Eur. Polym. J. Vol. 28, No. 3, pp. 293–297, 1992
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0014-3057/92 $5.00 + 0.00

THE SOLUBILITY PARAMETER OF POLY(DL-LACTIC ACID)

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(Received 4 June 1991)

Abstract—The solubility parameter δ as defined by Hildebrand was determined for amorphous poly(DL-lactic acid) by means of high precision density measurements. These measurements were used to obtain the partial specific volumes $\bar{V}$ of the polymer dissolved in a series of solvents characterized by different solubility parameters δ_s. The solubility parameter of the polymer δ_p was calculated from these values applying an approximation of the type

$$\bar{V} = \bar{V}_{max} - A \times (\delta_s - \delta_p)^2.$$

This curve is adduced from the polymer–solvent interaction and shows the highest partial volume for the polymer dissolved in the solvent with maximum solvation power. The fit on the base of seven solvents resulted in a solubility parameter of about 10.3 $cal^{0.5}\,cm^{-1.5}$ for poly(DL-lactic acid) at 25°C. An evaluation starting from the measurement of only two solutions, as described in the literature for low-molecular weight substances, gave no reliable results in this case. Determinations of the solubility parameter by means of viscosity numbers was performed for the most part using the same solvents and leads to a comparable value of about 10.0 $cal^{0.5}\,cm^{-1.5}$. These experimental results are compared with solubility parameters calculated by means of incremental methods.

INTRODUCTION

Poly(lactic acid) and its copolymers with other hydroxyacids are used in many medical applications, such as sutures [1], bone fixation, bone replacement [2] and depots for long-term drug release [3, 4]. The main advantages of these aliphatic polyesters are biocompatibility and biodegradability, yielding physiologically occurring degradation products. Rate of degradation (or stability), mechanical and diffusive properties can be adjusted by copolymerization, formulation or by other suitable measures [2, 5]. On the other hand, poly(lactic acid) and its copolymers have been considered as materials of the future to replace commonly used technical polymers, such as PVC or polystyrene [6].

The concept of solubility parameters was developed by Scatchard and Hildebrand on the basis of the theory of regular solutions [7, 8]. The Hildebrand solubility parameter at a given temperature

$$\delta = \left(\frac{(\Delta E_v)}{(V)}\right)^{0.5}, \qquad (1)$$

is given by the square root of the cohesive energy divided by the molecular volume or the square root of the cohesive energy density. The Hildebrand concept in the most simplified form is used in terms of a progression, attaching one solubility parameter δ to each solvent or solute. Substances with values of similar magnitude should be miscible or soluble. In many cases, the *exact* prediction of solubility is not possible by means of this progression. This fact originates from some assumptions and simplifications in the derivation of the Hildebrand parameter [9]. Therefore, various additions, refinements and extensions have been developed, in most cases based upon multicomponent parameters, to allow a stricter treatment of solubility and related phenomena [10–15]. Nevertheless, it should be apparent that the use of the simple Hildebrand solubility parameter of a substance can often be a useful tool, applicable to the solution of many practical problems, especially if there is a new material for particular application and only limited empirical knowledge about product properties.

In the context of poly(hydroxy acids), solubility parameters can be applied to accelerate the improvement of synthesis, purification, further processing and product properties. Examples for possible applications of biopolymers are given in the literature, e.g. the choice of suitable excipients (plasticizers) [16], of suitable polymer–drug combinations to optimize drug release [17], adjustment of appropriate swelling properties by changing the copolymer composition [18] and prediction of absorption/desorption rates after sterilization with ethylene oxide [19].

