

VAPOR PRESSURE STUDIES OF SELF-ASSOCIATION OF ALCOHOLS IN ISOCTANE. I. THE EFFECT OF CHAIN LENGTH

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SUMMARY

A study of the vapor pressures of the primary alcohols L-propanol through L-octanol as a function of their concentration in isooctane at 25°C has been interpreted in terms of a self-association model. The results suggest that in fairly dilute solutions (0.05–1 M), the self-association tendencies of these alcohols are independent of chain length and can be described adequately with a monomer–pentamer association model. At higher concentrations and in the pure liquids, the extent of association increases with increasing chain length. Standard free energies for the processes of transferring alcohol from its pure state to vapor, from its pure state to infinite dilution in isooctane, and from infinite dilution in isooctane to the vapor phase have been calculated. The methylene group contribution to the free energy of transfer of alcohol from infinite dilution in isooctane to the vapor phase has been shown to be a constant equal to 710 cal/mole of $-\text{CH}_2-$ groups.

INTRODUCTION

The relationship between the molecular structure of a drug molecule and its physical and biological behavior is of paramount importance in drug delivery. Designing a drug which can be efficiently delivered to a target site involves maximizing the release rate from a pharmaceutical formulation, controlling the rates of transport through physiological barriers, and favorably altering the partition coefficients between various compartments. All of these processes are directly related to the thermodynamic activity of the drug in the phases involved. Therefore, an understanding of the role of molecular structure in determining a drug's physical properties such as the thermodynamic activity of the drug substance in its pure state and in various solvent environments is essential for rational drug design.

Our long term interest has been the development of a rational basis for the a priori calculation of the thermodynamic activity of drug molecules in any given environment from

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a consideration of the molecular interactions which occur in solution between the dissolved drug and the surrounding solvent molecules. In this paper are presented the results of a study designed to identify the nature and extent of molecular interactions between primary alcohol molecules in alcohol-isooctane solvent systems and in the pure alcohols.

The self-association of alcohols has received considerable attention in the literature presumably because it has such a dramatic influence on the physical properties of alcohols. For example, a comparison of the boiling points of diethyl ether and butanol, both of which have the empirical formula $C_4H_{10}O$ but have boiling points of 35°C and 118°C , respectively, serves to illustrate the importance of hydrogen bonding effects on solution properties. The breaking of hydrogen bonds which occurs on dilution of alcohols in non-polar solvents results in changes in enthalpies, infrared and proton magnetic resonance spectra, vapor pressures, dielectric properties, partial molar volumes, and other properties, many of which have been used in investigations of self-association behavior.

Although a large amount of data is presently available in the literature, a continuing controversy exists over the number and size of associated species in solutions of primary alcohols. Much of the earlier research, as summarized by Pimentel and McClellan (1960), treated alcohol polymerization as a stepwise process resulting in a continuum of species with perhaps a preponderance of dimer. Recent work, however, suggests that a higher polymer of a specific size may be dominant. Fletcher and Heller (1967), for instance, have proposed that a monomer-tetramer model adequately explains their infrared data for the self-association of *L*-octanol in *n*-decane. On the other hand, Tucker et al. (1969) best explained their vapor pressure data for methanol in *n*-hexadecane and PVT measurements on methanol vapor by assuming trimers and octamers were dominant. The most commonly used model is the monomer-dimer-tetramer model where tetramer is the dominant polymer except in very dilute solutions. Examples of the application of this model can be found in the work of Aveyard et al. (1973) on the association of *n*-dodecanol and *n*-octanol in *n*-octane, and in a previous study in our laboratories on the enthalpies of dilution of *n*-alcohols in isooctane (Anderson et al., 1975).

Each of the available methods offers advantages in investigating particular characteristics of associated species. However, from a theoretical standpoint we felt that a study of the vapor pressures of alcohols above their solutions should be the most reliable method of obtaining a mathematical model of self-association, since the vapor pressure directly reflects monomer concentration in solution. Direct measurements of total vapor pressure have been made previously for methanol and *t*-butyl alcohol in the non-volatile solvent *n*-hexadecane, but measurements of total pressure are not as desirable for longer chain alcohols having lower volatility or for alkane solvents having shorter chain lengths and thus higher volatility than *n*-hexadecane. Since one of the goals of the present study was to determine the effect of chain length on the self-association of a series of primary alcohols, a method was required with which one could obtain precise vapor pressure data for dilute solutions of relatively non-volatile long chain alcohols. The method chosen consisted of the gas chromatographic analysis of the vapor in the head-space over solutions of alcohols in isooctane. Isooctane was chosen as the solvent since it has been previously shown by a number of workers that alkanes are more 'inert' toward alcohols than other non-polar solvents such as CCl_4 and benzene (Fletcher, 1969; Campbell et al., 1975; Wolff and Höppel, 1968; Woolley and Hepler, 1972). By using the gas chromato-

graphic head-space technique, the isooctane contribution to the total vapor pressure presented no problem since the components of the vapor were resolved, and alcohol vapors having partial pressures as low as ~ 0.003 torr could be analyzed accurately.

Monomer concentrations as a function of alcohol molarity were obtained from the vapor pressure data and evaluated by two methods, one of which involved no a priori assumptions regarding a self-association model. The results suggest that associated species larger than tetramers are important even in dilute solutions – a conclusion which is contrary to much of the data obtained by other techniques.

MATERIALS AND METHODS

Materials

The chemicals used were of the highest purity available from the supplier and were used without further purification. In some instances, the manufacturer's purity claim was verified by gas chromatographic analysis. The L-propanol and L-octanol were obtained from Aldrich Chemical Co. with purities of 99 + %; L-butanol was 99+ mol% from Matheson Coleman and Bell or $\geq 99.5\%$ puriss. grade from Fluka AG; L-pentanol and L-hexanol were $\geq 99\%$ from Fluka AG; L-heptanol was from Matheson Coleman and Bell with a purity of 99+ mol%; and the isooctane used was ≥ 99 mol% from Phillips Petroleum Company. All solvents were stored over Linde 4Å molecular sieves (Union Carbide Co.) to remove possible trace amounts of water.

Head-space technique

Samples used in the vapor pressure study were prepared by weight. Molarities were then calculated using the densities of the neat liquids to calculate total solution volume. Changes in partial molar volumes of the pure components on mixing were presumed to have a negligible effect on the total volume. Concentrations ranging from less than 0.005 M alcohol in isooctane to the neat alcohols were analyzed. The solutions were prepared in 50 ml, or 100 ml, bottles with screw caps in which a small hole was drilled. The bottles were sealed with teflon cap liners which were punctured prior to sampling. Rubber stoppers were avoided because of the possibility for loss of sample by partitioning into the rubber and leaching of impurities from the stopper into the solutions. The bottles were immersed up to the caps in a water bath maintained at 25.0°C. Equilibration time was at least 15 min.

