Isokinetic Relationship, Isoequilibrium Relationship, and Enthalpy–Entropy Compensation

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Contents

1. Introduction

Consider that there is a series of closely related chemical reactions (denoted by an index *i*). Such a series might comprise, for instance, a series of reactions of the same reactants in several different

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Lei Liu, born in 1977 in Chuzhou, China, received his B.S. degree in Chemistry with honors from the University of Science and Technology of China (USTC). From 1996 to 1999, he worked in the lab of Professor Qing-Xiang Guo for over three years, focusing on experimental and theoretical supramolecular chemistry. Now he is doing graduate work with Professor Ronald Breslow at Columbia University in the area of enzyme mimics.

Qing-Xiang Guo, born in 1950 in Gansu Province, China, graduated from Lanzhou University in 1975. After finishing his graduate study in the same university under supervision of Professor You-Cheng Liu, he joined the faculty of the Chemistry Department at Lanzhou University in 1981. As a research associate, he worked with Professor T. Ffrancon Williams on the structure and reactivity of radical ions in the University of Tennessee, Knoxville, from 1986 to 1989. He returned to Lanzhou University in 1990 and was assigned as Associate Professor in 1991. In 1994, he moved to the University of Science and Technology of China (USTC). He has been Professor since 1995. Now he serves as Chairman of the Department of Chemistry and Vice Dean of the School of Chemistry and Materials Science, USTC. Current research activities of his group include experimental and theoretical studies on the molecular recognition, electron-transfer reactions in supramolecular systems as well as design and synthesis of novel cationic lipids for gene delivery.

solvents or it might be a series of reactions differing only in a single substituent in one of the reactants. Then we have a series of values of enthalpy changes (ΔH_i), entropy changes (ΔS_i), and free energy changes (ΔG_i) individually related by eq 1

$$\Delta G_i = \Delta H_i - T\Delta S_i \tag{1}$$

If the Arrhenius equation and transition-state theory hold, we also have a series of values of rate constants (k_i), preexponential factors (A_i), activation energies ($E_{a,i}$), enthalpies of activation ($\Delta H_i^{\ddagger}$), and entropies of activation ($\Delta S_i^{\ddagger}$) individually related by eqs 2 and 3

$$k_i = A_i \exp(-E_{a,i}/RT) \tag{2}$$

$$k_i = \frac{k_B T}{h} \exp\left(\frac{\Delta S_i^{\ddagger}}{R}\right) \exp\left(-\frac{\Delta H_i^{\ddagger}}{RT}\right)(c^{\theta})^{1-m} \tag{3}$$

in which k_B, h, and R are Boltzmann's, Planck's, and the gas constants, respectively, c^{θ} is the concentration in the standard state to which the activation parameters $\Delta H_i^{\ddagger}$ and $\Delta S_i^{\ddagger}$ are referred, and m is the molecularity.

　　Sometimes, it is found that there is a linear relationship between the logarithm of the preexponential factors and the activation energies, between the enthalpies and entropies of activation, or between the enthalpy and entropy changes of the series of reactions, i.e.

$$\ln A_i = \alpha + E_{a,i}/R\beta \tag{4}$$

$$\Delta H_i^{\ddagger} = \alpha + \beta\Delta S_i^{\ddagger} \tag{5}$$

or

$$\Delta H_i = \alpha + \beta\Delta S_i \tag{6}$$

in which α and β are constants. This behavior is called the compensation effect or, more specifically, enthalpy−entropy compensation.

　　As the quantity β in the above equations has the dimension of temperature, it is often defined as the isokinetic (or isoequilibrium) temperature and the corresponding behavior is called an isokinetic (or isoequilibrium) effect because it seems that at the temperature β all the reactions in the series should have the same rate (or equilibrium) constant according to the following equations

$$\Delta G_i(\beta) = \Delta H_i - \beta\Delta S_i = \alpha \tag{7}$$

$$k_i(\beta) = A_i \exp(-E_{a,i}/R\beta) = \exp(\alpha) \tag{8}$$

and

$$k_i(\beta) = \frac{k_B\beta}{h} \exp\left(\frac{\Delta S_i^{\ddagger}}{R}\right) \exp\left(-\frac{\Delta H_i^{\ddagger}}{R\beta}\right)(c^{\theta})^{1-m} = \\ \frac{k_B\beta}{h}\exp\left(-\frac{\alpha}{R\beta}\right)(c^{\theta})^{1-m} \tag{9}$$

The above empirical relationships were discovered very early[1] and have been rediscovered time and time again in many different fields, often independently. Sometimes different names such as the Barclay−Butler rule,[2a] the Meyer−Neldel effect,[2b] the theta rule,[2c] and the Smith−Topley effect[2d] were also used for them. Because they lie outside the normal realm of thermodynamics, they are often called extrathermodynamic relationships. To date, these relationships have been found in an extremely wide range of fields such as micellization,[3a] Langmuir adsorption,[3b] enantiomer separation,[3c] water sorption,[3d] gas chromatography,[3e] liquid chromatography,[3f] solvation thermodynamics,[3g] thermal transitions,[3h] solution extraction,[3i] conformational equilibrium,[3j] ionic hydration,[3k] dielectric relaxation,[3l] hydrogen bonding,[3m] crystal melting,[3n] coordination chemistry,[3o] calixarene chemistry,[3p] cyclodextrin chemistry,[3q] crown ether chemistry,[3r] molecular capsules,[3s] van der Waals complexes,[3t] protein chemistry,[3u] lipid chemistry,[3v] nucleic acid chemistry,[3w] antibiotics dissociation,[3x] enzyme binding,[3y] and food chemistry.[3z] These relationships have also been established for the reactions including oxidation,[4a] thermal decomposition,[4b] thermal isomerization,[4c] hydrolysis,[4d] addition reaction,[4e] substitution reaction,[4f] redox reaction,[4g] electron transfer,[4h] photolysis,[4i] depolymerization,[4j] proton transfer,[4k] and photoisomerization.[4l]

　　Although a number of good reviews are available on these relationships, they are generally restricted to certain specific fields, such as molecular recognition or heterogeneous catalysis.[4] Also, because the three relationships have been found in so many seemingly unrelated fields, researchers in one field often overlook the work done by those in other disciplines. Thus, there remains a great deal of controversy and misunderstanding concerning the concepts and origins of the three relationships.

　　The primary aims of the present review are to clarify the concepts of the isokinetic relationship, isoequilibrium relationship, and compensation effect and to summarize the theories on them. The main concern is to make clear what is known, what is unknown, what the facts are, and what the artifacts are.

2. Relation and Difference between the Three Concepts

　　Historically, the isokinetic (or isoequilibrium) relationship and compensation effect were considered to be synonymous or different names for the same phenomenon. This is readily understandable because it seems obvious that if eqs 4−6 hold, eqs 7−9 will be correct, and vice versa.[6] However, it will be shown that this truism is misleading.

　　Table 1 lists the enthalpy and entropy changes of a set of hypothetical chemical reactions. (Herein, it should be emphasized these enthalpies and entropies are supposed to be the true values and hence error-free.) Plotting the enthalpy changes vs the entropy changes gives a straight line as shown in Figure 1a. Obviously, there is an excellent linear correlation between the enthalpy and entropy changes and, therefore, an excellent compensation effect. However,
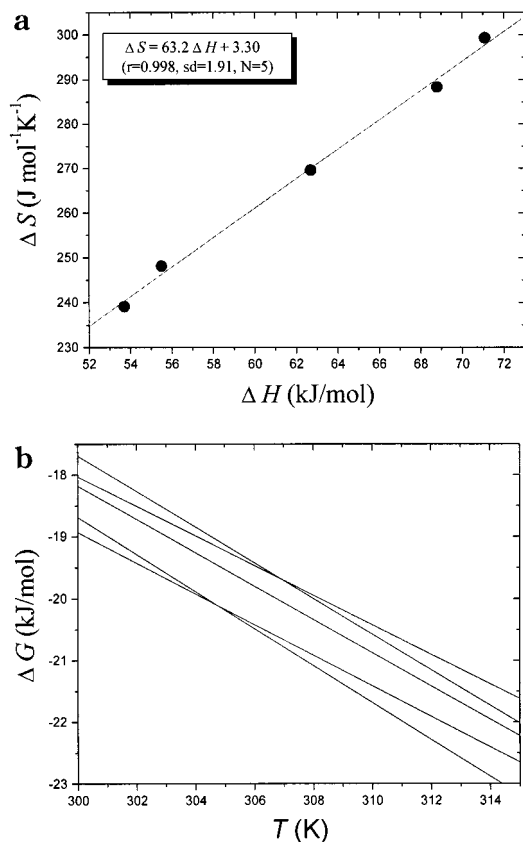
a

$\Delta S = 63.2 \Delta H + 3.30$
(r=0.998, sd=1.91, N=5)

b

Figure 1. Enthalpy−entropy compensation plot (a) and van't Hoff plot (b) of a series of hypothetical chemical reactions.

Table 1. Hypothetical Enthalpy and Entropy Changes of a Series of Chemical Reactions

ΔH (kJ/mol)	ΔS (J/mol·K)
68.8	288.3
53.7	239.1
62.7	269.6
71.1	299.3
55.5	248.1

Table 2. Hypothetical Enthalpy and Entropy Changes of Another Series of Chemical Reactions

ΔH (kJ/mol)	ΔS (J/mol·K)
−10.0	0.0
−5.0	150.0
−15.0	500.0
−8.0	700.0
−12.0	100.0

plotting the free energy changes vs the temperature (Figure 1b) indicates that there is no temperature such that all the equilibrium constants of the set of reactions are close to each other, i.e., there is no isoequilibrium effect at all. The same behavior was also observed by Petersen,[7a] Agrawal,[7b] and others.[7c,d]

Table 2 lists the enthalpy and entropy changes of another set of hypothetical chemical reactions. (Again, these values are assumed to be error free.) Plotting the free energy change changes vs the temperature (Figure 2a) shows that there is a temperature at which all the equilibrium constants of the set of reactions are fairly close to each other, i.e., there is an isoequilibrium effect. However, plotting the enthalpy vs the entropy (Figure 2b) indicates that the
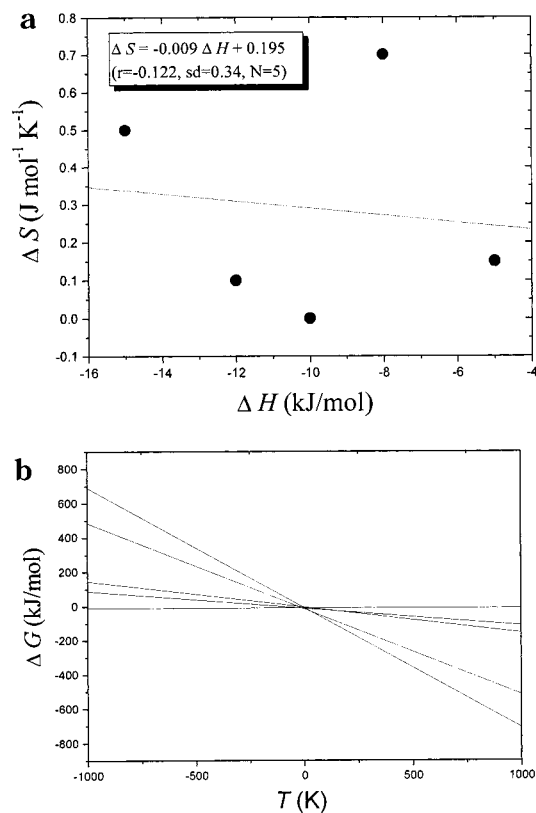
a

$\Delta S = -0.009 \Delta H + 0.195$
(r=-0.122, sd=0.34, N=5)

b

Figure 2. Enthalpy−entropy compensation plot (a) and van't Hoff plot (b) of another series of hypothetical chemical reactions.

correlation between them is rather poor, i.e., there is no significant compensation effect. The same behavior was also noticed by Hammett.[5e]

The above two examples demonstrate that the compensation effect and isokinetic (or isoequilibrium) effect are not necessarily synonymous, and the occurrence of one does not necessarily imply the occurrence of the other.

