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The Linear Relationship between Enthalpy and Entropy of Activation

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The frequently observed linear relationship between entropy and enthalpy of activation, also called the iso-kinetic relationship or the compensation effect, is discussed and illustrated with hypothetical kinetic data. It is shown that the linear entropy–enthalpy plot can be extremely deceptive and is not by itself an adequate demonstration of the existence of an iso-kinetic relationship.

The observation and reporting of linear relationships between entropies and enthalpies of activation have become common in kinetic studies of groups of similar organic reactions. Such a group might comprise, for example, a series of thermal decompositions of a single compound in several different solvents, or it might be a series of reactions differing only in a single substituent in one of the reactants.

Some years ago Leffler[1] reviewed a large number (over 75) of examples of this linear relationship which had appeared in the chemical literature and discussed the significance and interpretation of the relationship. Since that time a great many more examples have been reported.

More recently Leffler and Grunwald[2] have discussed the relationship in still greater detail, and have applied sophisticated interpretations to the phenomenon. In this work they limited their lists of examples (97) to those having correlation coefficients[1] greater than 0.95.

Petersen, Markgraf and Ross[3] have previously questioned the validity of all such observations of linear entropy–enthalpy of activation relationships. They pointed out that ΔH^* and ΔS^* are derived quantities, removed from experiment by a number of steps of computation, and their values are not obtained independently, but are both computed from a single equation. Specifically, it was shown that, if the observed variation in ΔH^* throughout a given series of reactions were due largely to random errors in the determinations of rate constants, exactly this linear relationship between ΔH^* and ΔS^* would be observed. They further noted that they had been unable to find a clearly valid linear ΔH^*–ΔS^* relationship in the literature.

The present paper will not repeat the previous discussion of errors,[3] but will discuss the linear entropy–enthalpy relationship from a more general point of view. The terminology will be that of activation parameters of absolute reaction rate theory for first-order reactions, but the discussion will clearly be applicable to higher-order reactions, to other activation theories, and, to some extent, to equilibrium situations.

The slope of a plot of enthalpy *vs.* entropy of activation has units of absolute temperature and it is called the iso-kinetic temperature. The name is derived from the fact that the existence of a linear ΔH^*–ΔS^* relationship for a series of reactions implies that all reactions in the series proceed at the same rate at the temperature defined by the slope of the ΔH^*–ΔS^* plot. The phenomenon is sometimes called the compensation effect because it implies that enthalpy variations through the series of reactions are exactly compensated by entropy changes.

Table I lists rate constants k_1 and k_2 at temperatures $T_1 = 300°$ K. and $T_2 = 315°$ K., respectively, for a series of hypothetical reactions a–e. The magnitudes and range of variation of these rate constants are typical of many appearing in the literature in cases where linear entropy–enthalpy relationships were observed.

TABLE I

Reaction	$k_1 \times 10^4$, sec.$^{-1}$ (T_1 = 300°K.)	$k_2 \times 10^4$, sec.$^{-1}$ (T_2 = 315°K.)
a	1.32	9.43
b	1.62	7.95
c	1.92	6.91
d	2.19	6.23
e	2.56	5.46

From absolute reaction rate theory, given a simple reaction path and a transmission coefficient of unity, ΔH^* and ΔS^* are computed from rate constants at two temperatures by the following equations (1 and 2),

$$\Delta H^* = 4.5753 \frac{T_2 T_1}{T_2 - T_1} \log \frac{k_2 T_1}{k_1 T_2} \tag{1}$$

$$\Delta S^* = -47.212 + \frac{\Delta H^*}{T} + 4.5753 \log \frac{k_1}{T_1} \tag{2}$$

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[1] J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).

[2] J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963.

[3] R. C. Petersen, J. H. Markgraf, and S. D. Ross, *J. Am. Chem. Soc.*, **83**, 3819 (1961).