Samples were withdrawn from the head-space in the bottles using a sample loop. Gas-tight syringes were originally used for sampling, but it became apparent when studying the longer chain alcohols that adsorption onto the glass walls of the syringe barrel and onto the metal surface in the needle adversely affected the precision and accuracy of the results. Heating the syringe prior to sampling improved precision considerably, but to be completely sure that all of the sample was being introduced onto the column, the previously mentioned sample loop was constructed. The device consisted of two Hamilton miniature inert teflon valves, a 6 in. X 0.076 in. i.d. teflon sample loop and a stainless steel bypass loop. The needle used for withdrawing sample was teflon. A Welch Duo-Seal vacuum pump was used to evacuate the sample loop while carrier gas flowed into the column through the bypass loop. Closing one valve maintained the vacuum in the loop

while the needle was inserted into the sample head-space. Sample could then be drawn into the teflon loop and introduced into the column by diverting carrier gas flow through the sample loop. Heating tape was used to minimize the potential for adsorption on all stainless steel lines through which the sample passed prior to reaching the column. Peak symmetry was excellent for all alcohols, but slightly more tailing was observed for L-heptanol and L-octanol peaks using the sample loop as compared to samples injected with a syringe. This may have been due to adsorption by metal surfaces or slight partitioning of sample into the teflon components as chain length increased.

Gas chromatography

All studies were performed with a Varian 2100 gas chromatograph using a flame ionization detector. A 6-ft long \times 4 mm i.d. glass column packed with 10% Carbowax 20 M on 80/100 mesh Gas-Chrom Q (Applied Science Laboratories, Inc.) was used for L-butanol through L-heptanol. Column temperatures were 95°C for L-butanol, 110°C for L-pentanol, 120°C for L-hexanol, and 130°C for L-heptanol. The L-propanol data were obtained on a 1-ft long \times 4 mm i.d. glass column packed with 100/200 mesh Chromosorb 102 (Johns-Manville) at a temperature of 155°C, and the L-octanol analyses were carried out using a 6-ft long \times 4 mm i.d. glass column packed with 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport (Supelco, Inc.) at a temperature of 120°C.

Standard curves for peak height versus amount of sample were obtained for each alcohol by injecting liquid samples of known concentration. The detector response was found to be linear over the working range for all alcohols. Relative vapor concentrations were obtained by comparing sample peak heights with the average peak height of a standard consisting of the vapor over the neat alcohol of interest.

RESULTS

Sample loop performance

In a study of interactions in solution, one cannot introduce an extraneous substance for use as an internal standard. Although this limited the precision attainable to some extent, peak heights from successive injections were still very reproducible. Standard deviations calculated from sets of injections of pure alcohol vapor often representing data over the course of several hours showed that precision decreased with decreasing concentration of alcohol in the vapor, ranging from $\pm 0.8\%$ of the mean for L-propanol to $\pm 2.7\%$ for L-octanol. Except for L-octanol, the standard deviations were $\leq 1.6\%$ of the mean peak height for all alcohols in this study.

Determination of monomer concentration

The underlying premise involved in obtaining monomer concentrations from vapor pressure data is that association of monomer in the vapor is negligible. Data of Cheam et al. (1970) for methanol vapor at 25°C show that at vapor pressures lower than 30–40 torr, self-association is negligible. If the higher straight chain alcohols behave similarly, non-ideality in the vapor phase can be neglected since the highest vapor pressure encountered in this study was 20.85 torr for neat L-propanol. If the vapor contains only monomer, measurement of vapor pressure gives directly the activity, a_1 , of monomer in the

liquid phase because the chemical potential of the monomer, μ_1 , must be the same in both phases at equilibrium. The standard state used here is a hypothetical 1 molar solution of monomer, the reference state being infinite dilution in isooctane. The chemical potential in the liquid phase is then expressed as

$$\text{liq}\mu_1 = \text{liq}\mu_1^0 + RT\ln a_1 \quad (1)$$

in which

$$a_1 = \gamma_1 \cdot c_1 = p_1/H \quad (2)$$

where p_1 is the vapor pressure over a solution of known molarity, c_1 , and H is the extrapolated vapor pressure in the standard state, or simply the Henry's Law constant. γ_1 is the activity coefficient of monomer. If it is assumed that, apart from association phenomena, the solution behaves ideally, then the activity coefficient of monomer is one and monomer concentration is obtained from the ratio p_1/H . Henry's Law constants were determined from the slopes of plots of vapor pressure versus total concentration up to about 0.02 M. These plots were linear in this region, within experimental error, indicating the absence of significant association. Literature values used for the vapor pressures of the pure alcohols, p^0 , and the calculated Henry's Law constants obtained from our vapor pressure data are reported in Table 1. Of course, the actual values for Henry's Law constants will depend on the literature values chosen for the pure alcohol vapor pressures, but monomer concentrations will not be affected by possible errors in the vapor pressures of the neat alcohols.

Monomer concentration as a function of total molarity over the entire concentration range are shown in Fig. 1 for the *n*-alcohols studied. The most striking feature of the data is the uniformity of the curves below about 1 M. This similarity in self-association ten-

TABLE 1
HENRY'S LAW CONSTANTS AND VAPOR PRESSURES OF THE PURE ALCOHOLS ^a

Alcohol	H (torr 1 mol ⁻¹)	P (torr)
Ethanol ^b	460	59.77
L-Propanol	127	20.85
L-Butanol	33.3	6.18
L-Pentanol	11.8	2.35
L-Hexanol	3.76	0.82
L-Heptanol	1.00	0.232
L-Octanol	0.293	0.075

^a Pure alcohol vapor pressures were obtained from literature data. Piddick and Bunger (1970) was the source for all values except L-heptanol's vapor pressure which was found by extrapolation of data from Jordan (1954).

^b An estimate of ethanol's Henry's Law constant was obtained from a preliminary study in our laboratories using a gas-tight syringe.