However, the above simple viewpoint has not been well understood, which resulted in a lot of debates in the past.[8] As pointed out by Larsson et al. recently,[9a] the compensation effect thus defined should only mean that there is a linear relationship between the logarithm of the preexponential factors and the activation energies, between the enthalpies and entropies of activation, or between the enthalpy and entropy changes of a series of similar reactions. On the other hand, the isokinetic (or isoequilibrium) effect should be defined only by the existence of a common intersection point of Arrhenius (or van't Hoff) lines describing the kinetics (or thermodynamics) of a series of similar reactions. This viewpoint was also earlier presented by Feizkhanov.[9b]

The difference between the compensation and isokinetic (or isoequilibrium) effect stems from the different statistical criteria that are used to decide their existences. For the compensation effect, the correlation coefficient of the linear plot is usually used as a criterion to judge its existence. It is common sense that the higher the correlation coefficient, the better the compensation. However, for the isokinetic (or isoequilibrium) effect, people usually base their judgments on how close the reaction rates (or equi-

Table 3. True and Experimental Values of the Enthalpy, Entropy, and Free Energy Changes of a Series of Chemical Reactions (T = 300 K)

ΔH (true) (kJ/mol)	ΔH (exp.) (kJ/mol)	ΔS (true) (J/mol·K)	ΔS (exp.) (J/mol·K)	ΔG (true) (kJ/mol)	ΔG (exp.) (kJ/mol)
−80.0	−83.2	−206.3	−217.3	−18.1	−18.0
−80.2	−75.5	−206.7	−190.3	−18.2	−18.4
−80.1	−80.3	−206.0	−205.7	−18.3	−18.6
−80.3	−74.5	−206.3	−188.0	−18.4	−18.1
−80.3	−83.5	−206.0	−215.7	−18.5	−18.8

librium constants) can be to each other at the isokinetic (or isoequilibrium) temperature. Therefore, eqs 4−6 leading to the compensation and eqs 7−9 leading to the isokinetic and isoequilibrium effect are both only obeyed statistically and the two types of statistical validities are not necessarily equivalent in mathematics. In fact, the compensation effect and the isokinetic (or isoequilibrium) effect might be equivalent only when the correlation coefficient in the compensation plot is exactly 1 or when the set of similar reactions have strictly the same reaction rate (or equilibrium constant) at a certain temperature,[10] which however is rarely possible in the real experiments. Furthermore, the superficial equivalency between eqs 4−6 and eqs 7−9 is based on the assumption of linear Arrhenius and van't Hoff relationships, which are only approximations to the real situations. This fact makes it more unlikely that the compensation effect and the isokinetic (or isoequilibrium) effect are equivalent to each other.

In summary, the compensation effect and isokinetic (or isoequilibrium) can be different.

3. Statistical Examinations on the Three Relationships

As the compensation and isokinetic (isoequilibrium) effects are empirical relationships generated from statistical analyses, it is important to establish certain statistical examinations to test the correctness and significance of these relationships. However, as the three relationships are not necessarily synonymous, the establishment of the compensation effect does not imply that the isokinetic (or isoequilibrium) relationship is operative at the same time. Likewise, the establishment of the isokinetic (or isoequilibrium) relationship does not mean that the compensation effect consequently exists.

3.1. Compensation Effect

According to the definition, if there is a linear correlation between the logarithm of the preexponential factors and the activation energies, between the enthalpies and entropies of activation, or between the enthalpy and entropy changes of a series of similar reactions, the compensation effect is true. However, this definition is proposed based on the assumption that the data used in the correlation are error free. In real experiments, errors of the measurements are unavoidable and the data used in the correlation are the estimators of the corresponding parameters. Therefore, it is possible that though the true values of the parameters have no correlation, their estimators have. This is the cause of the false compensation.

3.1.1. Experimental Values Are Obtained from Calorimetric Method

Usually the kinetic and thermodynamic parameters, namely, the enthalpy changes, entropy changes, preexponential factors, activation energies, enthalpies of activation, and entropies of activation, can be obtained via two methods. The first one is possible only with thermodynamic parameters, which consist of the determination of the enthalpy changes (ΔH) directly from calorimetry and combination with the free energy changes (ΔG) obtained from equilibrium constants, measured at a single temperature. The value of the entropy change (ΔS) is obtained from the equation

$$\Delta S = (\Delta H - \Delta G)/T \qquad (10)$$

Sometimes the experimental errors in ΔG are smaller or much smaller than errors in ΔH. Thus, regressions in the coordinates ΔH vs ΔS, frequently used in the literature, can be dangerous.

Table 3 lists the values of ΔH, ΔG, and ΔS of a set of hypothetical reactions. Both the true values and the experimental ones are given, in accordance with the assumption that the experimental errors in ΔG (herein, it is assumed to be 2%) are much smaller than errors in ΔH (herein, it is assumed to be 25%). Plotting the experimental enthalpies vs the experimental entropies gives a straight line with an excellent correlation coefficient (Figure 3a). However, it is obvious from Figure 3b that the true enthalpies and entropies have no correlation at all. The same behavior was earlier noticed by Exner.[11]

Exner[11] also suggested methods to avoid this danger. According to him, the regression in the coordinates ΔH vs ΔG should be employed to examine the enthalpy−entropy relationship. However, though this method is a correct statistical treatment, it is not relevant to the definition of the compensation effect. Table 4 gives the true values and experimental values of ΔH, ΔG, and ΔS of another set of hypothetical reactions. Again, it is assumed that the experimental errors in ΔG (2%) are much smaller than errors in ΔH (25%). In Figure 4a (for the experimental values) and 4b (for the true values), the plots of ΔH vs ΔS are shown, which both indicate an excellent compensation. However, plot of ΔH vs ΔG shows no correlation (Figure 4c). Therefore, plot of ΔH vs ΔG is not a correct method to examine the compensation effect. The compensation effect can occur when ΔG is approximately constant within the reaction series while ΔH and ΔS vary significantly.[12] As shown later, this kind of compensation is not a random phenomenon without any physical meaning.

Table 4. True and Experimental Values of the Enthalpy, Entropy, and Free Energy Changes of Another Series of Chemical Reactions (T = 300 K)

ΔH (true) (kJ/mol)	ΔH (exp.) (kJ/mol)	ΔS (true) (J/mol·K)	ΔS (exp.) (J/mol·K)	ΔG (true) (kJ/mol)	ΔG (exp.) (kJ/mol)
−100.0	−99.8	−272.7	−272.7	−18.2	−18.0
−120.0	−101.2	−340.0	−276.0	−18.0	−18.4
−140.0	−151.0	−406.0	−441.3	−18.2	−18.6
−160.0	−176.5	−473.3	−528.0	−18.0	−18.1
−180.0	−170.2	−539.3	−505.3	−18.2	−18.6
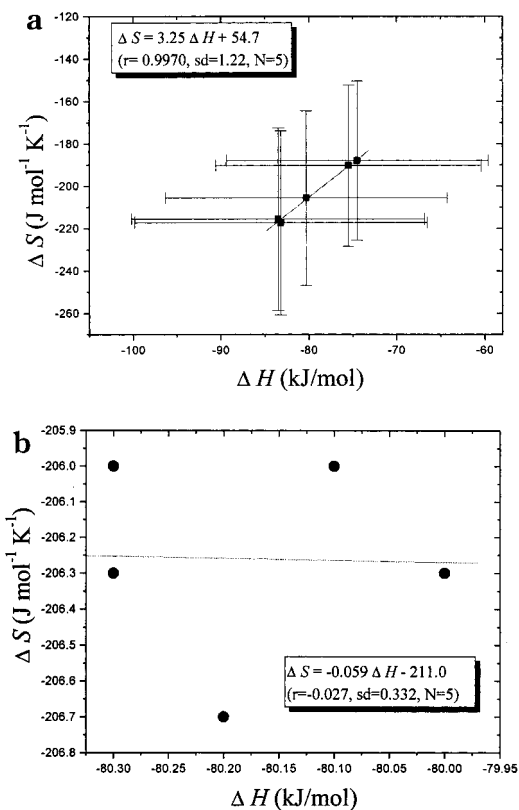
Figure 3. Compensation plot for the experimental (a) and true (b) enthalpy and entropy changes of a series of hypothetical chemical reactions.

In fact, examination of the compensation effect here is quite simple. In Figure 4a, the error bars of the experimental enthalpies and entropies are shown. From the error bars, it is obvious that the compensation in this case is correct. On the other hand, from the error bars in Figure 3a, it is also obvious that the compensation in that case is questionable. Therefore, plotting ΔH *vs* ΔS with error bars is a simple, clear, and correct method in the establishment of the compensation effect from the experimental data obtained via calorimetric measurements.

3.1.2. Experimental Values Are Obtained from Arrhenius or van't Hoff Plot

In many cases, the values of the kinetic or thermodynamic parameters cannot be measured directly. Then they can be derived from a linear Arrhenius or van't Hoff plot. In 1962, Petersen et al.[13] pointed out that if the activation enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) were measured for a series of reactions using the same two temperatures T and T' throughout the series, the experimental error in $\Delta S^{\ddagger}$ (denoted as σ) was directly proportional to the experimental error
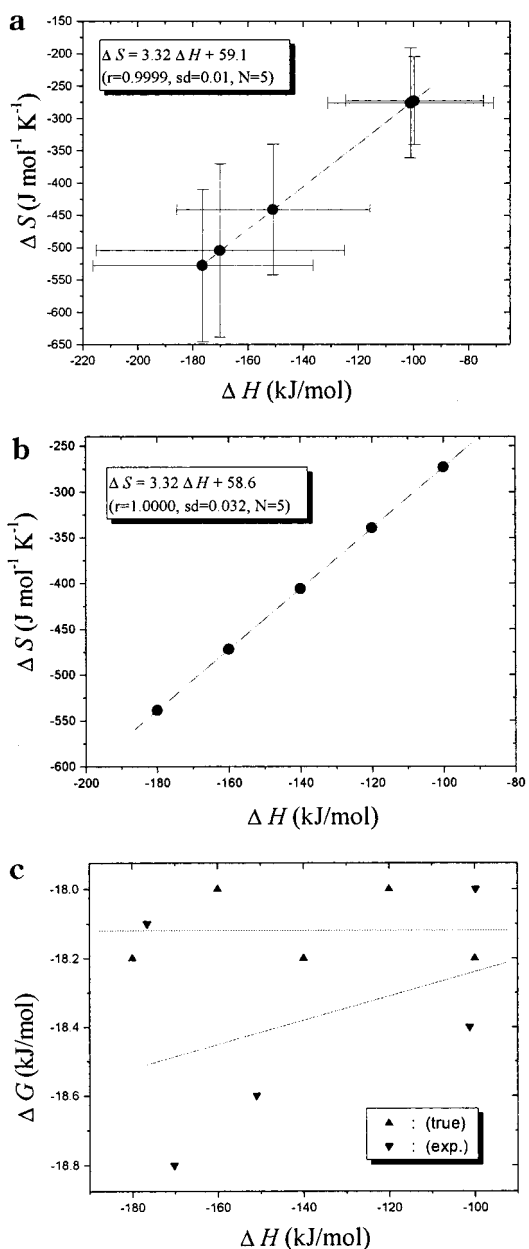
Figure 4. Compensation plot for the experimental (a) and true (b) enthalpy and entropy changes of a series of hypothetical chemical reactions, and the enthalpy−free energy plot (c) for the experimental and true enthalpy and free energy changes.

in $\Delta H^{\ddagger}$ (denoted as δ), obeying the following equation

$$\sigma = \frac{3T' - T}{2T' \cdot T} \cdot \delta \tag{11}$$

Thus, if the range of values of the true $\Delta H^{\ddagger}$ (or $\Delta S^{\ddagger}$) is not as large as that of the experimental error δ (or

σ), a plot of $\Delta H^{\ddagger}$ vs $\Delta S^{\ddagger}$ will be a straight line of slope $2T{\cdot}T'/(3T' - T)$. Usually $2T{\cdot}T'/(3T' - T)$ is approximately T, because T and T' are usually not very different. Thus, the observed enthalpy−entropy correlation is simply a demonstration of the experimental error and hence misleading.

The finding is important and has been rediscovered by many other scientists later, often independently.[14] In the 1970s, Exner carefully examined the problem in detail with advanced mathematical analyses.[15] The conclusion is basically the same as that of Petersen, i.e., the uncertainty in the estimates of ΔH and ΔS (or $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ or ln A and E_a) from a linear Arrhenius or van't Hoff plot are highly correlated. If the uncertainty is large enough, the inherent imprecision of the data will lead to a false compensation. Exner again suggested several methods for finding a real compensation effect. However, these methods are again irrelevant to the compensation effect as mentioned above. In fact, these methods should be applied to the isokinetic (or isoequilibrium) relationship.

In 1999, Wirz et al. reported an interesting compensation effect in the triplet−singlet intersystem crossing of 1,3-cyclopentanediyl diradicals.[16] Though the Arrhenius parameters were found to be not obeying the compensation relationship according to Exner's method, the 95% confidence regions of the datum pairs (ln A and E_a) were found to be much smaller than their total variation, which indicated that the compensation was real. Herein, the 95% confidence region is the region in the ln $A - E_a$ plane that the true values of the datum pair (ln A and E_a) should be located in at a confidence level of >95%. It can be drawn when the experimental error is known, and usually the experimental errors in ln A and E_a are correlated in such a way that the confidence region is of an elliptical shape.[17] Apparently, drawing the confidence regions is based on the same idea as drawing the error bars in Figure 3.