The solubility parameter of volatile substances can conveniently be obtained, e.g. by using the heat of vaporization and vapour–pressure–temperature data [8]. For high-molecular weight substances, these methods are inapplicable. Indirect methods must be used and they can be based on various kinds of measurements, such as osmotic pressure of solutions [20], swelling of cross-linked polymers in solvents having a wide range of δ-values [21, 22] or measurement of the intrinsic viscosities in a series of solvents [22, 23]. These methods are tedious and time consuming, and hence, a great deal of effort has been spent on discovering alternative ways of estimating solubility parameters. Gas–solid chromatography is a

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Table 1. Specific and partial specific volumes of poly(DL-lactic acid) in various solvents

Solvent	Solubility parameter[a]	V spec. (c = 0)[b]	Correlation coefficient	SEC[c]	Coefficient of determination	$\bar{V}$ spec.
1. Toluene	8.9	1.15998	−3.753e-03	5.1	0.9996	0.7847
2. Ethyl acetate	9.1	1.11838	−3.443e-03	2.6	0.9999	0.7741
3. Chloroform	9.3	0.67628	1.072e-02	1.5	0.9998	0.7835
4. Methylene chloride	9.7	0.75989	3.230e-04	0.6	0.9993	0.7922
5. Dioxane	10.0	0.97305	−1.814e-03	1.3	0.9999	0.7917
6. Acetophenone	10.6	0.97817	−1.818e-03	1.2	0.9999	0.7964
7. Acetonitrile	11.9	1.28782	5.171e-03	14.5	0.9985	0.7707

[a] Values from Ref. [30], dimension [$\text{cal}^{0.5}\,\text{cm}^{1.5}$].
[b] Specific and partial specific volume in [$\text{cm}^3\,\text{g}^{-1}$].
[c] Standard error of correlation × 10^5.

new and promising way to determine solubility parameters of solids [24], and even to obtain partial components δ_i of refined solubility concepts [25].

In recent years, another new method has been developed, made possible by new equipment for high-precision density measurement of solutions. In the paper by Liron and Cohen, the solubility parameters of low molecular weight compounds were investigated by this method [26]. In the present paper, the first attempt to determine the δ-value of a polymer by means of high-pressure density measurements of solutions is introduced [27].

EXPERIMENTAL PROCEDURES

1. Density method

Equipment. The density-measuring assembly consisted of a measuring cell unit and a density meter with digital display (DMA 601 and DMA 60, Anton Paar, Gretz, Austria). The density determination is based on measuring the period of oscillation of a vibrating U-shaped sample tube, which is filled with about 0.6 ml liquid [28]. The following relationship exists between period T and the density d

$$d = A \times (T^2 - B) \qquad (2)$$

A and B are instrument constants, determined by two calibration measurements with substances of known densities. In our case, air and distilled water were used. The achievable accuracy of this method depends upon the short term temperature stability. A variation of $\pm 0.01°\text{C}$ will yield an uncertainty of $\pm 5 \times 10^{-6}\,\text{g} \times \text{cm}^{-3}$ in the density determinations of aqueous solutions, and even more for organic solvents. Therefore, extreme effort must be taken to provide a high stability of temperature. The equipment was placed in a thermostatically controlled room and a high performance ultra-thermostat (Lauda Messgeraete, Lauda, Fed. Rep. Germany, Thermostat RCS 6) with a circulation of 15 l/min water, pumped through isolated tubes into the measuring unit. A temperature stability of $25 \pm 0.02°\text{C}$ was achieved.

Procedure. Calibration was performed with air (including barometric correction) and distilled and degassed water using tabulated values with an accuracy of $10^{-7}\,\text{g} \times \text{cm}^{-3}$. With each solvent, five polymer solutions were prepared in the range of 0.2–1.0% contents. Solvent and solutions were degassed by ultrasonic agitation just before the density measurements. After slow injection of the liquid into the measuring cell, the achievement of thermal equilibration was controlled by means of the oscillatory period. Thereafter, triple determination was taken as the basis for further calculation.

Calculation. Specific volume, the reciprocal of density, was plotted against the mass fraction of the solute. Curve fitting was made by a linear least-square regression analysis. Regression coefficient and standard error are given in Table 1. The partial specific volume $\bar{V}$ was calculated by extrapolating the specific volume to the polymer concentration of 100% [26]. The approximation to a given function was performed by employing the Marquardt–Levenberg method until a least-squares solution was reached (RS/1 software, BBN Corp., Cambridge, MA 02238, U.S.A.).

