Our calculations using formulae (6)–(13) with equal weights w_{ij} yielded the values $\beta = -1740^\circ\text{K}$, $y_0 = -1.817$ pK units, $s_0 = 0.089$, $s_{00} = 0.096$, $s_\infty = 0.241$, $s_S = 0.098$ pK units; s_x as function of x ($= T^{-1}$) is plotted in Fig. 3 by a full line, the dependence of y on x being shown by a dot-and-dash line. The unconstrained Arrhenius lines are shown on the same figure by light straight lines. This symbolism is maintained in the following diagrams, too. The value of s_{00} may be considered as the estimate of the experimental error; it is relatively large for these extremely weak bases and strongly affected by some 2–3 big errors. Since s_0 is lower than s_{00} , the isokinetic hypothesis must be accepted unconditionally, at any significance level. The same conclusion follows from Fig. 3 on the first inspection. Even so, the value of β is rather uncertain; if one allowed *e.g.* the error of 0.125 log units, (corresponding approximately to $\alpha = 0.01$), possible values of β would lie between -330 K and $-\infty$ or between $+2300$ K and $+\infty$. Hence, the hypothesis must be admitted that the reaction series is isoentropic; in fact it is not rejected even at $\alpha = 0.25$ according to the ratio of s_S and s_{00} . However, the series cannot be isoenthalpic according to the value of s_∞ (rejected at α much less than 0.005). The example shows once more the inaccuracy inherent in the value of β even when the validity of the isokinetic relationship is beyond any doubt.

Example 2. Kinetics of the proton transfer from nitromethane to anions of aliphatic and arylaliphatic carboxylic acids was studied⁹ in the whole for 19 acids, including 15 acids at the temperatures 15, 25, and 35°C, two at 10, 20, 30, and 40°C, and other two at 15, 20, 25, and 35°C. Estimation of the isokinetic temperature was attempted by the original authors using a principally incorrect method⁹ with the result $\beta = 102$ K. We have made two separate calculations according to formulae (6)–(13). In the first one weights have been introduced according to the reported standard errors of individual rate constants⁹, which varied strongly from 0.0006 to 0.086 log units with the median value of 0.0086. In this respect this example represents an exceptional case, the extreme values of weights being in the ratio 1:20 000. The calculation with weights yielded the results $\beta = -2820$ K, $y_0 = 12.841$ log units, $s_0 = 0.0077$, $s_{00} = 0.0043$, $s_\infty = 0.012$, $s_S = 0.0077$ log units, s_x as function of x is plotted in Fig. 4 with a full line. The value of s_{00} shows

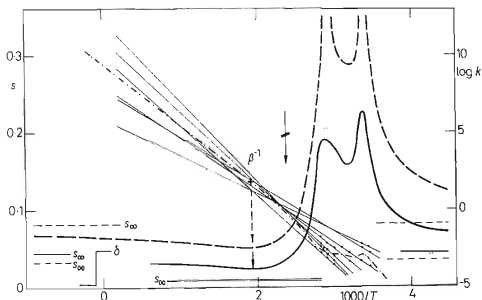


FIG. 5

Isokinetic Relationship for the Hydrolysis of Substituted 9-Chloroacridines^{15,16}

— With different weights, - - - with equal weights.

that less precise measurements have little influence on the overall accuracy, they are practically ruled out by their extremely low weights. The ratio of s_0 to s_{00} is significant even at the level $\alpha = 0.005$ (F -test used with an approximative validity). Hence the isokinetic hypothesis is to be rejected and so is, of course, also the particular case, the isoentropic hypothesis (according to the ratio of s_5 to s_{00} , F -test used rigorously). On the other hand the value of s_0 is still rather low when compared with other reaction series, so that one can speak about an approximate validity of the isokinetic relationship within given limits of accuracy, say 0.08 log units. The value of β has little significance when the isokinetic relationship does not hold; this is confirmed by attempting to construct its confidence interval. When *e.g.* the error of 0.012 log units is allowed, possible values of β are between 700 K and infinity, or any negative value. To conclude, the uneven precision combined with the narrow temperature interval does not allow more definite results.