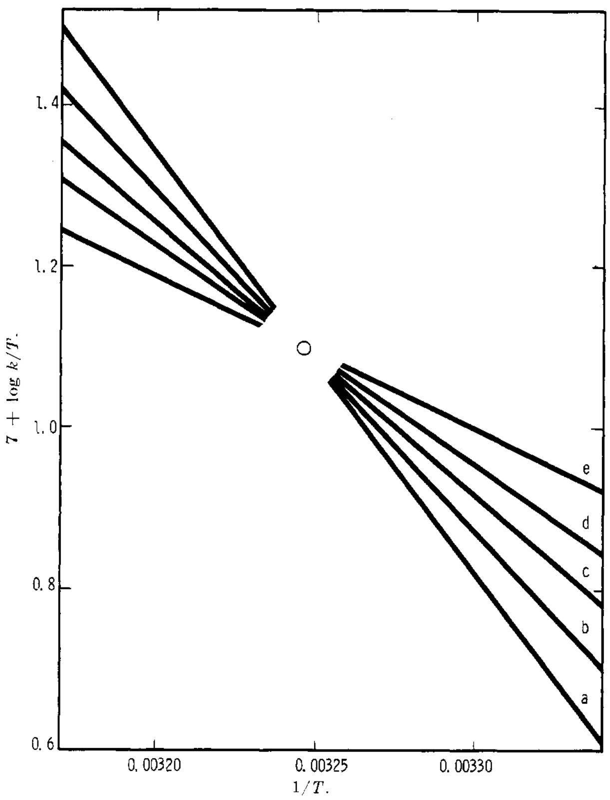

Fig. 1.—Activation plot for data of Table I.

where ΔH^* has units of cal./mole and ΔS^* is in cal./mole-deg. ΔH^* can also be determined graphically with the aid of eq. 3.

$$\frac{d(\log k/T)}{d(1/T)} = -\frac{\Delta H^*}{4.5753} \tag{3}$$

Figure 1 shows plots of log (k/T) *vs.* $1/T$ for the hypothetical reactions of Table I. These plots, whose slopes are described by eq. 3, differ only slightly from plots of log k *vs.* $1/T$, whose slopes give the Arrhenius activation energy.

The five lines of Fig. 1 all intersect at a single point, corresponding to a temperature of 308.1° K. This temperature is clearly an iso-kinetic temperature, since all five reactions must have the same k at this point.

Figure 2 shows the ΔH^*–ΔS^* plot for the data of Table I (and Fig. 1). As expected, Fig. 2 again indicates an iso-kinetic relationship. The line is drawn with a slope of 308°, although a variation of several degrees would be virtually undetectable, and each point falls perfectly on the line, again as expected.

Plots similar to Fig. 2 are common in the literature, while plots like Fig. 1 are certainly rare and perhaps nonexistent.

The data of Table II illustrate a more common state of affairs. Many examples much like this one could have been taken from the literature, but Table II, like Table I, uses hypothetical data.

TABLE II

Reaction	$k_1 \times 10^4$, sec.$^{-1}$ (T_1 = 300°K.)	$k_2 \times 10^4$, sec.$^{-1}$ (T_2 = 315°K.)
a	1.2	6.8
b	1.4	5.9
c	1.6	8.1
d	1.8	10.9
e	2.0	8.9

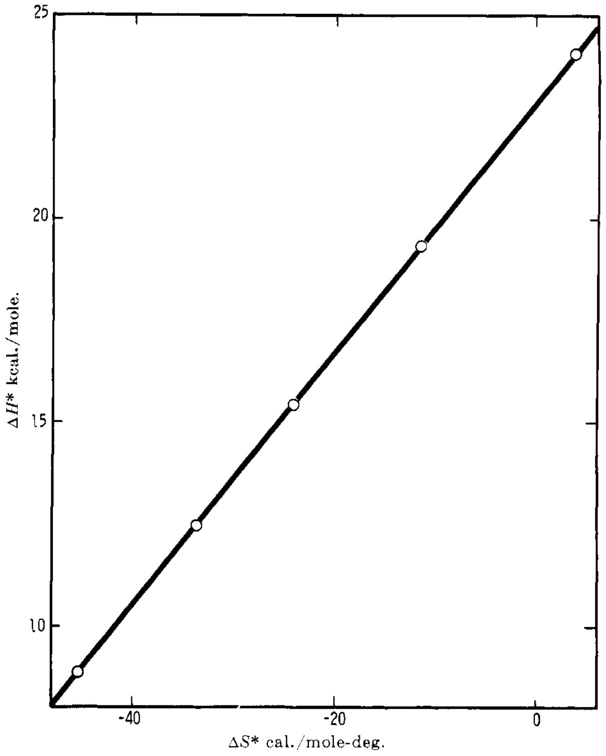

Fig. 2.—Plot of ΔH^* *vs.* ΔS^* for data of Table I.

