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Use of the Walden Product to Evaluate the Effect of Amino Acids on Water Structure

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Abstract—The Walden Product, the product of viscosity (η_0) and conductivity at infinite dilution of a solution (Λ_0), provides a measurement of the water-structuring activity of the solute. Measuring the effect of concentration on viscosity of solutions of amino acids, together with the conductivity of solutions of sodium chloride containing increasing concentrations of the amino acids, enabled Walden Products to be determined. The classical form of the Walden Product ($\Lambda_0\eta_0$) was used, together with a modified form, $\Lambda_0\eta_c$, in which η_c was the slope of the concentration/viscosity curve. Most amino acids demonstrated modest water-structure-breaking activity but L-lysine, L-glutamic acid and L-aspartic acid, and their respective salts, all showed relatively higher activity. Dextrose behaved as a classical water-structure maker and, when added progressively, reversed the breaking activity of L-lysine. It is speculated that effects seen in bulk water may also occur at emulsion droplet surfaces, thereby inducing structural changes associated with the occasional rapid instability experienced when making admixtures of phospholipid-stabilized emulsions and additives such as amino acids and dextrose.

Phospholipid-stabilized emulsions have been used for parenteral nutrition for 30 years, generally without significant pharmaceutical problems. It is widely recognized that multivalent cations can produce some instability, but admixtures with dextrose, amino acids and monovalent electrolytes have been prepared as required immediately before administration (Takamura et al 1984). Stepwise evaluation of stability by gross visual and microscopic examination was described by Ho & Higuchi (1967) and Frank (1973). Particle size of emulsions was measured by Black & Popovich (1981). Those authors used a Coulter Counter with a 100 μm-orifice tube and were unable to measure particles below 2 μm. This is unfortunate since the mean particle size has been reported by a number of workers to be well below 1 μm (Dawes & Groves 1978; Kawilarang et al 1980; Lee & Groves 1981; Takamura et al 1984; Washington 1992). Nevertheless, Black & Popovich (1981) confirmed the flocculation effects reported by Davis (1974) and others (Dawes & Groves 1978; Kawilarang et al 1980; Knutsen 1986). Other authors have developed this emphasis on stability as being a flocculation of the emulsion (Washington & Cattell 1989) without, at the same time, detecting significant effects on the overall particle size distribution. This was recently summarized by Li et al (1993) who noted that phospholipid-stabilized emulsions were extraordinarily stable under ambient conditions with no changes being detected by sedimentation field-flow fractionation and photon correlation spectroscopy. These authors also made the point that many previous workers, who did not have access to sensitive methods for droplet size characterization, were only detecting gross changes at the end of a destabilization process and not the subtle changes that may ultimately lead to creaming over a somewhat shorter time frame.

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Although sterile admixtures of lipid emulsions, electrolytes, minerals, vitamins and amino acids have been employed for some time, in recent years reports of instability have appeared (P. Wright, Coordinator, National TPN Group, UK, personal communication) which did not appear to be related to the relatively slow changes associated with initial flocculation and subsequent aggregation of phospholipid-stabilized emulsions. Washington (1990 a,b) has demonstrated changes on the addition of electrolytes that may be correlated to aggregation behaviour on the basis of the classical Deryaguin, Landau, Vervey and Overbeek (DLVO) view of colloid stability (Vervey & Overbeek 1948). The predictive ability of this approach appears to be relatively modest and it seems that an alternative approach to the problem of unpredictable emulsion breakdown is needed.

Water is generally recognized to be a heavily hydrogen-bonded material with a variable evanescent structure which is strongly influenced by temperature and the presence of additives (Franks 1984; Symons 1989). An attempt to determine the effect of various amino acids on bulk water structure is reported here since it is possible that, if an additive is able to disrupt the bulk water structure, in turn an effect may be produced on the vicinal water or on the mesophase between the oil and water phases. Accordingly, we report here measurements on the bulk properties of water induced by some amino acids.