2. Viscosity method

Equipment. Viscosities of poly(lactic acid) solutions were obtained with the capillary viscometer (Ubbelohde viscometer AVS/G and AVS/M, Schott-Geraete, Mainz). The open tube was provided with a drying device during conditioning of the capillary (type 0) and the measurements. The capillary unit was placed in a water bath at $20 \pm 0.1°\text{C}$.

Procedure. Solvents were dried and filtered through a 0.5 μm glass filter before use. The capillary was conditioned with the appropriate solvent. Five solutions with concentrations within the range of 0.15–0.8% were filtered and measured in the automated instrument. The efflux times of at least 360 sec were determined after temperature equilibration, four times for each solution, with an accuracy of ± 0.01 sec.

Calculation. All values were corrected according to Hagenbach. Specific viscosities were calculated by means of densities measured with an accuracy of $10^{-3}\,\text{g} \times \text{cm}^{-3}$. Reduced viscosities were extrapolated to zero concentration according to Huggins by a linear least-square fit to obtain the limiting viscosity number $[\eta]$, formerly known as 'intrinsic viscosity'. The results are summarized in Table 2.

3. Materials

Poly(DL-lactic acid) was synthesized by ring-opening polymerization of dilactide using stannous octoate as initiator [29]. Structure and purity were confirmed by ^{1}H-NMR and IR spectroscopy. Molecular weight was determined by gel permeation chromatography in tetrahydrofuran using Ultrastyragel columns and polystyrene standards. The results were $\bar{M}_w = 67{,}300$ and $\bar{M}_n = 42{,}000$.

Commercially available spectroscopy grade solvents with water contents of $\leqslant 0.05\%$ were used. It was observed in previous experiments that water contents due to hydroscopicity can disturb the determination; therefore great care was taken to measure under dry conditions.

Table 2. Limiting viscosity numbers of poly(DL-lactic acid) in various solvents

Solvent	Solubility parameter[a]	$[\eta]$[b]	SD[b]
1. Toluene	8.9	0.590	0.0500
2. Tetrahydrofuran	9.1	0.625	0.0786
3. Ethyl acetate	9.1	0.660	0.0600
4. Benzene	9.2	0.630	0.0500
5. Methylene chloride	9.7	0.980	0.0500
6. 1,4-Dioxane	10.0	0.690	0.0198
7. Acetonitrile	11.9	0.310	0.1100

[a] See note in Table 1.
[b] Dimension [$\text{cm}^3 \times \text{g}^{-1} \times 10^2$].

RESULTS AND DISCUSSION

1. Density method

The partial specific volume is defined

$$\bar{V}_i = \frac{(\delta V)}{(\delta c_i)} \quad T, p, i \neq j. \tag{3}$$

For a non-ideal two component system, the specific volume can be written as

$$V_{\text{spec}} = c_1 \times \bar{V}_1 + c_2 \times \bar{V}_2 . \tag{4}$$

When component-2 is polymer and component-1 solvent, $\bar{V}_2$ is the rate of the change of volume of the solution when an infinitely small amount of polymer is added. If the concentration is kept low and c_1 reaches unity, $\bar{V}_1$ does not change noticeably with concentration [31]. This point was established in our case at polymer concentrations below 1% by control of the linear least-square fit. Starting from this assumption, the calculation of the partial specific volume of the polymer was possible by linear extrapolation of equation

$$\bar{V}_{\text{spec}} = \bar{V}_1(c_2 = 0) + c_2 \times \bar{V}_2 \tag{5}$$

to $c_2 = 1$.

Extremely precise measurement is required to obtain accurate results from this extrapolation. With one exception, only series showing correlation coefficients of > 0.999 were used for further calculation (Table 1). The standard errors for the partial specific volumes were found to be $< 1\%$, except for the results for the solvent with highest solubility parameter (acetonitrile $\pm$ 7%) and the lowest one (toluene $\pm$ 2.4%). The reason for this behaviour might be the insufficient solubilization property of those solvents.