The rate constants used in Table II are similar to those of Table I and the temperatures are the same, but in this latter case there is nothing even remotely resembling a single iso-kinetic temperature. This is shown by Fig. 3, which is the activation plot of the data of Table II.

The five straight lines have ten intersections of pairs, only two of which appear in the figure (in contrast to Fig. 1). These ten intersections, which might be called iso-kinetic temperatures for pairs of reactions, occur over a 113° temperature range from 229 to 342° K.

In spite of this clear lack of an iso-kinetic temperature, the ΔH^*–ΔS^* plot, Fig. 4, shows a straight line with points deviating only slightly from the line. The correlation coefficient, as defined by Leffler,[1] for this plot is 0.998, and this then qualifies as an excellent example of an iso-kinetic relationship by the standards of Leffler and Grunwald.[2]

It is clear from this illustration that the mere observation of an apparently straight-line plot of ΔH^* *vs.* ΔS^* cannot substantiate a claim of an iso-kinetic relationship among a group of reactions.

The inadequacy of the ΔH^*–ΔS^* plot stems from its insensitivity to deviations from true iso-kinetic behavior, which in turn is a result of the interrelation between the equations used to compute ΔH^* and ΔS^*.

To substantiate the existence of an iso-kinetic temperature for a series of reactions it is necessary to go back one step closer to the experiment, to examine the activation plot (Fig. 1 and 3). If all of the lines on such a plot have a common point, as in Fig. 1, then that point is an iso-kinetic point and the iso-kinetic relationship is established. This author is not aware of any data in the literature which meet or approximate this condition.

The plot of log (k/T) *vs.* $1/T$ is also useful in estimating visually the magnitude and importance of experi-

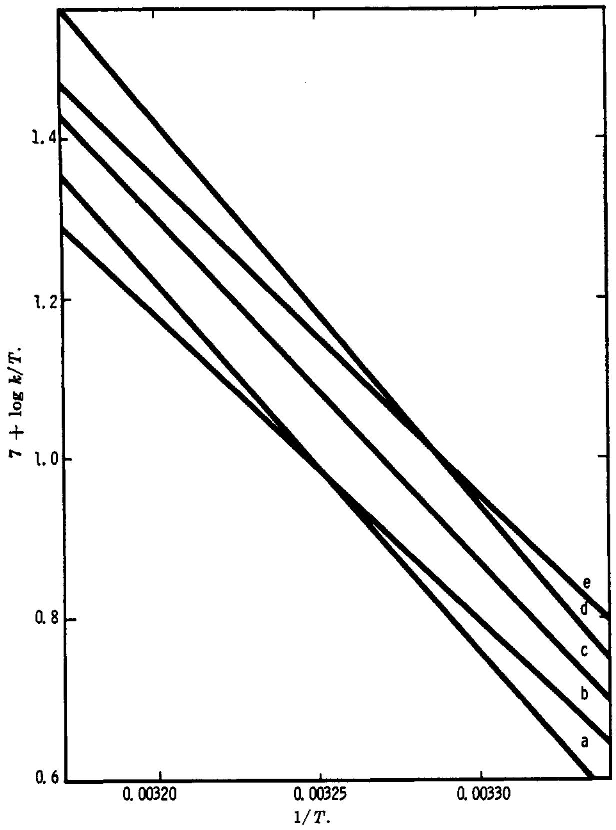

Fig. 3.—Activation plot for data of Table II.