Another method to determine the existence of the compensation effect from the data measured with the Arrhenius or van't Hoff approach was provided by Alper and Gelb.[18a] In the method, it is assumed that for each reaction i

$$\Delta H_i = \alpha + \beta \Delta S_i \qquad (12)$$

Thus, at each temperature T_{ij}

$$R \ln K_{ij} = -\Delta H_i / T_{ij} + \Delta S_i \qquad (13)$$

Taking α, β, and ΔS_i as adjustable parameters, the Levenberg−Marquardt algorithm was used to optimize them by minimizing χ^2

$$\chi^2 = \sum_i \sum_j (y_{ij} - Y_{ij})^2 / \sigma_{ij}^2 \qquad (14)$$

Herein, y_{ij} is the measured $R \ln K_{ij}$ and Y_{ij} is the calculated $R \ln K_{ij}$ by eq 13. σ_{ij} is the experimental uncertainty in the measured value of $R \ln K_{ij}$. Since β is calculated simultaneously with ΔS_i, the pseudo-compensation between enthalpy and entropy does not affect the value of β. The absence of compensation

can be determined by the fact that (1) $\beta = 0$ or the uncertainty in β is sufficiently large that the appropriate confidence interval about β encompasses 0 or (2) χ^2 is much larger than the number of degrees of freedom ($\sum N_i - n - 2$). The method is strict in statistics and has been applied to the compensation in cyclodextrin complexation.[18b] However, in the method it is assumed that the enthalpy and entropy are temperature independent. Therefore, the uncertainty in β can be large if it is far from the experimental temperature range.

In summary, a mere observation of correlation between the experimental ΔH and ΔS, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, or ln A and E_a cannot, by itself, be taken as evidence for the existence of the compensation effect. Explicitly drawing the error bars (or confidence region) in the correlation diagram is a simple, clear, and correct test for the existence of the compensation effect.

3.2. Isokinetic Effect and Isoequilibrium Effect

As mentioned above, the isokinetic (or isoequilibrium) effect can be different from the compensation effect. Therefore, the correlation between ΔH and ΔS, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, or ln A and E_a is not good evidence for the existence of the isokinetic (or isoequilibrium) relationship.

According to the definition, one way to find a real isokinetic (or isoequilibrium) relationship is to overlay rate (or equilibrium) constant data for all the reactions in the series of interest on a single Arrhenius (or van't Hoff) plot and look for a point of common intersection among the best-fit lines. If no point of common intersection exists within experimental error, then an isokinetic (or isoequilibrium) relationship cannot be said to hold for the series of reactions.

Exner suggested a simple method to evaluate the isokinetic relationship.[15a,b] It consisted of plotting the logarithms of rate constants at two temperatures ($T_2 > T_1$) against each other according to the equation

$$\log k_2 = a + b \log k_1 \qquad (15)$$

A linear plot implies a valid isokinetic relationship. From the graphically estimated slope b, the isokinetic temperature β is readily obtained.

$$\beta = T_1 T_2 (b - 1)/(b T_2 - T_1) \qquad (16)$$

This method is correct in statistics but has the shortcoming that it is only applicable to measurements at two temperatures. Furthermore, Leffler has pointed out the limitations of the method when two interaction mechanisms are operative and, thus, the extrathermodynamic relationship under this condition consists of two independent isokinetic effects.[19] It was also criticized by Lumry and Rajender[5d] that this correlation analysis exaggerated errors.

Exner has also given a stricter but more sophisticated method to test the isokinetic relationship based on least-squares fitting.[15c−e] In the method, linear regressions of experimental Arrhenius plots are done (i) individually for each reaction of the series and (ii) under the isokinetic constraint that all regression

lines intersect at some temperature $T = \beta$. As β is not known a priori, the residual sum of squares is calculated for trial values of β until the minimum, S_0, is found. This is compared to the residue sum of squares that is obtained when a separate straight line is fitted to the data of each reaction without any restrictions, S_{00}. The hypothesis of the isokinetic relationship is simply to be accepted if S_{00} is larger S_0. More sophisticatedly, an F-statistic can be calculated to test the hypothesis of isokinetic relationship, i.e., the null hypothesis H_0: the true (error-free) regression lines of all reactions intersect at one point, according to the following equation

$$F(f_0, f_{00}) \approx \frac{(S_{00} - S_0)/f_0}{S_{00}/f_{00}} \qquad (17)$$

Here, the degrees of freedom of the unconstrained regression (i) are f_{00} = number of datum points − 2 and those associated with introducing constraint (ii) are f_0 = number of reactions −2.

The above method is often called the Exner isokinetic method. Sometimes, it is also called the Linert−Exner method, because Linert has significantly improved the calculation procedure and the understandability of the method.[20] As the calculation procedure is still complicated to some extent, the method has been relatively little used.[21] Also, as the common intersection point is often calculated to lie well outside the range of experimentally accessible temperatures, the uncertainty in β obtained from this method is very large. In 1973, Wold and Exner[22] generalized the method to the cases when the activation parameters of the individual reaction series were temperature dependent. Interestingly, it was found that in some cases, enthalpy−entropy plots showed a large apparent scatter despite a very good fit of the isokinetic model to the experimental data.[23] This is another example showing that the isokinetic (or isoequilibrium) effect is not equivalent to the compensation effect.

In 1976, Krug et al.[24] demonstrated that the linear plots of enthalpy vs entropy did not necessarily imply that a chemical phenomenon was responsible for the observed correlation. It was found that the enthalpy and entropy estimates were distributed by experimental errors in elliptical probability regions that were very elongated and appeared as lines. They claimed that the compensation regression should be of enthalpy estimates on free energy estimates evaluated at the harmonic mean of the experimental temperatures instead of enthalpy on entropy because these parameters were not statistically correlated. However, as mentioned above, the plot of enthalpy vs free energy is only relevant to the problem of the isokinetic (or isoequilibrium) relationship and not applicable to the problem of enthalpy−entropy compensation. Despite this fact, the so-called Krug−Hunter−Grieger plot of ΔH vs ΔG was often used to show the existence of the isokinetic (or isoequilibrium) effect due to its simplicity.[25] Interestingly, in 1994, Gilli et al.[26] claimed the existence of the enthalpy−entropy compensation in drug−receptor binding despite the fact that ΔH and ΔG for the

complete set of data were totally uncorrelated. This again manifests the difference between the compensation and isokinetic and isoequilibrium relationships.

In addition to the above methods, there are several others that have been proposed to check the existence of an isokinetic or isoequilibrium relationship.[27] However, the basic ideas in these methods are the same as those mentioned above.

On the basis of the above methods, some authors have examined the correctness of the isokinetic or isoequilibrium relationships reported in the literature.[24,28] Because most of them have not noticed the difference between the compensation effect and the isokinetic (or isoequilibrium) effect, they tended to claim that most cases reported in the literature corresponded to the false compensation, which caused a great deal of controversy and debate in the literature.[29] Fairly speaking, although some cases of the compensation effect reported in the literature are false, most observed compensation relationships are correct. However, only a few cases reported in the literature can be said to correspond to the isokinetic (or isoequilibrium) effect, and the rest are only examples of compensation.

In summary, an isokinetic or isoequilibrium relationship cannot be determined from the compensation plot. They should be defined only by the existence of a common intersection point of Arrhenius (or van't Hoff) lines describing the kinetics (or thermodynamics) of a series of reactions.

4. Theories of the Three Relationships

4.1. Outline

One reason that the compensation effect and the isokinetic (or isoequilibrium) effect are in a state of great confusion is due to the general belief of the lack of a theory connecting the experimental observations with events at a molecular level.[30] In fact, from the very beginning of the study on the three relationships, a large number of theories have been proposed to explain them.

However, as most researchers did not recognize the difference between the three relationships, they often tried to establish models that could explain the three simultaneously, which is unfortunately impossible in principle. Furthermore, since the three relationships were discovered in many seemingly unrelated fields, often independently, theories proposed in one field are usually poorly known to scientists in the other fields.

Herein, theories on the three relationships are reviewed in different categories, according to which relationship the theory really addresses. Interestingly, a lot of seemingly unrelated theories are found based on the same ideas.

4.2. Pure Mathematical Explanations

Before we discuss the possible physical origins of the three relationships, let us first review the theories of the three relationships based on pure mathematical considerations of the kinetic or thermodynamic

models that are used to treat the experimental data. These theories are different from those of the false compensation caused by the experimental errors because they could still be applicable even if the experimental data were free of error.

The first theory in this category regards the compensation between the logarithm of the preexponential factors and the activation energies as a result of the linear relationship between Eyring's activation enthalpy and entropy.[31] It was criticized by Tudos and David,[32] who showed that the theory gave no additional or newer physical information on the compensation effect.

The second mathematical explanation of the compensation effect is quite amusing, i.e., the compensation is caused by the work habit of the kineticists.[33] Simply speaking, too fast or too slow reactions are generally difficult or even impossible to monitor. Therefore, kineticists tend to selectively study the reactions with modest reaction rates at normal temperature, so that all the reported reaction rates in logarithmic form usually fall inside a relatively small range. However, the extent of the temperature dependence of the reaction usually causes little trouble for the kineticists, which means that the reported preexponential factors and activation energies can vary greatly. Thus, in the equation

$$\ln k = \ln A - E_d/RT \qquad (18)$$

$\ln k$ and RT vary much less significantly than $\ln A$ and E_a. As a result, the compensation between $\ln A$ and E_a is necessary. This interesting theory is difficult to object to. It also teaches that if the series of reactions under study are not related in mechanism, the discussion of the compensation effect might be meaningless because the compensation relationship is so easy to establish. However, when the series of reactions are strongly similar in mechanism, the observed compensation still requires a deeper explanation rather than that mentioned above, i.e., why these similar reactions, with similar reactions rates, differ so much in their activation energies and preexponential factors?

In 1981, starting with the equation

$$\ln k_0 = c + rE \qquad (19)$$

where k_0 was the preexponential factor, E the activation energy, and c and r presumably constants, Feizkhanov et al.[34] through mathematical deductions "obtained" the equation $r = 1/RT$. Because at a given temperature the parameter r was the same for any reaction, the compensation effect described by eq 19 was argued to have no physical meaning and be therefore scientifically worthless. This paper is problematic because the compensation effect described by eq 19 requires that r and c be constants at the same time. In fact, eq 19 can be directly generated from the Arrhenius equation $k = k_0 \exp(-E/RT)$, where k is the rate constant of the reaction. However, if r equals $1/RT$ is a constant, c will equal $\ln k$ of each reaction and is therefore NOT a constant within the series of reactions. Thus, Feizkhanov's argument is unfortunately wrong.

Nevertheless, Feizkhanov's argument was re-proposed independently by several other authors,[35] who again considered the compensation effect as a mathematical consequence of the Arrhenius equation. Zsako, by citing the fact that the isokinetic temperature could be higher or lower than the temperature at which the reaction took place, criticized this viewpoint.[36]

In 1991, Audouin and Verdu studied the compensation effect in the thermal aging of polymers of electrotechnical interest.[37] It was shown that the Arrhenius equation was usually not justified for the overall kinetics. Numerical examples were given demonstrating that the non-Arrhenian character of the reaction could lead to the apparent compensation effect between the preexponential factor and the activation energy if the overall rate was deliberately fitted into the Arrhenius equation. This viewpoint, i.e., the compensation might be caused by the misuse (usually unconscious by the researchers) of the kinetic model, can be found in several other studies.[38] In 1996, Antal et al.,[39a] by developing the thermal lag model, suggested that the undetected thermal lag might be the underlying cause of the compensation effect observed in biomass pyrolysis. Later, Budrugeac et al. also showed that the compensation might be the consequence of using an overall rate equation instead of the real complex rate equation.[39b,c]

In 1994, Vyazovkin and Linert studied in detail the compensation effect found in the nonisothermal decomposition of solids.[40] They named the compensation caused by variation of (i) reaction model, (ii) conversion, or (iii) hearing rate as a "false" isokinetic relationship. However, since no statistical examination of the isokinetic relationship has been conducted in these studies, the so-called "false" isokinetic relationship is better named as a "false" compensation effect.