Amino acids have been previously reported to affect water structure. Kay & Evans (1966) found negative temperature coefficients, of the order of 1–3%, for the Walden Products of glycine, β-alanine and serine. This was considered evidence that these amino acids had weak water-structure-breaking activity. Similarly glucose, sucrose, raffinose, valine and leucine all had equally weak water-structure-making activity. The Walden Product, defined as the

product of the conductivity at infinite dilution (Λ_0) and solvent viscosity (η_0) (Walden 1906), was generally small numerically and although both constituent parameters may be measured accurately, the net effect is subject to experimental error which may obscure subtleties in the data. We have therefore attempted to measure conductivities at 25°C of increasing concentrations of the additive in the presence of increasing concentrations of sodium chloride. By extrapolating the data to the intercept, or the point at which the conductivity of sodium chloride is measured at infinite dilution, we have been able to demonstrate that some amino acids and their salts have considerable water-structure-breaking activity whereas most have only a modest effect, as noted by Kay & Evans (1966). This is despite the fact that sodium and chloride ions have their own effects on water structure, the former being strong water-structure-breakers and the latter border-line cases, having properties associated with both makers and breakers (Kay 1968).

The viscosity terms in the Walden Product

As noted, the viscosity term, η_0, is the viscosity of the continuous phase through which the ions and their counter ions are migrating. In principle, therefore, this term is not affected by the solution. This is also true for the Λ_0 term, since this is measured as an intercept at the point where, effectively, the solute ions also have no effect on the solvent. As will be demonstrated, the relationship between the viscosity at a fixed temperature and the concentration of the amino acids is linear, with an intercept that is the viscosity of the solvent (water) and a slope (η_c) that is unique to the individual amino acids. Since, numerically, the values of this modified Walden Product are lower, this suggestion has the advantage of being somewhat more sensitive and, at the same time, is not disturbed by inevitable fluctuations of individual measurements.

Materials and Methods

Materials

Amino acids, injectable grades, were supplied as gifts by Kabi-Pharmacia Inc. (Clayton, NC). Dextrose and urea were from Fisher Scientific (Itasca, IL). Sodium chloride, potassium chloride, lithium chloride and rubidium chloride were from Fluka Inc., (Ronkonkoma, NY) and were used as received. Distilled water was obtained from a Fi-Stream 4 (Barnstead-Sybron Inc., Boston, MA).

Methods

Viscosity was measured at 25·0 (± 0·1)°C using calibrated glass Cannon-Fenske viscometers (Boekel Industries Inc., Philadelphia, PA).

Conductivity was measured at 25·0 (± 1)°C with a CDM 83 conductivity meter equipped with a CDC 304 Immersion conductivity cell and a T801 temperature probe (Radiometer, Copenhagen, Denmark). The cell was calibrated at 25°C using 0·05% (w/w) sodium chloride and the absolute electrical accuracy was ± 0·75% over the range of 13–130 μS cm^{-1} for a nominal cell constant of 1·0 cm^{-1}. The conductance, in Siemens (S) (mhos or ohms^{-1}), is defined as:

$$C = \text{conductance} = k^{-1}\Sigma(\zeta_i c_i \lambda_i) \cdot 10^{-3}$$

where k = cell constant (cm^{-1}), c_i = molar concentration of the ith ion with charge ζ_i (positive) and λ_i = the equivalent conductivity of the ion (in infinitely dilute solution). The conductivity κ is the conductance per unit cube of the solution i.e. κ = C.k and is measured in S cm^{-1}.

The equivalent conductivity is defined as the ratio of the specific conductivity of a solution to the concentration expressed in g equivalents L^{-1} of solute, with units S cm^2 per equivalent.

By plotting the conductivity κ as a function of the electrolyte concentration, the intercept at the y-axis, effectively the conductivity at infinite dilution, becomes the specific conductivity, Λ_0. This was readily measured for sodium chloride but by repeating these measurements in fixed concentrations of additive, the effect of the additive on the specific conductivity could be determined. Repeating these measurements for increasing concentrations of additive enabled the effect of the additive on water structure to be determined. Intuitively, a positive slope of Λ_0 vs concentration of additive would indicate a decrease in resistance to ionic movement, a situation caused by an increasing breakdown of water-structure. Conversely, a decrease in slope would suggest a decrease in electrolyte ion mobility and an increase in water-structure.

