

ACCURATE NMR DATA EVALUATION FOR MONOMER SHIFT, DIMER SHIFT AND DIMERIZATION CONSTANT IN A SELF-ASSOCIATING SYSTEM

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Summary: A novel graphical method is proposed for the simultaneous determination of the monomer shift, dimer shift and dimerization constant from NMR dilution shift data for a self-associating system. Dilution shift data for the proton in N-H group of Valerolactam in CDCl_3 at 360K is used to demonstrate this method.

Nuclear magnetic resonance (NMR) has been widely used to investigate the problem of self-association in solutions [1-4]. Traditionally, monomer shifts are obtained by visual extrapolation to infinite dilution [5,6]. However, at high dilutions, the change of chemical shift with concentration is usually very steep and nonlinear. Consequently, it is difficult to obtain accurate values in monomer shifts from such extrapolations. Furthermore, errors in monomer shifts limit the accuracy in the evaluation of dimerization constants [2], which, in turn, make the determination of association enthalpy and entropy, using Van't Hoff's equation, unreliable.

In a system with monomer-dimer rapid exchange kinetics, the observed chemical shift, δ_{obs} , is an average of monomer shift, δ_{m} , and dimer shift, δ_{d} , weighted by their respective mole fractions, F_{m} , and F_{d} [7]. The mole fractions are, in turn, determined by the dimerization constant, K , and total concentration, C . For system with $\delta_{\text{d}} > \delta_{\text{m}}$, the equations governing the relations among those quantities were derived previously [8] as

$$\delta_{\text{obs}} = \delta_{\text{d}} - \frac{(\delta_{\text{d}} - \delta_{\text{m}})}{2K} \left(\frac{\delta_{\text{obs}} - \delta_{\text{m}}}{C} \right)^{1/2}; \quad \text{or} \quad (1)$$

$$\begin{aligned} \delta_{\text{obs}} &= \delta_{\text{m}} + (\delta_{\text{d}} - \delta_{\text{m}}) F_{\text{d}} \\ &= \delta_{\text{m}} + (\delta_{\text{d}} - \delta_{\text{m}}) \frac{(1 + 8KC)^{1/2} - 1}{(1 + 8KC)^{1/2} + 1}. \end{aligned} \quad (2)$$

In reference [8], an iteration scheme was employed to determine δ_m , δ_d , and K simultaneously from the dilution shift data. This scheme starts with a guessed δ_m to calculate $X = \{(\delta_{\text{obs}} - \delta_m)/C\}^{1/2}$ in eq. (1). Data of δ_{obs} vs. X are then regressed in terms of a quadratic (instead of a linear) polynomial to calculate a tentative value of δ_d from the intercept and a tentative value of K from the foregoing δ_d and limiting slope (slope at $X = 0$) of the regressed curve. The K thus obtained is then inserted into eq. (2) to calculate $F_d = \{(1 + 8KC)^{1/2} - 1\}/\{(1 + 8KC)^{1/2} + 1\}$. F_d is then used for regressing data of δ_{obs} vs. F_d based on eq. (2) in terms of a quadratic polynomial to obtain an improved value of δ_m from the intercept, and an improved value of δ_d from the foregoing δ_m and limiting slope. This newly obtained δ_m is then inserted in eq. (1) to initiate the second iteration to obtain further improved values of δ_d and K . The iteration procedure is repeated until the difference of two successive monomer shifts lies within the limit of a preset tolerance.

In this communication we propose an alternative graphical method. If a value of δ_m is correctly guessed, plots of δ_{obs} vs. X based on eq. (1) give a straight line. In such a case, the constant and linear terms obtained from quadratic regression are substantially equal to their respective counterparts obtained from the linear regression, while the quadratic term is negligibly small. This is tantamount to the fact that the values of K determined from either regression are identical, if a correct value of δ_m is used. On the other hand, if an incorrect value of δ_m is inserted into X , different values of K would be obtained from linear and quadratic polynomial regressions. This feature can be utilized to determine the "true values" of δ_m and K from the intersection of plots of regressed values of K vs. guessed values of δ_m obtained by quadratic and linear regression, respectively. By the same token, this unique point can also be determined from the intersection of plots of guessed values of K vs. regressed values of δ_m , respectively, for linear and quadratic regressions based on eq. (2). Ideally, these two intersections should coincide, since both of them are based on the same physical entities. Their departure may reflect the coexistence of other forms of dimers, extended clustering beyond dimerization, nonlinearity of solution and experimental errors. In practical applications, this departure, however, would provide a measure of consistency and a method of estimating error for the determination.