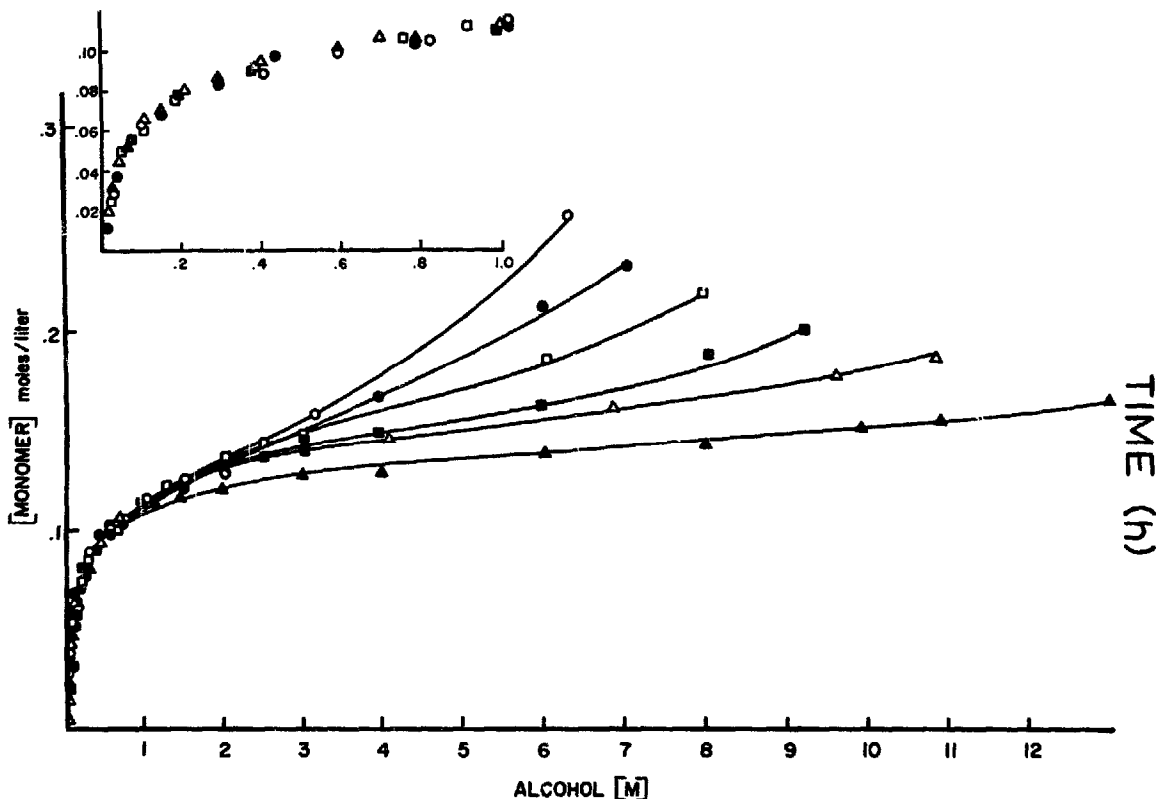


Fig. 1. Calculated monomer concentrations versus formal alcohol concentration for L-propanol (▲), L-butanol (△), L-pentanol (●), L-hexanol (◻), L-heptanol (◐), and L-octanol (○). The region between 0 and 1 M is expanded as shown in the insert.

dency at total concentrations below 1 M is more clearly illustrated in a plot of α , the ratio of monomer to total molarity, versus total molarity of alcohol up to 0.6 M as shown in Fig. 2.

As mentioned previously, two methods were employed in obtaining a model which best describes the experimental data. The first of these involves the assumption that only one polymeric species exists in equilibrium with monomer as characterized by the equilibrium constants, $K_{1,n}$, where n is the size of n -mer formed and:

$$K_{1,n} = \frac{(n\text{-mer})}{(\text{Mon})^n} \quad (3)$$

The total alcohol molarity, C_T , is then expressed by the following relation:

$$C_T = \text{Mon} + n \cdot K_{1,n} \cdot (\text{Mon})^n \quad (4)$$

and

$$\log(C_T - \text{Mon}) = \log(n \cdot K_{1,n}) + n \cdot \log(\text{Mon}) \quad (5)$$

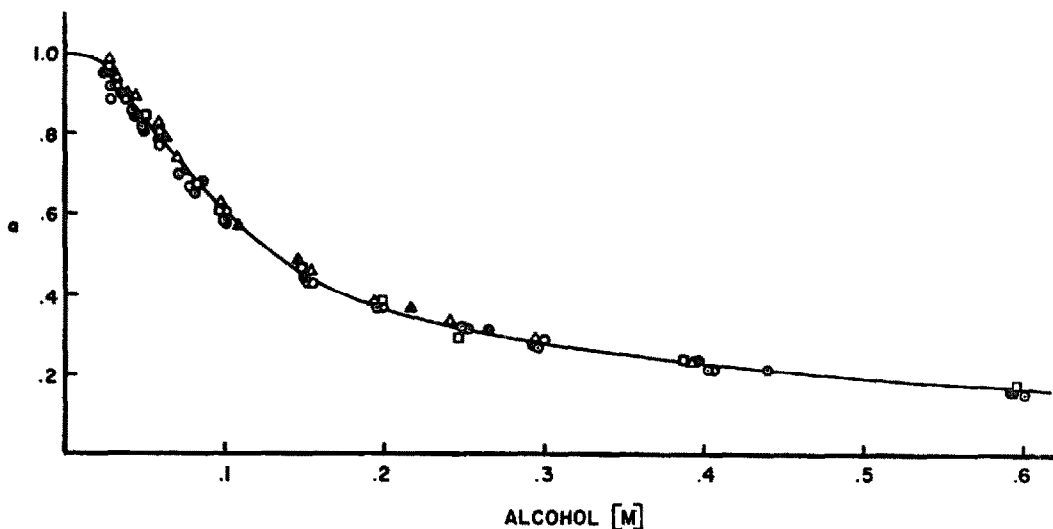


Fig. 2. Plot of α , the ratio of monomer to formal alcohol concentration, versus formal alcohol molarity for L-propanol (Δ), L-butanol (\blacktriangle), L-pentanol (\square), L-hexanol (\circ), L-heptanol (\hexagon), and L-octanol (\circ).

One can see from equation (5) that a plot of $\log(C_T - \text{Mon})$ vs. $\log(\text{Mon})$ should give a straight line with a slope of n if only one associated species is present. In interpreting such a plot, one is not restricted to a single polymer model. If more than one polymer is present, the result will be an upward curvature in the line. The log-log plots for the primary alcohols from ~ 0.04 M in iso-octane to the pure alcohol are combined in Fig. 3. The precision of the gas chromatographic data was not sufficient to attach quantitative significance to the data below 0.04 M because the difference $C_T - \text{Mon}$ rapidly approaches zero at lower concentrations. It is quite apparent from Fig. 3 that over a large concentration region the plots are parallel and nearly linear with a slope of 5, suggesting a dominance of pentamer. A linear regression fit of the data shown in Fig. 3 over the concentration range of ~ 0.05 to 1.0 M yielded slopes of 5.02 (L-propanol), 4.97 (L-butanol), 4.99 (L-pentanol), 4.69 (L-hexanol), 4.78 (L-heptanol), and 4.93 (L-octanol). The magnitudes of $K_{1,5}$ as represented by the intercept at $\log(\text{Mon}) = 0.0$ are also quite similar for all alcohols (see Table 2).

