NMR Study of ε-Caprolactam in various Solvents

Graphical Determination of Monomer Shift, Dimer Shift and Dimerization Constant from the Dilution Shift Data

Jenn-Shing Chen

Department of Applied Chemistry, National Chiao Tung University, Hsin Chu, Taiwan, 30050, Republic of China

A graphical method for the simultaneous determination of the monomer shift, dimer shift and dimerization constant of a self-association system from the dilution NMR shift data is proposed. This method avoids the conventional extrapolation to infinite dilution to obtain the monomer shift. Three self-association systems: ε-caprolactam in [²H₁]chloroform, [²H₆]acetone and [²H₃]acetonitrile were studied at various temperatures. The enthalpy and entropy of dimerization were also determined from van't Hoff plots.

The self-association of two monomers to give a dimer is the first step toward nucleation and colloidal flocculation.[1,2] It is also one of the factors that cause the thermodynamic properties of solution to deviate from ideality.[3,4] A variety of theoretical and experimental methods has been employed to investigate the equilibium and kinetic behaviour related to this phenomenon.[4-6] The advent of NMR spectroscopy has emerged as one of the most effective methods for those studies.[7,8]

Conventionally, in an NMR experiment, an estimated value of the monomer shift, Δv_m, is first obtained by extrapolating the dilution shift data to infinite dilution. A standard procedure is then followed to obtain a dimerization constant, K, and a dimer shift, Δv_d, by fitting an equation containing K and Δv_d as parameters. Unfortunately, the behaviour of the shift *vs.* concentration in the diluted region is inherently nonlinear, and the curve is so steep (especially in the case of strong association) that a precise determination of Δv_m is impossible. As a rule, such a determination is very sensitive to the assessed value of Δv_m, *i.e.* is prone to large errors in the determination of K and Δv_d because of an inaccurate estimation of Δv_m.

In order to have a more accurate determination of Δv_m, Δv_d and K, we propose a novel graphical method in which the conventional extrapolation is avoided. This graphical method is based on two physically equivalent, albeit different in form, equations governing the dependence of the observed chemical shift, Δv_{obs}, on the initial concentration of the solute, $[A]_0$, as a function of the parameters Δv_m, Δv_d and K. An accurate determination of K at various temperatures is considered to be a crucial step toward the accurate determination of the standard enthalpy and entropy change for self-association by using a van't Hoff plot. Thus our proposed graphical method would provide an additional powerful tool for a reliable thermodynamic investigation of self-association.

Theory

In a monomer–dimer equilibrium system, at a temperature where there is a rapid interconversion

$$A + A \rightleftharpoons A_2 \qquad (I)$$
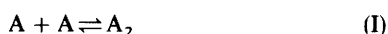
the observed chemical shift, Δv_{obs}, is the weighted average of the shifts of the monomer and dimer and was given by Gutowsky and Saika[9] as

$$\Delta v_{obs} = f_m \Delta v_m + f_d \Delta v_d = \frac{[A]}{[A]_0} \Delta v_m + \frac{2[A_2]}{[A]_0} \Delta v_d \qquad (1)$$

where $[A]_0$ is the initial concentration of solute and $[A]$ and $[A_2]$ are the concentrations of monomer and dimer at equilibrium. Δv_m and Δv_d are the monomer shift and dimer shift, respectively. f_m and f_d, the mole fractions of monomer and dimer, stand for their respective statistical weights. With the relation $f_m + f_d = 1$, one obtains

$$f_m = \frac{\Delta v_d - \Delta v_{obs}}{\Delta v_d - \Delta v_m} \qquad (2)$$

$$f_d = \frac{\Delta v_{obs} - \Delta v_m}{\Delta v_d - \Delta v_m} \qquad (3)$$

Furthermore, the dimerization constant K can be expressed in terms of mole fractions as

$$K = \frac{[A_2]}{[A]^2} = \frac{f_d}{2[A]_0 f_m^2} \qquad (4)$$

Substitution of eqn. (2) and (3) into eqn. (4) followed by taking the square root gives, after rearrangement

$$\Delta v_{obs} = \Delta v_d - \left(\frac{\Delta v_d - \Delta v_m}{2K}\right)^{1/2} \left(\frac{\Delta v_{obs} - \Delta v_m}{[A]_0}\right)^{1/2} \qquad (5)$$

For a simpler notation we denote the last square root term by X:

$$X = \left(\frac{\Delta v_{obs} - \Delta v_m}{[A]_0}\right)^{1/2} \qquad (6)$$

Thus, eqn. (5) explicitly expresses the observed chemical shifts as a linear function of X. In order to use eqn. (5), Δv_m should be known in advance in order to calculate X. A plot of Δv_{obs} *vs.* X then gives Δv_d and K from the intercept and slope.