The second calculation has been carried out with equal weights of all measurements and yielded rather different results $\beta = 640$ K, $y_0 = 4.148$ log units, $s_0 = 0.039$, $s_{00} = 0.023$, $s_{\infty} = 0.065$, $s_5 = 0.046$ log units, s_x as function of x is shown in Fig. 4 with a broken line. The large difference of the overall accuracy (s_{00}) against the first calculation is remarkable. It means that measurements denoted as less precise in fact deviated significantly from Arrhenius lines; their influence was suppressed by their low weights in the first case. The ratio of s_0 to s_{00} is significant at the level $\alpha = 0.005$, so that the isokinetic relationship is to be rejected as in the preceding calculation. The difference in β between the two calculations (the full and dashed arrows in Fig. 4) is unimportant when the isokinetic relationship does not hold. Note that relatively large differences between the two kinds of calculation are due to an extreme variability of weights. In fact the set of data is different in both cases since some points and one whole line are disqualified by their low weights. Sets of such uneven data are not convenient for processing, a better decision would be to disregard the least dependable ones completely.

In addition the third, approximate calculation was carried out according to the formulae of the explicit solution in the special case⁶. For this purpose two excessive measurements at 20°C were simply neglected and the data at 10, 20, 30 and 40°C (for two compounds) plotted in Arr-

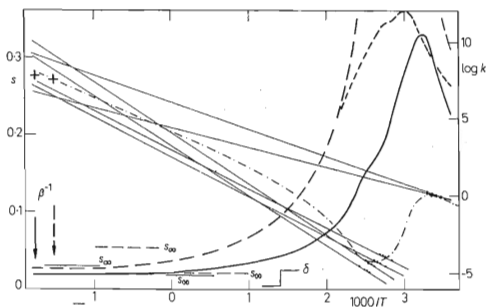


FIG. 6

Isokinetic Relationship for the Reaction of Chloro- and Bromo-nitronaphthalenes with Piperidine¹⁷

— With different weights, - - - - with equal weights.

henius graphs and replaced by the interpolated ones at 15, 25, and 35°C, accounting approximately even for the scatter. By this rather arbitrary procedure a homogenous set of 19×3 data was obtained and worked up on a desk calculator⁶ with the results $\beta = 622$ K, $y_0 = 3.916$ log units, $s_0 = 0.041$, $s_{00} = 0.024$, $s_\infty = 0.066$, $s_S = 0.047$ log units; the curve of s_x vs x (dotted line) differs little from the broken one in Fig. 4. The good agreement with the exact results thus makes even this crude approximation usable, particularly when the computer program is not available.

Example 3. The hydrolysis of 9-chloroacridine and its methyl-, methoxy-, and nitro-derivatives in all positions (altogether 13 compounds) in 80% acetic acid was kinetically studied^{15,16} at various temperatures in the range of 15–90°C; for an individual compound the temperature interval was between 10° to 40°. The value of $\beta = 417$ K was claimed^{15,16} (crossed arrow in Fig. 5). Fig. 5 also shows that the distribution of points is rather far from the regular "special case" and the computer treatment is thus inevitable. The first calculation has been carried out with unequal weights according the standard errors given^{15,16}, which again varied strongly from 0.0008 to 0.028 log units, but not so much as in the preceding example. We obtained the results $\beta = 516$ K, $y_0 = 1.584$ log units, $s_0 = 0.024$, $s_{00} = 0.009$, $s_\infty = 0.045$, $s_S = 0.034$ log units, s_x shown in Fig. 5 by the full curve. The whole pattern differs from previous examples by the double maximum on the s_x curve and by non-linear dependence of y on x (dot-and-dash line). However, these irregularities do not affect the region where the minimum is situated and cannot prevent its determining. The Arrhenius law is valid within the experimental error; again the most inaccurate result does not affect the accuracy. The isokinetic hypothesis is rejected at $\alpha = 0.005$ according to the ratio of s_0 to s_{00} . The value of β is unimportant when the isokinetic relationship does not hold.

A recalculation with equal weights yielded a similar qualitative picture, but a significantly lowered accuracy: $\beta = 518$ K, $y_0 = 1.800$ log units, $s_0 = 0.052$, $s_{00} = 0.032$, $s_\infty = 0.082$, $s_S = 0.065$ log units, s_x shown by the dashed curve in Fig. 5. The difference in s_{00} between the two calculations is clearly again caused by some imprecise measurements, which are disqualified by their low weights. The extreme values of weights are now in the ratio 1 : 1200; due to small number of points on one line, some lines are completely depreciated. Nevertheless the values