The second approach used in analyzing the data involved a computer fitting technique. The computer program employed the simplex method of least-squares described by Deming and Morgan (1973) to optimize equilibrium constants for each species allowed to compete for monomer. The only constraint on the equilibrium constants was the requirement that all values be non-negative, as a negative equilibrium constant would have no physical meaning. A comparison of standard deviations obtained from the best fits of a number of models enabled one to choose the model which best approximated the experimental data. The simplest models tested were monomer-single polymer models. Since the assumption of unity for the activity coefficient of monomer becomes less valid at higher concentrations, only the region from 0 to 1 M was chosen for computer optimization.

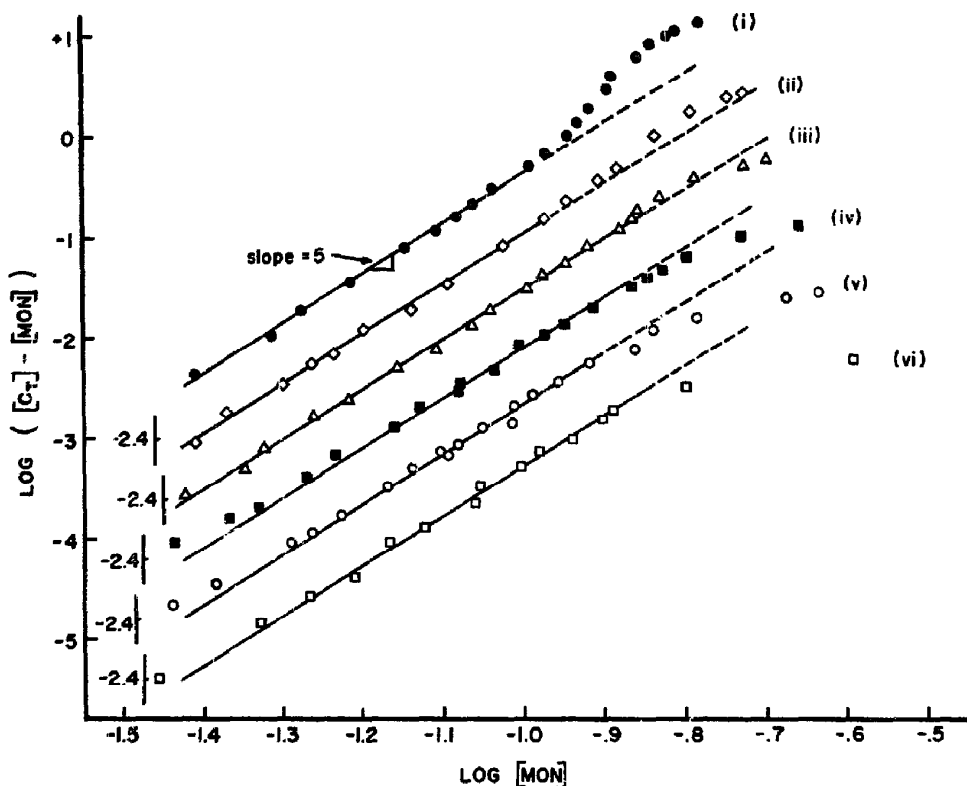


Fig. 3. Log-log plots for (i) L-propanol, (ii) L-butanol, (iii) L-pentanol, (iv) L-hexanol, (v) L-heptanol, and (vi) L-octanol data in iso-octane at 25°C (see equation 5). Ordinate is shifted downward 0.6 units for each alcohol after L-propanol as indicated. The straight lines having slopes of 5 represent the theoretical log-log plots based on the parameters in Table 3.

In every case, a monomer-pentamer model gave significantly lower standard deviations than other single polymer models. In addition, the equilibrium constants for pentamer formation were nearly identical for all the primary alcohols studied. (It should be kept in mind that a change of about 15% in the equilibrium constants results from an error of less than 3% in monomer concentration at a total molarity of one.) Table 2 sum-

TABLE 2
EQUILIBRIUM CONSTANTS AND FREE ENERGIES OF PENTAMER FORMATION

Alcohol	$K_{1,5} (1^4 \text{ mol}^{-4}) \times 10^{-3}$	$\Delta G_{1,5}^{\circ}$ (kcal/mole)
L-Propanol	8.6 ± 0.2	-5.4
L-Butanol	8.7 ± 0.3	-5.4
L-Pentanol	9.4 ± 0.2	-5.4
L-Hexanol	10.0 ± 0.4	-5.5
L-Heptanol	10.9 ± 0.5	-5.5
L-Octanol	10.3 ± 0.6	-5.5

TABLE 3
RESULTS OF COMPUTER FITS USING VARIOUS MODELS FOR L-BUTANOL DATA

Model	Std. dev. ($\times 10^3$)	Parameter values
1-3	8.1	$K_{1,3} = 129$
1-4	3.4	$K_{1,4} = 1,005$
1-5	0.75	$K_{1,5} = 8,700$
1-6	1.9	$K_{1,6} = 80,000$
1-2-5	0.75	$K_{1,2} \sim 0, K_{1,5} = 8,700$
1-3-5	0.75	$K_{1,3} \sim 0, K_{1,5} = 8,700$
1-4-5	0.75	$K_{1,4} \sim 0, K_{1,5} = 8,700$
1-4-6	0.51	$K_{1,4} = 358, K_{1,6} = 48,500$
1-3-8	1.3	$K_{1,3} = 41, K_{1,8} = 3.7 \times 10^6$

marizes the results from the computer optimization using the monomer-pentamer model. In addition to $K_{1,5}$ values, $\Delta G_{1,5}^0$ values for the formation of pentamer are included to more clearly illustrate the similarity in tendency to form pentamer among the various straight chain alcohols. The 90% confidence intervals listed are based on Fischer's F statistic and reflect the precision within each data set.

