

# Do Experimental Errors Really Cause Isoequilibrium and Isokinetic Relationships?

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(Received October 22, 2012)

## Abstract.

Numerical experiments simulating spectroscopic determination of equilibrium constants with normally distributed random noise in spectral amplitudes and temperatures have shown that the ‘statistical’ correlation between estimates of  $\Delta H^0$  and  $\Delta S^0$  only appears when measurements are performed on systems with  $\Delta H^0$  and  $\Delta S^0$  varying within an interval smaller than two standard deviations ( $\sigma$ ) of their estimates, *i.e.* when the precision of an instrument or a method is insufficient for studies of such small variations of chemical reactivity. Random variations of  $\Delta H^0 \pm \sigma_{\Delta H}$  and  $\Delta S^0 \pm \sigma_{\Delta S}$  completely destroy statistical correlation. This means that in properly designed experiments the experimental errors *cannot* be the origin of the observed correlations between  $\Delta H^0$  and  $\Delta S^0$ . This has been proven by numerical experiments on reaction series exhibiting compensation effect. When analysing experimental data of unknown precision the Exner-Linert method can be advantageously used to distinguish the ‘statistical’ compensation effect.

## 1. Introduction

Kinetic and equilibrium compensation effects are often considered (*e. g.* see in the ref. [1]) as dubious because of the ‘statistical’ interdependence between  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  or  $\Delta H^0$  and  $\Delta S^0$  when they are determined by linear regression of van’t Hoff or Arrhenius plots ( $\ln K$  or  $\ln k$  vs.  $1/T$ ). A recent paper by P. J. Barrie on the role of random errors [2] presents an analysis of the ‘mathematical’ origin of the compensation effect. The main result of this paper is that the random nature of experimental data may cause an apparent compensation effect with  $1/T_{iso}$  approximately equal the mean inverse temperature of experiment

$\langle 1/T \rangle = (1/n)\Sigma(1/T_i)$ . In such cases the significance ellipses should be calculated. Overlapping of such ellipses indicates the false compensation effect arising from experimental errors.

Several methods have already been developed [3 - 8] for distinguishing false compensation effect. They are based on the determination of the common point of intersection of the lines in Arrhenius (or van't Hoff) plots rather than on the analysis the linear dependence of  $\Delta H^\ddagger$  on  $\Delta S^\ddagger$  or  $\Delta H^0$  and  $\Delta S^0$  (compensation plot, or 'Constable plot' according to P. J. Barrie).

In the present paper it will be shown that the false compensation effect only reveals itself in badly designed experiments when the errors of determination of  $\Delta H^0$  and  $\Delta S^0$  ( $\Delta H^\ddagger$ ,  $\Delta S^\ddagger$ ) are larger than variations of these parameters in the investigated series of reactions. We shall mainly consider the equilibrium compensation effect (correlation of  $\Delta H^0$  and  $\Delta S^0$ , both estimated from the temperature dependence of equilibrium constants) because it is much easier to evaluate possible errors in equilibrium constants. However, the results can be extended to kinetic measurements as well. We shall further demonstrate that in the absence of any data on the errors of measurements the false compensation effect can be detected by applying the Exner-Linert method [3 - 8].

## 2. Compensation effect and isoequilibrium (isokinetic) relationships

The compensation effect is sometimes opposed [1] to the isoequilibrium or isokinetic relationship (IER, IKR) that manifest themselves in the intersection of several van't Hoff (Arrhenius) plots in one point (or in a vicinity of such a point). It is not difficult to demonstrate that an intersection of van't Hoff plots implies a linear correlation of  $\Delta H^0$  and  $\Delta S^0$  and *vice versa*.

Compensation effect is usually observed in systematic studies of *variations of chemical reactivity*. In such studies it is practically impossible to independently vary a single molecular parameter affecting chemical affinity. For example, by modifying a reactant we change molecular mass, electronic energy, frequencies of vibrational modes, inertia moments that determine molecular free energy, hence the value of the equilibrium constant. In a reaction series we have always a *vector* of varied parameters  $\{\eta_1, \eta_2, \dots, \eta_n\}$ .

An intersection of several van't Hoff plots in one point means that the equilibrium constant at a certain temperature ( $T_{iso}$ ) is independent of the varied parameters ( $\eta_i$ ). The effect

of variation of parameters on the chemical affinity depends on the parametrical sensitivities  $\partial\Delta H^0/\partial\eta_i$  and  $\partial\Delta S^0/\partial\eta_i$ . The condition of the invariance of  $\ln K$  at  $T_{iso}$  can be written as:

$$dR \ln K = \sum_i \left( \frac{\partial\Delta S^0}{\partial\eta_i} - \frac{1}{T_{iso}} \frac{\partial\Delta H^0}{\partial\eta_i} \right) d\eta_i = 0 \quad (1)$$

It is hardly probable that random variations of several parameters yield a single  $T_{iso}$ ; therefore it has been assumed [9] that when an IER (IKR) is observed the variation of only *one parameter* controls the variations of both  $\Delta H^0$  and  $\Delta S^0$ . However, there is another possibility for the observation of IER, arising from variations of several parameters controlling  $\Delta H^0$  and  $\Delta S^0$ , namely when a linear interdependence between these variations of parameters exists:

$$d\eta_i = a_i d\eta_k \quad (2)$$

The coefficient  $a_i$  depends on the actual mode of modification and fundamental laws connecting the variations of mass, charge, atomic or molecular radius, bond strength, *etc.* (see *e. g.* in refs. [10-12]). This possibility must be quite common in systematic studies of chemical reactivity in homological series, especially when variations of parameters are small. Assuming In such cases Eq. (1) can be transformed into:

$$\sum a_i \frac{\partial\Delta S^0}{\partial\eta_i} - \frac{1}{T_{iso}} \sum a_i \frac{\partial\Delta H^0}{\partial\eta_i} = 0 \quad (3)$$

Note that the sums in (3) are *complete derivatives*  $d\Delta S^0/d\eta_k$  and  $d\Delta H^0/d\eta_k$ :

$$\frac{d\Delta S^0}{d\eta_k} - \frac{1}{T_{iso}} \frac{d\Delta H^0}{d\eta_k} = 0 \quad (4)$$

$$T_{iso} = \frac{d\Delta H^0}{d\eta_k} \bigg/ \frac{d\Delta S^0}{d\eta_k} \quad (5)$$

A meaningful value of  $T_{iso}$  is obtained when both  $d\Delta S^0/d\eta_k$  and  $d\Delta H^0/d\eta_k$  are non-zero. By multiplying (4) by  $d\eta_k$ , we transform it into a linear relationship between  $\Delta H^0$  and  $\Delta S^0$ :

$$d\Delta S^0 = \frac{1}{T_{iso}} d\Delta H^0 \quad (6)$$

$$\Delta S^0 = \frac{1}{T_{iso}} \Delta E^0 + \Delta S_{iso} \quad (7)$$

in which  $\Delta S_{iso}$  is integration constant *independent of the variation of parameters*. The physical significance of  $\Delta S_{iso}$  can be obtained if the initial conditions for the integration of (6) can be rationally formulated. It is not always possible, therefore the isoequilibrium temperature  $T_{iso}$  is the parameter mostly discussed. Employing different theoretical models of IER and IKR one can develop certain ideas about the physical significance of  $T_{iso}$  (see *e. g.* in refs. [10 - 12]).