In the following we will demonstrate the utility of our technique by applying it to data obtained by Purcell *et al.* for the dilution shift of δ -valerolactam in CDCl_3 [9]. These authors applied the direct search procedure in which a preset value of monomer shift was assumed, the dimer shift and dimerization constant varied independently until the deviation of the fitting to the observed chemical shift vs. concentration reach a minimum. They concluded that while the dimer shift is fairly independent of the preset value of monomer shift, the dimerization constant is strongly dependent. We have particularly selected this system for testing our approach, since a wide range of value

Table 1: 60 MHz NMR dilution shift data for the proton in the N-H group of valerolactam in CDCl_3 at 306 K (data from reference [9]).

<u>conc.(m)</u>	<u>obed. shift (Hz)</u>	<u>conc.(m)</u>	<u>obed. shift (Hz)</u>
0.0839	382.0	0.8923	458.4
0.1695	408.8	1.4659	469.6
0.2569	420.7	2.1158	476.9
0.3551	426.6	2.8433	484.6
0.4557	442.7	3.5602	484.7
0.5396	451.0	4.6625	488.3
0.6542	444.8	5.7251	491.7
0.7519	453.3	6.7692	491.9
0.8316	459.5	7.9813	493.4

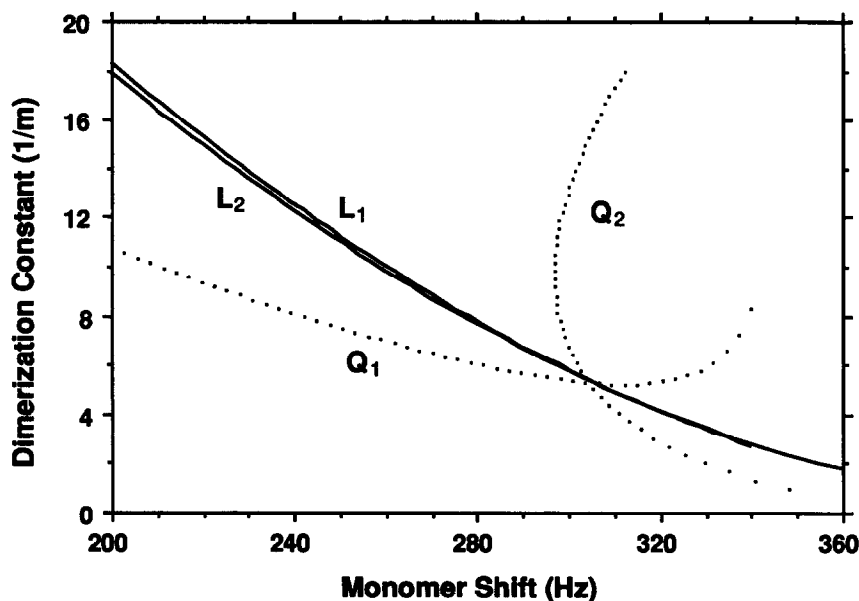


Fig. 1: Illustration of simultaneous graphical determination of monomer shift and dimerization constant from the data in Table 1. Solid and dotted curves represent the regressions using linear (L) and quadratic (Q) polynomials, respectively, while subscripts 1 and 2 denote the regressions based on eqs (1) and (2), respectively.

of pairs (δ_m and K) results in fits of nearly equal standard deviations (least square errors) and, hence, can not be accurately evaluated by the old approach.

The dilution shift data of the proton in the NH group of δ -valerolactam measured with a 60 MHz spectrometer at 298 K are listed in Table 1. Fig. 1 illustrates our evaluation approach. The solid curves represent the linearly regressed K values vs. guessed δ_m obtained from eq. (1), L_1 , and eq. (2), L_2 , respectively. The dotted curves, Q_1 and Q_2 are the result of the corresponding quadratic regressions. Note that the linear regression curves are almost indistinguishable and, thus, do not supply a well defined intersection. Additional use of quadratic regressions, on the other hand, generates well defined intersections which yield $\delta_m = 304.92 \pm 0.87$ Hz, $K = 5.35 \pm 0.06$ m⁻¹. Inserting this δ_m into X and performing a linear regression based on eq. (1) we then obtained $\delta_d = 516.86 \pm 0.5$ Hz. Note also the consistency check of the data set illustrated by the coincidence of the intersection "points" of the solid and dotted curves.

In conclusion, we have proposed an effective graphical method for the simultaneous determination of the monomer shift, dimer shift and dimerization constant from the dilution shift data in self-associating systems. The conventional explicit extrapolation to infinite dilution to determine the monomer shift is deliberately avoided. This new method is superior to the previous iteration scheme in that, in addition to a consistency check, it provides a means of estimating errors. The problem of divergence due to the inappropriate choice of initial guessed of δ_m can also be avoided. Due to its capability to offer a more accurate determination, we believe, this graphical method will lend itself to reliable thermodynamic investigations of self-associating systems.

Acknowledgement: This research was supported by the State of Alabama through the Center for Microgravity and Materials Research at the University of Alabama in Huntsville.

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