Several combinations involving more than one polymer were also considered for computer optimization. Generally, allowing one additional smaller species in addition to pentamer, such as dimer or trimer, did not significantly lower standard deviations. The most noticeable improvement in fit occurred for the monomer-tetramer-hexamer

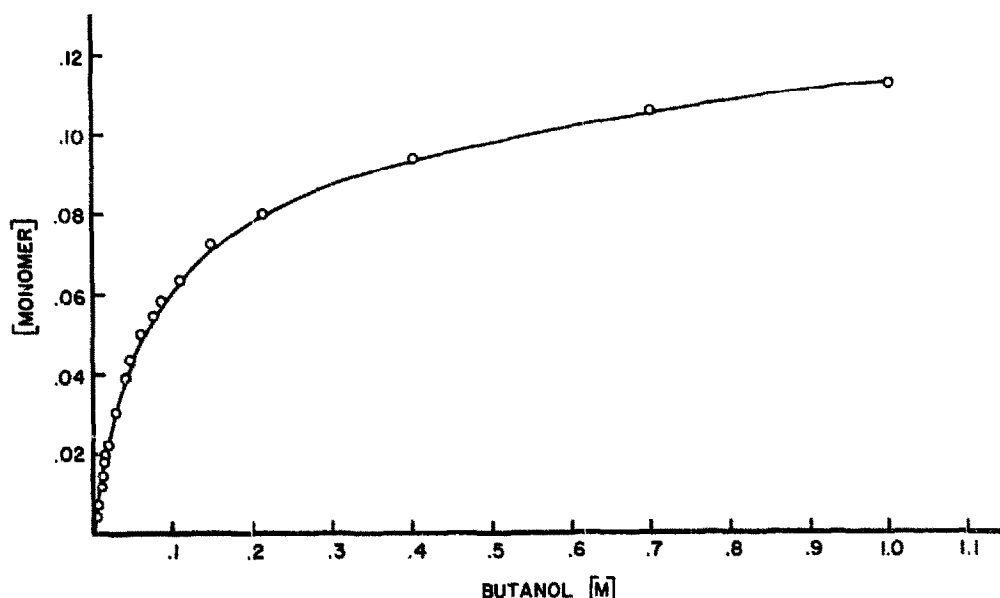


Fig. 4. Monomer concentration versus formal butanol molarity between 0 and 1 M. The solid line represents the best fit using a monomer-pentamer model. The line based on a monomer-tetramer-hexamer model was nearly indistinguishable from the line drawn.

model, but the gain in fit over the single polymer model based on a comparison of percent standard deviations was less than 1%. A summary of some of the models considered and the resultant standard deviations are presented in Table 3 for the L-butanol self-association data. A graphical comparison of the theoretical curve with the experimental data is shown in Fig. 4 for the monomer–pentamer model. The curve for the monomer–tetramer–hexamer model which yielded the lowest standard deviation was nearly superimposable on the monomer–pentamer curve.

DISCUSSION

The assumption that chemically distinct 'species' in addition to monomer exist in alcohols is implicit in our treatment of the vapor pressure data and perhaps the strongest argument for species formation comes from the success of association models in explaining alcohol behavior. As shown in this study, the pronounced deviations from ideality in the alcohol vapor pressures in dilute solutions can be explained quantitatively by a chemical theory of association. Because species formation is such an integral part of any self-association model, some consideration should be given to what is meant by 'species'. The fact that the extent of deviation from ideality in the alcohols studied here depends only on hydroxyl group concentration (independent of chain length) suggests that hydrogen bonding is the most important force involved, and is consistent with spectroscopic studies of alcohol solutions showing a correlation between OH stretching vibrations and solution behavior (Tucker et al., 1969). Therefore, the term 'species' as used here refers to chemically distinct entities formed by specific intermolecular interactions between functional groups. Certainly alcohol polymers do not have the lifetimes attributed to covalently bonded species. However, if the energy of a hydrogen bond is assumed to be roughly 5 kcal mol⁻¹, its average lifetime at 25°C will be several thousand vibrations. This should be a sufficient length of time to justify our referring to these associated molecules as species.

Dominance of pentamer

One of the most important conclusions which can be derived from this and other recent studies is that alcohol self-association does not occur by a continuous chain-like model such as the Kreschmer–Wiebe (1954) model, in which step-wise formation of the (n + 1)-th polymer from a monomer and an n-mer has the same equilibrium constant for all values of n. Rather, it follows from the large region of near-linearity in the plots of log(C_T – Mon) versus log(Mon) (Fig. 3) that an optimum polymer size exists.

An energy minimum with increasing polymer size is best explained by formation of a cyclic species. It would be difficult to rationalize a linear species having an optimum stability as it is generally acknowledged that formation of linear polymers leads to an enhanced acidity of the terminal hydrogen and thus should favor further hydrogen bonding (Bellamy and Pace, 1957). The formation of one additional bond in a cyclic species would provide the energy loss necessary for its stabilization. Perhaps the best experimental evidence for the presence of cyclic species comes from dielectric studies of alcohols in alkane solvents such as the work by Campbell et al. (1975) on octanols. A decrease in the apparent dipole moments of alcohols as a function of concentration was explained by the formation of low dipole moment cyclic polymers.

Much of the literature has been discussed in terms of tetramer formation and a previous calorimetric study, in our laboratories also suggested the monomer-tetramer model. However, the slopes of the log-log plots in Fig. 3 and the results of the computer optimization procedure clearly favor a species larger than tetramer. From an energetic standpoint, a cyclic pentamer should be a favorable structure. The H—O—H angle of a planar pentamer would be 108° which is close to the 109.1° found for the same angle in ice (Peterson and Levy, 1957). The estimate of 108° is based on the assumption that the O—H—O bond favors linearity. Much of the evidence for linear X—H—X bonds has been summarized by Franks (1973). In the case of a planar cyclic tetramer, the H—O—H bond angles would be constricted to 90° unless some bending of the O—H—O bonds occurs resulting in the introduction of strain energy in the hydrogen bond (Pauling, 1960).

Very little free-energy data on primary alcohols, such as vapor pressure data, exists in the literature. A study of vapor pressures of methanol in hexadecane resulted in a monomer-trimer-octamer model (Tucker et al., 1969) while a vapor pressure osmometry study (Aveyard et al., 1973) of dodecanol in *n*-octane was consistent with a monomer-dimer-tetramer model but was only carried out up to a concentration of 0.13 M. Consequently, most of the evidence for tetramer comes from infrared, NMR, and enthalpy of mixing data. For this reason, we feel it is necessary to review the inherent disadvantages of these techniques in arriving at a mathematical model of self-association. (Tucker and Becker (1973) have previously discussed the relative merits of vapor pressures, IR, and NMR techniques.) From equation 4, it can be seen that to evaluate a particular self-association model, one must obtain data for the concentration of monomer as a function of total molarity. As we discussed previously, the alcohol vapor pressures over their solutions are directly related to the monomer concentration in solution. The measureable quantity in both NMR and calorimetric techniques cannot be directly converted to monomer concentration. Also, additional parameters must be determined to completely define the system. For example, the chemical shift obtained from proton magnetic resonance measurements is a weighted average and includes contributions from monomer as well as higher polymers. Similarly, calorimetric studies often involve the measurement of a change in heat on mixing of alcohols in alkane solvents — a quantity which is again not directly related to monomer concentration. In addition, two parameters must be determined for each polymer present — a K and ΔH° of formation. Another difficulty with calorimetric studies lies in the assumption that the heat change measured can be attributed entirely to breaking of polymer bonds. Although correction for heats due to factors other than hydrogen bond breaking have been made (Van Ness et al., 1967; Smith and Brown, 1973), this requires another parameter in the model.

