

# STATISTICS OF THE ENTHALPY-ENTROPY RELATIONSHIP. I. THE SPECIAL CASE\*

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The relationship between activation energies and activation entropies in a series of related reactions presents difficult problems of a statistical nature, particularly the task of estimating its slope — the so-called isokinetic temperature  $\beta$ . In this paper the problem is formulated generally in the framework of the least squares method and solved explicitly for a special, but often observed case when all the reactions have been followed at corresponding temperatures. In addition to the estimate of  $\beta$ , the residual sums of squares are given enabling one to decide whether the isokinetic relationship is fulfilled or not; finally the reliability interval of  $\beta$  is estimated. In many practical examples  $\beta$  is estimated with a great uncertainty, hence its numerical value cannot be given any significance; the attention should be focused on the finding that the existence of an isokinetic relationship can be accepted as a hypothesis or that it can be disproved.

The linear relation between activation parameters in a series of related reactions is called the isokinetic relationship or compensation law; it is of fundamental importance in kinetics and in reactivity studies<sup>1-4</sup>. If it holds in a given series, the interpretation of reactivity retains its validity even when the temperature is changed; if it does not hold, any interpretation in temperature independent terms, as inductive and mesomeric effects, strain of rings *etc.*, is strictly speaking not allowed. The relationship can either connect the Arrhenius activation energy  $E^*$  and the preexponential factor  $A$  (1a), or the activation enthalpy  $\Delta H^\ddagger$  and activation entropy  $\Delta S^\ddagger$  (1b). Since there is no significant difference between the Arrhenius theory and the theory of the activated complex in the limits of common accuracy, we shall regard both formulations as equivalent.

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

The proportionality constant  $\beta$  is called the isokinetic temperature and represents the temperature at which all the reactions of the series proceed at the same rate<sup>1-4</sup>; the intercepts  $e_0$  and  $h_0$  are usually not attributed to any physical meaning.

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A similar relationship in thermodynamics (*Ic*), *i.e.* between the reaction enthalpy  $\Delta H^0$  and standard reaction entropy  $\Delta S^0$ , can be called the isoequilibrium relationship<sup>4</sup> but is usually included under the term isokinetic relationship, too.

$$\Delta H^0 = h_0 + \beta \Delta S^0, \quad (Ic)$$

In this paper we shall discriminate neither this equation and the quantities  $\Delta H$  and  $\Delta S$  without superscript will be used, relating either to kinetics or to thermodynamics as the case may be. Similarly the symbol  $k$  will denote either the rate or equilibrium constant.

Equations (*Ia-c*), as simple as they are, impose serious problems of statistical nature when they shall be experimentally verified and the values of coefficients estimated. It is because the two variables involved are usually loaded with considerable experimental error and — what is still more important — always mutually dependent.\* Particularly the simple plotting of  $\Delta H$  against  $\Delta S$  or the regression analysis in these coordinates are completely wrong procedures since the results obtained need not comply with the original kinetic data<sup>5,6</sup>. We showed previously by a theoretical analysis and on numerous examples that particularly the slopes obtained are erroneous and that the accuracy of fit, expressed *e.g.* by the correlation coefficient is overestimated<sup>5</sup>. At the same time we suggested a simple and statistically correct procedure which consists in plotting the logarithms of rate constants at two temperatures\*\* ( $T_2 > T_1$ ) against each other according to the equation

$$\log k_2 = a + b \log k_1, \quad (2)$$

From the graphically estimated slope  $b$ , the isokinetic temperature  $\beta$  is readily obtained<sup>5,8</sup>.

$$\beta = T_1 T_2 (b - 1) / (b T_2 - T_1). \quad (3)$$

The whole procedure can be described in terms of geometry as a coordinate transformation (affinity); its essential feature is that the original line is drawn in independent coordinates. The method has been applied several times to kinetic data<sup>9,10</sup>, however, it has the shortcoming that it is simply applicable to measurement at two temperatures only. In a more general case it is possible to construct an Arrhenius plot for each reaction of the series and to choose on it two smoothed values of  $\log k$  at fixed temperatures<sup>11</sup>, however, this procedure lacks simplicity. Alternatively part of the data remains simply not utilized, or the calculation was made for all available couples of temperatures<sup>9</sup>. The last approach is unpractical, of course, and gives no correct possibility to choose the most probable value among a lot of results. Other procedures have been advanced, no one of which is completely correct from the statistical point of view. An indirect determination is possible if a kind of linear free energy relationship holds for the given reaction series<sup>7,9,12</sup>. Then  $\beta$  can be calculated from the temperature dependence of the reaction constant  $g$ , however, it makes the result dependent on the values of constants  $\sigma$  and on the accuracy of correlation. Another procedure<sup>12</sup> is based on the multiple regression of the dependent variable

\* The only exception arises with the equation (*Ic*) when  $\Delta H^0$  has been directly determined by calorimetry<sup>1</sup>.

\*\* The original denotation by indexes<sup>5</sup> has been now interchanged in order to reach agreement with other references<sup>1,7,8</sup>.

$\log k_{ij}$  and independent variables  $\log k_{i1}$ ,  $T_j^{-1}$  and  $T_j^{-1} \log k_{i1}$ . This method has the shortcoming that an arbitrary temperature  $T_1$  and corresponding values  $k_1$  are given a special significance, thereby not weighing all measurements equally; in addition there is a principal defect that statistical estimates are used further to make new estimates.

With respect to the general meaning of the isokinetic relationship, we have tried in this paper to solve the problem in a statistically unobjectionable manner. Although an absolute mathematic accuracy is not claimed, attention is paid rigorously to the formulation of the model considered, so that in practical examples a decision should be possible whether the assumptions apply. With this provision the results enable one to obtain the best estimates of the isokinetic temperature, of the intercepts in equations (1a-c), and of the enthalpies and entropies under the isokinetic constraint; finally a decision is possible if the isokinetic hypothesis can be rejected on the basis of experiments or not.

### THEORETICAL

The formulation of the problem is based on the most general representation of the isokinetic relationship in the coordinates  $\log k$  vs  $T^{-1}$  (Fig. 1). The significance of this picture was advocated particularly by Petersen<sup>6</sup> and Malawski<sup>13</sup>, although it was known already to Schwab<sup>14</sup> and Gapon<sup>15</sup> with all its consequences. If the Arrhenius law holds for a given reaction, the corresponding points are situated on a straight line; if the isokinetic relationship holds, all the lines intersect in one point with the coordinates  $\beta^{-1}$  and  $-e_0/2.303R\beta$ .