In 1997, Stepanov proposed another mathematical explanation of the compensation effect.[41] On the basis of the assumption that k = constant for $0 < T \le T_0$, $k = f(T)$ for $T_0 < T \le T_1$, $k = A_1 \exp(-E_1/RT)$ for $T_1 < T \le T_2$, $k = A_2 \exp(-E_2/RT)$ for $T_2 < T \le T_3$, ..., $k = A_n \exp(-E_n/RT)$ for $T_n < T$,[42] the following equation was obtained

$$k = C \exp(E_n/RT_n)\exp(-E_n/RT) \qquad (20)$$

here C was constant. The compensation equation was obtained if $\ln C^i \approx \ln C^j$ held for different reactions of the same type, because it was argued that T_n^i did not differ much from one another. This model is not very convincing. In addition to the questionable validity of the abrupt changes in the energy of activation every few dozen degrees, the reason for $\ln C^i \approx \ln C^j$ is far from clear.

In summary, the compensation relationship is not difficult to establish because the work habit of the kineticists and the misuse of the kinetic model can cause compensation. Thus, not all of the observed compensations require a physicochemical explanation. Moreover, the change of the compensation relationship to its mathematically equivalent form cannot constitute a useful theory.

4.3. Theories of Compensation Effect

4.3.1. Exact Compensation Is Impossible

Before we review the theories on the compensation effect, it should be pointed out that the exact (or full) enthalpy−entropy compensation does not embrace the basic term and thus cannot extend to the overall $\{G, H, S\}$ of the formal components.

This conclusion can be drawn from the Benzinger's division of enthalpy and entropy. In 1971, Benzinger et al.[43a,b] showed that the entropy changes in an isothermal, isopiestic process were related through the heat integral in such a way that

$$S(T) = \frac{\int_0^T S(T')\, dT'}{T} + \frac{\int_0^T C_p(T')\, dT'}{T} \quad (21)$$

$$H(T) = H(0) + \int_0^T C_p(T')\, dT' \quad (22)$$

and

$$G(T) = H(0) - \int_0^T S(T')\, dT' \quad (23)$$

In eq 21, the first part of entropy was called the motive entropy while the second part was called the compensation entropy. Both parts of entropy are positive definite values, and it can be seen that the compensation entropy does not appear in the free energy G or its changes. The same theory has also been developed by several other authors.[43c]

Although many authors have raised objections to Benzinger's division of entropy in that such a separation might have no physical significance, Grunwald[5v] proved that full enthalpy−entropy compensation was a mirage based upon Benzinger's entropy division. From eqs 21 and 22, it can be seen that the thermal excitation part of S fails to compensate for the thermal-excitation part of H by a positive amount equal to $T^{-1}\int S\, dT$. For a reaction series, this portion of entropy would be a difference of such portions between reactants and products or between reactants and transition states. In either case, since this portion of entropy is nonzero, exact compensation is impossible. The same idea can be found in Rhodes's paper based on quantum thermodynamics.[44]

4.3.2. Entropic and Energetic Aspects of Chemical Bonding

Generally speaking, a stronger intermolecular interaction or bonding (related to the enthalpy) will lead to a greater reduction of the configurational freedom and hence greater order of the system (related to the entropy). This might be the cause of the enthalpy−entropy compensation.

In 1969, Thorn[45] tried to show the monotonicity of relation between ΔS and ΔH by considering the entropic and energetic aspects of chemical bonding. It was proven that for a sequence of reactions order → disorder, in which all the significant configurations of the reactants in the sequence are sufficiently equivalent and in which all the significant configurations of the products in the sequence are sufficiently equivalent, ΔS is a nondecreasing function of ΔH

such that a branch can occur at a low virtual temperature with negative curvature and a branch can occur at high virtual temperature with positive curvature. The monotonic relationship was considered a reason for the linear compensation effect observed for reactions involving organic compounds with varying substituents. However, as the $\Delta S - \Delta H$ relationship shown in the study was often extremely curved, the simple monotonicity cannot be satisfactorily used to explain the linear enthalpy−entropy compensation.

Later, Stolov et al. studied the compensation effect in the thermodynamics of conformational equilibria, i.e., the enthalpy (ΔH) and entropy (ΔS) differences of the conformers changed in the same direction when going from one solvent to another.[46] The explanation of the compensation started from the following equation, which can be easily generated from statistical thermodynamics

$$\Delta S = S_A - S_B = \frac{1}{2}\, R \ln\!\left(\frac{I_{rA}}{I_{rB}} \cdot \frac{K_B}{K_A}\right) \quad (24)$$

In eq 24, A and B are two conformers of a molecule, I_r is the reduced inertia moment, and K is the force constant for torsional vibrations. Thus, for the change of ΔS with a solvent, one obtains

$$\Delta\Delta S = \Delta S' - \Delta S = \frac{1}{2}\, R \ln\!\left(\frac{K_A}{K_A'} \cdot \frac{K_B'}{K_B}\right) \quad (25)$$

where K' is the force constant in the second solvent and I_r disappears because the reduced inertia moment of a molecule is a constant.

It was supposed that the dependence of the enthalpy upon a coordinate of the internal rotation obeyed the following equation

$$H = \frac{\Delta H_{AB}^{\ddagger}}{2}[1 - \cos(nq)] \quad (26)$$

Then

$$K_A = \frac{\partial^2 H}{\partial q^2}\bigg|_{q=0} = \frac{\Delta H_{AB}^{\ddagger}}{2}\, n^2 \quad (27)$$

Thus, S had been correlated with H explicitly via K, and finally it was obtained that

$$\frac{\Delta\Delta S}{\Delta\Delta H} \approx \frac{R}{2}\, \frac{m}{\Delta H^{\ddagger}} \quad (28)$$

where m was the number of coordinates responsible for the internal rotation process. This is a good explanation of the enthalpy−entropy compensation observed in a specific situation.

In the 1990s, William et al. studied in detail the enthalpy−entropy compensation in weak intermolecular interactions.[47] The theory rooted in a general curve for the monotonic dependence of the enthalpic benefit on the entropic cost in a simple exothermic bimolecular association as shown in Figure 5, which could be easily generated from the Morse potential of chemical bonding with statistical thermodynamics.[5q]
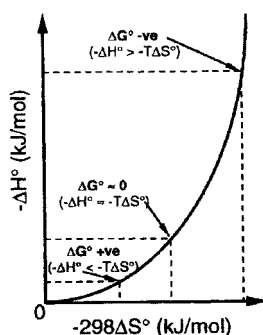
Figure 5. General form of the plot of the exothermicity of association (ΔH) $\mathbf{A} + \mathbf{B} \rightarrow \mathbf{A \cdot B}$ as a function of the entropic cost (ΔS) at a temperature of 298 K. There is a limit to the price in entropy to be paid (essentially due to loss of 1 mol of translational and rotational freedom per mole of $\mathbf{A}$ and $\mathbf{B}$), and this limit is approached before covalent bond strengths are reached. Weak interactions (typical hydrogen-bond strengths) occupy a region lower down the curve and closer to the origin. (Reprinted with permission from ref 47f. Copyright 1996 American Chemical Society.)

Experimental evidences from the associations in the gas phase and from the monatomic sublimations were shown to support the proposed relationship. Although the dependence of association enthalpy on association entropy is not linear, it was believed that this type of monotonicity constituted the physical origin of the enthalpy−entropy compensation observed in chemistry and biology. The systems that have been addressed included the binding of agonists versus antagonists, the interaction of macrocycles with neutral molecules, stacking of free bases and nucleotides, etc.

Fairly speaking, the compensation between the association energy and association entropy (though not strictly linear) is correct for the simple chemical systems bounded by weak intermolecular interactions. In fact, this effect has been proven by quantum chemical calculations[48] and by experimental observations on van der Waals molecules.[3t] However, it is far from straightforward to use the ideas derived from the study of the process of crystallization or gas-phase association on the much more complicated biochemical problems such as molecular recognition. The primary reason is that in biochemical processes, the solvation effect plays a very important role in determining the enthalpy and entropy of the systems. Though the solvent−solvent and solvent−solute interactions are weak intermolecular interactions, their mathematical consequences are not easy to predict.

In summary, the monotonic relationship between the energy and entropy of the weakly bonded chemical systems is true. However, this fact might not fully explain the compensation effect observed in chemistry and biology in general.

4.3.3. Compensation and Linear Free Energy Relationship

Both the compensation effect and the linear free energy relationship are empirical relationships. However, the linear free energy relationship has been understood much better, and the existence of linear free energy relationship has almost been accepted as an axiom in the textbooks. Therefore, people can ask

is it possible to explain the compensation effect from the better-understood theories of linear free energy relationship?

In 1955, Leffler[49] studied the entropy requirements of the Hammett relationship. He started with the following well-known equation

$$\Delta \Delta F^{\ddagger} = \rho \Delta \Delta F_s$$

where $\Delta \Delta F^{\ddagger}$ is the effect of a certain substituent on the free energy of activation, $\Delta \Delta F_s$ is the effect of the same substituent in an arbitrarily chosen standard reaction, and ρ is a constant characteristic of the reaction being correlated. Obviously, $\Delta \Delta F_s$ is independent of temperature, but $\Delta \Delta F^{\ddagger}$ and ρ might be not. Thus

$$\Delta \Delta F_1^{\ddagger} = \Delta \Delta H^{\ddagger} - T_1 \Delta \Delta S^{\ddagger} \tag{29}$$

$$\Delta \Delta F_2^{\ddagger} = \Delta \Delta H^{\ddagger} - T_2 \Delta \Delta S^{\ddagger} \tag{30}$$

$$\Delta \Delta S^{\ddagger} = \frac{\Delta \Delta F_1^{\ddagger} - \Delta \Delta F_2^{\ddagger}}{T_2 - T_1} = \frac{\rho_1 - \rho_2}{T_2 - T_1} \Delta \Delta F_s \equiv \lambda \Delta \Delta F_s \tag{31}$$

If $\lambda \neq 0$

$$\Delta \Delta H^{\ddagger} = \frac{\rho_1 + \lambda T_1}{\lambda} \Delta \Delta S^{\ddagger} \tag{32}$$

Therefore, $\Delta H^{\ddagger}$ is a linear function of $\Delta S^{\ddagger}$. In other words, the validity of the Hammett equation over a range of temperature requires the compensation relationship by thermodynamics. This idea was echoed later by Palm, Exner, and others.[50]

However, the explanation that the compensation effect is simply a result of the validity of the linear free energy relationship at variable temperature is not convincing. First, it is possible that the compensation occurs while at the same time the linear free energy relationship does not.[51] On the other hand, it was also shown that linear free energy relations are sometimes valid without the simultaneous validity of the compensation model.[52] In fact, both the compensation (eq 5) and linear free energy relationships (eq 29) are only obeyed statistically, and hence, the mathematical transformation from eq 29 to eq 5 may be questionable. As shown in section 2 of this review, any mathematical transformation of the statistically valid equations can be dangerous in that the equivalence it involves might be only superficial.

Moreover, if any theory of the compensation effect based on the linear free energy relationship can be said at a molecular level, it must involve an explanation of the linear free energy relationship at a molecular level. However, to date, the physical origin of the linear free energy relationship is not fully clear yet, i.e., why are free energies, which are composites of two quantities with independent molecular explanations, often correlated with one or two parameters?[53] The difficulty of answering this question arises from the tricky solvation enthalpy and entropy, which are very difficult to calculate or to correlate, either with another quantity or among themselves.

Interestingly, Hepler[54] conducted a series of theoretical studies relevant to the problem. He formally partitioned the total free energy of an isodesmic reaction into internal and external enthalpies and entropies.

$$\delta\Delta G = \delta\Delta H_{int} - T\delta\Delta S_{int} + \delta\Delta H_{ext} - T\delta\Delta S_{ext} \tag{33}$$

The internal terms represent pure substituent effects in the gas phase, and external terms represent the substituent effects due to the solvation. It was suggested that the internal entropy could be neglected, i.e., $\delta\Delta S_{int} = 0$ and that the external enthalpy and entropy compensated each other, i.e.

$$\delta\Delta H_{ext} = \beta_{ext}\delta\Delta S_{ext} \tag{34}$$

If the above relations are correct, the observed $\delta\Delta G$ in solution equals approximately $\delta\Delta H_{int}$. This should explain the success of the linear free energy relationship: the experimental free energy in solution should be very near to the theoretically much simpler quantity, the enthalpy in the gas phase. This theory, though criticized by some scientists,[23,55] has been successfully employed in several studies.[56] Its implication is interesting, i.e., the explanation of the linear free energy relationship might require the involvement of enthalpy–entropy compensation.

Recently, Horvath et al.[57] studied the enthalpy–entropy compensation in liquid chromatography. On the basis of the theory of group additivity, linear exothermodynamic relationships were found between thermodynamic quantities including enthalpy, entropy, and free energy and the properties (n) of the eluite, the eluent, or the stationary phase, which typically read like

$$\Delta H = a_h\varphi + b_h \tag{35}$$

$$\Delta S = a_s\varphi + b_s \tag{36}$$

and

$$\Delta G = a_g\varphi + b_g \tag{37}$$

Consequently, the enthalpy–entropy compensation was clear from itself. The theory is correct, as it has experimental evidence. However, the application of the theory to the generally observed compensation effect in chemistry and biology seems limited, because a relationship like eq 35 or 36 is not frequently found. Besides, as the validity of eqs 35–37 has not been explained from the first principle, the theory is not at a molecular level. As pointed out by Lumry,[5r] the linear enthalpy–entropy compensation due to additivity is deceptive in promising more than it delivers, because its profundity goes no farther than indicating that the members of a series share a single source of additivity.