The reverse is also true: if Eq. (7) is valid then:

$$\ln K(T_{iso}) = \frac{\Delta S^0}{R} - \frac{1}{RT_{iso}} \Delta E^0 = \frac{\Delta S_{iso}}{R} \neq f(\eta_1, \eta_2 \dots \eta_n) \quad (8)$$

Deriving the complete derivative of  $\ln K(T_{iso})$  with respect to  $\eta_k$  in the case of linear interdependence of parameters controlling  $\Delta H^0$  and  $\Delta S^0$  (Eq. (2)) it is not difficult to obtain the condition of the intersection of van't Hoff plots in one point:

$$\frac{d \ln K(T_{iso})}{d\eta_k} = \sum_i \frac{\partial \Delta S^0}{\partial \eta_i} a_i - \frac{1}{T_{iso}} \sum_i \frac{\partial \Delta E^0}{\partial \eta_k} a_i = 0 \quad (9)$$

### 3. Analysis of van't Hoff plots using pseudo-experimental data

Let us now consider the effects of the random errors in the evaluation of  $\Delta H^0$  and  $\Delta S^0$ . An overwhelming majority of such data have been obtained by estimating parameters of the linear regression equation:

$$Y_i = \beta_0 + \beta_1 X_i + \varepsilon_i \quad (10)$$

in which  $Y_i = \ln K_i$ ,  $X = T_i^{-1}$ ,  $\beta_1 = -\Delta H^0/R$ ,  $\beta_0 = \Delta S^0/R$ , and  $\varepsilon_i$  is the random error. Regression methods yield corresponding *estimates*  $b_0$  and  $b_1$  derived from the conditions of the minimum of the  $\sum \varepsilon_i^2$  with respect to  $\beta_1$  and  $\beta_0$  (see *e.g.* in ref. [13]). *If experimental points are not symmetrically arranged* with respect to  $X = 0$ , then these estimates are intrinsically correlated. In the case of van't Hoff and Arrhenius plots such arrangement is impossible:  $X = T^{-1} \neq 0$ , therefore the estimates  $b_0$  and  $b_1$  (hence  $\Delta H^0$  and  $\Delta S^0$ ) are correlated.

In order to quantify the role of this correlation in the analysis of the compensation effect let us follow the whole procedure of the experimental evaluation of  $\Delta H^0$  and  $\Delta S^0$  from spectroscopic data. Consider a simple monomolecular equilibrium, *e.g.* a keto-enol tautomerism:

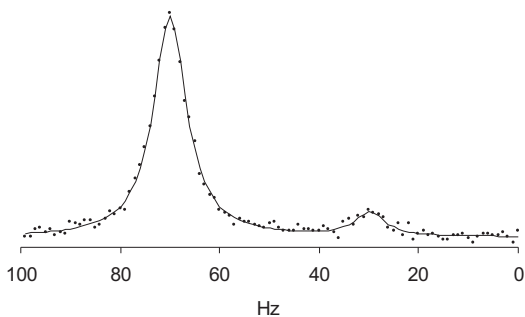


These equilibria have been studied by NMR spectroscopy [14] under the conditions of slow exchange when A and B species yield separate well-resolved signals. The composition of such a system can be obtained by integrating spectra or by approximating spectra as a set of Lorentzian lines. The latter method (deconvolution) is time consuming but it usually yields better precision. Pseudo-experimental spectra of the reaction mixture (11) can be obtained by generating them according to:

$$A(\nu) = A_0 \left[ \frac{x_B}{\Delta\nu_B} \frac{1}{1 + \Delta\nu_B^2 (\nu - \nu_{0B})^2} + \frac{1 - x_B}{\Delta\nu_A} \frac{1}{1 + \Delta\nu_A^2 (\nu - \nu_{0A})^2} \right] + Noise \quad (12)$$

in which  $x_B$  is the fraction of B species,  $\Delta\nu_{A(B)}$  are line widths,  $\nu_{0A(B)}$  are peak positions,  $A_0$  is the normalisation factor, *Noise* is a normally distributed random value characterised by the ratio  $S/N = A(\nu)_{\max}/Noise$ . The deconvolution is, of course, done according to (12) excluding the noise; it can be performed using any non-linear regression program that yields estimates of the above mentioned parameters and mean square errors of these estimates ( $\sigma$ ). Fig. 1 shows an example of a spectrum of the system (11) generated according to (12) and then deconvoluted. True parameters and their estimates are shown in Table 1. Obtained estimates of  $x_B$  are well defined, they lie within two mean square errors of estimation ( $\pm 2\sigma$ ) from the true values and can be used for the determination of equilibrium constants.

Due to the limited dynamic range of spectrometers the dependence of  $\ln K$  on  $1/T$  is usually followed by varying the temperature achieving standard degrees of conversion that can be reliably measured. Therefore pseudo-experimental spectra have been generated and deconvoluted for the true values  $x_B = 0.1, 0.2, 0.3, 0.5, 0.7, 0.8, 0.9$  with  $S/N = 50$ . Results are shown in Table 2. Corresponding ‘true’ temperatures have been calculated to meet the ‘true’ values of  $\Delta H^0/R = 3000$  K and  $\Delta S^0/R = 10$  at the ‘true’ values of  $x_B$ .