Let us formulate the problem in the following way; its applicability to real systems will be discussed in the next section. In the coordinates  $x \equiv T^{-1}$  and  $y \equiv \log k$  a family of  $l$  straight lines is given ( $l \geq 3$ ) with the slopes  $b_i$  ( $i = 1, 2, \dots, l$ ) and with a common point of intersection ( $x_0, y_0$ ). The  $i$ th line is determined by  $m_i$  points ( $m_i \geq 2$ ) with coordinates  $(x_{ij}, y'_{ij})$  where  $j = 1, 2, \dots, m_i$ . Instead of true coordinates

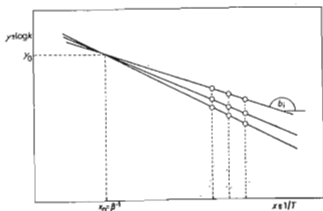


FIG. 1  
Representation of the Isokinetic Relationship in the Coordinates  $\log k$  vs  $T^{-1}$

$y'_{ij}$  only the values  $y_{ij} = y'_{ij} + e_{ij}$  are available, where  $e_{ij}$  are random variables with zero average values and a constant variance  $\sigma^2$ . The task is to estimate the parameters  $x_0 (= \beta^{-1})$ ,  $y_0 (= -e_0/2 \cdot 303R\beta)$ ,  $b_i$  and  $\sigma$ . In the framework of the least squares method the basic condition reads

$$\sum_{ij} [y_{ij} - y_0 - b_i(x_{ij} - x_0)]^2 = \min. \quad (4)$$

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

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

where  $x_{i.}$  stands for  $\sum_j x_{ij} / m_i$ ,  $y_{i.} = \sum_j y_{ij} / m_i$  and  $y_{..} = \sum_j y_{ij} / \sum_i m_i$ .

This system of  $l + 2$  equations is non-linear and for this reason probably has not received attention in the treatises of the least squares method<sup>16,\*</sup>. An explicit solution can be obtained easily in the special case when  $x_{ij} = x_j$  and  $m_i = m$  for all values of  $i$ ; this means that all reactions of the series were kinetically followed at the same set of temperatures (nor necessarily equidistant, only the same for all reactions). It is this special case to which this paper is confined, a more general case being reserved for a later publication<sup>17</sup>. The problem can easily be formulated still more generally with variances  $\sigma_{ij}$  changing from one point to another, *i.e.* with different weights attributed to individual points<sup>17</sup>.

To solve explicitly the special case outlined let us still introduce

$$p_i = \sum_j x_j y_{ij} / m - \bar{x} y_i, \quad (6)$$

where  $\bar{x}$  is the mean value of  $x$ . The searched estimate  $\hat{x}_0$  is obtained, by solving the equations (5), in the form

$$\hat{x}_0 = u_0 + \bar{x} = u_0 + \sum_j x_j / m, \quad (7)$$

where  $u_0$  is a root of the quadratic equation

\* Quite recently Thorn has derived essentially identical set of normal equations, when analysing the vapor pressure-temperature dependence<sup>18</sup>; he did not deal with its solution.

$$\begin{aligned}
 & -u^2 \sum_i (p_i - \bar{p})(y_i - y_{..}) + u[\sum_i (p_i - \bar{p})^2 - \frac{1}{m} \sum_j (x_j - \bar{x})^2 \sum_i (y_i - y_{..})^2] + \\
 & + \frac{1}{m} \sum_j (x_j - \bar{x})^2 \sum_i (p_i - \bar{p})(y_i - y_{..}) = 0. \quad (8)
 \end{aligned}$$

This equation has two real solutions except an unrealistic degenerate case, when the coefficient at  $u^2$  equals zero. From the two real roots this one corresponds to the minimum sum of squares, *i.e.* to the searched value  $x_0 = \beta^{-1}$  which is computed with a positive sign at the square root [cf. Eq. (12)]. When  $u_0$  is once found,  $\hat{y}_0$  and  $\hat{b}_i$  are given by the equations

$$\hat{y}_0 = y_{..} + (u_0 m \sum_i p_i) / [l \sum_j (x_j - \bar{x})^2], \quad (9)$$

$$\hat{b}_i = [p_i + u_0(\hat{y}_0 - y_i)] / [u_0^2 + \frac{1}{m} \sum_j (x_j - \bar{x})^2]. \quad (10)$$

Clearly  $b_i$  is different from the slope  $b_{i,0}$  of the  $i$ th regression line computed without the constraint of a common point of intersection. It is given according to common formulae of linear regression<sup>19</sup> as

$$b_{i,0} = m p_i / \sum_j (x_j - \bar{x})^2. \quad (11)$$

Further the residual sum of squares  $S_0$  is given by the equation

$$S_0 = \sum_{ij} (y_{ij} - y_{..})^2 - m^2 [\sum_i p_i^2 - u_0 \sum_i (p_i - \bar{p})(y_i - y_{..})] / \sum_j (x_j - \bar{x})^2 \quad (12)$$

and has  $f = (m - 1) l - 2$  degrees of freedom; accordingly the corresponding standard deviation  $s_0$  can serve as an estimate of  $\sigma$ . In addition  $S_0$  may be compared to the sum of squares  $S_{00}$  computed from the free regression lines without the constraint of a common point of intersection.  $S_{00}$  is given by the usual formula of linear regression<sup>19</sup>, which reads in the symbols introduced

$$S_{00} = \sum_{ij} y_{ij}^2 - m \sum_i y_i^2 - m^2 (\sum_i p_i^2) / \sum_j (x_j - \bar{x})^2 \quad (13)$$

with  $f = (m - 2) l$  degrees of freedom. Of course  $S_0$  is always larger or at most equal to  $S_{00}$  since the relation holds:

$$\sum_i (y_i - y_{..})^2 \sum_i (p_i - \bar{p})^2 \geq [\sum_i (p_i - \bar{p})(y_i - y_{..})]^2. \quad (14)$$

The equality represents the special case when all the unconstrained regression lines intersect in one point. It is of course identically fulfilled for  $l = 2$  when there are only two lines. Usually  $S_0$  is distinctly larger than  $S_{00}$ . By comparing the corresponding standard deviations  $s_0$  and  $s_{00}$  with an estimate of the experimental error  $\delta$  the following conclusions can be drawn. If  $s_{00}$  is not significantly larger than  $\delta$ , the Arrhenius equation is valid within experimental errors. (If it is significantly smaller, probably the experimental error has been overestimated). If  $s_0$  is not significantly larger than  $s_{00}$ , the hypothesis of a common point of intersection cannot be rejected. (A point of intersection at an infinite distance is included into the hypothesis). Quite rigorously the F-test must not be applied to  $S_0$  ( $s_0$ ) since the problem is not linear. However, even a qualitative comparison of  $s_0$ ,  $s_{00}$ , and  $\delta$  may be sufficient in most instances; in such qualitative manner the F-test is referred to in later examples.