Replacing $1 - f_d$ by f_m in eqn. (4), and solving for f_d gives

$$f_d = \frac{(1 + 8K[A]_0)^{1/2} - 1}{(1 + 8K[A]_0)^{1/2} + 1} \qquad (7)$$

The dependence of Δv_{obs} on $[A]_0$ can then be written:

$$\begin{aligned} \Delta v_{obs} &= \Delta v_m + f_d(\Delta v_d - \Delta v_m) \\ &= \Delta v_m + (\Delta v_d - \Delta v_m)\frac{(1 + 8K[A]_0)^{1/2} - 1}{(1 + 8K[A]_0)^{1/2} + 1} \end{aligned} \qquad (8)$$

Eqn. (8) explicitly expresses the dependence of Δv_{obs} on f_d in a linear form. With the knowledge of K to calculate f_d, one may obtain Δv_m and Δv_d from the intercept of the plot of Δv_{obs} *vs.* f_d at $f_d = 0$ and $f_d = 1$, respectively.

Eqn. (5) and (8), albeit in different forms, carry the same physical meaning. Both equations, however, are our pivotal results and are the basis of the following proposed graphical method.

Proposed Graphical Method

Purcell et al. have studied a similar self-association system of δ-valerolactam in $CDCl_3$.[10] They applied the direct-search procedure[11] in which an initial monomer shift is assumed, and then the dimer shift and dimerization constant are varied independently until the standard deviation for non-linear fitting (the shift vs. concentration data) reach a minimum. They concluded that the regressed dimer shift is fairly independent of the initial trial monomer shift, within the range of the latter. However, the regressed dimerization constant depends strongly on the initial trial monomer shift. The uncertainty in final values of monomer shift and dimerization constant is large because a wide range of pairs of (monomer shift, dimerization constant) values are found to have nearly equal least-square fitting errors. Such a formidable short-coming prompts us to propose an alternative algorithm to treat the dilution shift data associated with the monomer–dimer equilibrium.

In an earlier investigation,[12] we employed an iteration scheme to determine Δv_m, Av_d and K simultaneously from the dilution shift data. This scheme starts with a guessed Δv_m to calculate $X = \{(\Delta v_{obs} - \Delta v_m)/[A]_0\}^{1/2}$ in eqn. (5). Data of Δv_{obs} vs. X are then regressed in terms of a quadratic (instead of a linear) polynomial to calculate a tentative value of Δv_d from the intercept and a tentative value of K from the foregoing Δv_d and limiting slope (slope at $X = 0$) of the regressed curve. The K thus obtained is then inserted into eqn. (7) to calculate f_d which is used for regressing data of Δv_{obs} vs. f_d based on eqn. (8) in terms of a quadratic polynomial, to obtain an improved value of Δv_m from the intercept, and an improved value of Δv_d from the foregoing Δv_m and limiting slope. This newly obtained Δv_m is then inserted in eqn. (5) to initiate the second iteration to obtain further improved values of Δv_d and K. The iteration procedure is repeated until the difference of two successive monomer shifts is less than a preset tolerance.

Based on eqn. (5) and (8), we propose an alternative graphical method. The primary results have been published elsewhere.[13] It should be noted in advance that the validity of eqn. (5) and (8) is tacitly based on the following assumptions: only dimerization takes place and the thermodynamic behaviour of the solution is so ideal over the concentration range studied that only one value of the dimerization constant prevails. In this ideal case, if a value of Δv_m in X of eqn. (6) is correctly guessed, a linear regression on the data of Δv_{obs} vs. X based on eqn. (5) gives a line of perfect fitting to the experimental data i.e. its correlation coefficient is unity. The 'true' values of Δv_d and K can then be derived from the intercept and slope of this line. If, on the other hand, a quadratic instead of a linear equation is used in the regression, the same perfectly fitted line is restored, i.e. the quadratic term becomes identically zero. If, however, the value of Δv_m is not guessed correctly, the curves from linear and quadratic regressions are not the same. In particular, the linear part of the regressed quadratic equation is not equal to the regressed linear equation as before. Nevertheless, it still provides a pair of regressed values of Δv_d and K from the linear part of the quadratic equation. This is tantamount to saying that guessing a correct value of Δv_m results in a correct value of K irrespective of whether a linear or quadratic form is used in the regression. Conversely, an incorrect guessed value of Δv_m leads to different regressed values of K for linear and quadratic regressions. If we plot regressed values of K vs. guessed

values of Δv_m generated from linear and quadratic regressions, respectively, two distinct curves will be obtained. The intersection P1, having the common values of Δv_m and K from linear and quadratic regressions, determines the 'true' values of Δv_m and K for the self-association system based on eqn. (5).