In summary, there is certainly some relation between the linear free energy relationship and the compensation effect. However, it is not clear which one can be used to explain the other or if neither can. Since both behaviors are empirical and have not been

fully explained, any theory merely based upon them cannot be regarded as being at a molecular level.

4.3.4. Compensation Due to the Solvation Effect

Apparently no theory can anticipate at what temperature a given experiment will be carried out.[55] Therefore, it is hard to understand why the coefficient β (sometimes called as "compensation temperature") in eq 4–6 is often found near the experimental temperature. In fact, a number of authors prefer to describe the compensation relationship with the following equation instead of, for example, eq 6.

$$\Delta H_i = a + b(T_i\Delta S_i) \tag{38}$$

In this equation, the constant b is usually said to be the "extent" to which the entropy compensates the enthalpy and the "compensation temperature" is usually not mentioned at all. (For example, see the recent series of studies on the enthalpy–entropy compensation in molecular recognitions by Inoue et al.[58])

Equation 38 has some advantages over eq 6 in describing the compensation relationship. First, as the compensation and isokinetic (or isoequilibrium) effect can be different, the introduction of the "compensation temperature" β in eq 6 is misleading. Second, few enthalpies and entropies in the compensation series are strictly temperature independent. Hence, it is advisable or necessary to contain the temperature information in the compensation model. Third, eq 38 makes the explanation of the "compensation temperature" unnecessary and the problem raised above changes to a much simpler one, i.e., why the experimental entropy often offsets the experimental enthalpy to nearly 100%.

The first explanation of this problem was given by Lumry et al.[5d] As his examples of enthalpy–entropy compensation often corresponded to aqueous solution reactions, he suggested that the compensation might be a consequence of the properties of water. He employed the idea of two phenomenological species of water, and he supposed that reaction $A \rightarrow B$ was coupled to a second reaction in which n water molecules in state $W1$ underwent a transition to state $W2$, i.e., $n\,(H_2O)_{W1} \rightarrow n\,(H_2O)_{W2}$. The overall enthalpy and entropy changes for the reaction then became

$$\Delta H = \Delta H_{A\rightarrow B} + n\Delta H_{W1\rightarrow W2} \tag{39}$$

and

$$\Delta S = \Delta S_{A\rightarrow B} + n\Delta S_{W1\rightarrow W2} \tag{40}$$

It was suggested that in the range of 250–320 K, which corresponded to the normal experimental temperature, $\Delta G_{W1\rightarrow W2} \approx 0$. Also, in many reactions it was believed that $n \gg 1$. Thus, the compensation was easy to understand.

The above theory of enthalpy–entropy compensation is interesting and has been quoted or re-proposed in many later studies.[59] However, the theory is not perfect in that it involves the use of a two-state hydration model. Traditionally it was believed that when hydrated, the structure of the water molecules

in the near vicinity of the nonpolar solute will be enhanced.[60] This idea of "structure making" and "structure breaking" was frequently employed in the explanation of hydrophobicity.[61] Sometimes the idea was even overemphasized, resulting in the postulation of the iceberg- or clathrate-like structures of the hydrophobic hydration shell. However, this microscopic picture of hydration was greatly challenged recently. Neither the neutron scattering measurements nor the computer simulations indicated any evidence that the structure of the hydration water close to a nonpolar group was more ordered than that of water in the bulk.[62] Thus, it seems that at least eqs 39 and 40 are not fully correct. Furthermore, since the compensation effect has been found in other solvent systems, the idea that enthalpy–entropy compensation is a ubiquitous property of water is not exact.

Nevertheless, it is certain that there is some relation between solvation and the compensation effect.[63] In fact, in the field of computational chemistry, theoreticians have found that the calculated enthalpy and entropy of solvation often compensate for each other. In 1988, Karplus et al. showed theoretically that only averages over the solute–solvent interaction energy contribute to the free energy and that the solvent–solvent interaction term, which contributes to the so-called cavity (solvent reorganization) term to the energy, is canceled exactly by a corresponding term in the entropy.[64] In fact, this viewpoint had been proposed before[65] and was re-proposed later by several other authors,[66] especially Lee et al.[67] Furthermore, in recent computer simulations of solvation, more and more numerical results were shown to support the idea.[68] Unfortunately, the theory remains hardly known by the chemists outside the field of computer simulation. Apparently, although the physics involved in the theory is straightforward, its mathematical form is not friendly enough to the experimentalists.

Recently, Grunwald provided an interesting model to explain the enthalpy–entropy compensation.[5v,6] This theory, though based on the idea similar to that mentioned above, is much easier to understand. According to the theory, the enthalpy–entropy compensation can be caused by two types of interactions, i.e., solvent reorganization and molar shift.

The description of the solvent reorganization is based on the idea of distinguishable subspecies of the same compound in a solution. As theoretically proven,[70] in most liquid solutions, the solvent molecules that are adjacent to a solute molecule (denoted as $A\backslash x$) are distinguishable from those that reside in the "bulk solvent" (denoted as $A\backslash a$). Thus, for example, in the solvation of gaseous X in liquid A (in the absence of bonded complex formation), the quantities of the two distinguishable subspecies $A\backslash x$ and $A\backslash a$ will change. Consequently, two processes occur during the solvation of X, i.e.

$$X(g) \rightarrow X\backslash a \qquad (41)$$

and

$$n\,A\backslash a \rightarrow n\,A\backslash x \qquad (42)$$

where n is the number of moles transferred from $A\backslash a$ to $A\backslash x$ per mole of $X(g) \rightarrow X\backslash a$. Equation 41 is called the nominal process, while eq 42, the environmental process, describes the solvent reorganization. It can be proven that the free energy change contributing from the environmental process is zero, so that only the nominal process accounts for the observed free energy change associated with the solvation. On the other hand, the enthalpy and entropy contributing from the environmental process are usually nonzero and in consequence must offset each other exactly. If this portion of enthalpy and entropy is substantial or even much larger than the free energy contributed from the nominal process, a net enthalpy–entropy compensation effect will be observed.

The theory of molar shift is also based on the idea of distinguishable species or subspecies. For example, 1,2-dichloroethane is an equilibrium mixture of trans and gauche forms. When the 1,2-dichloroethane component is heated to a new equilibrium state, the whole process can be viewed as occurring in two parts. The first process is an isomolar one in which the temperature is raised without a change in the gauche/trans ratio. It causes a departure from equilibrium. Then there is an isothermal process in which the gauche/trans ratio returns to equilibrium but at a new temperature. This isothermal process is a molar shift. It can be proven that the change in free energy contributing from the molar-shift part is zero. Hence, for the molar-shift part, the enthalpy must offset the entropy exactly. As a result, molar shift causes compensation. Interestingly, the molar shift can happen within the solvent molecules themselves. As shown by Grunwald, in pure liquid water there are at least two environmental isomers, $W\backslash 4w$ and $W\backslash 5w$.[71] In $W\backslash 4w$, the water molecules interact with four neighbors, while in $W\backslash 5w$, they have five neighbors. It was thought that the addition of nonpolar solutes could induce strong molar shifts in the water, which could be used to explain the concept of hydrophobicity. Moreover, a molar shift can happen in the host–guest complexation, if the complexed molecules can exist in several distinguishable forms such as "weakly bound" and "strongly bound" ones.

The above interesting theory is basically correct. However, from the point of view of the present authors, the theory could be unified into a more general form. Herein, let us suppose that in a mixture (not necessarily a solution) there are several species $(X_1, X_2, ..., X_S)$, each of which exists in several distinguishable subspecies (for example, X_i has the subspecies $X_i^1, X_i^2, ..., X_i^{m_i}$). Initially the system is in a thermodynamic equilibrium and its enthalpy is

$$H = \sum_{i=1}^{S} \sum_{j=1}^{m_i} n_{X_i^j}\, h_{X_i^j} \qquad (43)$$

where $n_{X_i^j}$ and $h_{X_i^j}$ are the amount and partial molar enthalpy of the species, respectively. On the other hand, the thermodynamic quantities of the above system can be written as a state function of $n_{X_1}, n_{X_2}, ..., T, P, ...$, where n_{X_1} describes the composition of the system and T, P, etc. describe the thermodynamic condition of the system. Thus

$$H = f(n_{X_1}, n_{X_2} ..., n_{X_S}, T, P, ...) \quad (44)$$

Interestingly, from the above two equations we can do the following calculations

$$\frac{\partial H}{\partial n_{X_p}} = \sum_{i=1}^{S} \sum_{j=1}^{m_i} \left(h_{X_i^j} \frac{\partial n_{X_i^j}}{\partial n_{X_p}} + n_{X_i^j} \frac{\partial h_{X_i^j}}{\partial n_{X_p}} \right) \quad (45)$$

and

$$\frac{\partial H}{\partial T} = \sum_{i=1}^{S} \sum_{j=1}^{m_i} \left(h_{X_i^j} \frac{\partial n_{X_i^j}}{\partial T} + n_{X_i^j} \frac{\partial h_{X_i^j}}{\partial T} \right) \quad (46)$$

Herein, the calculation of $\partial H/\partial T$ can also be done on $\partial H/\partial P$, etc. Similarly, we have

$$\frac{\partial S}{\partial n_{X_p}} = \sum_{i=1}^{S} \sum_{j=1}^{m_i} \left(s_{X_i^j} \frac{\partial n_{X_i^j}}{\partial n_{X_p}} + n_{X_i^j} \frac{\partial s_{X_i^j}}{\partial n_{X_p}} \right) \quad (47)$$

and

$$\frac{\partial S}{\partial T} = \sum_{i=1}^{S} \sum_{j=1}^{m_i} \left(s_{X_i^j} \frac{\partial n_{X_i^j}}{\partial T} + n_{X_i^j} \frac{\partial s_{X_i^j}}{\partial T} \right) \quad (48)$$

However, in the case of free energy, there is some difference. Since initially the system is in equilibrium, the chemical potential of every subspecies of the same species should be the same, i.e., $\mu_{X_i^1} = \mu_{X_i^2} = ... = \mu_{X_i^{m_i}} = \mu_{X_i}$. Also, it is apparent that

$$\sum_{j=1}^{m_q} \frac{\partial n_{X_q^j}}{\partial n_{X_p}} = \frac{\partial n_{X_q}}{\partial n_{X_p}} = 0 \quad (\forall p \neq q) \quad (49)$$

and

$$\sum_{j=1}^{m_q} \frac{\partial n_{X_q^j}}{\partial T} = \frac{\partial n_{X_q}}{\partial T} = 0 \quad (\forall q) \quad (50)$$

Thus

$$\frac{\partial G}{\partial n_{X_p}} = \sum_{i=1}^{S} \sum_{j=1}^{m_i} \left(\mu_{X_i^j} \frac{\partial n_{X_i^j}}{\partial n_{X_p}} + n_{X_i^j} \frac{\partial \mu_{X_i^j}}{\partial n_{X_p}} \right) = $$
$$\sum_{i=1}^{S} \sum_{j=1}^{m_i} n_{X_i^j} \frac{\partial \mu_{X_i^j}}{\partial n_{X_p}} + \mu_{X_p} \quad (51)$$

and

$$\frac{\partial G}{\partial T} = \sum_{i=1}^{S} \sum_{j=1}^{m_i} n_{X_i^j} \frac{\partial \mu_{X_i^j}}{\partial T} \quad (52)$$

In other words, the following portion of free energy is zero

$$\sum_{i=1, i \neq p}^{S} \sum_{j=1}^{m_i} \mu_{X_i^j} \frac{\partial n_{X_i^j}}{\partial n_{X_p}} = \sum_{i=1}^{S} \sum_{j=1}^{m_i} \mu_{X_i^j} \frac{\partial n_{X_i^j}}{\partial T} = 0 \quad (53)$$

However, since in general $h_{X_i^1} \neq h_{X_i^2} \neq ... \neq h_{X_i^{m_i}}$ and $s_{X_i^1} \neq s_{X_i^2} \neq ... \neq s_{X_i^{m_i}}$, the corresponding portions of enthalpy and entropy are generally not zero. Consequently, they must offset each other exactly. As the enthalpy, entropy, and free energy changes can be written in integration forms such as

$$\Delta H = \int \left(\frac{\partial H}{\partial n_{X_1}} dn_{X_1} + \frac{\partial H}{\partial n_{X_2}} dn_{X_2} + ... + \frac{\partial H}{\partial n_{X_S}} dn_{X_S} + \right.$$
$$\left. \frac{\partial H}{\partial T} dT + \frac{\partial H}{\partial P} dP + ... \right) \quad (54)$$

the above argument also holds for the total enthalpy, entropy, and free energy changes. Thus, if the compensated portion of enthalpy and entropy are substantial, significant compensation will occur between the total enthalpy and entropy. Moreover, it is noteworthy that exact compensation is not possible according to the present theory. In eq 52, there is always a portion of free energy that the compensation cannot make disappear.