In the past the value of  $\beta$  was determined erroneously as the slope in the graph  $\Delta H$  vs  $\Delta S$  (cf. <sup>2-4,7</sup>). This procedure has been already criticized in the special case of measurement at two temperatures<sup>5</sup>; now we can show generally that it yields wrong values of  $\beta$ . The relative enthalpy for each reaction is proportional to the negative slope  $b_{i,0}$  of the corresponding line, see equation (11); the relative entropy is proportional to the intercept of this line, i.e. to  $y_i - \bar{x}b_{i,0}$ . The regression coefficient  $\beta^*$  of these two variables is, according to common regression formula<sup>19</sup>, given by the equation:

$$\frac{1}{\beta^*} = \bar{x} - \frac{\bar{x} \sum_j (x_j - \bar{x})^2 \sum_i (p_i - \bar{p}) (y_i - y_{..}) - (1/m) [\sum_j (x_j - \bar{x})^2 \sum_i (y_i - y_{..})^2]}{\bar{x}m \sum_i (p_i - \bar{p})^2 - \sum_j (x_j - \bar{x})^2 \sum_i (p_i - \bar{p}) (y_i - y_{..})} \quad (15)$$

This expression is different from the right values  $\beta^{-1} = x_0$ , given by equations (7) and (8). Both expressions give the same result only in the special (unrealistic) case when relation (14) holds as the equality. In this case also  $b_i$  equals  $b_{i,0}$  for each line.

Finally a confidence interval for  $u_0(x_0)$  can be constructed by the following procedure. Let us solve from the beginning a similar but easier problem in which the abscissa of the common point of intersection is known and denoted  $x_l = \bar{x} + u$ . The task is to estimate its ordinate  $y_u$  and the slopes  $b_{i,u}$  and to calculate the residual sum of squares  $S_u$ . Similarly as in the more general problem we get for  $y_u$  and  $b_{i,u}$  the equations identical with (9) and (10) with  $u$  instead of  $u_0$ , and  $S_u$  is given as

$$S_u = \sum_{ij} (y_{ij} - y_{..})^2 - \frac{\sum_i p_i^2 - 2u \sum_i (p_i - \bar{p}) (y_i - y_{..}) + u^2 [\sum_i (y_i - y_{..})^2 + (m/l) (\sum_i p_i)^2 / \sum_j (x_j - \bar{x})^2]}{\sum_j (x_j - \bar{x})^2 + mu^2} \quad (16)$$

with  $f = (m - 1)l - 1$  degrees of freedom.

By substituting  $u_0$  for  $u$  into (16) we get  $S_u = S_0$ , of course; *vice versa* from the condition  $S_u = S_0$  it follows  $u = u_0$ .

The calculation of  $S_u$  can be repeated for various values of  $u$  and  $S_u$ , or  $s_u$  represented as a function of  $u$ . Generally it is a rational curve of the third degree with a horizontal asymptote given by the value  $S_\infty$

$$S_\infty = \sum_{ij} y_{ij}^2 - m \sum_i y_i^2 - (m^2/l) (\sum_i p_i)^2 / \sum_j (x_j - \bar{x})^2. \quad (17)$$

Of course by taking the derivative of equation (16) with respect to  $u$ , the same value for the extremes is obtained as given by the equation (8). Hence the function has one maximum and one minimum given by the two roots of equation (8) and in addition three inflexions. A typical form is given in Fig. 2; a sharp maximum and flat minimum are characteristic. If one now chooses a fixed value of  $s_u$  as an admissible limit, one obtains the confidence interval of  $\beta$  from the graph.

On the other hand the functional dependence of  $y_u$  on  $u$  is simply a straight line according to the equation (9); its slope  $b_\infty$  is given by

$$b_\infty = (m/l) \sum_i p_i / \sum_j (x_j - \bar{x})^2. \quad (18)$$

The values of  $b_\infty$  and  $S_\infty$  represent the solution of a further particular problem, *i.e.* to draw parallel lines through a given set of points; this problem corresponds to an isenthalpic reaction series.

A graph like Fig. 2 and the following ones, in real examples (Figs 3–6) represents the ultimate result of the analysis since it enables one not only to read off the most probable value of  $\beta$ , but also to visualize its confidence interval. It may happen, and in fact does quite often, that the isokinetic hypothesis itself cannot be rejected while the isokinetic temperature  $\beta$  cannot be given any more definite value.

Concluding the mathematical analysis we shall discuss several special degenerate cases. Since they cannot occur practically in real chemical examples, they will be mentioned only briefly and in this point the present analysis remains uncomplete. All the cases considered are characterized by the condition

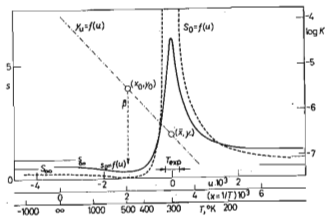


FIG. 2

Dependence of the Residual Sum of Squares  $S_u$  and the Corresponding Standard Deviation  $s_u$  on the Supposed Isokinetic Temperature  $x^{-1}$  (real example<sup>24</sup>)

$$\sum_i (p_i - \bar{p})(y_{i.} - y_{..}) = 0, \quad (19)$$

which reduces the quadratic equation (8) to a linear one with the only root  $u = 0$ . At the same time the function  $S_u = f(u)$  in equation (16) is simplified and has only one extreme or it is even linear with no extreme. It depends on the value of the expression

$$m \sum_i (p_i - \bar{p})^2 - \sum_j (x_j - \bar{x})^2 \sum_i (y_{i.} - y_{..})^2 \cong 0. \quad (20)$$