Similarly, putting a guessed value of K into the f_d of eqn. (7) followed by regressing Δv_{obs} vs. f_d using linear and quadratic equations based on eqn. (8) will produce, from the intercept, the same value of Δv_m, if the guessed value is correct, or different values if not. Plots of guessed values of K vs. regressed values of Δv_m for linear and quadratic regressions, generate two distinct curves. Again, the intersection P2 determines the true values of Δv_m and K based on eqn (8). Ideally, the two intersections, P1 and P2, should coincide, since they represent the same physical entities. The departure, however, may reflect (1) the experimental error of shift and/or solute concentration measurement; (2) extended association beyond dimerization and (3) the non-ideal thermodynamic behaviour of the solution. The last possibility arises from the fact that the equilibrium constant depends on the solute concentration in a non-ideal thermodynamic solution. This behaviour is inconsistent with the underlying assumption that the equilibrium constant should be a constant value throughout the concentration range studied. In practical applications, this non-coincidence of P1 and P2 would provide a consistency check and a method of estimating errors for this graphical determination. We then give equal weight to both determinations from P1 and P2. Accordingly, the average and standard deviation of Δv_m and/or K from two determinations are taken as the finally determined values and errors of Δv_m and K.

The finally determined value of Δv_m is then put into X, followed by a linear regression on Δv_{obs} vs. X based on eqn. (5) to obtain the true value of Δv_d from the intercept. The finally determined value of K is also put into f_d followed by linear regression on the data of δ_{obs} vs. f_d based on eqn. (8) to obtain the true value of Δv_d by evaluating the foregoing regressed linear equation at $f_d = 1$. The average and standard deviation of Δv_d from two determinations are then taken as the finally determined value and error of Δv_d.

Our previous scheme of iteration[12] determines the intersection of the curve plotted for regressed values of K vs. guessed values of Δv_m based on eqn. (5), and that plotted for guessed values of K vs. regressed values of Δv_m based on eqn. (8); both are in terms of quadratic regression. Hence, the iteration scheme takes only the intersection of Q1 and Q2 into account. An extensive comparison of fitting the experimental data to the theoretical curves of eqn. (5) and (8), using the parameters Δv_m, Δv_d and K obtained from the two methods, demonstrates that the new graphical method is superior to the previous iteration method.

Results and Discussion

We have carried out NMR spectroscopy on three self-association systems: ε-caprolactam in [²H₁]chloroform, [²H₆]acetone and [²H₃]acetonitrile at various temperatures. The 300 MHz proton spectra were taken on a Varian Unity-300 NMR spectrometer equipped with a variable temperature controller, model VTC4, whose precision was calibrated, using ethylene glycol as standard, to be within ±1 K. All chemicals were the highest grade from Aldrich and were used without further purification. Samples of different concentration (expressed in units of molality) of solute, with a trace of TMS as a reference, were prepared gravimetrically in small vials with the help of microsyringes. The samples were

then transferred into 5 mm od NMR tubes and sealed without further degassing.

The peak for monitoring shift change with concentration is from the proton in the amine group of ε-caprolactam. The average of readings from five spectra taken repeatedly without removing the tube from the magnet were referred to as the observed value of each shift. The measured NH shift may include errors induced by a trace of water in the solvents. The nominal water level in various solvents is within the range 0.01–0.05%. We estimated that there was only a negligible effect on the NH shift measurement, since the solvents are overwhelming predominant and, moreover, have a strong capability for hydrogen bonding with water molecules.