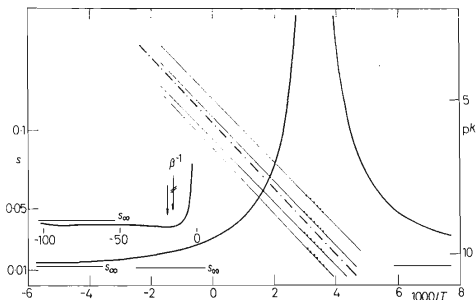


FIG. 7

Isoequilibrium Relationship for the Dissociation of *meta*-Substituted Phenols¹⁸

The remote part of the curve is shown separately on the left on a smaller scale.

of β and the whole pattern are rather similar, they seem not to be affected by several gross errors. Another difference is that the isokinetic relationship is now rejected only at the 0.05 level according to the s_0 to s_{00} ratio; it would be, however, accepted at any lower α . For β even a confidence interval, although a broad one, may be constructed. *E.g.* for the error of 0.06 log units it would extend from 435 to 1160 K. The final decision is thus affected by gross errors in this sense that these mask smaller systematic deviations and do not allow significant rejecting of the isokinetic hypothesis.

Example 4. The nucleophilic substitution of nitro-substituted chloro- and bromonaphthalenes with piperidine in benzene was followed¹⁷ at different temperatures (between 10 to 140°C) due to different reactivity, each reaction only in the interval of 15–20°. The standard errors of individual rate constants vary less than in the previous examples, *i.e.* from 0.0013 to 0.026 log units, nevertheless the extreme values of weights are thus in the ratio 1 : 400. Hence the difference is not so striking between the two calculations with and without weights. In the first case, with unequal weights, we obtained the results $\beta = -569$ K, $y_0 = 7.702$ log units, $s_0 = 0.018$, $s_{00} = 0.018$, $s_{\infty} = 0.029$, $s_s = 0.022$ log units, s_x shown as a function of x by the full curve in Fig. 6. Since the distribution of points is again rather irregular, the whole pattern differs from the "special case"; characteristic is the double maximum of the s_x -curve (shown on a different scale) and the non-linear y -curve (dot-and-dash). The isokinetic hypothesis is to be accepted unconditionally ($s_0 < s_{00}$), even the isoentropic one is rejected only at $\alpha = 0.10$, *i.e.* also admitted. Fig. 6 also reveals that any confidence interval of β would be very broad, including high positive and almost all negative values.

The second calculation, with equal weights, yielded the results: $\beta = -659$ K, $y_0 = 7.470$ log units, $s_0 = 0.025$, $s_{00} = 0.020$, $s_{\infty} = 0.054$, $s_s = 0.035$ log units, s_x shown by a broken line in Fig. 6. The small difference of s_{00} of the two calculations suggest that there are no gross errors (with low weights) within the measurements. There is also no striking difference between the two values of the isokinetic temperature. The isokinetic hypothesis is still accepted (it would be rejected only at $\alpha = 0.10$) but the isoentropic one is rejected more significantly (at $\alpha = 0.01$). In agreement the confidence interval of β is somewhat closer than in the first calculation (Fig. 6)

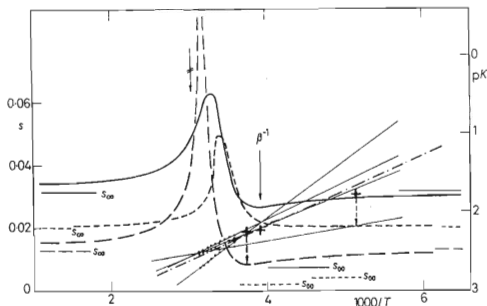


Fig. 8

Isoequilibrium Relationship for the Dissociation of Substituted Cyanoacetic Acids¹⁹

The full line corresponds to the whole temperature interval, broken lines to its two halves.

even when still rather broad. To conclude it should be pointed out that the basic set of data is rather inhomogenous and arose by mixing two subgroups of compounds with very different reactivities. Such sets cannot be recommended for significant testing of the isokinetic relationships and the results obtained must be judged cautiously.