Results

Viscosity

Validation of our procedure was obtained by reference to literature values for sodium chloride (Eisenberg & Kautzman 1969) and indicate (Fig. 1) that our data are within ± 1% over the entire range of concentrations measured. A typical viscosity/concentration curve is shown in Fig. 2 and all data for amino acid solutions in water are listed in terms of their y-intercepts, slopes and correlation coefficients (Table 1). The y-intercepts are effectively the viscosity of the solvent, water, and may be compared with data in the literature. The viscosity of water at 25·0°C is or 0·8904 × 10^{-3} Pa s (Swin-

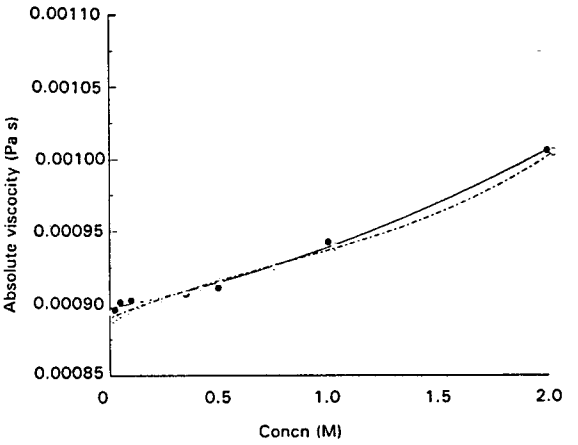

FIG. 1. Comparison of experimental and literature values of sodium chloride viscosities at 25°C. ● Measured viscosity, ○ literature value (Eisenberg & Kautzman 1969).

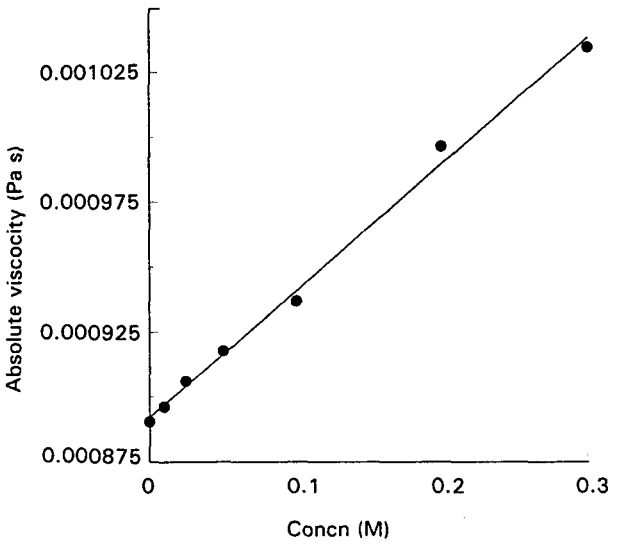

FIG. 2. Measured viscosities of L-lysine solutions in water at 25°C.

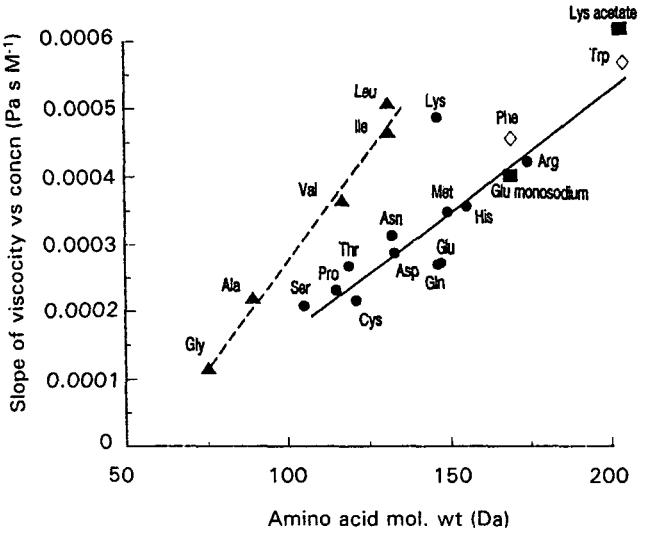

FIG. 3. The slope of the viscosity vs concentration curves (η_c) plotted against mol. wt. ▲ Aliphatic amino acids, ◇ aromatic amino acids, ■ salts of glutamic acid and lysine, ● remaining amino acids.