The solubility parameter as defined by Hildebrand can be related to short-range interactions between polymer and solvent molecules. The concept fails in the case of specific interactions. If the interactions are not specific and the geometric mean rule is valid in a suitable solvent [9], the partial specific volume is higher when adding a solvent of better solubilization properties than for a solvent of poorer solubilization properties. That causes a lower gross density and a more diluted polymer coil for a 'better' solvent. This feature is demonstrated by a plot of the partial specific volume of the polymer against the solubility parameters of the solvents (Fig. 1).

A fit to a quadratic equation results in a maximum of

$$\bar{V}_2 = 0.784 \pm 0.004 \text{ cm}^3 \text{ g}^{-1}$$

and

$$\delta = 10.29 \pm 0.13 \text{ cal}^{0.5} \text{ cm}^{-1.5}.$$

For comparison, the calculated specific volume of amorphous poly(DL-lactic acid) at 25°C is 0.787 cm^3 g^{-1}.

In solvents with poorer solubilization properties, the partial specific volume generally tends to be lower than the specific volume of the amorphous polymer [32]. The use of the density method for determination of solubility parameters requires solvents covering a wide range of solubility parameters. That condition was not met in previous studies determining partial volumes. An additional advantage of the use of a range of solvents to determine solubility parameters is the possibility that small differences caused by more specific interactions due to solvent properties can be compensated. As a consequence, the choice of the solvent is critical if the range of solvent probes has to be reduced for practical reasons [25]. Comparisons of the evaluation using the same five solvents as for our viscosity measurement resulted in nearly the same value, but with a higher standard deviation $\delta = 10.22 \pm 0.24$ $\text{cal}^{0.5}$ $\text{cm}^{-1.5}$.

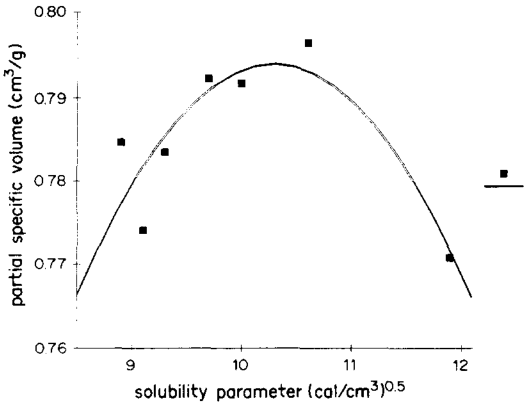

Fig. 1. Partial specific volume of poly(DL-lactic acid) in various solvents. Data were fitted to the equation $\bar{V} = \bar{V}_{\max} - A \times (\delta_s - \delta_p)^2$.

It was claimed in the literature that the determination of solubility parameters of solid compounds from partial volumes should be generally applicable. The method according to Liron and Cohen [26] depends upon an equation of Hildebrand describing the mixture of liquids in terms of the regular solution theory.

$$\frac{\bar{V}_2 - \bar{V}_2^\circ}{V_2^\circ} = \frac{(\delta_s - \delta_p)^2}{(\delta E_s / \delta V)_T} \tag{6}$$

$\bar{V}_2$ stands for the partial specific volume, $\bar{V}_2^\circ$ for the standard volume of the solute as a supercooled liquid at the reference temperature, and δ_s and δ_p for solubility parameters of solvent and polymer respectively. $(\delta E_s/\delta V)$ is the so-called 'internal pressure' of the solvent at the reference temperature. The authors proposed a determination of the solubility parameter of the solute by measurement in only two reference solutions, followed by calculation of the unknown V_2° and δ_p by means of a quadratic equation derived from equation (6). Unfortunately, the parameters required to solve equation (6) are not entirely reliable, e.g. solubility parameters of solvents depend on their origin (see Table 3) and literature values for internal pressures can differ by $> 10\%$ in special cases, depending on the method of determination [27, 3, 34, 35]. It is obvious that solution of the quadratic equation derived from equation (6) may result in serious errors under these conditions. Nevertheless, 21 pairs of solvents were evaluated by means of the calculation [26]. The results in Table 4 show clearly that the calculated solubility parameters δ_p

Table 3. Comparison of solubility parameters and internal pressures $[\delta E_s/\delta V]_T$ of the investigated solvents