Infrared studies are the most commonly employed of all the techniques in studying alcohol self-association. Although workers using this technique often assume that the monomer band accurately reflects monomer concentration over the entire range of interest, end hydroxyl group absorption of chain polymers may overlap the monomer peak causing an error in the apparent monomer concentration. This was shown to occur in the *t*-butyl alcohol-hexadecane system by Tucker and Becker (1973). Their data indicated that the upper limit for direct use of monomer absorbance data was at approximately 0.1 M *t*-BuOH.

Certainly, the IR, NMR, and calorimetric techniques offer advantages over the vapor pressure technique in the kinds of information they provide, but in light of the limitations inherent in these methods, we feel that vapor pressure data should be the most reliable means for obtaining a mathematical self-association model. It should be pointed out, however, that even vapor pressure data can probably not be obtained with sufficient precision to enable one to support one particular model to the exclusion of all other possibilities. The computer fits summarized in Table 3 show that the tetramer-hexamer model actually resulted in a better fit of the data for L-butanol. This was also true for the other alcohols, but the magnitudes of $K_{1,4}$ and $K_{1,6}$ fluctuated considerably from alcohol to alcohol. Therefore, the advantage gained in describing the vapor pressure data by including another term in the model, when weighed against the resulting loss in physical significance, and the difficulty in making comparisons between alcohols did not seem to justify the tetramer-hexamer model over the pentamer model.

Evidence for dimer

Considerable discussion exists in the literature over the existence and importance of dimers. Fletcher (1969) maintained that dimers did not exist in sufficient quantity to be considered in the material balance equations for L-octanol in *n*-decane. Aveyard et al. (1973) estimated that the maximum amount of dimer in L-octanol-octane systems was just over 5% at 0.1 M while Tucker and Becker (1973) insist that a trimer is actually better supported by their methanol and *t*-BuOH data in hexadecane.

The vapor pressures obtained in this study are not of sufficient precision to unequivocally conclude that dimers exist but not trimers, or vice versa. It is our opinion that a number of small species may form to a slight degree, but the computer fits of the vapor pressures were not significantly improved by considering dimers or trimers as demonstrated in Table 3. The most important consideration here is that the experimental vapor pressures can be explained to within approximately $\pm 3\%$ for the entire region from 0–1 M for all alcohols studied using the monomer-pentamer model (see Fig. 4). The simplicity of a single polymer model and the uncertainty in identifying smaller species causes us to favor the monomer-pentamer model, while recognizing that other species may exist in small amounts.

Effect of chain length on self-association

Fig. 2 and Table 2 display the remarkable similarity in association among the *n*-alcohols from propanol to octanol up to 0.6 M. Fletcher (1972) has earlier proposed that the extent of self-association in saturated hydrocarbon solvents for *n*-alcohols is in the order L-octanol > L-butanol > ethanol- d_1 > methanol. The evidence presented here suggests that self-association tendency in dilute solutions is independent of alcohol chain length. Apparently the loss in entropy accompanying the formation of a complex is not appreciably altered by the addition of methylene groups to the alkyl chain. At higher concentrations, distinct differences in association appear as shown in Fig. 1, with the extent of association in the neat state in the order: L-propanol > L-butanol > ... > L-octanol. A comparison of the experimental and theoretical vapor pressures versus total concentration for L-propanol and L-hexanol (Fig. 5) illustrates a significant deviation from the pentamer model in their self-association patterns above 1 M. For alcohols having short chain

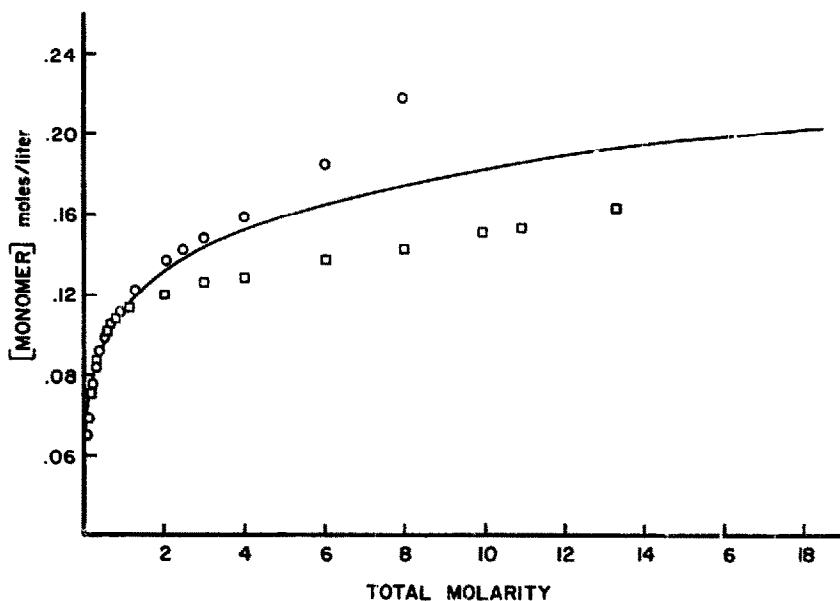


Fig. 5. Plot of monomer concentration versus formal alcohol molarity for L-propanol (□) and L-hexanol (○) showing the deviation from a simple monomer-pentamer model (solid line assuming a $K_{1,5} = 10,000 \text{ l}^4 \text{ mol}^{-4}$) at higher concentrations.

lengths such as L-propanol the experimental vapor pressures are lower than predicted by the monomer-pentamer model at higher concentrations. (Negative deviation was also observed for L-butanol but to a smaller extent.) On the other hand, the longer chain alcohols such as hexanol exhibit positive deviations from the pentamer curve at higher molarities.

Several factors having opposing effects are probably coming into play at higher alcohol concentrations. Further association to form higher polymers or networks could account for the lowered activity seen for L-propanol. Brink et al. (1977) and Smith (1977) have postulated that network formation occurs through formation of two hydrogen bonds to one atom resulting in polymers with side chains. It is conceivable that such network formation would occur less readily in long-chain alcohol systems due to the bulk of the alkyl chains. Smith (1977) has also explained the differences between concentrated alcohol solutions in terms of dipole-dipole interactions between polymers. Again this phenomenon would be more pronounced in the smaller alcohols since long alkyl chains would have a screening effect inhibiting short range dipole-dipole interactions. Data from the study of Tucker et al. (1969) on the self-association of methanol in hexadecane indicates that higher association occurs at very low concentrations in this system with a slope of ~ 7 in their log-log plots at a total concentration of $\sim 0.08 \text{ M}$. Some preliminary data on ethanol vapor pressures in isoctane obtained in our laboratories also suggest that higher polymers than pentamer form at concentrations above 0.2 M which is consistent with the apparent trend that network formation or higher polymerization becomes significant at lower concentrations as the chain length is decreased.