Example 5. Dissociation constants of four 3-substituted phenols were measured¹⁸ in water at the temperatures between 5 and 50°C, or between 5–60°C, increasing by 5°C. The isokinetic temperature $\beta = -69$ K was claimed¹⁸ (the crossed arrow in Fig. 7). Since there is little difference in temperatures for individual reactions, the overall pattern is almost regular, the numerical data obtained being $\beta = -52$ K, $y_0 = -14.686$ pK, $s_0 = 0.0117$, $s_{00} = 0.0108$, $s_\infty = 0.0126$, $s_g = 0.030$ log units. In the original literature, the data were worked up by a non-linear equation, whereas our treatment was restricted to linear Arrhenius law. Even so, the value of s_{00} reveals a quite satisfactory accuracy. The isokinetic relationship cannot be rejected even at $\alpha = 0.25$. However, any reasonable confidence interval for β cannot be constructed, as it follows at the first inspection from Fig. 7. *E.g.* for the error 0.016 log units (corresponding approximately to $\alpha = 0.01$ based on s_0) this interval would be -250 – 50 K, including thus the isenthalpic hypothesis $\beta = 0$. In addition Fig. 7, particularly the remote part of the curve, pictured on the left on a changed scale, reveals that there are several local minima and the right one is not easy to find. Hence the only reasonable decision is to consider this reaction series to be isenthalpic, in fact this hypothesis can be rejected only at $\alpha = 0.25$ but not at $\alpha = 0.1$. The isoentropic hypothesis is rejected safely ($\alpha \ll 0.005$).

Example 6. Dissociation constants of cyanoacetic acid and three its derivatives were measured very accurately¹⁹ at nine temperatures increasing by 5° from 5° to 45°C. The results were processed by a non-linear equation for the temperature dependence and an isokinetic relationships was found by a wrong procedure with β somewhat dependent on temperature, *viz.* 322–328 K. Our calculations yielded the results $\beta = 259$ K, $y_0 = 2.237$ pK units, $s_0 = 0.027$, $s_{00} = 0.007$, $s_\infty = 0.032$, $s_g = 0.033$ log units. The value of s_{00} confirms the accuracy of the measurements and approximate validity even of the linear relationships. Any isokinetic relationships is clearly non-existent, it could be rejected at α much less than 0.005. The curve in Fig. 8 is characteristic by its low maximum (due to small differences of reactivity between individual compounds) and flat but high situated minimum. This finding is in no connection with the non-linear temperature dependence since essentially the same results are obtained, when dividing the data into two halves, those at higher and lower temperatures (dashed curves in Fig. 8). The two pertinent isokinetic temperatures differ significantly (dashed arrows) but the comparison of s_0 with s_{00} yields the same results as formerly. This example shows once more, that improper statistical treatment can produce results which completely disagree with original experimental data; the crossed arrow, corresponding to the erroneous values¹⁹ of β , is situated near the maximum of the curve. The original data are again inhomogenous and not suitable for isokinetic investigations since the reactivity of one compound is quite different from the others.

DISCUSSION

Along the lines given in the preceding section we have analyzed further reaction series where data of sufficient quality and quantity were available. The results in principle confirmed out previous views⁶ as to the nature and significance of the isokinetic relationship, so that relatively little can be added to the discussion.

In the following we summarize, what kind of information can be obtained from such analysis and particularly from individual numerical quantities.

The value of s_{00} may either represent an estimate of the experimental error or the deviation from the Arrhenius law. A decision is possible by comparing with another estimate of the former, obtained *e.g.* from fits to a particular kinetic equation or from repeated experiments. We believe that the Arrhenius equation is sufficient for most routine work in solution kinetics, or, at least, the effort connected with a more elaborate treatment^{1,20,21} is usually not proportionate to the improvement achieved. Hence, we regard s_{00} in most cases as an estimate of the experimental error, and in this function it is in our opinion more reliable than separate estimates from individual kinetics runs. For this reason we do not recommend⁶ to put individual rate constants⁸ into equations (6)–(13) with different weights, unless significant differences in their accuracy have been proved, *e.h.* by the *F*-test. Examples 4 and even 3 show that including of weights sometimes does not alter the final results significantly; when it does, a gross error can be suspected. Then the effort of the experimenter must be directed to bring all the measurements to the same level of accuracy. Very low weights in fact eliminate the pertinent data from the computation.

In the other case, when s_{00} and δ differ significantly, the former represents deviation from the Arrhenius equation and our whole treatment is not exactly applicable. Either the temperature interval must be divided (Example 6), or, if the accuracy of data allows, a more general treatment²² with temperature variable activation parameters can be attempted.

The values of s_0 represents the most important result and its comparison with s_{00} is the clue to the whole analysis. Although the *F*-test may not be used rigorously to this purpose, a qualitative comparison is usually sufficient. The result can either be that the isokinetic hypothesis is rejected, or, that it cannot be rejected on the basis of the available data.