Solvent	Density method	Viscosity method	Solubility parameter ^{a}	Solubility parameter ^{b}	Internal pressure (cal cm^{-3})^c
			(cal$^{0.5}$ cm$^{-1.5}$)		
Toluene	Yes	Yes	8.9	8.91	84.8
Ethyl acetate	Yes	Yes	9.1	9.1	84.5
Tetrahydrofuran	No	Yes	9.1	9.52	—
Benzene	No	Yes	9.2	9.15	90.5
Chloroform	Yes	No	9.3	9.21	86.6
Methylene chloride	Yes	Yes	9.7	9.93	89.6
1,4 Dioxane	Yes	Yes	10.0	10.00	119.3
Acetophenone	Yes	No	10.6	9.68	109.3
Acetonitrile	Yes	Yes	11.9	11.9	90.5

^{a} and ^{b} see note ^{a} in Table 1.
^{c}Data from Refs [26, 33–35].

depend upon δ_s of the solvent probes. The combination of solvents having high solubility parameters yielded a high value for the dissolved polymer and vice-versa. Further, in some cases irregular results are obvious. In Table 4, combinations with ethyl acetate showed a negative square root as the solution of equation (6), or a value below the range for normal organic compounds. This effect could be caused by a wrong literature value for the internal pressure. Apart from this series, the results scatter in the range between $\delta = 8.2$–12.7 cal$^{0.5}$ cm$^{-1.5}$. Similar observations were reported by the above mentioned authors in a later publication, referring to the 'chameleonic' behaviour of organic solutes [36]. This behaviour is defined by a virtual increase of the solubility parameter of a semi-polar solute as the result of increasing polarity and solubility parameter of the solvent. On the molecular level, that effect can partially be explained by self-association of the solute to dimers or more complex aggregates. These complexes expose the non-polar surface to non-polar solvents with a low solubility parameter, or in a polar environment expose a more polar surface towards the solvent. Different approaches have been proposed to overcome this difficulty, but a more exact estimate of δ using two solvents seems to be reliable only for highly non-polar compounds. One has to note that the more general aspect of the 1-dimensional Hildebrand parameter is better demonstrated by a mean curve resulting from a method involving a range of solvents, with a maximum solubility for the optimum δ value and the information for suitable solvents, showing decreasing solvation probability the larger becomes the difference $(\delta_s - \delta_p)^2$.

2. *Viscosity method*

The second experimental way to determine solubility parameters described in this paper needs measurement of the limiting viscosity numbers $[\eta]$ and is a typical range of solvents method. Usually, the $[\eta]$ values or swelling coefficients are arranged in the form of a gaussian shaped curve [22, 23].

$$[\eta] = [\eta]_{\max} \times \exp[-A \times (\delta_s - \delta_p)^2] \qquad (7)$$

The maximum $[\eta]_{\max}$ is attributed to the solvent with the highest solvation power and is expected when $\delta_s = \delta_p$. This maximum appears because of the maximal coil extension or hydrodynamic volume after solvation by the most effective solvent. No theoretically well-founded explanation was given for the fit to a gaussian equation. Other authors use an approximation to a quadratic equation in evaluating swelling measurements of polymers in a series of solvents [21]. Both evaluation methods were performed, resulting in $\delta_p = 10.0 \pm 0.2$ cal$^{0.5}$ cm$^{-1.5}$ using equation (7) (Fig. 2) and $\delta_p = 10.12 \pm 0.18$ cal$^{0.5}$ cm$^{-1.5}$ using the equation

$$[\eta] = [\eta]_{\max} - A'(\delta_s - \delta_p)^2. \qquad (8)$$

The standard deviation of both regression procedures was about the same. Based on the five solvents used also in the density measurements, the result of the viscosity method was $\delta_p = 9.9 \pm 0.3$ cal$^{0.5}$ cm$^{-1.5}$ for both fits.