The positive deviations of the vapor pressures of higher alcohols from those pre-

dicted by a monomer–pentamer model can be explained by a breakdown in our assumption that the activity coefficient of monomer is one. Certainly the change in environment on going from infinite dilution in isooctane to a solution which is composed primarily of alcohol polymers will alter the monomer's activity coefficient. An increase in the monomer activity coefficient would account for the upward curvature in the vapor pressure curves seen at concentrations approaching the neat state.

Calculation of the thermodynamics of transfer processes and the methylene group contribution

The ability to predict solution behavior from the physical properties of the pure components would have many useful physical and biological applications. One of the methods which has achieved some success in this context is the semi-empirical group contribution approach. A recent review of this concept has been prepared by Davis et al. (1974). The basic premise made in this method is that the free energy is additively composed of independent contributions from the constituent functional groups.

From the data for the Henry's Law constants of *n*-alcohols in isooctane, we can calculate the molar free energies for the process of transferring alcohol at infinite dilution in isooctane to the vapor phase, $\Delta_{\text{iso}}^{\text{vap}}G_1^0$. For the vapor phase,

$${}^{\text{vap}}\mu_1 = {}^{\text{vap}}\mu_1^0 + RT \ln p_1 \quad (6)$$

where ${}^{\text{vap}}\mu_1^0$ is the chemical potential of the alcohol in the vapor at a pressure, p_1 , of 1 atm. For the alcohol at infinite dilution in isooctane,

$${}^{\text{iso}}\mu_1 = {}^{\text{iso}}\mu_1^0 + RT \ln X_1 \quad (7)$$

where ${}^{\text{iso}}\mu_1^0$ is the chemical potential of the neat alcohol (mole fraction = $X_1 = 1$). At equilibrium, ${}^{\text{iso}}\mu_1 = {}^{\text{vap}}\mu_1$, and

$$\Delta_{\text{iso}}^{\text{vap}}G_1^0 = {}^{\text{vap}}\mu_1^0 - {}^{\text{iso}}\mu_1^0 = -RT \ln(p_1/X_1) = -RT \ln(H_x/760) \quad (8)$$

where H_x is the Henry's Law constant in torr based on mole fraction concentration units. Values for H_x and $\Delta_{\text{iso}}^{\text{vap}}G_1^0$ are listed in Table 4. A plot of $\Delta_{\text{iso}}^{\text{vap}}G_1^0$ versus carbon number, shown in Fig. 6, results in a straight line from which one can calculate the contribution of a methylene group to the transfer process by measurement of the slope. The value obtained is 710 cal/mole of $-\text{CH}_2-$ groups, which is very close to the average value of 700 cal/mole found by Davis et al. (1972) in a survey of the literature.

The free energy of transfer of alcohol from its neat state to an isooctane environment, $\Delta_{\text{alc}}^{\text{iso}}G_1^0$, can also be calculated. For the pure alcohol, ${}^{\text{alc}}\mu_1 = {}^{\text{alc}}\mu_1^0$, and a calculation similar to the above procedure (eqns. 6–8) can be used to obtain the value for $\Delta_{\text{alc}}^{\text{vap}}G_1^0$, the standard free energy of transfer from neat alcohol to the vapor:

$$\Delta_{\text{alc}}^{\text{vap}}G_1^0 = {}^{\text{vap}}\mu_1^0 - {}^{\text{alc}}\mu_1^0 = -RT \ln p_1^0/760 \quad (9)$$

where p_1^0 is the vapor pressure over the pure alcohol at 25°C obtained from the literature values reported in Table 1.

TABLE 4

STANDARD FREE ENERGIES OF TRANSFER OF ALCOHOL FROM ISOCTANE TO VAPOR AND FROM ALCOHOL TO ISOCTANE

Alcohol	H_x (Törr)	$\Delta_{iso}^{vap} G_1^0$ (kcal/mole)	$\Delta_{alc}^{iso} G_1^0$ (kcal/mole)
L-Propanol	765	-0.004	+2.13
L-Butanol	200	+0.79	+2.06
L-Pentanol	71	+1.40	+2.02
L-Hexanol	22.6	+2.08	+1.96
L-Heptanol	6.02	+2.86	+1.93
L-Octanol	1.76	+3.59	+1.87

The standard free energy of transfer of alcohol from its neat state to infinite dilution in isooctane is then,

$$\Delta_{alc}^{iso} G_1^0 = {}^{iso}\mu_1^0 - {}^{alc}\mu_1^0 = -RT \ln(p_1^0/H_x) \quad (10)$$

These values are also listed in Table 4. The steady decline in the free energies of transfer again reflect the decreased association in the neat state, resulting in a higher escaping tendency for monomer in the higher alcohols. Data for standard free energies of solution of alkanols in alkanes from Aveyard and Mitchell (1969) suggest the

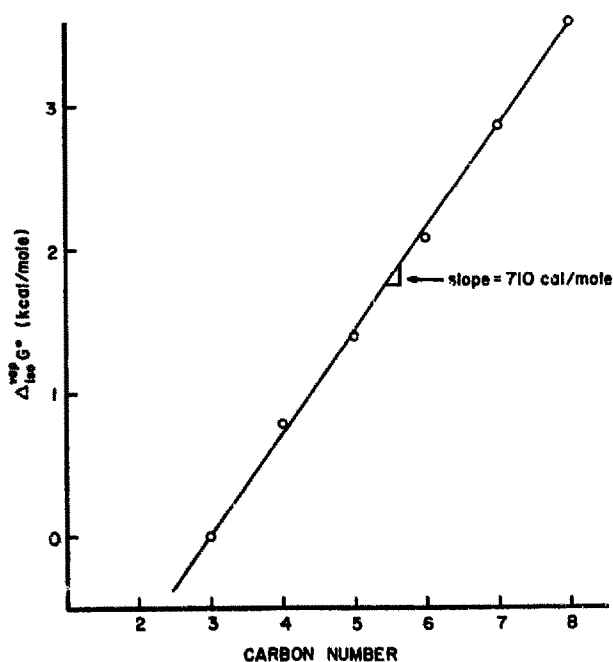


Fig. 6. Standard free energy of transfer of alcohol from isooctane to the vapor phase versus alcohol chain length. The slope gives the methylene group contribution to the transfer process.

opposite trend with chain length. Their results, however, were based on the distribution of alcohols between water and alkane solvents and the free energies of solution of the alcohols in water. The effect of water on the distribution behavior of alcohols is unknown, but may have affected their results.