**Figure 1:** Simulated spectrum of a binary reaction mixture, solid line represents the approximation of pseudo-experimental points by a sum of two Lorentzian lines. Estimates of parameters are given in Table 11

**Table 1:** Parameters of simulated NMR spectrum (Fig. 1,  $S/N \approx 50$ ) and their estimates obtained by non-linear regression

|             | $\nu_B$<br>Hz  | $\nu_A$<br>Hz    | $\nu_A$<br>Hz | $\nu_A$<br>Hz   | $x_B$             | $A_0$             |
|-------------|----------------|------------------|---------------|-----------------|-------------------|-------------------|
| True values | 30.00          | 70.00            | 4.000         | 4.000           | 0.100             | 1.000             |
| Estimates   | $29.7 \pm 0.4$ | $70.01 \pm 0.05$ | $3.6 \pm 0.6$ | $4.03 \pm 0.07$ | $0.087 \pm 0.008$ | $0.989 \pm 0.012$ |

**Table 2:** Pseudo-experimental data on the temperature dependence of  $\ln K$  of a binary equilibrium simulated for true values  $\Delta H^0/R = 3000$  K and  $\Delta S^0/R = 10$

| $x_B$<br>(true) | $\ln K$<br>(true) | $T_{true}$<br>K | $T_{exp}$<br>K | $x_B$<br>(exper.) | $\sigma(x_B)$<br>(exper.) | $1000/T_{exp}$<br>K <sup>-1</sup> | $\ln K$<br>(exper.) | $\sigma(\ln K)$<br>(exper.) |
|-----------------|-------------------|-----------------|----------------|-------------------|---------------------------|-----------------------------------|---------------------|-----------------------------|
| 0.1             | -2.1972           | 246.0           | 245.9          | 0.0872            | 0.0083                    | 4.1405                            | -2.3483             | 0.1048                      |
| 0.2             | -1.3863           | 263.5           | 263.9          | 0.2005            | 0.0082                    | 3.8688                            | -1.3831             | 0.0514                      |
| 0.3             | -0.8473           | 276.6           | 276.8          | 0.3040            | 0.0071                    | 3.6797                            | -0.8283             | 0.0336                      |
| 0.5             | 0.0000            | 300.0           | 300.0          | 0.4991            | 0.0044                    | 3.3819                            | -0.0038             | 0.0175                      |
| 0.7             | 0.8473            | 327.8           | 327.6          | 0.6924            | 0.0065                    | 3.0931                            | 0.8112              | 0.0304                      |
| 0.8             | 1.3863            | 348.3           | 348.4          | 0.7942            | 0.0080                    | 2.9030                            | 1.3502              | 0.0488                      |
| 0.9             | 2.1972            | 384.5           | 384.5          | 0.8914            | 0.0105                    | 2.6250                            | 2.1050              | 0.1087                      |

However, experimental temperatures differ from these values due the limited precision of the thermostating device and fluctuations of the gas flow through the probehead. Therefore temperatures used in the analysis of van't Hoff plots ( $T_{exp}$ ) also contained normally distributed

errors of the thermostating device (in NMR spectroscopy the mean square error  $\sigma_T$  usually equals  $\pm 0.5$  K). Such numerical experiments reproduce a common situation when an experimenter completely relies on the readings of the thermostating device. This introduces additional random error into  $\ln K$ :

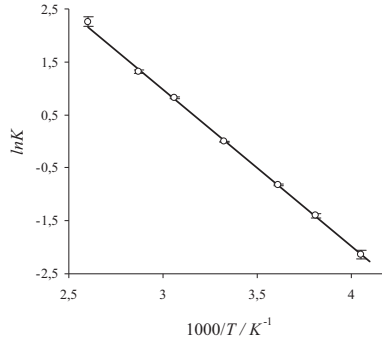
$$\sigma^2(\ln K(T)) = \sigma_T^2 \left( \frac{\partial \ln K}{\partial T} \right)^2 = \sigma_T^2 \frac{(\Delta H^0)^2}{R^2 T^4} \quad (13)$$

For  $\sigma_T = 0.5$  K,  $T = 300$  K and  $\Delta H^0/R = 3000$  K this component equals  $2.7 \cdot 10^{-4}$  which is considerably smaller than the mean value of  $\sigma^2(\ln K)$  arising from the uncertainty of the composition (see Table 2):

$$\sigma^2(\ln K(x_B)) = \sigma^2(x_B) \left( \frac{\partial \ln K}{\partial x_B} \right)^2 = \frac{\sigma^2(x_B)}{x_B^2 (1-x_B)^2} \quad (14)$$

The error of  $\ln K$  varies in a wide range therefore the estimation of  $\Delta H^0$  and  $\Delta S^0$  must be done using the weighted linear least square method (see *e.g.* in ref. [13]). Fig. 2 shows an example of the van't Hoff plot of these data along with the weighted linear regression line. The regression of these data yields well-defined estimates of  $\Delta H^0$  and  $\Delta S^0$  shown in the first row of Table 3. The ratio of variances  $s^2(\text{regression})/s^2(\text{reproducibility})$  equals 3.76, which is smaller than the tabulated value of the F-criterion for the actual number of degrees of freedom and significance level 0.95:  $F(5, 7, 0.95) = 3.97$ , *i.e.* these data do not contradict the assumption of temperature independent  $\Delta H^0$  and  $\Delta S^0$  (*i.e.* van't Hoff plots can be considered as straight lines). We see that in the absence of systematic errors (distortions of the line-shape, curvature of the baseline, *etc.*) the deconvolution of spectra yields well-defined estimates of  $\Delta H^0$  and  $\Delta S^0$  even at a comparatively high noise level ( $S/N = 50$ ) for systems with  $x_B$  varying from 0.1 to 0.9.

Similar numerical experiments in a narrower range of compositions ( $x_B = 0.35, 0.40, 0.45, 0.5, 0.55, 0.60$  and  $0.65$ ) yield larger errors of estimates (second row in Table 3). The ratio of variances  $s^2_{\text{reg}}/s^2_{\text{rep}} = 37.3$  is much larger than the tabulated value of the  $F$ -criterion, therefore these data do not support the assumption of temperature independent  $\Delta H^0$  and/or  $\Delta S^0$ , *i.e.* the test for linearity of the van't Hoff plot must be done using a wider range of compositions.



**Figure 2:** Pseudo-experimental van't Hoff plot generated in the range  $x_B = 0.1 - 0.9$  ( $S/N = 50$ ).

**Table 3:** First row: results of the weighted linear least square regression of data from Table 2. Second row shows results of a similar numerical experiment in a narrower range of compositions

| Composition range | $s^2$ reprod. | $s^2$ regr. | $\Delta H^0/R$ K | $\sigma(\Delta H^0/R)$ K | $\Delta S^0/R$ | $\sigma(\Delta S^0/R)$ | $\rho(\Delta S^0, \Delta H^0)$ |
|-------------------|---------------|-------------|------------------|--------------------------|----------------|------------------------|--------------------------------|
| 0.1 - 0.9         | 0.0026        | 0.0099      | -2946            | 36                       | 9.81           | 0.12                   | 0.997                          |
| 0.35 - 0.65       | 0.0003        | 0.011       | -3041            | 52                       | 10.15          | 0.18                   | 0.999                          |

Although optimal precision for the determination of  $x_B$  is achieved for systems with compositions close to  $x_B = 0.5$  (see Table 2), the errors in  $\Delta H^0$  and  $\Delta S^0$  become smaller when a system is investigated in a wider range of compositions.