Fig. 1 illustrates the graphical determination of Δv_m and K for the system ε-caprolactam in [$^2H_1$]chloroform at 298 K. The curves L1 and Q1 represent the plots of regressed values of K vs. guessed values of Δv_m for linear and quadratic regressions based on eqn. (5). The intersection P1 then corresponds to the determined values of Δv_m and K based on eqn. (5). Likewise, the curves L2 and Q2 represent the plots of guessed values of K vs. regressed values of Δv_m for linear and quadratic regressions based on eqn. (8). The intersection P2 then corresponds to the determined values of Δv_m and K based on eqn. (8). The difference in P1 and P2 is indicative of the errors discussed earlier. From P1 and P2, the values of Δv_m, K and Δv_d and their errors can then be determined. The results for the three systems at various temperatures are listed in Table 1. As seen from this table, K for any system decreases with increase in temperature. This indicates that the dimerization is an exothermic process. Also from Table 1, decrease of Δv_m and Δv_d with increase in temperature implies that increasing temperature will weaken the molecular association within a dimer or a monomer–solvent complex. This phenomenon has also been observed by other authors.[14,15]

In the systems studied it is more appropriate to represent the equilibrium (I) as A–solvent + A–solvent $\rightleftharpoons$ A$_2$. A near-infrared investigation[16] of similar systems of δ-valerolactam in various solvents with strong hydrogen-bonding capability led to the same conclusion. We also observed that in the system of ε-caprolactam in CDCl$_3$ the proton shift from a trace of undeuteriated chloroform increases with the concentration of the solute. An NMR study of lactam–chloroform complexation is now underway in our laboratory.

The 'goodness' of the determination can be appraised by comparing the experimental values of Δv_{obs} with its theoretical counterpart calculated from the final determined values of
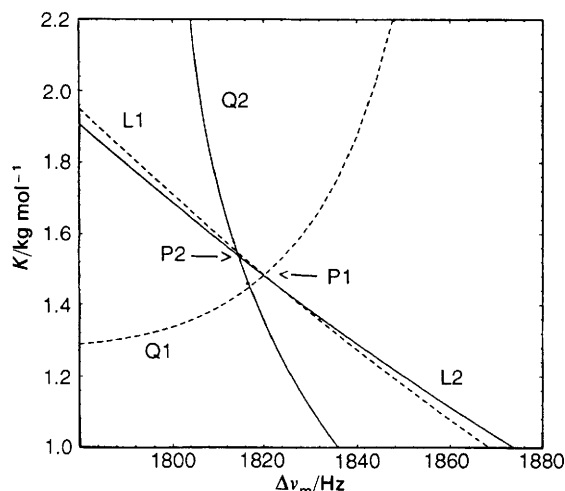
Table 1 Monomer shift, dimer shift and dimerization constant for ε-caprolactam in deuteriated chloroform, acetone and acetonitrile at various temperatures

solvent	T/K	$\Delta v_m/Hz$	$\Delta v_d/Hz$	$K/kg\ mol^{-1}$
[$^2H_1$]chloroform	268	1900.8 ± 1.3	2745.4 ± 0.1	2.698 ± 0.016
	283	1846.0 ± 1.2	2697.8 ± 0.2	2.080 ± 0.012
	298	1817.2 ± 2.8	2644.5 ± 0.3	1.513 ± 0.025
	313	1797.7 ± 2.5	2602.8 ± 0.5	1.158 ± 0.039
	328	1772.8 ± 2.1	2565.0 ± 0.6	0.905 ± 0.015
[$^2H_6$]acetone	298	1956.4 ± 1.8	2520.7 ± 0.1	0.456 ± 0.010
	305	1942.5 ± 0.6	2500.2 ± 0.1	0.416 ± 0.003
	313	1919.7 ± 0.3	2474.5 ± 0.2	0.409 ± 0.001
	328	1889.6 ± 0.6	2430.8 ± 0.0	0.353 ± 0.031
[$^2H_3$]acetonitrile	298	1858.2 ± 1.8	2600.0 ± 2.9	0.143 ± 0.005
	318	1829.9 ± 2.3	2526.1 ± 6.1	0.124 ± 0.007
	338	1803.0 ± 1.5	2483.9 ± 8.9	0.097 ± 0.004
	348	1795.8 ± 1.4	2466.7 ± 8.2	0.086 ± 0.001

Δv_m, Δv_d and K by the different methods. Fig. 2 shows the plots of Δv_{obs} vs. X for ε-caprolactam in [$^2H_1$]chloroform at various temperatures. Similar plots for Δv_{obs} vs. f_d, and Δv_{obs} vs. initial concentration of solute for the same system at various temperatures are shown in Fig. 3 and 4.