Pharmaceutical implications

Information of this type allows one to obtain thermodynamic activities of the various alcohol species in solution. For example, a current study in this laboratory of the effects of self-association on mass transport between phases has shown that the rate of transport of phenol is proportional to the thermodynamic activity of the monomer. Another study in progress in this laboratory has examined the increases in solubility observed in hydrocarbon alcohol mixtures for several solutes which are capable of hydrogen bonding. These increases are accounted for quantitatively by complexation with both the monomeric and polymeric species described in this study. Thus, this type of data should be of value in understanding and predicting the solubility and other thermodynamically controlled properties of many substances of pharmaceutical interest.

CONCLUSION

The vapor pressure data for primary alcohols (L-propanol to L-octanol) in isooctane from 0–1 M can be accounted for by assuming that the important species are monomers and pentamers. This clearly contradicts several recent IR, NMR, and calorimetric studies which have suggested that a tetramer is predominant. Although the cause for this discrepancy has not been resolved, we have pointed out some of the problems inherent in the IR, NMR, and calorimetric techniques in obtaining accurate values for monomer concentration. Obtaining the exact distribution of all species existing in these systems is of course unattainable from vapor pressure data, so that the monomer–pentamer model must be viewed as the simplest model which adequately explains the data. Certainly a species larger than tetramer must be included to obtain reasonable agreement with the vapor pressure data. Inclusion of dimers and trimers did not significantly improve the computer fits.

Alcohol self-association at low concentration was shown to be independent of chain length, but at high molarities the formation of larger polymers or networks increased with shorter chain lengths. The activities of the pure alcohols reflect the degree of association in the neat state which is in the order L-propanol > L-butanol > ... L-octanol.

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REFERENCES

- Anderson, B.D., Rytting, J.H., Lindenbaum, S. and Higuchi, T., A calorimetric study of the self-association of *n*-alcohols in isoctane. *J. Phys. Chem.*, 79 (1975) 2340.
- Aveyard, R. and Mitchell, R.W. Distribution of *n*-alkanols between water and *n*-alkanes. *Trans. Faraday Soc.*, 65 (1969) 2645.
- Aveyard, R., Briscoe, B.J. and Chapman, J., Activity coefficients and association of *n*-alkanols in *n*-octane. *J. Chem. Soc., Faraday Trans.*, 1 (1973) 69, 1772.
- Bellamy, L.J. and Pace, R.J., Hydrogen bonding by alcohols and phenols – I. The nature of the hydrogen bond in alcohol dimers and polymers. *Spectrochim. Acta*, 22 (1957) 525.
- Brink, G., Campbell, C. and Glasser, L., Hydrogen bonding structure in alcohols and their solutions. *S. Afr. J. Sci.*, 73 (1977) 11.
- Campbell, C., Brink, G. and Glasser, L., Dielectric studies of molecular association. Concentration dependence of dipole moment of L-octanol in solution. *J. Phys. Chem.*, 79 (1975) 660.
- Cheam, V., Farnham, S.B. and Christian, S.D., Vapor phase association of methanol. Vapor density evidence for trimer formation. *J. Phys. Chem.*, 74 (1970) 4157.
- Davis, S.S., Higuchi, T. and Rytting, J.H., Determination of thermodynamics of the methylene group in solutions of drug molecules. *J. Pharm. Pharmac.*, 24 (1972) 31.
- Davis, S.S., Higuchi, T. and Rytting, J.H., Determination of thermodynamics of functional groups in solutions of drug molecules. In Beam, H.S., Beckett, A.H. and Carless, J.E. (Eds.) *Advances in Pharmaceutical Sciences*, Vol. 4, Academic Press, New York, 1974, pp. 73–261.
- Deming, S.N. and Morgan, S.L. Simplex optimization of variables in analytical chemistry. *Anal. Chem.*, 45 (1973) 278A.
- Fletcher, A.N., The effect of carbon tetrachloride upon the self-association of L-octanol. *J. Phys. Chem.*, 73 (1969) 2217.
- Fletcher, A.N., Molecular structure of ethanol- d_1 solutions. A near-infrared study of hydrogen bonding. *J. Phys. Chem.*, 76 (1972) 2562.
- Fletcher, A.N. and Heller, C.A., Self-association of alcohols in nonpolar solvents. *J. Phys. Chem.*, 71 (1967) 3742.
- Franks, F., In *Water – A Comprehensive Treatise*, Vol. II, Plenum Press, New York, 1973, p. 272.
- Jordan, T.E., *Vapor Pressure of Organic Compounds*, Interscience, New York, 1954.
- Kretschmer, C.B. and Wiebe, R., Thermodynamics of alcohol–hydrocarbon mixtures. *J. Chem. Phys.*, 22 (1954) 1697.
- Morgan, S.L. and Deming, S.N., Simplex optimization of analytical chemical methods. *Anal. Chem.*, 46 (1974) 1170.
- Pauling, L., *The Nature of the Chemical Bond*, 3rd. ed., Cornell University Press, Ithaca, New York, 1960, p. 453.
- Peterson, S.W. and Levy, H.A., A singly-crystal neutron diffraction study of heavy ice. *Acta Cryst.*, 10 (1957) 70.
- Pimentel, G.C. and McClellan, A.L., *The Hydrogen Bond*, Freeman, San Francisco, 1960.
- Riddick, J.A. and Bunger, W.B., *Techniques in Chemistry. Vol. II. Organic Solvents: Physical Properties and Methods of Purification*, 3rd. ed., Wiley-Interscience, New York, 1970.
- Smith, F., Properties of *n*-alcohol + *n*-alkane mixtures. *Aust. J. Chem.*, 30 (1977) 43.
- Smith, F. and Brown, I., Thermodynamic properties of alcohol and alkane mixtures II. contributions to the excess energies other than those due to hydrogen bonding. *Aust. J. Chem.*, 26 (1973) 705.
- Tucker, E.E. and Becker, E.D., Alcohol association studies. II. Vapor pressure, 220-MHz proton magnetic resonance, and infrared investigations of tert-butyl alcohol association in hexadecane. *J. Phys. Chem.*, 77 (1973) 1783.
- Tucker, E.E., Farnham, S.B. and Christian, S.D., Association of methanol in vapor and in *n*-hexadecane. A model for the association of alcohols. *J. Phys. Chem.*, 73 (1969) 3820.
- Van Ness, H.C., Van Winkle, J., Richtol, H.H. and Hollinger, H.B., Infrared spectra and the thermodynamics of alcohol–hydrocarbon systems. *J. Phys. Chem.*, 71 (1967) 1483.
- Wolff, H. and Hoppel, H.E., Die Assoziation von Methanol in Tetrachlorkohlenstoff (nach Dampfdruckmessungen). *Ber Bunsenges Phys. Chem.*, 72 (1968) 1173.
- Woolley, F.M. and Hepler, L.G., Molecular association of hydrogen bonding solutes. Phenol in cyclohexane and benzene. *J. Phys. Chem.*, 76 (1972) 3058.