In the latter case there are two possible explanations: Either the isokinetic relationship is in fact valid, or it is not, but the data are not sufficient for proving it. Possible reason may be the low accuracy of individual rate constants, small number of data, insufficient differences in reactivity between individual reactions, or a narrow temperature interval; particularly the last factor is usually the limiting one and often invalidates otherwise ample and careful work.

Having in mind the approximate character of the isokinetic relationship, we must understand the term of its validity in a quantitative sense, *i.e.* within the limits of a given accuracy and in a given temperature interval. The comparison with s_{00} need not be the only criterion, since the experimental accuracy can be in principle always improved and finally almost any isokinetic relationship could be disproved. While the ratio s_0/s_{00} gives answer to the question, whether the relationship is valid with respect to the attained experimental accuracy, one can ask another question, whether it is approximately valid with respect to requirements and usual accuracy of other extrathermodynamic relationships. Then one can choose an arbitrary value of standard deviation and speak about the validity of the isokinetic relationship within

this accuracy (Example 2). We hope to return to this fundamental question once more.

The dependence of s_x on x is a much telling result, particularly when combined with the Arrhenius plot and plot of y vs x . In a graph of this type (Figs 3-8) the value of s_0 is included, of course. The graph enables us to control the remaining results and, when there are several minima on the curve, to identify the absolute one. In addition the shape of the curve gives a general idea about the validity of the isokinetic relationship and reliability of the results obtained. A very irregular pattern (like Fig. 2, or Fig. 6) does not allow to define the temperature range in which the isokinetic relationship holds; such extreme cases should be disregarded. On the other hand very flat plain curves (Fig. 7 of ref.⁶ or Fig. 8 of this paper) are usually due to a too narrow temperature interval, or small differences in reactivity and do not allow any more definite conclusion.

Referring to the postulates of the preceding paragraphs we may summarize that the validity of the isokinetic relationship should be examined in a temperature interval not too narrow (with respect to the accuracy) and not too large (with respect to the limited validity), and all the reactions should be studied at nearly the same temperatures ("regular" pattern). The validity of the isokinetic relationship, when proved, is always restricted to the temperature interval studied; of course such a limitation holds for many concepts of theoretical chemistry.

Among the values of s_x there are two of particular interest: s_∞ at $T = 0$ and s_g at $T \rightarrow \infty$. They enable us to test, whether the reaction series may be isenthalpic or isoentropic, respectively. Particularly s_∞ should be ever compared with s_{00} , and when the difference is not significant, the isenthalpic hypothesis is accepted and preferred to any other value of β (Example 5). Of course, an apparently isenthalpic reaction series is found always when the data are inaccurate or temperature interval too narrow. The result should be then formulated that the poor information does not allow to reject any hypothesis, hence neither the isokinetic one. The isoentropic reaction series seem to be less common, much less than it was formerly supposed⁴.

The isokinetic temperature β is a characteristic constant, usually attributed a much more importance than it in fact has. Our mathematical procedure always yields a single value of β , even when the isokinetic relationship does not hold at all, or, on the other hand, when possible values of β lying in a broad interval must be admitted. Such values have a purely mathematical meaning of course. Let us still remember that negative values are quite often (Examples 1, 4, 5) and that high values are loaded with a large error since the reciprocal is primarily determined. For this reason the quantity $\gamma = \beta^{-1}$ would be more objective and less misleading as to its physical meaning, however, this symbol has been also used in another sense⁴.

It follows that an interval estimate of β would be of much value, it is, however, very difficult to give its general definition. The graph s_x vs x allows to determine the confidence interval for β provided that a value of the permissible standard de-

viation is given. It is usually estimated on the basis of s_{00} (or δ) and a chosen α , but when s_0 is significantly higher than s_{00} , a narrow interval for β is obtained, simulating a high precision. Instead, the correct interpretation would be that the isokinetic relationship is probably invalid, or, if valid, only values of β in a narrow interval are permissible. An alternative estimate of the confidence interval of β , based on s_0 and a certain α , would characterize the shape of the curve near its minimum, irrespective of the validity of the isokinetic relationship. This is a valuable information in itself, however, it can give a wrong idea if the isokinetic relationship is invalid. Thus the only unambiguous statement is a confidence interval together with a corresponding permissible standard deviation and the main result of the discussion is that the meaning of β should not be overestimated and attention focused rather to the values s_0 , s_{00} , s_x , and to the question whether the isokinetic relationship can be rejected or not.