With dimerization constants known at different temperatures, a van't Hoff plot of log K vs. $1/T$ can then be employed to determine the standard enthalpy, ΔH^0, and standard entropy, ΔS^0, of dimerization. Such plots are shown in Fig. 5 for the three systems. The determined values and errors of ΔH^0 and ΔS^0 for each system are listed in Table 2. The errors are calculated by a standard procedure described elsewhere.[17] A dimerization process which involves attracting two separate entities together usually reduces the intermolecular potential energy (i.e. it is exothermic) and the randomness
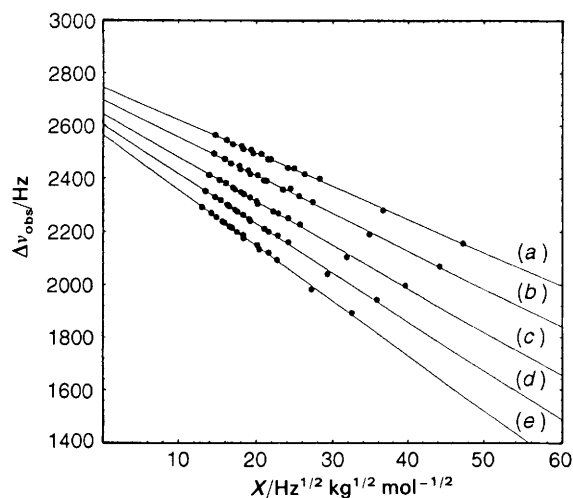
Fig. 2 Comparison of theoretical curves with experimental data for Δv_{obs} vs. X for ε-caprolactam in [$^2H_1$]chloroform at (a) 268, (b) 283, (c) 298, (d) 313 and (e) 328 K

Fig. 1 Graphical determination of monomer shift and dimerization constant for ε-caprolactam in [$^2H_1$]chloroform at 298 K

Table 2 Standard enthalpy and entropy of dimerization for ε-caprolactam in various solvents

solvent	$\Delta H^0/kJ\ mol^{-1}$	$\Delta S^0/J\ mol^{-1}\ K^{-1}$
[$^2H_1$]chloroform	−13.52 ± 0.38	−41.91 ± 1.34
[$^2H_6$]acetone	−6.57 ± 0.92	−28.68 ± 3.01
[$^2H_6$]acetonitrile	−8.83 ± 1.05	−45.64 ± 3.18
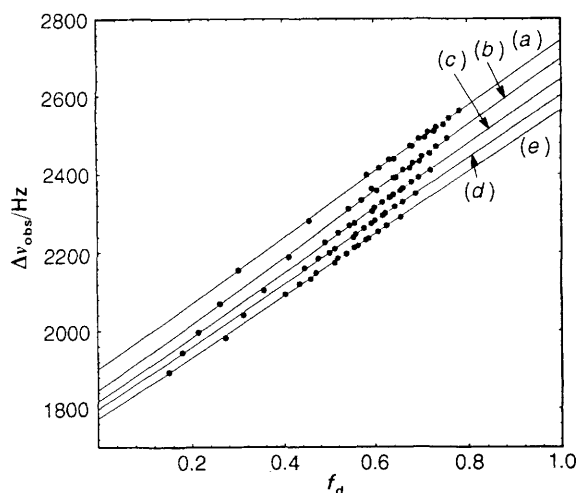
Fig. 3 Comparison of theoretical curves with experimental data for $\Delta\nu_{obs}$ vs. f_d for ε-caprolactam in $[^2H_1]$chloroform at temperatures (a)–(e) as in Fig. 2

of the system. In this regard, the negative values of ΔH^0 and ΔS^0 seem to be physically justified.

Franzen and Stephens[18] used dielectric polarization to study the dimerization of ε-caprolactam in solvents of relative
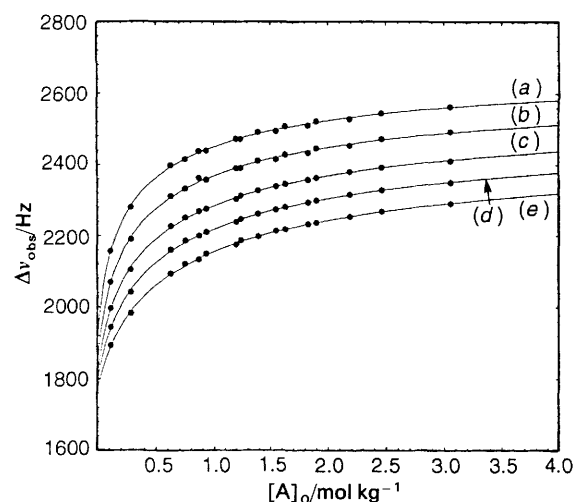