1. If this is negative,  $S_u$  is an even function of  $u$  with a maximum at  $u = 0$  and a horizontal asymptote,  $u_0$  as well as  $y_0$  lie at infinity,  $S_0$  equals  $S_\infty$ , and all  $b_i$  equal  $b_\infty$ . This is the representation of an isoenthalpic series. If still  $\sum_i p_i$  equals zero, all the lines are horizontal with  $b_i = b_\infty = 0$ , corresponding to the series with a zero enthalpy. 2. If the expression (20) is positive,  $S_u$  is an even function of  $u$  with a minimum at  $u = 0$  and a horizontal asymptote,  $S_0 < S_\infty$ . Except the symmetry this case gives a normal picture. 3. If the expression (20) equals zero,  $S_u$  is constant for all values of  $u$  and equals  $S_0$  as well as  $S_\infty$ . Any value of  $u$  complies with the equation (8) and no isokinetic temperature exists. All these cases are only of theoretical interest since in practice the critical expressions can never be exactly equal to zero.

Previously we suggested a simple method<sup>5</sup>, limited to measurements at two temperatures, whereby one estimates  $\beta$  using the equations (2) and (3). The last task of the present analysis is to show that this procedure is, in its range of validity, essentially equivalent to that one developed here. The first step is to estimate the slope  $b$  of the regression equation (2) in the coordinates  $\log k_1 \equiv y_{i1}$  and  $\log k_2 \equiv y_{i2}$ . The common regression procedure is inadequate, although it has been applied<sup>9</sup>, since both variables are equally loaded with errors. A suitable regression minimizes the squared deviations normal to the regression line<sup>16</sup>, the slope  $b = \operatorname{tg} \varphi$  is given by the relation

$$\operatorname{tg} 2\varphi = \frac{2b}{1 - b^2} = \frac{2 \sum_i (y_{i1} - y_{.1})(y_{i2} - y_{.2})}{\sum_i (y_{i1} - y_{.1})^2 - \sum_i (y_{i2} - y_{.2})^2}. \quad (21)$$

When solving this equation for  $b$  and introducing into (3) we get for  $\beta$  the equation

$$\tau \left( \beta^{-1} - \frac{T_1 + T_2}{2T_1 T_2} \right) \left[ \sum_i (y_{i1} - y_{.1})^2 - \sum_i (y_{i2} - y_{.2})^2 \right] = -2 \sum_i (y_{i1} - y_{.1})(y_{i2} - y_{.2}) - \sqrt{\left\{ 4 \left[ \sum_i (y_{i1} - y_{.1})(y_{i2} - y_{.2}) \right]^2 + \left[ \sum_i (y_{i1} - y_{.1})^2 - \sum_i (y_{i2} - y_{.2})^2 \right]^2 \right\}}, \quad (22)$$

where the symbol  $\tau$ , characterizing the broadness of the temperature interval, has been introduced:





are fulfilled. 1. The fundamental presumption is the validity of the Arrhenius law, at least within the interval of experimental temperatures and with a reasonable accuracy, comparable with the experimental error. This assumption is tested using the value of  $S_{00}$ ; if the test is negative, no further conclusions can be drawn. In organic chemistry the Arrhenius law is valid in a larger majority of examples, due mainly to narrow intervals of temperature. Even when more complex equations are used in the literature, the simple Arrhenius treatment may give satisfactory results (Example 3). When a non-linear equation is necessary, statistics of the isokinetic relationship becomes very difficult and is not elaborated as yet; for some remarks in this direction see<sup>1</sup>. 2. In developing the formulae, temperature was not considered as a random variable but as an exact quantity. Apart from the usually small errors in temperature measurement, this assumption can be generally substantiated by the following approach. Let us denote by  $T$  the exact value at which one intended to carry out the kinetic measurement; experimental errors in thermostating are simply manifested as errors in  $\log k$ . In this conception one is justified in introducing  $T$  in all regression formulae as if it would be free of error<sup>20</sup>. 3. If the isokinetic relationship holds, the quantities  $e_{ij}$  are identified with experimental errors in  $\log k$  and their standard deviation  $\sigma$  with the standard error  $\delta$ . The method of least squares is fully justified when the distribution of  $e_{ij}$  is normal, however, its application is not limited to this case. In kinetic measurements it is usually assumed that the distribution of  $\log k$  rather than of  $k$  is normal<sup>21,22</sup>. The model considered by us supposes further that the absolute error in  $\log k$  is constant at different temperatures and in all the reactions of the series. This assumption corresponding to the constant relative error in  $k$  is quite natural<sup>21,22</sup>; however, the alternative procedure was also advocated<sup>23</sup> giving each rate constant a particular weight according to the accuracy of the corresponding kinetic experiments. In our opinion it can be dangerous to give different weights to individual reactions of a series since they are *a priori* of the same importance. At any rate the different accuracies should be proved rigorously by statistical tests before such decision is made, and the experimenter must always try rather to bring all measurements to the same level. Alternatively, the reactions can be divided into subgroups *etc.* Variable accuracy according to temperature may be encountered more frequently and does not represent such a shortcoming. It also can be incorporated easily into our mathematical model by simple multiplying by appropriate weights. 4. The set of experimental data must be complete, *i.e.* each reaction followed at all temperatures. In practice one

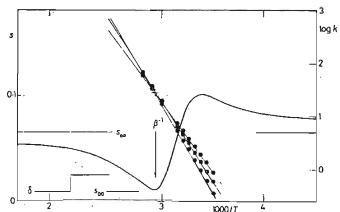


FIG. 5

Isokinetic Relationship for the Reaction of Malachite Green Derivatives with Hydroxyl Ions<sup>25</sup> (5 derivatives)

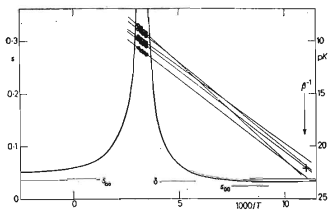


FIG. 6

Isoequilibrium Relationship of  $pK$  Values of 3- and 4-Substituted (4'-Methoxybenzal)-anilines in Acetonitrile<sup>26</sup> (6 derivatives)

lacking figure from a set of, say, twenty may be completed by interpolation or extrapolation, without affecting the overall results. Otherwise it is necessary to have recourse to the general method<sup>17</sup>. 5. Some directions for practical calculations on a desk calculator are suggested in the Appendix. In fact the explicit solution is of value only in connection with this technique. If a computer should be used, the derived formulae have no advantage and the general program<sup>17</sup> may be applied to all cases.