3. *Comparison of results obtained by different methods*

When comparing the solubility parameter of poly(DL-lactic acid) obtained by the experimental procedures, one has to consider the slightly different temperatures of measurement. The temperature dependence of the enthalpy of mixing is small. It follows from the definition of the Hildebrand solubility parameter that it should decrease with increasing temperature. For non-polar substances, a temperature dependence of about $\Delta\delta/\Delta T = -0.015$ cal$^{0.5}$ cm$^{-1.5}$ K^{-1} was found [9]. The change of the solubility

Table 4. Influence of the selection of solvent combination on the resulting solubility parameter using equation [6]. Parameters used see Table 3

	Toluene	Ethyl acetate	Chloroform	Methylene chloride	Dioxane	Acetophenone	Acetonitrile
Toluene	X	—	—	—	—	—	—
Ethyl acetate	12.4	X	—	—	—	—	—
Chloroform	9.3	5.0	X	—	—	—	—
Methylene chloride	8.8	7.5	8.2	X	—	—	
Dioxane	9.0	i	8.6	9.9	X	—	—
Acetophenone	9.3	8.8	9.3	11.4	9.8	X	—
Acetonitrile	10.6	10.5	10.9	11.4	11.8	12.7	X

i = result is an imaginary number.

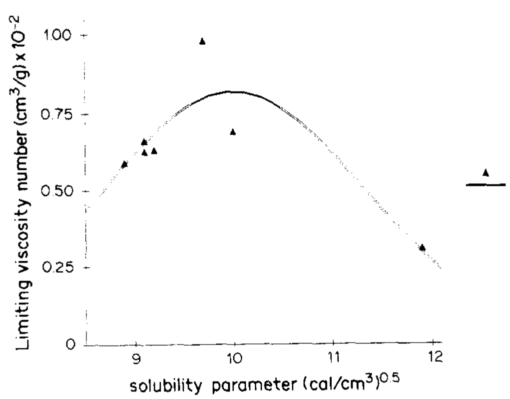

Fig. 2. Limiting viscosity number of poly(DL-lactic acid) in various solvents. Data were fitted to the equation $[\mu] = [\mu]_{\max} \times \exp[-A' \times (\delta_s - \delta_p)^2]$.

parameter for a temperature change of 5°C is supposed to be in the range of the experimental error for the substances and methods described.

There are different calculation methods for the estimation of solubility parameters starting from tabulated incremental values for the structural units of substances. To some extent, these methods need knowledge of the density of the compound [30]. The results of those methods together with the experimental values are summarized in Table 5. The influence of the choice of the δ-base for the solvents (see Table 3) was elucidated additionally. The results, using two different parameter sets, was shown to be not significantly different based on experimental determination with seven solvents. Generally, the calculated values tend to be lower than the experimental. The calculation method after Fedors seems to be not very suitable for polymeric compounds (Table 5).

In conclusion, the proposed new density method depending on the use of a range of solvents, the limiting viscosity number approach and the calculation of structural increments according to Hoy and Small gave comparable results for the solubility parameter of poly(DL-lactic acid). This value lies in the range of $\delta = 9.8\text{–}10.2\ \text{cal}^{0.5}\,\text{cm}^{-1.5}$ and is similar to those for polymers such as poly(ethyl acrylate) or ethylcellulose.

Table 5. Comparison of experimental and calculated solubility parameters for poly(DL-lactic acid) (density $1.27\ \text{g} \times \text{cm}^{-3}$)

	Solubility parameter
Determination method	($\text{cal}^{0.5} \times \text{cm}^{-1.5}$)
Density in solution[a]	10.25 ± 0.16
Density in solution[b]	10.29 ± 0.13
Limiting viscosity number[a]	10.0 ± 0.2
Limiting viscosity number[b]	10.05 ± 0.23
Increment methods	
Small[c]	9.7
Hoy[c]	9.9
Van Krevelen[d]	9.4
Fedors[e]	11.1

[a] Based on solubility parameters for solvents according to Ref. [30].

[b] Based on solubility parameters for solvents according to Hansen [10].

[c] Tabulated values from Ref. [30].

[d] Tabulated values from Ref. [9].

[e] Tabulated values from Ref. [20].

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