Fig. 4 Comparison of theoretical curves with experimental data for $\Delta\nu_{obs}$ vs. initial concentration f_d for ε-caprolactam in $[^2H_1]$chloroform at temperatures (a)–(e) as in Fig. 2
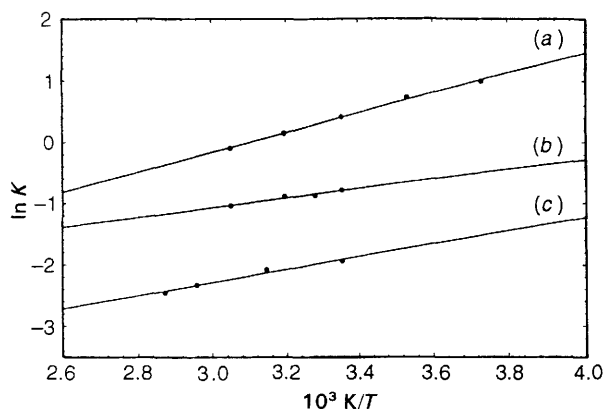

Fig. 5 Plot of ln K vs. $1/T$ for dimerization of ε-caprolactam in deuteriated (a) chloroform, (b) acetone and (c) acetonitrile

permittivity, ε, ranging from 2.25 to 9.13. They obtained at 298 K in chloroform a value for the dimerization constant, K, of 1.55 dm^3 mol^{-1} or 1.05 kg mol^{-1}. This is in fair agreement with our result of 1.51 kg mol^{-1}. They also found that within the range of relative permittivity studied K can be expressed as a linear function of $1/\varepsilon$. While we have also observed the tendency of K to increase with $1/\varepsilon$, a good linear relation is not obtained. This may be explained by the fact that, in addition to providing a dielectric environment for the dimerization process, the solvents may have some specific interaction with the monomer of the solute.

Conclusion

We have proposed an effective graphical method for a simultaneous determination of the monomer shift, dimer shift and dimerization constant from the dilution shift data of self-associating systems. The conventional extrapolation to infinite dilution for an estimation of the monomer shift is deliberately avoided. This new method, in addition to a consistency check, provides a means of estimating errors. Because it can offer a more accurate determination of equilibrium constant and spectrometric parameters for self-association, we believe this graphical method will lend itself to reliable thermodynamic investigations of such a system.

References

1 J. Frankel, *Kinetic Theory of Liquids*, Oxford University Press, Oxford, 1946.
2 Aggregation Processes in Solutions, ed. E. Wyn-Jones and J. Gormally, Elsevier, Amsterdam, 1983.
3 P. Hobza and R. Zahradnik, *Weak Intermolecular Interactions in Chemistry and Biology*, Elsevier, Amsterdam, 1978.
4 J. M. Praunitz, R. N. Lichtenthaler and E. G. de Azevedo, *Molecular Thermodynamics of Fluid Phase Equilibrium*, Prentice-Hall, Englewood Cliffs, New Jersey, 2nd edn., 1986.
5 J. C. Dore and J. Teixeira, *Hydrogen Bonded Liquids*, Kluwer, Dordrecht, 1989.
6 P. Hobza and R. Zahradnik, *Intermolecular Complexes*, Elsevier, Amsterdam, 1988.
7 J. S. Davies and K. K. Deb, *Adv. Magn. Reson.*, 1970, **4**, 201.
8 *Molecular Association*, ed. R. Foster, Academic Press, London, 1975.
9 H. S. Gutowsky and A. Saika, *J. Chem. Phys.*, 1953, **21**, 1688.
10 J. M. Purcell, H. Susi and J. R. Cavanaugh, *Can. J. Chem.*, 1969, **49**, 3655.
11 R. Hooke and J. A. Jeeves, *J. Assoc. Comput. Mach*, 1961, **8**, 212.
12 J. S. Chen and R. B. Shirts, *J. Phys. Chem.*, 1985, **89**, 1643.
13 J. S. Chen and F. Rosenberger, *Tetrahedron Lett.*, 1990, **31**, 3975.
14 N. Muller and R. C. Reiter, *J. Chem. Phys.*, 1965, **42**, 3265.
15 Soon Ng, *Spectrochim. Acta, Part A*, 1980, **36**, 927.
16 H. Susi and J. S. Ard, *Arch. Biochem. Biophys.*, 1966, **117**, 147.
17 R. Bevington, *Data Reduction and Error Analysis for Physical Science*, McGraw-Hill, New York, 1969, ch. 6.
18 J. S. Franzen and R. E. Stephens, *Biochemistry*, 1963, **2**, 1321.