The following examples show the standard treatment of a reaction series and some typical results which may be obtained.

*Example 1.* Equilibrium constants of the reaction of twenty substituted dinitromethanes with formaldehyde were determined<sup>24</sup> at 10, 20, 35 and 50°C. The isokinetic relationship was stated to be valid for eleven derivatives and the value of  $\beta = 690 \pm 90$  K was found by our method<sup>5</sup> using the data at 10 and 50°C and the improper common regression. From the plot of  $\log k_{50}$  against  $\log k_{10}$  (Fig. 3) we found a rather exact isokinetic relationship for the group of nine derivatives only (No 5–10, 12, 14, 15) and an approximate one, but covering a broader range of  $K$  values, for fourteen derivatives of the type  $RCH_2CH(NO_2)_2$  (in addition No 2–4, 17, 18). Calculations were carried out for the two sets separately and gave  $\beta = 491$  K,  $y_0 = 5.225 \log$  units,  $s_0 = 0.031$ ,  $s_{00} = 0.035$ ,  $s_{\infty} = 0.085 \log$  units, for the former, and  $\beta = 1879$  K,  $y_0 = 4.171 \log$  units,  $s_0 = 0.061$ ,  $s_{00} = 0.032$ ,  $s_{\infty} = 0.126 \log$  units for the latter;  $s_u$  as function of  $u$  (or  $T^{-1}$ ) is shown in Fig. 4 with a full line for the former group and with a broken line for the latter. The values of  $s_{00}$  indicate that the experimental error, given<sup>24</sup> from 0.01 to 0.02 log units, may be somewhat underestimated. In the narrower set the isokinetic hypothesis must be accepted unconditionally ( $s_0 < s_{00}$ ); however, the confidence interval of  $\beta$  is at least from 425 to 700 K (for  $\delta = 0.04 \log$  units). In the broader set the isokinetic hypothesis can be rejected even at the confidence level  $\alpha = 0.005$ , any reliable value for  $\beta$  cannot be given. The isenthalpic hypothesis is to be rejected in both sets ( $s_{\infty}$ ).

This example shows a complete treatment of a given reaction series which may consist of the following steps: the Arrhenius plot (Fig. 4), a preliminary plot of two  $\log k$  against each other<sup>5</sup> (Fig. 3), the statistical treatment concluded by the graph of  $s_u$  (Fig. 4) and by calculation of  $\Delta H$ ,  $\Delta S$ , and isokinetic  $\Delta H$ ,  $\Delta S$  (see Discussion). A conventional  $\Delta H$  vs  $\Delta S$  plot (Fig. 9) is not necessary; it can only serve to demonstrate the weakness of this treatment<sup>5</sup>. The following examples are treated less thoroughly.

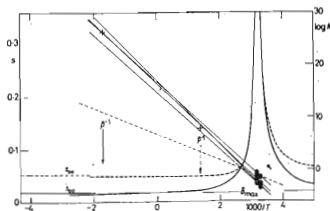


FIG. 7

Isokinetic Relationship for the Lossen Rearrangement of Salts of Dihydroxamic Acids<sup>27</sup>  
 Broken line for all 23 derivatives, full line one deviating derivative omitted.

*Example 2.* Kinetics of the reaction of Malachite Green like dyestuffs with hydroxyl ions<sup>25</sup> is one of the best proven examples of the isokinetic relationship, however, if it is confined to five *meta*- and *para*-substituted derivatives which were followed kinetically at 10, 15, 20, 25, 30, 35, 40, 55, 65 and 75°C. In this well-behaved case even the simple plot of  $\log k$  against  $T^{-1}$  gave a reasonable estimate<sup>25</sup>  $\beta = 331 \pm 4$  K. Our calculations yielded  $\beta = 335$  K,  $y_0 = 1.460$  log units,  $s_0 = 0.011$ ,  $s_{00} = 0.009$  and  $s_{\infty} = 0.066$  log units, the dependence of  $s_u$  on the supposed isokinetic temperature is shown in Fig. 5. The experimental accuracy was estimated to be from 2% (0.009 log units in  $\log k$ ) up to 6% (0.025 log units). It follows that the hypotheses of the validity of the Arrhenius equation ( $s_{00}$ ) as well as of the isokinetic equation ( $s_0$ ) must be accepted, the latter with the values of  $\beta$ , say, 325–350 K (corresponding to accuracy of 5% in  $k$ ). The hypotheses can be surely rejected that the reaction series is isoenthalpic ( $s_{\infty}$ ) or isentropic ( $s_u = 0.061$ ). However, the test of significance of the difference  $S_0 - S_{00}$  against  $S_{00}$  is positive even at  $\alpha = 0.005$ . The result should thus be formulated that the isokinetic relationship is acceptable with respect to the experimental accuracy and to the accuracy of the Arrhenius law; however, releasing of the isokinetic constraint produces still a significant improvement. The relatively definite conclusions in this example were made possible first of all by the unusually broad temperature interval.

*Example 3.* The  $pK_a$  values of six 3- and 4-substituted (4'-methoxybenzal)-anilines were measured<sup>26</sup> in acetonitrile at the temperatures 15, 25, 35 and 50°C. By our method<sup>5</sup>, but improperly with the common regression, the values of  $\beta = 12$  or 183 K were found, according to whether the couples of temperatures 15 and 50 or 25 and 35°C were used<sup>26</sup>. Our recalculation yielded  $\beta = 91$  K,  $y_0 = 22.14$  pK units,  $s_0 = 0.034$ ,  $s_{00} = 0.023$ ,  $s_{\infty} = 0.036$  pK units, and  $s_u$  shown in Fig. 6. The "experimental accuracy" was estimated<sup>26</sup> to 0.03 pK units, hence the Arrhenius law and even the isokinetic relationship can be accepted. The good fit with the Arrhenius law makes a more elaborate treatment<sup>26</sup> unnecessary. The hypothesis of an isentropic reaction series can be rejected ( $s_u = 0.060$ ), but the isoenthalpic series must be admitted ( $s_{\infty}$ ). Here again — like in Example 2 — the ratio of  $s_0$  and  $s_{00}$  is insignificant at  $\alpha = 0.05$ , but the difference  $S_0 - S_{00}$  is significant at  $\alpha = 0.01$ . The isokinetic temperature can hardly be given any more distinct value, if, say, the standard deviation 0.05 pK units is admitted, the confidence interval of  $\beta$  is from -75 to +155 K. In fact the reaction series would be isoenthalpic, were it not for the first reaction from the top in Fig. 6, which causes that  $\beta$  is lower than the experimental temperature.