dells 1982). Here the average of extrapolated values (Table 1) is $0{\cdot}8924 \times 10^{-3}$ Pa s (n = 21), a result within 0·20% of the literature consensus.

Plotting the slopes of the viscosity concentration curves (η_c) against mol. wt (Fig. 3) suggested a strong linearity for most of the amino acids ($r^2 = 0{\cdot}946$, n = 15). However, some aliphatic amino acids were clearly separated, with a slope almost double that of the remainder (0·00644 vs 0·00363) and a stronger correlation ($r^2 = 0{\cdot}992$, n = 5).

Conductivity

Comparison of the data obtained here against literature values for the conductivity of sodium chloride solutions (Robinson & Stokes 1959) showed satisfactory agreement over the range of concentrations examined (Fig. 4).

The effect due to urea, a known water-structure breaker, (Beauregard & Barrett 1968; Barone et al 1970) and dextrose, which behaves as a classical water-structure maker, are shown in Fig. 5. The effects due to glycine and lysine are shown in Fig. 6 and the data for all amino acids and their salts are shown in Table 1. The effects due to individual monovalent electrolytes (lithium, sodium, potassium and rubidium chlorides) on lysine were super-

Table 1. Viscosities and Walden Products of amino acids at 25°C.

L-Amino acid	Mol. wt (Da)	*y*-intercept η_0 (Pa s 10^{-3})	Slope (η_c) (Pa s $M^{-1}10^{-3}$)	Correlation coefficient (r^2)	Classical Walden Product ($\Lambda_0\eta_0$)	Modified Walden Product ($\Lambda_0\eta_c$)
Alanine	89·09	0·8937	0·2169	0·9979	0·706	0·171
Arginine	174·20	0·8921	0·4231	0·9963	1·132	0·537
Asparagine	132·10	0·8934	0·3136	0·9835	1·464	0·514
Aspartic acid	133·10	0·8920	0·2879	0·9914	5·153	1·663
Cysteine	121·20	0·8944	0·2157	0·9938	1·006	0·243
Glutamic acid	147·13	0·8921	0·2729	0·9818	6·432	1·968
Mono sodium glutamate	169·12	0·8897	0·4026	0·9996	44·82	20·28
Glutamine	146·15	0·8927	0·2703	0·9950	1·244	0·377
Glycine	75·07	0·8918	0·1142	0·9971	0·168	0·021
Histidine	155·16	0·8916	0·3580	0·9979	1·526	0·613
Isoleucine	131·20	0·8922	0·4640	0·9992	0·581	0·302
Leucine	131·17	0·8906	0·5063	0·9970	0·496	0·282
Lysine (free base)	146·12	0·8920	0·4880	0·9976	5·413	2·961
Lysine acetate salt	202·60	0·8901	0·6188	0·9993	40·13	24·84
Methionine	149·21	0·8940	0·3488	0·9923	0·782	0·305
Phenylalanine	169·19	0·8906	0·4568	0·9994	0·619	0·317
Proline	115·13	0·8935	0·2298	0·9926	0·978	0·252
Serine	105·09	0·8938	0·2078	0·9904	0·594	0·138
Threonine	119·12	0·8940	0·2679	0·9942	0·636	0·190
Tryptophane	204·22	0·8919	0·5694	0·9885	0·112	0·072
Tyrosine[a]	181·19				0·186	0·096*
Valine	117·10	0·8946†	0·3636	0·9942	0·467	0·190

* η_c estimated from Fig. 3 and the measured Λ_0. † η_0 average (n = 21) = $0{\cdot}8924 \times 10^{-3}$ Pa s (s.d. = 0·0014). [a] Parameters for tyrosine could not be determined due to very low water stability.