APPENDIX

Computation according to the equations (6)–(13) was programmed for the small digital computer Odra 1013 in the autocode Most-1. In the input the following data are given: The starting value of x ($= T^{-1}$), length of the step in x , number of steps, accuracy in finding S_0 , number of reactions (l), number of points in each reaction (m_i), set of data temperature - rate (equilibrium) constant - its error. Temperature may be given in °C or in reciprocal K, rate (in s^{-1} or in $\text{mol}^{-1} \cdot \text{l s}^{-1}$) or equilibrium constants either as k or $\log k$, errors in $\pm \delta k$ or in $\pm \delta \log k$; the program is modified with buttons as the case may be. With another button, rate and equilibrium data are distinguished.

In the output we obtain sets of values x , y , S_x , s_x for each step, computed according to the equations (6)–(9), in addition S_∞ , s_∞ , S_{00} , s_{00} according to the equations (12) and (11). Then the minimum of S_x is found by successive halving of the appropriate interval of x with the programmed accuracy and the values x_0 , y_0 , S_0 , s_0 , β in K and in °C, are printed, in addition b_i for each line and b_∞ according to the equations (7) and (13), respectively. If there is no minimum within the interval investigated, this statement is printed instead of the numerical values and the program continued. Further the unconstrained parameters are printed for each reaction, *i.e.* ΔH^0 and ΔS^0 in the case of equilibrium and E^* , $\log A$, ΔH^\ddagger and ΔS^\ddagger in the case of kinetics. Finally the same parameters appear constrained by the isokinetic condition, *i.e.* the so-called isokinetic parameters⁵. When no minimum has been found, these parameters are computed assuming an isoenthalpic series, *i.e.* from the value b_∞ for all the reactions. Of course the reaction series need not to be in fact isoenthalpic, it may happen that the minimum escapes due to the improperly chosen interval of computation. In this case the procedure is to be repeated with changed values of starting parameters.

We recommend to combine the computation with the graphical representation like Figs 3–8. It enables one to correct the interval investigated, if necessary, to discern the isoenthalpic series *etc.* In most series the interval from $x = -0.002$ to $x = 0.005$ (corresponding to -500 and $+200$ K respectively), is sufficient, a convenient step width is 0.0002.

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LIST OF SYMBOLS

A	preexponential factor
$b_i, b_{i,0}, b_{i,x}$	slopes of the Arrhenius lines (isokinetic, unconstrained, constrained, isenthalpic, isentropic)
$b_{\infty}, b_{i,S}$	isenthalpic, isentropic
e_{ij}	random variable (error)
e_0	intercept in the equation (1a)
E^*	Arrhenius activation energy
f	degrees of freedom
h_0	intercept in the equations (1b) and (1c)
ΔH	symbol for the activation or reaction enthalpy
ΔH^0	reaction enthalpy
ΔH^\ddagger	activation enthalpy
ΔH_{iso}	isokinetic enthalpy (of activation or reaction)
i	index pertinent to a straight line (reaction)
j	index pertinent to a point (temperature)
k	symbol for rate or equilibrium constant
l	number of straight lines (reactions)
m_i	number of points on the i -th line
s_0, s_{00}, s_x	standard deviations (isokinetic, unconstrained, constrained, isenthalpic, isentropic)
s_{∞}, s_S	isenthalpic, isentropic
S_0, S_{00}, S_x	residual sums of squares (isokinetic, unconstrained, constrained, isenthalpic, isentropic)
S_{∞}, S_S	isenthalpic, isentropic
ΔS	symbol for activation or reaction entropy
ΔS^0	reaction entropy
ΔS^\ddagger	activation entropy
ΔS_{iso}	isokinetic entropy (of activation or reaction)
w_{ij}	weight of a measurement
x_{ij}	independent variable ($= T^{-1}$)
x, x_0	abscissa of the point of intersection (supposed or actual)
X_i	auxiliary function defined by Eq. (8)
y_{ij}	dependent variable ($= \log k$)
y, y_0	ordinate of the point of intersection (supposed or actual)
α	significance level
β	isokinetic temperature
γ	reciprocal value of β
δ	experimental error
σ_{ij}^2	variance of the variable e_{ij}

Note added in proof: The whole computation, as well as the simpler procedure in the special case⁶, have been also programmed for the Hewlett-Packard calculator 9820 A. Programs are available on request and will be submitted to the H. P. Users Club.

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