#### 4. Analysis of the compensation plot

The statistical interdependence between the estimates  $\Delta S^0/R$  and  $\Delta H^0/R$  obtained above is very strong:  $\rho(b_0, b_1) = 0.997$  (and even higher when data are collected in a narrower temperature range). This correlation coefficient mainly depends on the arrangement of the points along the independent variable axis. For measurements of  $Y = \ln K$  (Eq. 10) with equal precision  $\rho(b_0, b_1)$  obviously does not depend [13] on the errors of determination of  $\ln K$ :

$$\rho(b_0, b_1) = -\frac{\sum_{i=1}^M X_i}{\sqrt{M \sum_{i=1}^M X_i^2}} \quad (15)$$



When the error in  $\ln K$  varies with temperature (which is typical for such measurements, see Table 2)  $\rho(b_0, b_1)$  depends on errors characterised by weighting factors  $w_i = 1/\sigma_{Y_i}^2$ :

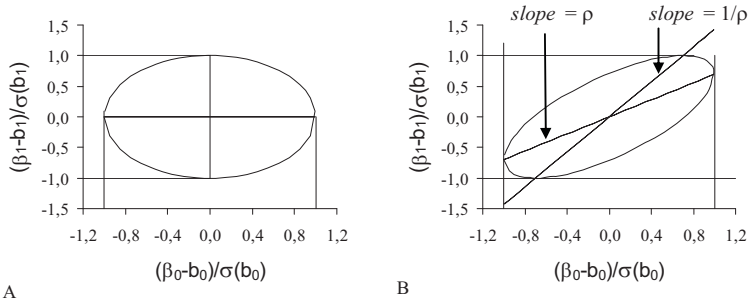
$$\rho(b_0, b_1) = - \frac{\sum_{i=1}^M w_i X_i}{\sqrt{\sum_{i=1}^M w_i \sum_{i=1}^M w_i X_i^2}} \quad (16)$$

The correlation coefficient  $\rho(b_0, b_1)$  does not depend on the absolute value of errors in  $\ln K$ : spectra with  $S/N = 100$  yield the same correlation coefficient  $\rho(b_0, b_1) = -0,997$ . Assuming that  $\ln K(T)$  in Table 2 have been obtained with equal precision one obtains  $\rho(b_0, b_1) = -0,989$ . For symmetric distribution of errors with respect to  $T_{1/2}^{-1}$   $\rho(b_0, b_1) = -0,993$ . Therefore the *distribution* of errors affects the values  $\rho(b_0, b_1)$  but not considerably.

The correlation coefficient  $\rho(b_0, b_1)$  along with the standard deviations ( $\sigma$ ) of  $\Delta H^0$  and  $\Delta S^0$  define the shape and size of the *joint significance ellipse* of the estimates of parameters (Fig. 3) according to [13]:

$$y^2 + x^2 - 2\rho xy = 1 - \rho^2 \quad (17)$$

in which  $x = \kappa(\beta_0 - b_0)/\sigma(b_0)$ ,  $y = \kappa(\beta_1 - b_1)/\sigma(b_1)$ ;  $\kappa = 1/2$  for the significance level 0.95 and  $\kappa = 1/3$  for the significance level 0.997. If  $b_0$  and  $b_1$  are uncorrelated (i.e.  $\rho(b_0, b_1) = 0$ ) then the axes of the ellipse are parallel to the coordinate axes (Fig. 3A). If  $\rho(b_0, b_1)$  considerably deviates from zero then the ellipse becomes narrow with axes at an angle to the coordinates (Fig. 3B).



**Figure 3:** Joint significance ellipse ( $\kappa=1$ ), corresponding to independent estimates  $b_0, b_1$ ,  $\rho(b_0, b_1) = 0$  (A). Graph (B) shows a similar ellipse for correlated estimates with  $\rho(b_0, b_1) = +0.7$

When the correlation between estimates complicates the interpretation of results the regression equation can be transformed in such a way that the estimates become independent:

$$Y = \ln K = Y(X_0) + b_1(X - X_0) = b'_0 + b_1 Z \quad (18)$$

in which  $Z = X - X_0$ . Assuming  $X_0 = \langle X \rangle$  one obtains  $Z_i$  symmetrically arranged around zero. The van't Hoff equation thus transforms into:

$$\ln K = b'_0 - \frac{\Delta H^0}{R} (T^{-1} - T_0^{-1}) \quad (19),$$

where

$$b'_0 = \ln K(T_0) = \frac{\Delta S^0}{R} - \frac{\Delta H^0}{R} T_0^{-1} \quad (19a)$$

Note that  $T_0$  is not a random value. Pseudo-experimental data from Table 2 being analysed according to (19) yield weakly correlated estimates of  $b_1$  and  $b'_0$  shown in Table 4. If  $T_0$  has been selected close to the half conversion temperature ( $T_{1/2}$ ) the correlation coefficient approaches zero. By choosing  $T_0$  above or below  $T_{1/2}$  one can obtain positive or negative correlation coefficients. However this transformation does not help in destroying the correlation between  $\Delta H^0$  and  $\Delta S^0$  because these values are now connected *via* the Eq. (19a).

Table 4: Results of the weighted linear least square regression of data from Table 2 according to Eq. (19).

| $T_0$<br>K | $\Delta H^0/R$<br>K | $b'_0$       | $\rho(\Delta H^0/R, b'_0)$ |
|------------|---------------------|--------------|----------------------------|
| 320        | 2972±39             | 0.606±0.013  | 0.604                      |
| 300        | 2972±39             | -0.013±0.010 | -0.046                     |
| 280        | 2972±39             | -0.720±0.014 | -0.694                     |

It is also possible to rewrite the van't Hoff equation in a non-linear (with respect to parameters) form:

$$\ln K = -\frac{\Delta H^0}{R} (T^{-1} - T_{1/2}^{-1}) \quad (20)$$

in which  $T_{1/2}$  is a *parameter* (i.e. a random value):

$$T_{1/2} = \Delta H^0 / \Delta S^0 \quad (21)$$

In order to estimate parameters of this equation one has to use non-linear regression methods. These methods have certain advantages: for example one can discard linearising transformations and write the regression equation with respect to variables obtained directly from experiment ( $x_B$  and  $T$  in the considered case):

$$x_B = \left[ 1 + \exp\left(\frac{\Delta H^0}{R}(T^{-1} - T_{1/2}^{-1})\right) \right]^{-1} \quad (22)$$

Although the errors of  $x_B$  in Table 2 vary, they can be made constant by a proper choice of the number NMR scans. Regression of data in Table 2 according to this equation indeed yields practically non-correlated estimates of  $\Delta H^0/R = 2978 \pm 42$  K;  $T_{1/2} = 300.7 \pm 0.5$  K with  $\rho(\Delta H^0, T_{1/2}) = 0.10$ . One can therefore safely correlate the values of  $\Delta H^0$  and  $T_{1/2}$ , however, the estimates of  $\Delta H^0$  and  $\Delta S^0$  (that possess clear *physical significances*) remain strongly correlated *via* Eq. (21).