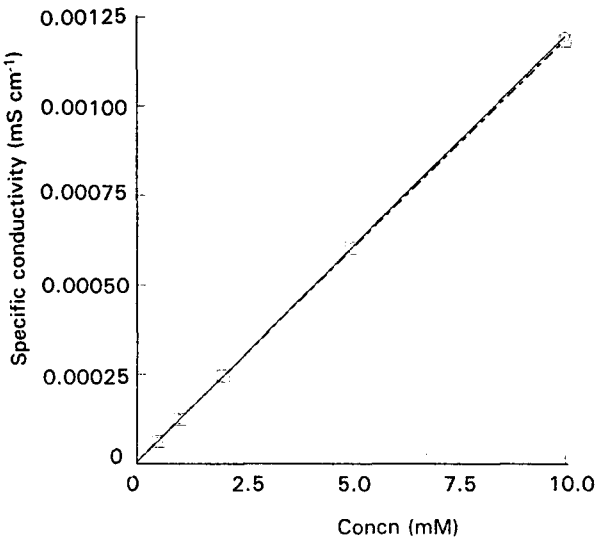

FIG. 4. The specific conductivities for sodium chloride solutions at 25°C compared with literature values. ○ Observed ($r^2 = 0{\cdot}9999$), □ literature (Robinson & Stokes 1959).

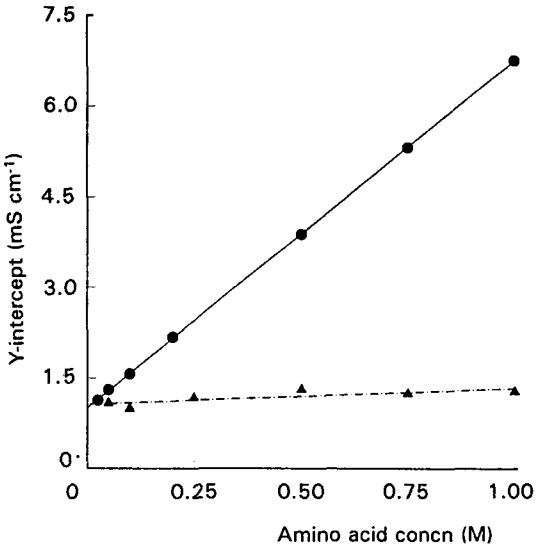

FIG. 6. Specific conductivities at infinite dilution (Λ_0) for L-lysine base (●) and L-glycine (▲) solutions at 25°C as a function of concentration. Lysine: slope = +6·068, $r^2 = 0{\cdot}9985$ (n = 7). Glycine: slope = +0·092, $r^2 = 0{\cdot}9600$ (n = 6).

imposable. The influence of temperature on the conductivities of lysine and glycine is shown in Fig. 7. Water-structure-breaking activity of L-lysine was incrementally reduced by the addition of dextrose.

Discussion

The Walden Product ($\Lambda_0\eta_0$) is effectively a conductivity corrected for any effect the solute viscosity may have on the movement of the ionic species. The viscosity term, η_0, is the viscosity of the solvent and, as shown in Table 1, experimentally the average intercept for the amino acids examined is within 0·2% of the accepted literature value for water at the temperature of measurement. It does not, therefore, represent any effect that the solute itself may have on the properties of the solution. A more effective parameter might be the slope of the viscosity-concentration curve, here termed η_c which, as noted, is relatively unaffected by inevitable experimental fluctuations in measurements. This parameter is unique to each amino acid and does appear to represent a fundamental property which can be related to mol. wt (Fig. 3) and, perhaps in the special case of the aliphatic amino acids the structure (Table 2).