The above model, though similar with that of Grunwald, describes the solvent reorganization and molar shift in one form, i.e., redistribution of the subspecies upon the change of the system. Since all the subspecies of the same species are in equilibrium before the change, the free energy change due to the redistribution of the subspecies is zero. This constitutes the origin of the compensation effect. To better understand it, let us discuss a simple example, i.e., the solvation of gaseous X in liquid A at constant temperature and pressure.

As mentioned above, in the solution the solvent molecule A has two subspecies, $A\backslash a$ and $A\backslash x$. Thus, there are in total three subspecies in the solution, i.e., $A\backslash a$, $A\backslash x$, and $X\backslash a$ (herein, the solution is supposed to be very dilute so that solute−solute interaction is negligible). Upon addition of an infinitesimal amount of X, the infinitesimal enthalpy, entropy, and free energy change of the solution are

$$dH = h_{A\backslash a} dn_{A\backslash a} + n_{A\backslash a} dh_{A\backslash a} + h_{A\backslash x} dn_{A\backslash x} +$$
$$n_{A\backslash x} dh_{A\backslash x} + h_{X\backslash a} dn_{X\backslash a} + n_{X\backslash a} dh_{X\backslash a}$$
$$= h_{A\backslash a} dn_{A\backslash a} + h_{A\backslash x} dn_{A\backslash x} + h_{X\backslash a} dn_{X\backslash a}$$
$$\text{(Gibbs−Duhem)}$$
$$= (h_{A\backslash a} - h_{A\backslash x}) dn_{A\backslash a} + h_{X\backslash a} dn_{X\backslash a}$$
$$(dn_{A\backslash a} + dn_{A\backslash x} = dn_A = 0) \quad (55)$$

$$dS = (s_{A\backslash a} - s_{A\backslash x}) dn_{A\backslash a} + s_{X\backslash a} dn_{X\backslash a} \quad (56)$$

and

$$dG = (\mu_{A\backslash a} - \mu_{A\backslash x}) dn_{A\backslash a} + \mu_{X\backslash a} dn_{X\backslash a}$$
$$= \mu_{X\backslash a} dn_{X\backslash a} \quad (\mu_{A\backslash a} = \mu_{A\backslash x}) \quad (57)$$

Obviously, there is a portion of enthalpy compensated by the corresponding portion of entropy. Now, let us consider the magnitudes of the portions. First, it should be noted that $dn_{A\backslash a}$ is always larger than $dn_{X\backslash a}$, because the number of solvent molecules that are adjacent to a solute molecule is always larger

than one. In water solution, the difference between $dn_{A\backslash a}$ and $dn_{X\backslash a}$ can even be very large, because water molecules are extremely small. Second, the magnitude of $(h_{A\backslash a} - h_{A\backslash x})$ can be significantly large. As shown by Grunwald, $(h_{A\backslash a} - h_{A\backslash x})$ in water solution was likely to be on the order of several kJ/mol.[71] Thus, $(h_{A\backslash a} - h_{A\backslash x})$ might be comparable to or even larger than $h_{X\backslash a}$, especially when the interaction between the solvent and solute molecules is very weak. In consequence, it is possible that $(h_{A\backslash a} - h_{A\backslash x})dn_{A\backslash a} \gg h_{X\backslash a}dn_{X\backslash a}$. Similarly, it is also possible that $(s_{A\backslash a} - s_{A\backslash x})dn_{A\backslash a} \gg s_{X\backslash a}dn_{X\backslash a}$. If they both happen, the net effect will be enthalpy−entropy compensation.

It should be mentioned that the above theory does not rely on the details of the solvent−solvent and solvent−solute interactions. Nor does it require the solvent to be water, though in water solution the compensation effect may emerge more easily. Furthermore, according to the theory, the occurrence of enthalpy−entropy compensation does not require any necessary relationship between ΔG and ΔS or between ΔG and ΔH, which is in agreement with many experimental observations.[72]

The only problem of the theory is that it is too general. The fact that it does not rely on the details of the interaction makes the theory unable to predict or explain the enthalpy and entropy of a specific reaction. For that purpose, computer simulation is still necessary. Nevertheless, the theory has successfully explained the compensation, and it seems that more and more scientists have begun to employ the theory to interpret their observations.[73] Besides, in a recent paper, Qian et al. explained the enthalpy−entropy compensation as a result of perturbation and relaxation in thermodynamic systems.[74] They divided the thermodynamic quantities of a system into two classes: one (including the chemical potential) was only determined by the equilibrium distribution of the system and the other (including the partial molar entropy and enthalpy) was sensitive to the environment constraints. Obviously, the model is the same as that of Grunwald.

In summary, the redistribution of the subspecies can lead to enthalpy−entropy compensation. Most observed compensations, especially those related to aqueous solution and biochemical molecules, in which no concrete relation could be found between the entropy and free energy or between the enthalpy and free energy, can be explained by this model.

4.3.5. Compensation in Heterogeneous Catalytic Reactions

The extrathermodynamic relationship found in heterogeneous catalysis is in a state of greater confusion than that found in the solution phase or biochemical reactions, because in this field both the compensation effect and the isokinetic relationship are frequently found. On the basis of statistical examinations, it turns out that sometimes only one relationship is correct, sometimes both, and sometimes neither. Herein, let us focus on the theories of compensation.

The first group of theories concerning the compensation effect in heterogeneous catalysis is purely mathematical, i.e., the compensation effect is caused by the use of "apparent" rather than "true" Arrhenius parameters. As suggested by several authors,[75,76] the surface of the catalyst might actually be an array of energetically different sites, with the property that the catalytic reaction on a different group of sites requires a different activation energy. The overall rate constant is expressed by the summation

$$k = \sum A_i \exp(-E_i/RT) \tag{58}$$

Thus, the composite reaction does not strictly obey the Arrhenius equation. As seen in section 4.2, using an overall rate equation instead of the real complex rate equation could lead to a compensation relationship. Needless to say, this type of compensation is not interesting.

The second group of theories are based on the argument expressed by Benson, "This compensation is perhaps more easily understood in the language of statistical mechanics, where we associate decreases in enthalpy (exothermic changes) with "tighter" binding and consequently with less entropy ("freedom of motion")".[77] Obviously, the idea is similar to that described in section 4.3.2. In the field of heterogeneous catalysis, this type of compensation is proposed to occur between the adsorption enthalpy and entropy, and this point of view can be found in works as early as in the 1950s.[78]

In 1982, Conner offered a general explanation for the compensation.[79a] From the fundamental statistical thermodynamics, he proposed that reduction of the activation energy resulted in a narrower transition state and hence decreasing entropy. This idea can also be found in early studies.[79b,c] However, Galwey criticized the theory with various arguments, and his biggest objection was that the theory might be too simple to describe the complex catalytic reactions.[80a] Though Conner[80b] disputed Galwey's objections by pointing out that the compensation was not unique to catalysis, his theory remained barely accepted. As argued, in the compensation effect the values of the enthalpy usually extend over far too wide a range so that the simple monotonic relationship between the two-body interaction energy and entropy is not able to account for the general large linear compensation.[81a]

Recently, Rooney et al.[81] proposed that the total reaction on the catalysts could be described by the following equation

$$k_{exp} = y \cdot kT/h \cdot \Pi K \cdot K^{\ddagger} \tag{59}$$

where ΠK is a multiple or quotient of the individual equilibrium constants for all the sequences of steps preceding the activation step (such as chemisorption, complexation, etc.), k_{exp} is the experimental rate constant, and y is the transmission coefficient. If the enthalpy and entropy corresponding to ΠK compensate each other and they are much larger than the activation enthalpy corresponding to $K^{\ddagger}$, the observed compensation between the kinetic parameters is caused not by the kinetics, but by the thermodynamic compensation in the equilibriums of the reactants on the catalysts prior to the activation or rate-determin-

ing step. This theory has been used to explain the isokinetic temperature,[82a] which, however, is not quite evident because the compensation effect and the isokinetic effect are not necessarily the same.

One problem of Rooney's theory is that it is only a formal description, which cannot explain why the compensation occurs in a specific case.[82b] Nevertheless, more and more experimental results indicate that the compensation effect observed in heterogeneous catalysis might be caused by the enthalpy−entropy compensation in chemisorption.[83] It has also been concluded from computer simulations that[84] (1) the adsorbate−adsorbate interaction can alter the adsorbate−substrate potential-energy surface and, hence, alter the activation energy and preexponential terms of the rate coefficient, (2) variations in the distribution of local configurations of pairs of reactant molecules as a function of temperature and fractional surface coverage can be responsible for the experimental compensation effect, and (3) the apparent preexponential factor is calculated to vary by over 11 orders of magnitude based on a simple lattice−gas model of surface reactions with pairwise-additive adsorbate interactions. Apparently, the above simulation results have well explained the compensation in heterogeneous catalysis. It is also not difficult to understand the results since they can be easily explained with the generalized Grunwald theory of compensation shown in section 4.4.3, in which the system of compensation can be any mixture (not necessarily being a solution) of species with distinguishable subspecies. As mentioned by Grunwald, a reorganization of adsorbate molecules among distinguishable adsorption sites on the surface might be the molecular mechanism of the compensation in surface chemistry.[85a] Kreuzer and March also held this viewpoint. In their words, "all that one needs to invoke in this latter case is that adsorbed molecules perturb the atomic mesh of the surface".[85a]

In summary, the compensation observed in heterogeneous catalysis can be the result of misuse of the kinetic model or the result of adsorption thermodynamics. It is more likely a many-particle effect rather than a simple single- or several-particle one.

4.3.6. Other Theories

In addition to the above theories, there are still a number of theories of enthalpy−entropy compensation which, however, cannot be put into any of the above categories. Some of them are based on general considerations and are reviewed below. On the other hand, the others usually rely heavily on the details of the interactions involved in the system under investigation[86] and, hence, are neither generally applicable nor of wide interest. Therefore, they are not discussed here.

In 1974, Melander[87] proposed a macroscopic model of enthalpy−entropy compensation. A simple system was considered in which only an ionic interaction was operative and hence the Coulombic product decided the total energy of the system. Assuming that the dielectric constant ϵ of water has the form $\epsilon = A + BT + CT^2 + DT^3$, the author calculated the enthalpy and entropy of the system. It was shown that over

the temperature range of 0−30 °C, the entropy compensated for the enthalpy dramatically. Thus, the thermal dependence of the dielectric constant was concluded to cause the compensation. Unfortunately, though this theory may be correct under the condition that the author described, the fact that it was based on many unrealistic assumptions (ionic mechanism, temperature dependence of ϵ, and no reaction series) made it unable to explain the compensation in general. Furthermore, Simeon and Ivicic[88] proved in their study that the compensation could not be predicted by the crude electrostatic theory.

Interestingly, the viewpoint that electrostatic theories could explain the enthalpy−entropy compensation was also held by Likhtenshtein et al.[89] In their study, the free energy, enthalpy, and entropy were written as $\Delta F = A$, $\Delta S = AL$, and $\Delta H = A(1 + LT)$, whereas $A = z_1 z_2 e^2/rD$ and $L = -d \ln D/dT$. Obviously, this model is the same as that of Melander, whose validity for compensation is questionable. Despite this fact, one thing in the study is instructive. From analyses of the enthalpy and entropy of gas-phase reactions, it was concluded that in the vast majority of cases systems had different values of enthalpy while the variation in entropy was small. This phenomenon shows why the general explanation of compensation with simple models by Conner et al. mentioned in section 4.4.4 is questionable.

In 1989, Boots and Bokx introduced an equivalent formulation of the enthalpy−entropy compensation, i.e., when the enthalpy−entropy compensation occurs, ΔG can be defined as the product of a temperature-dependent, system-independent factor and of a temperature-independent, system-dependent factor.[90] By relating ΔG to small variations in the one- and many-body potentials, they proved that in the similar systems having similar potential energies, whether differences in one-body potentials or in many-body potentials dominate can cause the enthalpy−entropy compensation. They also proved that the combined effects of one-body and many-body potential differences would not generally lead to the enthalpy−entropy compensation. However, since it is often difficult to determine whether combined effects dominate in a process, the applicability of the model is limited.