It might be concluded that the pair of estimates  $\Delta H^0$ ,  $\Delta S^0$  always remain correlated for purely statistical reasons. However, this purely statistical correlation *only appears in cases of perfectly constant* true values of  $\Delta H^0$  and  $\Delta S^0$ , i.e. when we repeat the experiments *on one and the same* system. Fig. 4 shows the results of 30 such numerical experiments (according to the procedure described above) with fixed true values  $\Delta H^0/R = 3000$  K and  $\Delta S^0/R = 10$ . The errors in  $\ln K$  and fluctuations of temperature bring about variations in the estimates of  $\Delta H^0$  and  $\Delta S^0$ . Thus numerically generated data indeed show an ‘excellent’ linear correlation between  $\Delta H^0$  and  $\Delta S^0$  characterised by  $T_{iso} = 306 \pm 7$  K  $\approx \langle T \rangle$  (Fig. 4). This correlation only occurs within a small range not exceeding  $2\sigma(b_1)$  and  $2\sigma(b_0)$ . As expected, the significance ellipse computed according to (17) at the significance level 0.95 ( $\kappa = 2$ ) contains all pseudo-experimental points.

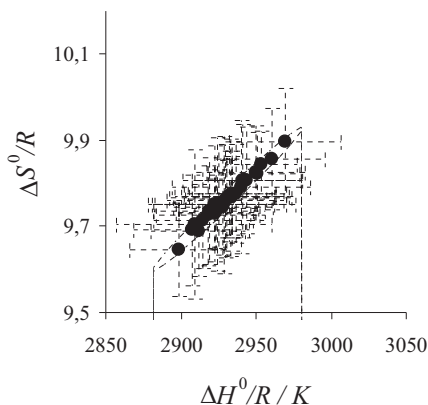
In real physico-chemical experiments measurements on the same system are only done in the determination of the reproducibility error. When a large number of *physically distinguishable systems* are investigated one should expect (in the worst possible case) *at least random variations* of  $\Delta H^0$  and  $\Delta S^0$  within *two errors of estimation*, arising, for example, from the variations of the minor parameters  $\eta_j$ .

Numerical simulations for a set of 30 equilibria with the ‘true’ values of  $\Delta H^0$  and  $\Delta S^0$  randomly varying within  $\Delta H^0/R = 3000$  K  $\pm \sigma_{\Delta H/R}$  and  $\Delta S^0/R = 10 \pm \sigma_{\Delta S/R}$  show that the linear correlation between the estimates of  $\Delta H^0$  and  $\Delta S^0$  *completely disappears* (Fig. 5, Table 5): the correlation coefficient approaches zero; points randomly fill the ellipse corresponding to  $\rho_{xy} = 0.035$  and standard deviation equal  $3\sigma$  (the latter value can be interpreted as  $1\sigma$  due to the errors of measurements and  $2\sigma$  due to the variation of  $\Delta H^0$  and  $\Delta S^0$ ). The ellipse

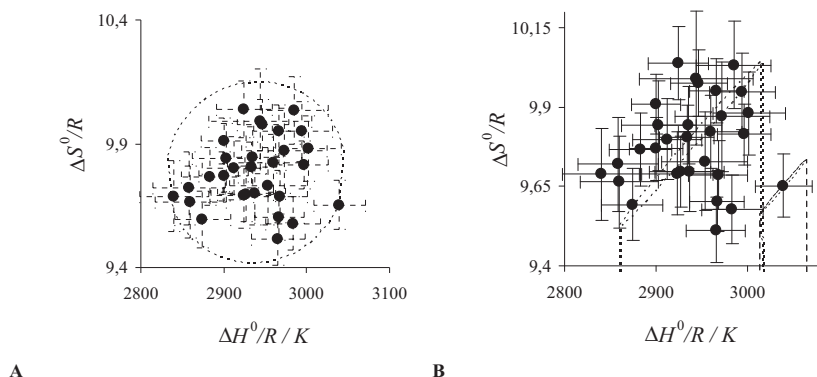
corresponding to  $\rho(\Delta H^0, \Delta S^0) = 0.997$  drawn around the mean values of  $\Delta H^0$  and  $\Delta S^0$  only contains few points (Fig. 5B).

A random variation of parameters within  $\pm 1\sigma$  thus *completely cancels the purely statistical correlations* of  $\Delta H^0$  and  $\Delta S^0$ . Therefore the statistical correlation shown in Fig. 4 merely describes the *ellipsoidal shape of an individual experimental point* (as shown in Fig. 5B)

However, when random variation of these parameters occurs within  $\pm 0.5\sigma$  the statistical correlation returns: in the compensation plot  $\rho(\Delta H^0, \Delta S^0) = 0.714$  and isokinetic temperature was shifted to the experimental range  $T_{iso} = 367 \pm 68$  K. Such numerical experiments simulate cases when the *precision of an instrument is insufficient* for the investigation of small variations of chemical affinity.



**Figure 4:** Correlation between  $\Delta S^0$  and  $\Delta H^0$  (compensation plot) of a purely statistical origin: ‘true’ values of these parameters remain constant ( $\Delta H^0/R = 3000$  K,  $\Delta S^0/R = 10$ ). The joint significance ellipse (dashed) has been drawn according to (17) with  $\kappa = 2$  and  $\rho = 0.997$



**Figure 5:** Graph A shows the compensation plot for systems with random variation of  $\Delta H^0/R = 3000K \pm \sigma$  and  $\Delta S^0/R = 10 \pm \sigma$  with significance ellipse computed (Eq. (17)) with  $\kappa = 1/3$ ,  $\rho = 0.079$  around the mean values. Graph B shows a part of the plot in graph A with significance ellipses computed using  $\kappa = 1/3$ ,  $\rho = 0.997$  around the mean values and  $\kappa = 1$ ,  $\rho = 0.997$  around the point (3040, 9.65).