Although not pronounced, the evident difference in slopes of these materials may indicate some form of self-association. The way in which the viscosity increases with increased concentrations, (η_c), is a manifestation of the association or interaction between all molecular species, but may not necessarily be due to hydrophobic or micellar forces as seen under other experimental conditions that apply, for example, when measuring diffusion coefficients. Paduano et al (1990) noted that the limiting diffusion coefficient of phenylalanine differed from that of linear amino acids by the associated presence of an aromatic

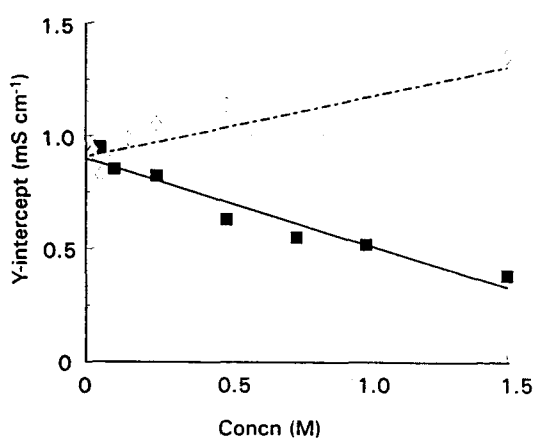

FIG. 5. Intercept of specific conductivity at infinite dilution (Λ_0) for urea (◇) and dextrose (■) in water at 25°C as a function of concentration. Urea: slope = +0·3750, $r^2 = 0{\cdot}708$ (n = 11). Dextrose: slope = −0·3782, $r^2 = 0{\cdot}9647$ (n = 7).

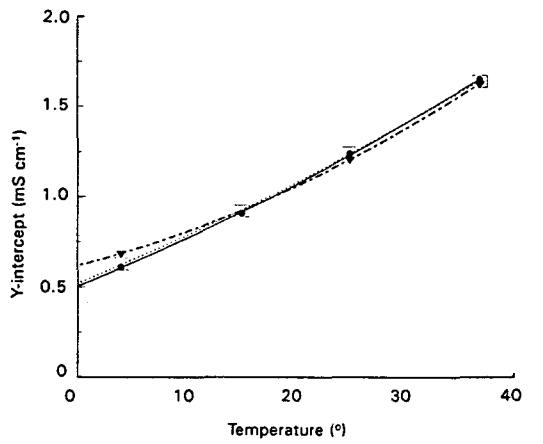

FIG. 7. The effect of temperature on the specific conductivity at infinite dilution (Λ_0) for solutions of amino acids and electrolytes. □ Sodium chloride, ▲ sodium chloride and L-lysine base, ● sodium chloride and L-glycine.

Table 2. Structural elements involved in the apparent association of some aliphatic amino acids evident in Fig. 3.

Amino acid	Side chain	Ratio η_c:mol. wt (from Fig. 3)
Glycine	$-H$	1·52
Alanine	$-CH_3$	2·43
Valine	$-(CH_3)_2$	3·11
Isoleucine	$-CH(CH_3)-CH_2-CH_3$	3·54
Leucine	$-CH_2-CH_2(CH_3)_2$	3·86

ring which would favour non-bonding interactions. On the other hand, Mukerjee (1974) suggested that compounds with rigid aromatic ring structures could associate by non-micellar processes involving face-to-face stacking of molecules, one on top of the other. Of the five aliphatic amino acids that appear to interact more rapidly than the remainder under these present experimental conditions, leucine and valine have branched terminal groups (dimethyl) and alanine, isoleucine and, arguably, glycine have linear aliphatic groups projecting away from the charged terminal groups which, in all cases, are adjacent to each other. This may be their only common feature (Table 2). The increasing hydrophobicity of these aliphatic groups may allow some form of weak self-association. Tryptophan, histidine and phenylalanine, also with adjacent amino and acidic groups, possess planar terminal groups which may not be capable of reacting in the same way under these conditions.