*Example 4.* The Lossen rearrangement of salts of dihydroxamic acid was followed only at two temperatures, 30 and 40°C, on 24 compounds<sup>27</sup>. (For several compounds  $\log k$  at 40°C was obtained<sup>5</sup> by extrapolation from  $\log k$  at 20°C). The data were already treated<sup>5</sup> by the graphical method and an approximate values of  $\beta = -4664$  K found, when one badly deviating point (No 4) was eliminated. Leffler on the basis of an insufficient statistical treatment offered the meaning that no isokinetic relationship exists<sup>4</sup>. The calculations have now been performed exploiting some simplifications shown in the Appendix for  $m = 2$ . The values of  $\beta = 714$  K,  $y_0 = 8.14$  log units,  $s_0 = 0.048$ ,  $s_{\infty} = 0.053$  log units and  $s_u$  shown in Fig. 7, (broken line), change dramatically when the deviating point is omitted, i.e. to  $\beta = -581$  K,  $y_0 = 26.48$  log units,  $s_0 = 0.016$ ,  $s_{\infty} = 0.017$  log units,  $s_u$  as shown by the full line. The improvement is highly significant ( $\alpha \ll \ll 0.05$ ) so that the elimination of the deviating compound (dotted straight line) was justified. The experimental accuracy was given from 0.004 to 0.016 log units for individual compounds<sup>27</sup>, the upper limit being probably more realistic. Hence the isokinetic hypothesis cannot be rejected, however, the isokinetic temperature cannot be given any definite value, any value higher than 600 K and any negative one being admissible. This example shows clearly the weakness of all conclusions based on insufficient number of measurements in a narrow temperature range, the larger number of reactions investigated being of little use.

## DISCUSSION

The improved statistical procedure enabled us to reinvestigate a lot of reaction series and to draw more definite conclusions than formerly as to the occurrence, usual accuracy and significance of the isokinetic relationship, further as to the meaning and possible values of the isokinetic temperature  $\beta$ . The isokinetic temperature  $\beta$ . The existence of this temperature, connected with the reversal of reactivity, is a puzzling corollary of the isokinetic relationship<sup>14,15</sup>. Especially if the reactivity in a reaction series is interpreted in theoretically significant terms, as inductive and mesomeric effect, steric strain *etc.*, it is hard to believe that those effects could change their sign with temperature. The question thus becomes important whether the isokinetic temperature may be in principle experimentally accessible or not. With our simple graphical reexamination we were able to show<sup>5</sup> that all values within the experimental interval, claimed in the literature<sup>2,4,7</sup>, are artefacts due to an erroneous statistical treatment. We offered the meaning that the constant  $\beta$  mostly results from a linear extrapolation of a non-linear dependence of  $\log k$  on  $T^{-1}$  and that it lacks any immediate physical meaning<sup>5,11</sup>. This view was supported by the existence of negative isokinetic temperatures<sup>5,28</sup> and recently by a theoretical approach of Likhtenshtein<sup>29</sup> who represented  $\beta$  as a non-linear function of the experimental temperature. Petersen<sup>6</sup> believed that no isokinetic temperature lying in the experimental interval had been reported. However, its existence in Fig. 5 can hardly be doubted although only in the limited series of reactions<sup>25</sup>; other examples, even when restricted to small subgroups<sup>30</sup>, have also been reported, particularly in the heterogeneous catalysis<sup>31</sup>. It must probably be accepted that a reversal of reactivity with temperature is principally possible even when rare. In these series the mechanism is certainly complicated and any straightforward interpretation in terms of substituent effects not allowed. The second question concerning the isokinetic temperature is whether it can attain arbitrary values differing from one reaction series to the other, or whether there is one, or several characteristic values of general validity. The second meaning was advocated by several theoretical arguments<sup>3,32,33</sup> and by observations<sup>34,35</sup> based on incorrect statistical treatment. However, considering the evidence now available, we can assert that these theories are experimentally disproved. Positive, negative, high and low values of  $\beta$  are possible, although positive ones, higher than the experimental temperature, seem to be the most frequent. The reported values<sup>34,35</sup> centered round an average, close to the experimental temperature, are with certainty artefacts of the computational procedure. It is true that the value of  $\beta$  is determined only very approximately by any procedure. However, considering the lack of its physical meaning, its exact determination is not the main task of the mathematical analysis of the isokinetic relationship.

*Classification of reaction series.* Blackadder and Hinshelwood<sup>36</sup> distinguished three types of reaction series: a) with a constant entropy of activation *i.e.* enthalpy



increasing selectivity ( $\beta < T_{\text{exp}}$ , Fig. 8d). The isenthalpic series represents the borderline ( $\beta = 0$ , Fig. 8a). The first case may be seen as a rule and agrees with the common sense; accordingly an extremely reactive reagent would react with all substrates at the same rate. The second case is an exception<sup>5</sup> (Fig. 6) and each such series should be studied carefully in order to detect the actual meaning of this classification. The possibility is given that this abnormal behaviour is caused by a complex reaction mechanism.