**Table 5:** Parameters of the compensation plot in Fig. 5.

| $1/T_{iso}$<br>K <sup>-1</sup> | $\Delta S_{iso}/R$ | $T_{iso}$<br>K        | $\rho(\Delta H^0, \Delta S^0)$ |
|--------------------------------|--------------------|-----------------------|--------------------------------|
| $(1.1 \pm 5.8) 10^{-4}$        | $9.46 \pm 1.7$     | $(9.2 \pm 49.3) 10^3$ | 0,035                          |

In fact, a properly designed physico-chemical experiment rarely deals with systems showing random variations of  $\Delta H^0$  and/or  $\Delta S^0$  within  $\pm 1\sigma$ . For example, parameters of the keto-enol equilibrium of acetylacetone dissolved in different solvents vary [14] within at least  $10\sigma$ . Larger (*ca.* 50%) variations of  $\Delta H^0$  and  $\Delta S^0$  are observed for the equilibrium between square-planar and tetrahedral forms of a Ni(II) complex in different solvents [15]. The latter data exhibit compensation effect discussed in ref [16].

Let us now consider *an isoentropic series of equilibria* showing variations of  $\Delta H^0/R$  within 2500 - 4000 K (such as observed for the conformational equilibria of Ni complexes [15]) modulated by random fluctuations within  $\pm 2\sigma_{\Delta H/R}$ , whereas the standard entropy only experiences fluctuations within  $\pm 2\sigma_{\Delta S/R}$  around a constant value (such fluctuation in  $\Delta H^0$  and  $\Delta S^0$  might arise from variations of minor parameters):

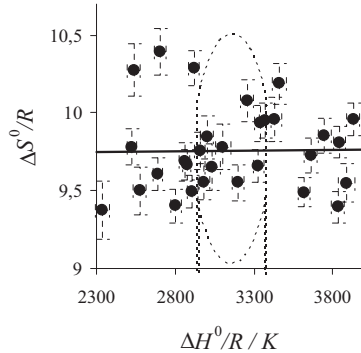
$$\Delta H^0/R = 2500 + (i - 1) * 50 + 2Rand(\sigma(\Delta H^0/R)) \quad (23)$$

$$\Delta S^0/R = 10 + 2Rand(\sigma(\Delta S^0/R)) \quad (24)$$

in which  $i$  is the experiment's number,  $Rand(\sigma(P))$  is a normally distributed variation in terms of the error of corresponding estimates. The results of these numerical experiments are shown in Fig. 6 and Table 6. The significance ellipse, drawn according to Eq. (17) with  $\kappa = 1/6$  and  $\rho = 0.015$  (Table 6) around the mean values of  $\Delta H^0/R$  and  $\Delta S^0/R$  only contains a part of experimental data. This indicates that some non-random variation of  $\Delta H^0$  occurs. As expected for isoentropic systems  $1/T_{iso} = 0$  within the error of its determination (Table 6). The large value of the correlation coefficient computed for individual measurement of  $\Delta H^0/R$  and  $\Delta S^0/R$  does not affect the estimate of  $T_{iso}$  of this exo-statistical connection between these parameters.

**Table 6:** Parameters of the compensation plot in Fig. 6.

| $1/T_{iso}$<br>K <sup>-1</sup> | $\Delta S_{iso}/R$ | $T_{iso}$<br>K      | $\rho_{xy}$ |
|--------------------------------|--------------------|---------------------|-------------|
| $(9.5 \pm 114) 10^{-6}$        | $9.73 \pm 0.36$    | $(1,1 \pm 12) 10^5$ | 0,015       |



**Figure 6:** Compensation plot computed for *isoentropic* systems with non-statistical variations of  $\Delta H^0/R$  from 2500 K to 4000 K and constant  $\Delta S^0 = 10R$ , both modulated by random fluctuations variations within  $\pm 2\sigma$ . The dashed ellipse was computed (Eq. (17)) with  $\kappa = 1/6$  and  $\rho = 0.015$

Suppose now that a physically based correlation exists between the ‘true’ values of  $\Delta H^0$  and  $\Delta S^0$ , characterised by  $T_{iso} = 400$  K (similar to that observed for the conformational equilibria of Ni complexes [15]):

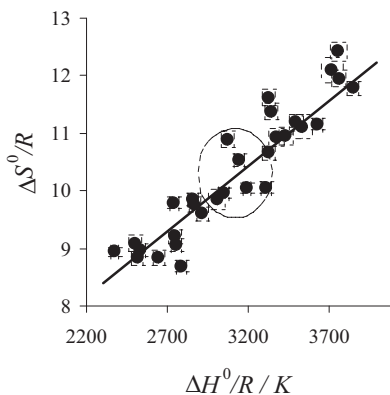
$$\Delta H^0/R = 2500 + (i-1)*50 + 2Rand(\sigma(\Delta H^0/R)) \quad (25)$$

$$\Delta S^0/R = \frac{3500 + (i-1)*50}{400} + 2Rand(\sigma(\Delta S^0/R)) \quad (26)$$

The results of these numerical experiments are shown in Fig. 7 and Table 7.

**Table 7:** Parameters of the compensation plot in Fig. 7.

| $1/T_{iso}$<br>K <sup>-1</sup> | $\Delta S_{iso}/R$ | $T_{iso}$<br>K | $\rho_{xy}$ |
|--------------------------------|--------------------|----------------|-------------|
| $(2,25 \pm 0,18) 10^{-3}$      | $3,22 \pm 0,54$    | $444 \pm 35$   | 0,921       |



**Figure 7:** Compensation plot computed for systems with non-statistical correlation between  $\Delta H^0/R$   $\Delta S^0$  modulated by random variations with  $\pm 2\sigma$ . The significance ellipse was computed (Eq. (17)) with  $\kappa = 1/6$  and  $\rho = 0$  around the mean values of  $\Delta H^0$  and  $\Delta S^0$ .

The significance ellipse in Fig. 7 shows that both  $\Delta S^0$  and  $\Delta H^0$  experience non-statistical variations. The correlation coefficient of the compensation plot  $\rho_{xy} = 0.921$  therefore reflects the reliability of the observed exo-statistical correlation. The estimate of  $T_{iso} = 444 \pm 35\text{K}$  practically coincides with the ‘true’ value within the error of estimation.

An exo-statistical (having some physical origin) correlation between  $\Delta H^0$  and  $\Delta S^0$  can thus be detected when the range of variations of these parameters considerably exceeds two errors of estimation. This shows the importance of the knowledge of the errors of estimation of thermodynamic parameters, however, when no data on errors are present there is still a way of distinguishing false IER.

## 5. Analysis of the isoequilibrium (isokinetic) plot

In the absence of data on errors of estimates of  $\Delta H^0$  and  $\Delta S^0$  (or  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ ) one can distinguish between purely statistical and real IER (IKR) by comparing  $T_{iso}$  resulted from the compensation plot and from the abscissa of the point of intersection of van't Hoff plots (Arrhenius plots). One of the authors of this paper has developed a computer program [5, 6] that searches for the most probable coordinates of the point of intersection corresponding to the minimum of the characteristic function S (see Section 6).