Conductivity measurements, on their own, indicate some form of water-structure modifying behaviour. Under our conditions, urea is seen to have structure-breaking activity and dextrose water-structure-making activity (Fig. 5). It should be noted that these measurements were achieved in the presence of sodium chloride. The chloride ion itself is strongly water-structure breaking (Kay 1968), so it may be argued that the measurements obtained here for urea are superimposed upon those obtained for a strong electrolyte. Data for glycine, with weak activity and lysine with stronger activity are shown in Fig. 6.

The argument that the Λ_0 is obtained at a point of infinite dilution where the carrier electrolyte is no longer influential is clearly not valid. Under the conditions of our measurements, the Λ_0 measured is a function of the added solute, irrespective of the effects due to the strong electrolyte itself and would be anticipated to be the same for any monovalent electrolyte employed. Experimentally this was confirmed with lithium, sodium, potassium and rubidium chlorides.

The effect of temperature on glycine and lysine is evident (Fig. 7) and is consistent with a reduction of the thickness of the layer of ordered water molecules around each solute molecule (Kay & Evans 1966; Kay 1968).

Taking the data acquired here and treating it in terms of a Walden Product ($\Lambda_0\eta_0$) or a modified Walden Product in the form of $\Lambda_0\eta_c$ we see that, in the event, most amino acids have a modest water-structure-breaking activity (Table 1). This is in substantial agreement with the investigation of the effect of temperature on the Walden Product (in the form $\Lambda_0\eta_0$) for glycine, β-alanine and serine (Kay & Evans 1965, 1966). On the other hand, these workers also found water-structure-making activity for α-alanine, valine, norleucine and leucine. In all cases these effects were modest ($\pm$ 3%). Assuming most of the amino acids had marginal activity, Table 1 shows that, in contrast, there is a marked water-structure-breaking activity due to lysine, glutamic acid and aspartic acid and, especially, of their respective salts. All three compounds are uniquely characterized by additional amine (lysine) or carboxylic acid (glutamic and aspartic acids) groups which might be anticipated to be strong water attracting moieties. An analogy can be made from the review of Abu-Hamdiyyah (1965) who suggested that water-breaking entities such as urea acted by orientating adjacent water molecules, thereby restricting their participation in surrounding hydrogen-bonded water molecule clusters.

Of interest was the demonstration that dextrose could progressively inhibit the bulk water-structure breaking activity of L-lysine. This would suggest that the order of mixing may be critical for the stability of an emulsion system affected by any water-structure-modifying activity associated with dextrose or amino acids when added to the emulsion as a component of an injectable total parenteral nutritional system.

The Walden Product in its modified form ($\Lambda_0\eta_c$) appears to be a valuable tool in that considerable water-structure-breaking activity, in the presence of sodium chloride, can be detected and measured. It appears reasonable to conclude that some amino acids may exert considerable structure-breaking activity on bulk water.

From a pharmaceutical perspective, the next stage is to determine if this activity can be detected in the vicinal water surrounding emulsion droplets and, beyond that, to measure any effects produced on the structural integrity of the intact emulsion itself.

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References

Abu-Hamdiyyah, M. (1965) The effect of urea on the structure of water and hydrophobic bonding. J. Phys. Chem. 69: 2720–2725

Barone, G., Rizzo, E., Vitagliano, V. (1970) Opposite effect of urea and some of its derivatives on water structure. J. Phys. Chem. 74: 2230–2232

Beauregard, D. V., Barrett, R. E. (1968) Ultrasonics and water structure in urea solutions. J. Chem. Phys. 49: 5241–5244

Black, C. D., Popovich, N. G. (1981) A study of intravenous emulsion capability: effects of dextrose, amino acids and selected electrolytes. Drug Intell. Clin. Pharm. 15: 184–193

Davis, S. S. (1974) Pharmaceutical aspects of intravenous fat emulsions. J. Hosp. Pharm. 32: 165–170

Dawes, W. H., Groves, M. J. (1978) The effect of electrolytes on phospholipid-stabilized soybean oil emulsions. Int. J. Pharm. 1: 141–150

Eisenberg, D., Kautzman, W. (1969) The Structure and Properties of Water. Oxford University Press, Oxford, p. 223