Another interesting explanation of enthalpy−entropy compensation relates the compensation effect to the phase transition. In 1986, Estrup et al.[91a] pointed out that a compensation effect might follow from the equality on the chemical potentials of two phases at a transition. Recently, Gilbert concluded that the enthalpy of fusion was compensated by the entropy of fusion for over 700 organic compounds.[91b] Basically this viewpoint is correct. However, considering the fact that in phase transitions the enthalpy change ΔH and the entropy change ΔS are connected via the phase-transition temperature T in the equation $\Delta S = \Delta H/T$, the compensation in these cases merely says that the phase-transition temperature is roughly the same among the series.

4.3.7. Summary

A real compensation effect (i.e., statistically correct) is not difficult to establish. An inappropriate or

incomplete description of a kinetic model can cause the compensation, which is obviously of little meaning. The monotonic relationship between the energy and entropy of the weakly bonded chemical systems can also cause the compensation, which is applicable to two-body weak associations. Compensation due to the group additivity is straightforward but contains little information. Finally, redistribution of distinguishable subspecies including solvent reorganization and molar shift can cause large enthalpy−entropy compensation, which is relevant to most observed compensation phenomena.

4.4. Theories of Isokinetic and Isoequilibrium Relationships

Since the isokinetic and isoequilibrium relationship are not necessarily equivalent to the compensation effect, the many theories of the enthalpy−entropy relationship might not be used to explain the isokinetic (or isoequilibrium) relationship. In fact, any theory that might explain the isokinetic (or isoequilibrium) relationship must explicitly demonstrate that there is a temperature at which all reactions in the series will have the same rate (or equilibrium) constant. However, few researchers have noticed this fact, and hence, there are so far only a few theories on the isokinetic and isoequilibrium relationship.

In 1929, Schwab et al.[92a] attributed the isokinetic relationship to a thermal energy distribution of the active centers at the preparation temperature, assuming that very active centers of low activation energy are rare and that weak centers of high activation energy are numerous. In this case, the isokinetic temperature would be the preparation temperature at which the catalysts reached thermal surface equilibrium for the last time. This theory is interesting, and initially a number of examples were found supporting it. However, it was concluded later from a more detailed analysis of the experimental data that this explanation was not applicable in general.[92b]

Since the 1980s, Linert and co-workers have done a series of studies on the isokinetic and isoequilibrium relationship.[93] They validated the two relationships from analyses of experimental data, proposed reasonable theoretical models, and found applications of the two relationships. In brief, Linert's theory of the isokinetic relationship is based on Kramer's theory of rate constants. In the theory, the reactant molecules are assumed to become activated through their collisions with other molecules of the surrounding medium, which acts as a constant-temperature "heat bath". After a random walk over discrete energy levels of the reactants, they reach the highest point of the barrier, a point of no return. The crossing over this barrier constitutes the chemical reaction rate. Mathematically, this process can be expressed in the following equation

$$\frac{d\sigma_l(t)}{dt} = Z\left[-\sum_{l<m}P_{ml}N^-\sigma_l(t) + \sum_{l<m}P_{ml}N^+_{ml}\sigma_l(t) + \sum_{m<l}P_{lm}N^+_{lm}\sigma_m(t) + \sum_{m>l}P_{lm}N^-\sigma_m(t)\right] \quad (60)$$

In the equation, σ_l is the time-dependent density of the reactants to the discrete level l, P_{lm} is the transition probability per collision for the transition from level m to l (presumably, $P_{0,-1} = 0$), Z is the collision number, and N^+_{lm} is the concentration of heat bath molecules which have sufficient energy to excite a molecule from a given level l to a higher level m ($m > l$). N^- is the concentration of heat-bath molecules able to de-excite a reactant molecule from m to l ($m > l$).

Suppose that the heat-bath molecules obey the Boltzmann distribution, thus

$$N_{lm} = \exp(\Delta E/kT)N_{ml} \quad (61)$$

where ΔE is the energy difference between two heat-bath energy levels. Under this condition, the equilibrium of the system can be represented by

$$\frac{d\sigma_l(t)}{dt} = 0 \quad (62)$$

Equation 60 can be rewritten in a differential equation by assuming l to be continuous

$$\frac{\partial\sigma(t)}{\partial t} = \frac{\partial}{\partial l}R(l)\left[\frac{\partial\sigma}{\partial l} + \frac{1}{k_BT}h\frac{\partial}{\partial l}\varpi(l)\sigma\right] + g(l) \quad (63)$$

Here, $g(l)$ is a source term for particles, so that a steady-state solution (eq 64) of eq 63 can be obtained under the condition of large barriers with a point of no return at the energy barrier and connected with a surrounding heat-bath.

$$k = \phi(s_N)\left\{\int_0^{s_N}dl\cdot\exp\left(-\frac{h}{RT}\int_0^l\varpi(l')dl'\right) \times \int_0^{s_N}dl'\frac{\exp\frac{1}{RT}\int_0^{s_N}\varpi(l')dl'}{P(l')}\phi(l')\right\}^{-1} \quad (64)$$

Assuming that the energy barrier is much larger than kT, eq 64 can be solved as

$$k \cong A_0(h\varpi/kT)P_{s_N,s_{N-1}}\exp(-s_Nh\varpi/kT) \quad (65)$$

In the above equation, s_N is the highest reactant level (i.e., the point of no return). Thus, the understanding of isokinetic relationship becomes how to express the quantum-mechanical transition probability $P_{s_N,s_{N-1}}$.

According to Linert, an appropriate transition probability for a vibrational−vibrational energy transfer is

$$P_{lm} = l\exp(\varpi/\nu) \quad (66)$$

where a resonance condition of the form

$$\nu\cdot m = \varpi\cdot l \quad (67)$$

is included, implying that energy is exchanged with the highest probability at equal energies (m is the number of the heat-bath level, ν is the associated frequency, ϖ and l are the respective parameters of

the reactant system). Thus, the rate constant can be written as

$$k = A_0 s_N (h\varpi/k_B T_{exp})^2 \exp[-s_N(\varpi/v - h\varpi/k_B T_{exp})] \tag{68}$$

Considering a series of reactions in which ϖ is the only changeable parameter, the isokinetic relationship can be expressed mathematically as

$$\left.\frac{\partial \ln k(\varpi)}{\partial \varpi}\right|_{T_{iso}} = 0 \tag{69}$$

Thus, the isokinetic temperature is found to obey the following relationship

$$1/RT_{iso} = 1/E + 1/N_L h v \tag{70}$$

where N_L is Avogadro's number and v the predominant active heat-bath frequency. In condensed phase, it was suggested that $1/E$ is negligible compared to $1/N_L h v$ and as a result

$$T_{iso} = N_L h v / R \tag{71}$$

In short, based on two major approximations, i.e., the heat-bath activating reaction rate theory and the vibrational−vibrational energy exchange mechanism, a temperature can be found at which all reactions in a series exhibit the same reaction rate. This temperature is only dependent on the predominant active heat-bath frequency. In other words, the theory indicates that the isokinetic relationship might stem from the environmental molecules interacting with the reactants, which force the reaction to proceed in accordance with their own energy distribution and exchange mechanism. Under this condition, the rate of the reaction is determined mainly by the environmental molecules and not by the interaction between the reactants themselves. Obviously, the theory can explain the isokinetic effect found in the cases where a series of reactions with different reactants occur on the same solid support or in the same liquid solution. In addition, since any equilibrium reaction can be expressed as a net effect of a forward reaction and a reverse reaction, the isoequilibrium effect can be understood as a special case of the isokinetic relationship.

Another interesting theory of isokinetic relationship was given by Larsson and co-workers.[94] According to the theory, the catalyst system and the reactant molecule vibrate at the frequency of ω and v, respectively. The coupling force between them is defined as $F(t)$. Thus, the equation of motion on the basis of classical physics is

$$d^2 x/dt^2 + 1/\tau \, dx/dt + v^2 x = F(t)/M \tag{72}$$

in which τ is the relaxation time.

It is again assumed that the reactant molecules are activated by the catalyst and the energy transfer per unit of time P can be obtained from eq 72.

$$P = P_{res}(\omega^2/\tau^2)/[(v^2 - \omega^2)^2 + \omega^2/\tau^2] \tag{73}$$

In eq 73, P_{res} is the energy transfer rate at resonance, i.e., when $\omega = v$. Defining the quality factor Q as $Q = v\tau$, we can formulate the efficiency of energy transfer R (defined as $R = P/P_{res}$) as

$$R = \frac{1}{(v^2 - \omega^2)^2 Q^2/\omega^2 v^2 + 1} \tag{74}$$

The above equation is applicable to any specified set of v, v, and τ. However, usually the whole reaction system is not homogeneous. Thus, to correctly express the total efficiency of energy transfer S we have to sum all the R-terms

$$S = \int R \, dQ = \int \frac{dQ}{(v^2 - \omega^2)^2 Q^2/\omega^2 v^2 + 1} = \\ v\frac{\omega}{v^2 - \omega^2}\left(\pm\pi/2 - \text{arctg}\frac{v\omega}{2(v^2 - \omega^2)}\right) \tag{75}$$

Consider that the reactant molecules vibrate at different energy levels and the vibration potential is anharmonic (i.e., $v_i \neq v_{i+1}$). Obviously eq 75 is valid for every vibrational level. Thus, the total energy transfer efficiency to promote the reaction, which can be represented by the multiplication of the energy transfer efficiency at every vibrational level up to the level of no return, is described in the following equation

$$S_Z = \Pi \exp(S_i) = \\ \Pi \exp\left(v_i\frac{\omega}{v_i^2 - \omega^2}\left(\pm\pi/2 - \text{arctg}\frac{v_i\omega}{2(v_i^2 - \omega^2)}\right)\right) \tag{76}$$

Larsson assumed that the preexponential factor A could be expressed as the following equation

$$A = ZS_Z \tag{77}$$

where Z is a nonenergy-related coefficient. Thus

$$\ln k = \ln Z + \\ \sum v_i\frac{\omega}{v_i^2 - \omega^2}\left(\pm\pi/2 - \text{arctg}\frac{v_i\omega}{2(v_i^2 - \omega^2)}\right) - E/RT \tag{78}$$

Supposing that the all the v_i are approximately of the same magnitude and that the energy difference between two consecutive vibrational levels is $\Delta E_i = hcv_i$, we can simplify eq 78 into

$$\ln k = \ln Z + \\ \frac{\omega}{v^2 - \omega^2}\left(\pm\pi/2 - \text{arctg}\frac{v\omega}{2(v^2 - \omega^2)}\right)\sum\Delta E_i/hc - \\ E/RT \tag{79}$$

Since $N\sum\Delta E_i - E$ (N is the Avogadro's number), we get

$$\ln k = \ln Z + E/R(1/\Theta - 1/T) \tag{80}$$

Here, $\Theta = (Nhc/R)\cdot[(v^2 - \omega^2)/\omega]\cdot 1/\{\pm\pi/2 - \text{arctg}[v\omega/2(v^2 - \omega^2)]\}$ is the isokinetic temperature. If $\omega = v$, the isokinetic temperature can be simplified as $\Theta = Nhcv/2R$.

Interestingly, the above theory is similar with that of Linert. The only difference is that Linert put the emphasis on the vibration of the heat bath (the catalyst) while Larsson put the emphasis on the vibration of the reactant molecules. According to Linert's theory, one heat bath should show a single isokinetic temperature irrespective of the reactants. However, from Larsson's model, the reactions of the molecules with the similar vibration frequency (or more specifically the breaking of the same type of chemical bond) should exhibit the isokinetic effect. Although both authors have found concrete experimental evidences for their theories, it remains unclear which theory is more generally applicable.

In summary, any theory of the isokinetic effect must be able to explain why at a certain temperature all the reactions in a series exhibit the same rate constant. Two mechanisms are especially appealing, i.e., the catalyst-dominating one and the reactant-dominating one. In the former mechanism, the isokinetic temperature is determined by the vibration frequency of the catalyst, which is invariable for different reactant molecules. In the latter mechanism, the isokinetic temperature is determined by the vibration frequency of a specific chemical bond, which is roughly the same for different substituent groups.

5. Applications and Relations with Other Concepts

Enthalpy−entropy compensation, the isokinetic relationship, and the isoequilibrium relationship, fundamentally important as they are, have found a number of applications in many fields. Also, a number of chemical concepts relevant to them have been developed. Herein, we summarize those that are most relevant to the understanding of the three extrathermodynamic relationships.