We made 4 series of numerical experiments characterised by: (A) constant  $\Delta H^0$ ,  $\Delta S^0$ , (B) randomly varying  $\Delta H^0$  and  $\Delta S^0$ , (C) constant  $\Delta S^0$  and varying  $\Delta H^0$ , and (D) varying  $\Delta S^0$  and  $\Delta H^0$ , as described in the preceding Section. Each series involved measurements of the temperature dependence of  $\ln K$  (7 points) on 12 systems. In order to test this method thoroughly we made our numerical experiments more complicated. Standard (true) degrees of conversion experience random variations within  $r_{xi} = \pm 5\%$  of actual values ( $x_B = 0.1, 0.2, 0.3, 0.5, 0.7, 0.8, 0.9 \pm r_{xi}$ ). This method simulates the experimental procedure of performing a test integration of an NMR spectrum at a given temperature (common error  $\pm 5\%$ ) before starting accumulation. Errors in  $\ln K$  arising from the uncertainty of the temperature measurements have also been taken into account.

In the case of purely statistical correlation (series A,  $\Delta H^0/R = 3000\text{K}$  and  $\Delta S^0/R = 10$ ) the analysis of the compensation plot yields a linear correlation with  $\rho_{xy} = 0.984$  and  $1/T_{iso} = (3.6 \pm 0.2) 10^{-3} \text{ K}^{-1}$  practically coinciding with the  $\langle 1/T \rangle = 0.33 \cdot 10^{-3} \text{ K}^{-1}$ . However, this correlation can be rejected because the search for the intersection point does not yield a minimum of the characteristic function S in the region of  $T_{iso}$ : the graph reveals rather a maximum of S in this region (Fig. 8A).



In the case of random variations of  $\Delta H^0$  and  $\Delta S^0$  around the above values within  $2\sigma$  (series B) the analysis of the compensation plot yields a poor correlation with  $\rho_{xy} = 0.07$ , characterised by  $1/T_{iso} = (1.4 \pm 6.5) 10^{-4} \text{ K}^{-1}$ . The search for the intersection point does not yield a minimum of the characteristic function (see Fig. 8B).

On the other hand, the analysis of the compensation plot of isoentropic series (C), in which  $\Delta H^0/R$  varies from 2400 to 4000 K whereas  $\Delta S^0/R$  remains constant (both modulated by random variations within  $2\sigma$ ) yields  $1/T_{iso} = -(3.2 \pm 1.6)10^{-4} \text{ K}^{-1}$ , in agreement with the search for the intersection point indicated by a sharp minimum of the characteristic function at  $1/T_{iso} = -1.9 10^{-4} \text{ K}^{-1}$  (Fig. 8C).

A similar result has been obtained for a linear exo-statistical correlation of  $\Delta H^0$  and  $\Delta S^0$  described by Eqs. (25), (26) (series D). The analysis of the compensation plot ( $\rho_{xy} = 0.973$ ) yields  $1/T_{iso} = (2.09 \pm 0.15)10^{-3} \text{ K}^{-1}$ . The search for the intersection point yields  $1/T_{int} = (1.75 \pm 0.1)10^{-3} \text{ K}^{-1}$  which agrees with the value obtained from the isoequilibrium plot within  $2\sigma$ . Both  $1/T_{iso}$  and  $1/T_{int}$  are slightly smaller than the theoretical  $1/T_{iso} = 0.0025 \text{ K}^{-1}$  following from Eq. (25). This shows that a random modulation of a linear relationship between  $\Delta H^0$  and  $\Delta S^0$  (that might arise from variations of parameters of minor importance) can shift the value of  $T_{iso}$  but not considerably.

## 6. Methods

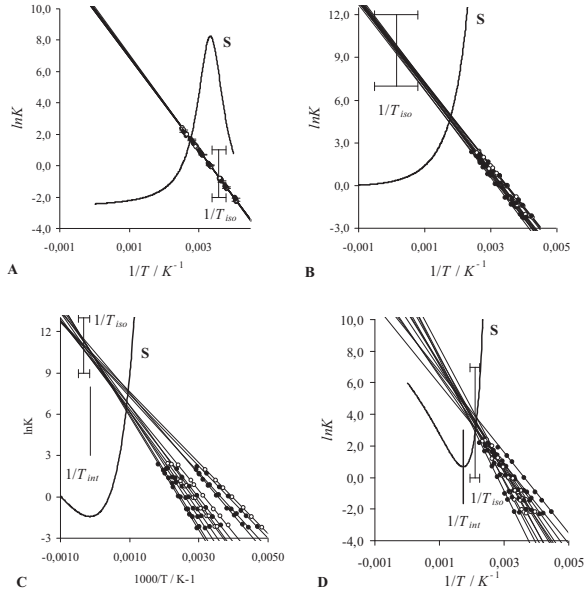
The pseudo-experimental spectra with a given signal to-noise ratio and  $x_B$  have been generated by a FORTRAN program employing the 'rand()' statement and further computation of normally distributed random numbers using the Box-Muller transformation [17]. In all spectra the added noise was fixed with respect to the largest peak in a spectrum (this means that in real experiments at compositions  $x_B = 0.5$  some additional scans must be provided).

These spectra have then been deconvoluted using non-linear regression program supplied with the book [18]. All six parameters of Eq. (10) have been adjusted in order to realise the most difficult scenario in which neither positions nor linewidths of peaks are exactly known.

Further analysis has been performed in the Excel worksheets also employing the rand() function and obtaining normally distributed random numbers by the Box-Muller transformation. The procedure of generating pseudo-experimental van't Hoff plots has been

described above in Section 3. Formulae of the weighted linear least square method can be found in [13].

The major problem of the regression analysis of the compensation plot is that both variables (dependent and independent) are random values. This does not contradict the calculation of the estimates of isoequilibrium parameters. However, when computing errors of the estimates of parameters the independent variable is supposed to be a non-random value. Therefore, obtained significance intervals for  $T_{iso}$  are rather illustrative. Using the weighted linear least square method in the analysis of the compensation plot one should also take into account the uncertainties in both  $\Delta H^0$  and  $\Delta S^0$ . We did this by computing weighting factors not as  $w = 1/\sigma_Y^2$  but as  $w = 1/(\sigma_Y\sigma_X)$ .



**Figure 8:** Van't Hoff plots for systems with constant (A)  $\Delta H^0/R$  and  $\Delta S^0/R$ , random variations of  $\Delta H^0/R$  and  $\Delta S^0/R$  within  $2\sigma$  (B), isoentropic series with  $\Delta H^0/R$  varying within 2500 - 4000 K and constant  $\Delta S^0/R = 10$  (both modulated by random fluctuations within  $\pm 2\sigma$ ), and isoequilibrium series (C) characterised by  $T_{iso} = 400$  K (exo-statistical variations of  $\Delta H^0/R$  and  $\Delta S^0$  modulated by random fluctuations within  $\pm 2\sigma$ ). Curves S in these graphs represent the characteristic function of the Exner-Linert method, the minimum of which indicates the abscissa of the intersection point ( $1/T_{int}$ ). Values of  $1/T_{iso}$  have been obtained from the compensation plot.