Frank, J. T. (1973) IV additive review. Intralipid compatability study. Drug Intell. Clin. Pharm. 7: 351

Franks, F. (1984) Water, Revised 1st edn. Royal Society of Chemistry, London

Ho, N. F. H., Higuchi, W. I. (1967) Kinetics of aggregation of

denatured proteins I. Methodology based on the multichannel particle size analyzer. J. Pharm. Sci. 56: 248–258

Kawilarang, C. R. T., Georghiou, K., Groves, M. J. (1980) The effect of additives on the physical properties of a phospholipid-stabilized soybean oil emulsion. J. Clin. Hosp. Pharm. 5: 151–155

Kay, R. L. (1968) The effect of water structure on the transport properties of electrolytes. Adv. Chem. Series, Am. Chem. Soc., Washington, DC 73: 1–17

Kay, R. L., Evans, D. F. (1965) The conductance of the tetra-alkylammonium halides in deuterium oxide solutions at 25°. J. Phys. Chem. 69: 4216–4221

Kay, R. L., Evans, D. F. (1966) The effect of solvent structure on the mobility of symmetrical ions in aqueous solution. J. Phys. Chem. 70: 2325–2335

Knutsen, O. H. (1986) Stability of Intralipid fat emulsion in amino acid solutions. Crit. Care Med. 14: 638–641

Lee, G. W. J., Groves, M. J. (1981) A pragmatic approach to the particle sizing of submicrometre emulsions using a laser nephelometer. Powder Technol. 28: 49–54

Li, J., Caldwell, K. D., Anderson, B. D. (1993) A method for the early evaluation of the effects of storage and additives on the stability of parenteral fat emulsions. Pharm. Res. 10: 535–541

Mukerjee, P. (1974) Micellar properties of drugs: micellar and nonmicellar patterns of self-association of hydrophobic solutes of different molecular structures–monomer fraction, availability, and misuses of micellar hypothesis. J. Pharm. Sci. 63: 972–981

Paduano, L., Sartario, R., Vitagliano, V., Costantino, L. (1990) Transport and thermodynamic properties of the systems (D,L) nor-leucine-water and (L) phenylalanine-water at 25°C. J. Mol. Liquids 47: 193–202

Robinson, R. A., Stokes, R. H. (1959) The variation of conductivities and transport numbers with concentration. In: Electrolyte Solutions. Butterworths Scientific Publications, London, pp 133–173

Swindells, J. F. (1982) Handbook of Chemistry and Physics 63rd edn. CRC Press Inc., Boca Raton, FL, F-40

Symons, M. C. R. (1989) Liquid water—the story unfolds. Chem. Br. 25: 491–498

Takamura, A., Ishii, F., Noro, S., Tanifuji, M., Nakajima, S. (1984) Study of intravenous hyperalimentation: effect of selected amino acids on the stability of intravenous fat emulsions. J. Pharm. Sci. 73: 91–94

Vervey, E. J. W., Overbeek, J. T. G. (1948) Theory of Stability of Lyophobic Colloids. Elsevier Science Publishers B.V., Amsterdam

Walden, P. (1906) Über organische lösungs—und Ionisierungsmittel. III. Innere Reiburg und deren zusammenhang mit dem Leitvermögen. Z. Physik. Chem. Heft. 6: 207–249

Washington, C. (1990a) The electrokinetic properties of phospholipid-stabilized fat emulsions. II. Droplet mobility in mixed electrolytes. Int. J. Pharm. 58: 13–18

Washington, C. (1990b) The electrokinetic properties of phospholipid-stabilized fat emulsions. III. Interdroplet potentials and stability ratios in monovalent electrolytes. Int. J. Pharm. 64: 67–73

Washington, C. (1992) Particle size distribution in parenteral fat emulsions by flow ultramicroscopy. J. Pharm. Pharmacol. 44: 1073

Washington, C., Cattell, R. J. (1989) Predictive models of TPN mixture stability: a simple binding-site model. J. Pharm. Pharmacol. 41 (Suppl.): 163P