*Meaning of the activation parameters.* As we showed previously<sup>11</sup>, the activation free energy (logarithm of the rate constant) at a chosen temperature affords a more reliable basis for any structure discussion than the activation energy. If the isokinetic relationship holds for a reaction series, the activation parameters yield in fact no additional information since all the quantities  $\Delta G$ ,  $\Delta H$  and  $\Delta S$  change in a parallel manner. When an attempt is made to discuss  $\Delta H$  and  $\Delta S$  separately in their structure dependence, it may happen that it is the experimental errors which are in fact discussed. To avoid this possibility we suggest defining the isokinetic enthalpies  $\Delta H_{\text{iso}}$  and isokinetic entropies  $\Delta S_{\text{iso}}$  as values computed with the isokinetic constraint. *E.g.* the values of  $\Delta S_{\text{iso}}$  are obtained directly from  $b_i$  in equation (10) through the relation

$$(\Delta H_{\text{iso}}^{\ddagger})_i = -2.303Rb_i - RT. \quad (26)$$

In the expression for  $\Delta H_{\text{iso}}^{\ddagger}$  the term  $-RT$  drops out. The values of  $\Delta S_{\text{iso}}$  are obtained from  $\Delta H_{\text{iso}}$  and  $\Delta G$ . The relation of isokinetic and unconstrained activation parameters is visualized in Fig. 9. The computed<sup>24</sup> values of  $\Delta H^{\ddagger}$  and  $\Delta S^{\ddagger}$  are shown for the same reaction as in Figs 3 and 4 together with their estimated errors<sup>24</sup>. Since the errors in  $\Delta H^{\ddagger}$  and  $\Delta S^{\ddagger}$  are dependent, each point can move only in one direction shown by a given line, the slope of which equals the mean experimental temperature (error slope<sup>4,34,36</sup>). The point of intersection of this given line (prolonged if necessary)

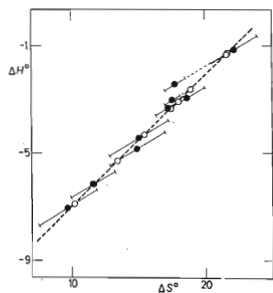


FIG. 9  
Isokinetic (○) and Unconstrained (●) Reaction Enthalpies (kcal) and Entropies, ( $\text{cal } \sigma^{-1}$ ) (Experimental data<sup>24</sup> the same as in Figs 3 and 4)

with the isokinetic line determines  $\Delta H_{\text{iso}}^0$  and  $\Delta S_{\text{iso}}^0$ . The values may differ distinctly from the unconstrained  $\Delta H^0$  and  $\Delta S^0$  although the differences only seldom exceed the standard error in the example given.

If the reaction series is isoenthalpic, the isoenthalpic enthalpy and entropies may be defined as a special case of isokinetic values. The isoenthalpic enthalpy is of course constant for all reactions of the series and is connected with  $b_\infty$  from the equation (18). On the other hand, when the reaction series is isoentropic, the isoentropic enthalpies and entropy may be defined. The former ones are obtained from  $b_0$  given by equation (10) with  $u = -\sum_j x_j/m$ , the latter is constant and equals  $2.303R(y_0 - \log T - 10.75)$  in kinetics and  $2.303Ry_0$  in thermodynamics.

We conclude that the isokinetic (isoenthalpic, isoentropic) activation parameters are more reliable than the common values in all cases when the isokinetic relationship has been proven to hold (as in Example 1, the narrower set). When it cannot be disproved but yet would cause a reduction of the over-all accuracy (Examples 2, 3), we recommend the calculation of both the isokinetic and common parameters. The main problem remains concerning how to judge reaction series, where the isokinetic relationship is valid only roughly or not at all; *i.e.* whether  $\Delta G$  or  $\Delta H$  is the appropriate quantity for structure-reactivity correlations. An experimental solution is in principle possible by comparing  $\Delta G$  and  $\Delta H$  of two related reaction series<sup>11, 37</sup>, however, it would require much more experimental material than available at present.

*Meaning of the isokinetic relationship.* The mathematical treatment enables one to estimate the isokinetic temperature  $\beta$  on the one hand and to judge the validity and accuracy of the isokinetic relationship on the other hand. We have seen that the numerical value of  $\beta$  is in general of little use; in most cases it is enough to decide whether it is higher or lower than the experimental temperature. Hence the second result is by far more important. In statistical terms it may be formulated either that the isokinetic hypothesis is rejected on a certain significance level, or, that there are not sufficient grounds to reject it. The weight of the decision will depend on several factors such as the experimental accuracy, the number of reactions in the series, the number of measurements for one reaction, and the broadness of the temperature interval. Particularly if this interval is narrow, the isokinetic hypothesis cannot be rejected in any case and a broad range of  $\beta$  values must be admitted, including those for the isoenthalpic and isoentropic series (see Example 4). The insufficient temperature range cannot be outweighed by a great number of reactions.

To distinguish isokinetic and non-isokinetic series is in our opinion one of the primary tasks of structural chemistry, since the interpretation of reactivity should be different in both. The isokinetic relationship could thus help to define with more precision the term reaction series in a proper sense<sup>38</sup>; its validity should be a necessary, but not a sufficient condition for a set of reaction to form a "series". A lot of attempts has been made to derive the isokinetic relationship in terms of various theories<sup>1-3</sup>;



they have a common shortcoming of being either quite general or confined only to reactions in the condensed phase, and offer no possibility to distinguish isokinetic and non-isokinetic series. There is the task of the future theory to incorporate the term "reaction series" and to enable prediction in which systems it is realized.

## APPENDIX

For practical calculation on the desk calculator the following procedure is recommended: The new independent variable  $u$  is introduced first

$$u = T^{-1} - \frac{1}{m} \sum_j T_j^{-1}, \quad (7')$$

dependent variable being  $y = \log k$ . The auxiliary quantity  $p_i$  is defined on the basis of Eq. (6),

$$p_i = \frac{1}{m} \sum_j u_j y_{ij}. \quad (6')$$

Further auxiliary symbols  $X, Y, Z, P, Q, U$  are defined as follows

$$\begin{aligned} X &= \frac{1}{m} \sum_j (x_j - \bar{x})^2 = \frac{1}{m} \sum_j u_j^2, \\ Y &= m \sum_i (y_{i.} - y_{..})^2 = \frac{1}{m} \sum_i (\sum_j y_{ij})^2 - \frac{1}{ml} (\sum_{ij} y_{ij})^2, \\ Z &= \sum_{ij} (y_{ij} - y_{..})^2 = \sum_{ij} y_{ij}^2 - \frac{1}{ml} (\sum_{ij} y_{ij})^2, \\ P &= m \sum_i p_i = \sum_{ij} u_j y_{ij}, \\ Q &= m \sum_i p_i^2 = \frac{1}{m} \sum_i (\sum_j u_j y_{ij})^2, \\ U &= 2m \sum_i (p_i - \bar{p}) (y_{i.} - y_{..}) = \frac{2}{m} \sum_i (\sum_j u_j y_{ij} \sum_j y_{ij}) - \frac{2}{ml} (\sum_{ij} u_j y_{ij}) (\sum_{ij} y_{ij}). \end{aligned} \quad (27)$$