The Exner-Linert method, in its simplest form, consists in the calculation of the characteristic function  $S_x$  which is the residual sum of squares of the deviations of experimentally measured points from their associated van't Hoff or Arrhenius line under the assumption of a common point of intersection of these lines. The abscissa  $x$  equals  $1/T$  whereas the associated value of  $y = \ln K(x)$  (respectively  $\ln k(x)$ ) is calculated as using the least means square estimates of the van't Hoff (Arrhenius) parameters at a given  $x$ .

$$S_x = \sum_{i,j} y_{ij}^2 + ly^2 - \sum_i \frac{\left( \sum_j y_{ij} + y \right)^2}{m_i + 1} - \sum_i \frac{\left[ \sum_j x_{ij} y_{ij} + xy - \frac{1}{m_i + 1} \left( \sum_j x_{ij} + x \right) \left( \sum_j y_{ij} + y \right) \right]^2}{\sum_j x_{ij}^2 + x^2 - \frac{1}{m_i + 1} \left( \sum_j x_{ij} + x \right)^2} \quad (27)$$

$$y = \frac{\sum_j y_{ij} - \sum_i \frac{\left( \sum_j x_{ij} - m_i x \right) \left( \sum_j x_{ij} y_{ij} - x \sum_j y_{ij} \right)}{\sum_j x_{ij}^2 - 2x \sum_j x_{ij} + m_i x^2}}{\sum_i m_i - \sum_i \frac{\left( \sum_j x_{ij} - m_i x \right)^2}{\sum_j x_{ij}^2 - 2x \sum_j x_{ij} + m_i x^2}} \quad (28)$$

in which  $i$  denotes each individual van't Hoff or Arrhenius line and varies from 1 to  $l$  (number of straight lines) and  $j$  varies from 1 to  $m_i$  (number of points associated with each line).

The quantitative analysis of the possibility of the intersection point is derived from the comparison of variances  $S_0$  (the minimal value of  $S_x$  as a function of  $x$ , *i.e.* the residual sum of squares of optimally constrained by passing through the common point of intersection regression lines) and  $S_{00}$  (without the constraint of the common point of intersection):

$$S_{00} = \sum_{ij} y_{ij}^2 - \sum_i \frac{\left( \sum_j y_{ij} \right)^2}{m_i} - \sum_i \frac{\left( \sum_j x_{ij} y_{ij} - \frac{1}{m_i} \sum_j x_{ij} \sum_j y_{ij} \right)^2}{\sum_j x_{ij}^2 - \frac{1}{m_i} \left( \sum_j x_{ij} \right)^2} \quad (29)$$

If the ratio  $F$ :

$$F = \frac{|S_0 - S_{00}|f_2}{S_{00}f_1} \quad (30)$$

(in which  $f_1 = l - 1$ ,  $f_2 = \Sigma m_i - 2l$ ) is less than the tabulated value of the F-criterion for the given degrees of freedom ( $f_1$  and  $f_2$ ) and chosen significance level then the occurrence of the common point of intersection can be considered as statistically possible. If, on the other hand,  $S_0$  is significantly larger than  $S_{00}$ , then the hypothesis of the common point of intersection must be rejected. Much stronger is the condition of testing the value  $1/F$  which statistically leads to a rejection of the hypothesis "There is no common point of intersection". In case this hypothesis can be rejected statistically we have to accept the common point of intersection at a certain significance level. More information can be found in refs. [5 - 9].

## 7. Conclusions

Numerical experiments simulating spectroscopic determination of equilibrium constants that take into account normally distributed random noise in spectral amplitudes and temperatures for the cases of isoentropic reaction series and those exhibiting isoequilibrium relationships have shown that even at comparatively high level of random noise in spectral data and theoretical values of  $\Delta H^0$  and  $\Delta S^0$  the estimates of isoequilibrium temperatures obtained from the analysis the compensation plot ( $\Delta S^0$  vs.  $\Delta H^0$ ) are in a satisfactory agreement with theoretical data. The necessary requirement is that the range of variation of  $\Delta H^0$  and  $\Delta S^0$  should exceed two standard errors of their estimation, which is usually complied with in properly designed physico-chemical experiments.

The so-called 'statistical' correlation between estimates of  $\Delta H^0$  and  $\Delta S^0$  only appears when measurements are performed on systems with perfectly stable  $\Delta H^0$  and  $\Delta S^0$ , i.e. on one and the same system. A random variation of  $\Delta H^0$  and  $\Delta S^0$  within two standard deviations of estimation ( $\Delta H^0 \pm 1\sigma_{\Delta H}$ , and  $\Delta S^0 \pm 1\sigma_{\Delta S}$ ) completely destroys this statistical effects causing a decrease in the correlation coefficient from  $\rho(\Delta H^0, \Delta S^0) = 0.997$  to  $\rho(\Delta H^0, \Delta S^0) = 0.079$ . The large correlation coefficient computed for an individual measurement of  $\Delta H^0$  and  $\Delta S^0$  thus defines the ellipsoidal shape of an individual experimental point. Smaller random variations of parameters (e.g. within  $\pm 0.5\sigma$ ) might cause a false compensation effect characterised by  $1/T_{iso}$  approaching  $\langle 1/T \rangle$ . However such results merely show that the precision of the experimental data is insufficient for the investigation of the chosen set of reactions.

Therefore, if a linear correlation between  $\Delta H^0$  and  $\Delta S^0$  ( $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ ) characterised by  $1/T_{iso} \approx \langle 1/T \rangle$  and large correlation coefficients has been experimentally established, then the range of variations of these parameters should be compared with the errors of their estimation. When the range of variation exceeds  $2\sigma$  then most probably the compensation effect is real. However, there is still a possibility that the error of estimation has been determined on other samples and/or in a different range of the values of  $\Delta H^0$  and  $\Delta S^0$  ( $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ ). In such cases the reproducibility errors of measurements should be specially tested.

When analysing literature data that do not give any reference with respect to the errors of measurements the false compensation effect can be distinguished by the Exner-Linert method of the determination of the intersection of van't Hoff (or Arrhenius) plots. In fact, this method (see Section 6) takes into account the scatter of experimental points respective linear dependence, *i.e.*, implicitly, the errors of parameters estimated in the regression procedure.

### Acknowledgments:

Thanks for financial support are due to the Austrian Science Foundation under Project 19335-N17.

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