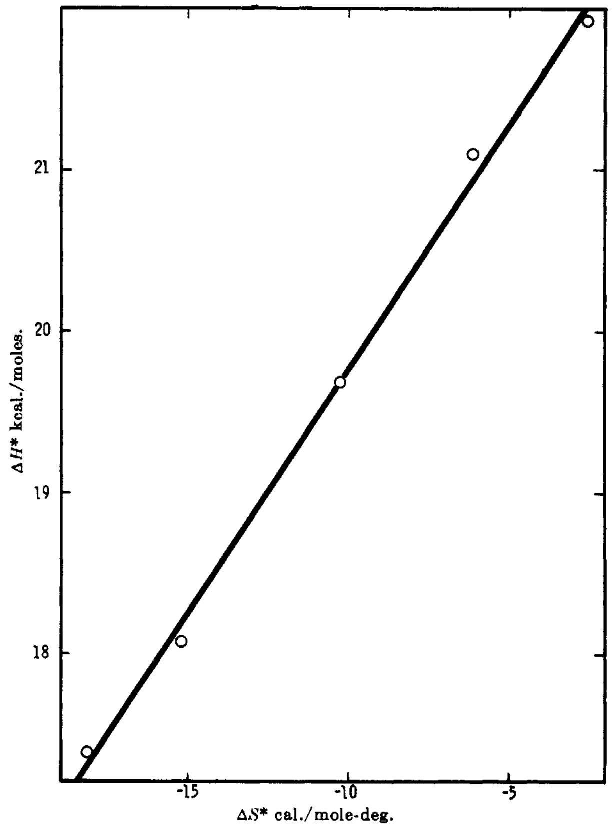

Fig. 4.—Plot of ΔH^* *vs.* ΔS^* for data of Table II.

mental errors, while the ΔH^*–ΔS^* plot has little value for this purpose.

If the iso-kinetic temperature suggested by the ΔH^*–ΔS^* plot does not fall within the range of the measurements, then additional measurements should be made around this suggested temperature.

If the indicated iso-kinetic temperature is not accessible, iso-kinetic temperature for all possible pairs of reactions in the series can be computed and compared (eq. 1 and 2). If these agree well with one another it is reasonable to conclude that an iso-kinetic relationship exists.

In no case can the linear ΔH–ΔS^* plot be taken by itself to be an adequate demonstration of the existence of an iso-kinetic relationship.

The Effect of Axial Alkyl Groups on the Base Strengths of Cyclic Amines

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The pK_a values of 3,3-dimethyl and 3,3,5,5-tetramethyl derivatives of piperidine and N-methylpiperidine were compared with those of the parent amines to determine the effects of 1,3-methyl interactions on pK_a values. Similarly, the pK_a values of 3-azabicyclo[3.2.2]nonane and its N-methyl derivative were compared with those of the corresponding hexamethylenimines to determine the effect of an ethylene bridge. The reductions in pK_a values were all very small and were consistent with a minor polar effect rather than steric hindrance of hydration of the ammonium ions.

An earlier report[1] showed, by pK_a measurements, that secondary ammonium ions are hydrated in solution. The size of the hydrated secondary ammonium ion may be evaluated by determining the extent of its interaction with an axial 3-substituent in a piperidine ring,[2,3] which would lower the pK_a value. Similar substitution in N-methylpiperidine would affect the pK_a value to a lesser extent because tertiary ammonium cations are much less hydrated.[1,4,5]

The possible effects of an ethylene bridge on the pK_a of hexamethyleneimine and N-methylhexamethylene-

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(1) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957).

(2) The size of the hydrated *primary* ammonium cation has been determined by two groups: (a) J. Sicher, J. Jonas, and M. Tichy, *Tetrahedron Letters*, 825 (1963); (b) E. L. Eliel, E. W. Della, and T. H. Williams, *ibid.*, 831 (1963).

(3) W. Simon, G. H. Lyssy, A. Moerikofer, and E. Heilbronner ["Collection of Apparent Dissociation Constants in Solvent System Methyl Cellosolve–Water," Juris-Zerlag, Zurich, 1959, p. 62] give a pK_a value of 8.60 for 3,3,5,5-tetramethylpiperidine compared with a value of 9.72 for piperidine, but no details have been given.

(4) E. Folkers and O. Runquist, *J. Org. Chem.*, **29**, 830 (1964).

(5) J. F. King, in "Technique of Organic Chemistry," Vol. XI, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 342.