In practical calculation the right-handed sides of equations (27) are used. The quantities needed are then given by the relations

$$u_0 = \beta^{-1} - \frac{1}{m} \sum_j T_j^{-1} = \{Q - P^2/ml - XY - \sqrt{[(Q - P^2/ml - XY)^2 + XU^2]}\}/U \quad (8')$$

$$y_0 = \frac{1}{ml} (\sum_{ij} y_{ij} + u_0 P/X), \quad (9')$$

$$b_i = \frac{p_i + u_0(y_0 - \sum_j y_{ij}/m)}{X + u_0^2}, \quad (10')$$

$$S_0 = Z - \{Q + P^2/ml + XY + \sqrt{[(Q - P^2/ml - XY)^2 + XU^2]}\}/2X, \quad (12')$$

$$f = (m-1)l - 2$$

$$S_{00} = Z - Y - Q/X, \quad f = (m-2)l \quad (13')$$

$$S_u = Z - [Q - uU + u^2(Y + P^2/mlX)]/(X + u^2) \quad f = (m-1)l - 1. \quad (16')$$

From  $b_i$  the isokinetic enthalpies are obtained according to the equation (23).

The procedure is considerably simplified when there are only two experimental temperatures ( $T_2 > T_1$ ), the dependent variables being denoted  $y_{i1} = \log k_{i1}$  and  $y_{i2} = \log k_{i2}$ . Here the number of auxiliary symbols is restricted by the constraint  $S_{00} = 0$ . Let us introduce  $\tau$  according to the equation (21) and the following symbols

$$L = \sum_i y_{i1}^2 - \frac{1}{l} (\sum_i y_{i1})^2,$$

$$M = \sum_i y_{i1} y_{i2} - \frac{1}{l} (\sum_i y_{i1}) (\sum_i y_{i2}), \quad (28)$$

$$N = \sum_i y_{i2}^2 - \frac{1}{l} (\sum_i y_{i2})^2.$$

The searched quantities are then given by the equations

$$u_0 = \beta^{-1} - \frac{T_1 + T_2}{2T_1 T_2} = \frac{\tau}{N - L} \{2M + \sqrt{[4M^2 + (N - L)^2]}\}, \quad (8'')$$

$$y_0 = \frac{1}{2l} \sum_{ij} y_{ij} + \frac{u_0}{2l\tau} (\sum_i y_{i1} - \sum_i y_{i2}), \quad (9'')$$

$$b_i = \frac{\tau(y_{i1} - y_{i2}) + u_0(2y_0 - y_{i1} - y_{i2})}{2\tau^2 + 2u_0^2}, \quad (10'')$$

$$S_0 = \frac{1}{2} \{L + N - \sqrt{[4M^2 + (N - L)^2]}\} \quad f = l - 2, \quad (12'')$$

$$S_u = \frac{L + N}{2} + \frac{\tau^2 M - u\tau(N - L) - u^2 M}{\tau^2 + u^2}. \quad f = l - 1 \quad (16'')$$

#### LIST OF SYMBOLS

- $A$  preexponential factor  
 $b$  proportionality constant in Eq. (2)  
 $b_i, b_{i,0}, b_{iu}, b_{\infty}$  slopes of the Arrhenius lines (isokinetic, unconstrained, constrained)

$e_{ij}$	random variable (error)
$e_0$	intercept in Eq. (1a)
$E^*$	Arrhenius activation energy
$f$	degrees of freedom
$h_0$	intercept in Eq. (1b) or (1c)
$\Delta H$	activation or reaction enthalpy
$\Delta H^0$	reaction enthalpy
$\Delta H^\ddagger$	activation enthalpy
$\Delta H_{iso}$	isokinetic (activation or reaction) enthalpy
$i$	subscript denoting the straight line (reaction)
$j$	subscript denoting the point (temperature)
$k$	symbol for rate or equilibrium constant
$l$	number of straight lines ( <i>i.e.</i> reactions)
$m$	number of points on a line ( <i>i.e.</i> temperatures)
$L$	auxiliary symbols defined by Eqs (28)
$M$	auxiliary symbols defined by Eqs (28)
$N$	auxiliary symbols defined by Eqs (28)
$p_i$	function of variables defined by Eq. (6)
$P$	auxiliary symbols defined by Eqs (27)
$Q$	auxiliary symbols defined by Eqs (27)
$s_0$	standard deviations (isokinetic, unconstrained, constrained)
$S_0$	residual sums of squares (isokinetic, unconstrained, constrained)
$S_{00}$	residual sums of squares (isokinetic, unconstrained, constrained)
$S_u$	residual sums of squares (isokinetic, unconstrained, constrained)
$S_\infty$	residual sums of squares (isokinetic, unconstrained, constrained)
$\Delta S$	symbol for activation or reaction entropy
$\Delta S^0$	reaction entropy
$\Delta S^\ddagger$	activation entropy
$\Delta S_{iso}$	isokinetic (activation or reaction) entropy
$u$	independent variable introduced by Eq. (7)
$u_0$	independent variable introduced by Eq. (7)
$U$	auxiliary symbols defined by Eqs (27)
$X$	auxiliary symbols defined by Eqs (27)
$Y$	auxiliary symbols defined by Eqs (27)
$Z$	auxiliary symbols defined by Eqs (27)
$x_{ij}$	independent variable ( $= T^{-1}$ )
$x_j$	independent variable ( $= T^{-1}$ )
$\bar{x}$	mean values of $x$
$x_0$	abscissa of the point of intersection ( $= \beta^{-1}$ )
$y_{ij}$	dependent variable ( $= \log k$ )
$y_{i1}$	dependent variable ( $= \log k$ )
$y_{i2}$	dependent variable ( $= \log k$ )
$y_i$	mean values of $y$
$y_{.1}$	mean values of $y$
$y_{.2}$	mean values of $y$
$y_0$	ordinate of the point of intersection
$y_u$	ordinate of the point of intersection
$\alpha$	confidence level
$\beta$	isokinetic temperature (real and erroneous)
$\beta^*$	isokinetic temperature (real and erroneous)
$\delta$	experimental error
$\sigma^2$	variance of $e_{ij}$
$\tau$	broadness of the temperature interval, defined by Eq. (23)
$\varphi$	inclination of the special regression line, Eq. (21)

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