5.1. Isoselective Relationship

The temperature dependence of the reaction selectivity is an interesting topic, though it has drawn relatively little attention. In the 1970s, Giese studied the competition experiments in which a series of compounds X_i reacted with two reagents Y_1 and Y_2. The reaction rates of each X_i with Y_1 and Y_2 were defined as $k_{i,1}$ and $k_{i,2}$, and it was found that the plot of $\log(k_{i,1}/k_{i,2})$ against $1/T$ for each X_i was a straight line. Interestingly, it turned out that the straight lines for several compounds in the series often cross at a single value of $1/T_{is}$. The temperature was called the isoselective temperature, and the behavior was defined as an isoselective relationship.[95]

Mathematically, the isoselective relationship can be described with the following equation

$$\delta \log \frac{k_{i,1}}{k_{i,2}} = 0 \qquad (81)$$

According to the Eyring equation, the following equation also holds

$$\log \frac{k_{i,1}}{k_{i,2}} = \frac{\Delta H_{i,2}^{\ddagger} - \Delta H_{i1}^{\ddagger}}{2.3RT} - \frac{\Delta S_{i,2}^{\ddagger} - \Delta S_{i,1}^{\ddagger}}{2.3R} \qquad (82)$$

Then we have

$$\delta(\Delta H_{i,2}^{\ddagger} - \Delta H_{i,1}^{\ddagger}) = T_{is}\delta(\Delta S_{i,2}^{\ddagger} - \Delta S_{i,1}^{\ddagger}) \qquad (83)$$

Thus, the isoselective relationship can be built up by two isokinetic reaction series.[96] However, the explanation of the isoselective relationship from the first principle remains unclear.

5.2. Isoinversion Principle

Consider the reactions in which a pair of diastereomers is produced. The quantity P is defined as the ratio of the experimental rate constants for the formation of these diastereomers or the ratio of the diastereomers produced in the reaction. Plots of $\ln P$ versus the inverse of the absolute temperature $(1/T)$ are normally linear, and the difference between the enthalpies $(\Delta\Delta H^{\ddagger})$ or entropies $(\Delta\Delta S^{\ddagger})$ of activation of the reactions leading to the two diastereomers can be calculated from the plots.

In 1989 Buschmann et al.[97] found that some plots of $\ln P$ vs $1/T$ had maxima, and the temperature corresponding to the maximum was named the inversion temperature, T_{inv}. Two sets of parameters of activation could be calculated from the plot for each system, namely, $\Delta\Delta H_1^{\ddagger}$ and $\Delta\Delta S_1^{\ddagger}$ for the high-temperature range $(T > T_{inv})$, and $\Delta\Delta H_2^{\ddagger}$ and $\Delta\Delta S_2^{\ddagger}$ for the low-temperature range $(T < T_{inv})$. Defining $\delta\Delta\Delta H^{\ddagger}$ as the difference between $\Delta\Delta H_1^{\ddagger}$ and $\Delta\Delta H_2^{\ddagger}$ and $\delta\Delta\Delta S^{\ddagger}$ as the difference between $\Delta\Delta S_1^{\ddagger}$ and $\Delta\Delta S_2^{\ddagger}$, Buschmann et al. found that plots of $\delta\Delta\Delta H^{\ddagger}$ vs $\delta\Delta\Delta S^{\ddagger}$ were linear. This linear relationship was called the principle of isoinversion, and the slope of the regression was defined as the isoinversion temperature. Thus, it seems that the isoinversion principle has certain relation with the enthalpy−entropy compensation.

Initially, the isoinversion principle was explained as the result of a temperature-dependent change in the mechanism of the reactions, and it has been used for both the optimization of selectivities and rationalization of reaction mechanisms in a number of stereoselective, regioselective, or chemoselective reactions.[98,99] However, in a recent calculation by Hale and Ridd[100] on model systems with two potentially rate-determining steps on a single reaction pathway, it was concluded that the maximum in the plot of $\ln P$ vs $1/T$ did not necessarily imply that the values of $\Delta\Delta H^{\ddagger}$ for the two possible rate-determining steps were of opposite sign. Therefore, an abrupt change in the rate-determining step is not necessary in producing the isoinversion effect. Interestingly, it was concluded that the calculated $\delta\Delta\Delta H^{\ddagger}$ and $\delta\Delta\Delta S^{\ddagger}$ had no simple physical meaning, and hence, the isoinversion relationship involving these quantities was not a conventional enthalpy−entropy relationship.

5.3. Enthalpy and Entropy Convergence

Protein unfolding is an interesting topic. In 1979, Privalov first reported that the enthalpy (ΔH_{un}) and

entropy (ΔS_{un}) of the unfolding of different proteins phenomenon converged at some characteristic temperature around 100 °C when normalized with respect to the number of amino acid residues in the proteins.[101] This intriguing behavior has been carefully reexamined in many following studies, but it still remains controversial to some extent.

Theoretical explanations for the behavior have been provided. The possible origins of the behavior were proposed to be (1) hydrophobic interaction,[102] (2) the linear correlations of ΔH_{un} and ΔS_{un} with a temperature-independent molecular property,[103] (3) protein evolution,[104] (4) nonpolar and peptide backbone hydration,[105] and (5) solvation effect.[106] However, firm conclusions have not been reached.

Recently, we studied the enthalpy−entropy compensation in protein unfolding.[107] It was shown that while at 298 K excellent enthalpy−entropy compensation occurred, at the enthalpy and entropy convergence temperature (around 383 K) the correlation between the enthalpy and entropy changes became very poor. The same observation was also reported in a recent study.[108] It suggested that hydration was the primary cause for both the compensation and the convergence phenomenon observed in protein unfolding. On the basis of Grunwald's theory of enthalpy−entropy compensation, we developed a model for the thermodynamics of protein unfolding and suggested that the convergence temperature was the one at which the enthalpy and entropy due to solvent reorganization became zero.

5.4. Nonlinear Enthalpy−Entropy Compensation

As the mechanism of compensation effect has been unclear for many years, many authors questioned why the compensation plot should always be linear. As a result, the concept of nonlinear compensation relationship appeared.

In 1975, Good et al.[109] proposed a "more general" approach to analyze the compensation relationship. Criticizing the previous methods such as plotting log k_1 vs log k_2 or plotting E vs log A, they argued that the compensation plot should be established in four steps. (i) Rank the members of the series of reactions according to ascending values of a physical characteristic χ such as concentration, atomic number, etc. (ii) Plot points in the log k_1 vs χ and log k_1 vs χ planes. (iii) Fit smooth curves through the points in each of the two planes. (iv) Plot both the actual and fitted points in the log k_1 vs log k_2 and in the E vs log A planes and hence the fitted curves.

In short, the compensation relationship should be defined by a curve fitted through the datum points consecutively according to certain monotonic physicochemical characteristic of the series.

The above method has been used in several studies,[110] and usually the compensation curve was found to be nonlinear. However, it should be pointed out that although the linear compensation might only be an approximation, the use of nonlinear model on such a relationship is even more dangerous. First, the compensation can be badly complicated by the experimental errors, and hence, the statistical validity of a nonlinear model should be carefully examined

before being used. Second, when the number of data points is small, the validity of any nonlinear regression is certainly more questionable than that of a linear one because the former has more unknown parameters. On the other hand, when the number of data points is large, the nonlinear compensation relationship usually becomes a too complicated curve to deserve any theoretical explanation. In short, though nonlinear compensation is interesting, cautious examination should be done before any conclusion can be generated.

In addition to the nonlinear compensation, some authors have mentioned the anticompensation.[111] In that case, the slope of the enthalpy−entropy plot is the reverse of that in the normal compensation so that the enthalpy and entropy reinforce each other producing a larger net free energy. This behavior is very intriguing, but no theory has been proposed to explain it.

5.5. Applications

Since the compensation effect and the isokinetic (or isoequilibrium) effect remain theoretically enigmatic to many researchers, the applications of these empirical relationships were questioned from the beginning[112] and even sometimes criticized as being "theoretical sterile".[113] However, many scientists still try to apply these relationships to chemistry. These studies were usually interesting, informative, and sometimes important because they promoted further studies to understand the three relationships.

The first and most important application of the compensation effect and the isokinetic (or isoequilibrium) effect was based on the inference that such behaviors constitute evidence for a dominant mechanism throughout the correlated series. To date, a number of papers have been proposed in which single or multiple mechanisms were operative for different systems based on this point of view.[114] However, as the several reasonable theories on the compensation effect do not show any mechanism relation among the reaction series, the argument based on the compensation relationship is questionable. In fact, the analysis of the reaction mechanism and the structure−activity relationship is often not eased but complicated or obfuscated by the observed enthalpy−entropy compensation.[115] On the other hand, if the isokinetic (or isoequilibrium) relationship is valid, it is possibly true that only one mechanism is operative.[116] Nevertheless, since the theory of the isokinetic relationship remains unclear, it is still advisable to be cautious in drawing such conclusions.

In 1977, Ranganathan et al. reported application of the compensation effect to the chemistry of catalysts.[117] They showed that the compensation effect could be used to differentiate the effects of surface properties (e.g., surface area, pore volume, and particle size) and bulk properties (e.g., heat of formation of catalyst oxides and latent heat of sublimation which characterize the catalyst) in evaluating catalysts. They found that the bulk properties of catalysts could be correlated with ln k_{iso}, while catalysts having similar bulk properties but having different surface properties exhibited the same ln k_{iso}.

In 1986, Feakins et al.[118] used the compensation principle in explaining the lowering of the viscosity of water by the electrolytes. It was argued that compensation between enthalpic and entropic contributions from solute-induced structural changes occurred in both the ground- and transition-state solvents. Therefore, the viscosity could not be influenced by changes in the structure of the solvent. Instead, it was suggested that in aqueous solution, the enhanced fluidity by the electrolytes stemmed from ion−solvent bond making in the transition state.

Another interesting application of the compensation law is to predict or estimate the thermodynamic quantities based on the linear correlation between enthalpy and entropy. In 1984, Tomlinson showed that the compensation analysis could be a useful tool for investigating biological and biochemical processes of relevance to QSAR of drugs.[119] Recently, Ruthven et al.[120] studied the adsorption thermodynamics of linear paraffins. The correlations between the adsorption energy and carbon number and between the entropy and enthalpy of adsorption were found to be a concise way to predict the adsorption behavior of the higher paraffins. Also, this approach made it possible to predict the heats of vaporization and heats of adsorption of a large number of organic compounds in a recent study by Goth et al.[121] On the basis of a combination of the enthalpy−entropy compensation relationship and the linear free energy relationship, Giering et al. quantitatively analyzed the ligand effects and determined the values of stereoelectronic parameters of phosphines.[122] Interestingly, in a recent ab initio study, the compensation between the binding enthalpies and entropies was used to estimate the entropy contributions to the free energies for stacking and hydrogen bonding of nucleic acid bases in aqueous solution.[123]

Furthermore, the compensation models were also found useful in some less well-known fields such as the cooperative relaxation kinetics in thermally stimulated process,[124a] the sorption and browning of garlic,[125b] etc.

6. Conclusions

Few concepts in chemistry have reached a state of such confusion as the enthalpy−entropy compensation, the isokinetic relationship, and the isoequilibrium relationship. Because they are complicated with so many artifacts and misunderstandings, many scientists even warn that the exploitation of these extrathermodynamic relationships is perhaps dangerous.

As shown in the present review, the compensation effect and the isokinetic (isoequilibrium) relationship are not necessarily equivalent. The compensation effect thus defined should only mean that there is a linear relationship between the logarithm of the preexponential factors and the activation energies, between the enthalpies and entropies of activation, or between the enthalpy and entropy changes of a series of similar reactions. On the other hand, the isokinetic (or isoequilibrium) effect should be defined only by the existence of a common intersection point of Arrhenius (or van't Hoff) lines describing the kinetics (or thermodynamics) of the reaction series.

Statistical examination is necessary in establishing any of the three relationships, because the experimental errors can lead to an apparent correlation. The simplest method to examine the validity of the compensation is to draw the error bars or confidence regions in the compensation plot. On the other hand, to test the isokinetic (or isoequilibrium) relationship, putting all of the Arrhenius (or van't Hoff) lines describing the kinetics (or thermodynamics) of the reaction series in one plot is necessary.

Relatively, the compensation effect can be well understood at the present stage. The misuse of the kinetic model can lead to compensation, which is of little importance. The monotonic relationship between the binding energy and binding entropy is a kind of compensation which, however, is not generally applicable. For the often-observed large compensation effects, especially those involving solution or biomolecules, redistribution of the energy-distinguishable subspecies is most likely the physical origin. Usually two forms of redistributions play the major roles, i.e., the solvent recognition and the molar shift.

On the other hand, the theory of an isokinetic (or isoequilibrium) relationship is not evident enough. Though it is established that the isokinetic (or isoequilibrium) relationship is a result of certain energy resonance between the reacting molecules and their environments, the detailed mechanism requires further investigation.

8. References

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