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A novel approach to the characterization of polar liquids Part 1: pure liquids

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Abstract

Liquid dosage forms, generally based on aqueous solutions, take an important role in drug administration. The approaches to a theoretical description of solvent and solubility properties have not yet proved completely satisfying. In this work, the Debye equation, which describes well polar and nonpolar molecules in an ideal gas, is extended to liquids. For this purpose, the Debye equation was modified and the term (E_i/E) was introduced (E_i = internal electric field, E = applied external electric field). Pure polar and nonpolar solvents were measured between 290.7 and 343.2 K. The values of (E_i/E) were compared with the correlation factor g of the Kirkwood–Fröhlich equation, a measure for molecular pair correlations. For polar solvents, the relationship $E_i/E = m(1/T) + b$ as a function of temperature T was found. Associating compounds showed negative values of (E_i/E) with a strong temperature dependency; the latter can be expressed by the slope m. A correlation between $|m|$ and the corresponding Hildebrand solubility parameter δ could be established. This new approach allows to describe polar hydrogen-bonding liquids and provides a tool for a more rational design of liquid dosage forms.

Keywords: Clausius–Mossotti equation; Debye equation; Dielectric permittivity; Modification of Clausius–Mossotti/Debye equation; Regular solutions; Solubility parameter

1. Introduction

In drug administration, liquid dosage forms play an important role, e.g. as oral solutions for children and elderly patients, ophthalmic formulations, injectible drug preparations, etc. It is evident that for physiological reasons aqueous solutions are the preferred dosage forms. Unfortunately, a large number of important drugs are only poorly soluble in water. Thus, the addition of cosolvents or surfactants is necessary to prepare an aqueous drug solution.

There have been many attempts to describe the properties of solvents and solvent mixtures, in order to develop liquid dosage forms more rationally and to obtain robust formulations. Most theories so far are based on the description of cohesive and adhesive forces between molecules, leading to the concept of regular solutions. Regu-

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lar binary solutions of liquids are described by the Hildebrand–Scatchard-equation (Eq. (1.1)) (Hildebrand and Scott, 1950). Accordingly, the solubility of liquid B in liquid A can be expressed as follows:

$$\ln X_B = -(\delta_A - \delta_B)^2 \frac{V_B \varphi_A^2}{RT} \tag{1.1}$$

where X_B, solubility of liquid B in liquid A, expressed as molar fraction; δ_A, solubility parameter of liquid A [(J m^{-3})$^{0.5}$; (MPa)$^{0.5}$] (1000 (J m^{-3})$^{0.5}$ = 1 (MPa)$^{0.5}$); V_B, molar volume (m^3 mol^{-1}) of liquid B at temperature T; ϕ_A, volume fraction of solvent A = $X_A V_A/(X_A V_A + X_B V_B)$: R, gas constant = 8.314 J mol^{-1} K^{-1}; T, temperature (K).

δ_A^2, δ_B^2 correspond to the volume specific cohesion energy expressed in J m^{-3} of the respective pure liquid:

$$\delta_A^2 = \frac{\Delta H_A - RT}{V_A}. \tag{1.2}$$

where ΔH_A is the molar vaporization enthalpy (J mol^{-1}) of liquid A at temperature T.

$\delta_A \delta_B$ can be related to the volume specific adhesion energy between unlike molecules A, B. If $\delta_A = \delta_B$, the liquids A, B show full miscibility and the regular solution becomes an ideal one. In practice, the regular solution theory works only well within the two classes of polar and nonpolar liquids according to the well-known rule of thumb 'like dissolves like'. Unlike solvents, i.e. polar and nonpolar liquids are in general not miscible.

Hansen (1967) extended empirically the concept of solubility parameters of individual pure liquids by introducing partial solubility parameters, considering volume specific cohesive energy contributions by nonpolar dispersion forces δ_d^2, by polar forces δ_p^2, and by hydrogen bonds δ_h^2.

The following relationship holds for an individual pure liquid A:

$$\delta_A^2 = \delta_{A_d}^2 + \delta_{A_p}^2 + \delta_{A_h}^2. \tag{1.3}$$

To describe the solubility of a solid substance in a liquid, Eq. (1.1) was later modified (Restaino and Martin, 1964), treating the solid as an undercooled melt.

These approaches did not prove satisfactory, especially for systems containing water with its high dielectric constant (ε = 78.4 at 298.2 K (Riddick and Bunger, 1970)). In addition, it has to be kept in mind that the solubility parameter δ is temperature dependent, not easily accessible through experiment for non-volatile compounds, and that the partial solubility parameters were determined empirically (Hansen and Beerbower, 1971).

The aim of this work is to extend the Debye equation, which describes well nonpolar and polar molecules in the ideal gas phase, to pure liquids. The results obtained by this new approach are compared with the Kirkwood–Fröhlich factor g, a measure for molecular pair correlations in polar liquids, and to the solubility parameter δ.

1.1. Theoretical background

Pure pharmaceutical solvents, for example water and ethanol, are dielectrics, i.e. insulating materials. When brought into an external electric field E, permanent dipoles are orientated and a small displacement of the electrons relative to the nuclei occurs; the electric field E polarizes the dielectric.

In static or low-frequency fields of moderate intensity the following linear relationship for the polarization P is valid (Alonso and Finn, 1992):

$$P = \chi_e \varepsilon_0 E = (\varepsilon - 1)\varepsilon_0 E. \tag{1.4}$$

where P is polarization, dipole density (C m^{-2}); χ_2 is electric susceptibility; ε_0 is electric field constant in vacuum = 8.854 × 10^{-12} (C^2 J^{-1} m^{-1}); ε is relative permittivity, dielectric constant; E is electric field (V m^{-1}).

In order to describe macroscopic properties, such as the polarization P and the relative permittivity ε, by molecular ones (e.g. dipole moment μ_g, polarizability α), the following equations have been developed.

1.1.1. The Onsager and Kirkwood–Fröhlich equations

The Onsager equation (Eq. (1.5)) (Onsager, 1936) is based on the model of a spherical cavity with radius a in a continuous dielectric with the dielectric constant ε. In the centre of the cavity is a point dipole.

$$\frac{(\varepsilon - n^2)(2\varepsilon + n^2)}{\varepsilon(n^2+2)^2} = \frac{N_A}{9\varepsilon_0 kT}\frac{\rho}{M_r}\mu_g^2 \tag{1.5}$$

where n is refractive index, usually measured at $\lambda = 589.3$ nm; N_A is Avogadro's number $= 6.023 \times 10^{23}$ (mol^{-1}); k is Boltzmann's constant $= 1.38 \times 10^{-23}$ (J K^{-1}); ρ, density; M_r, molecular weight; μ_g, dipole moment in the gas phase (C m).

The Onsager equation (Eq. (1.5)) is only valid if no strong short range interactions like hydrogen bonding and dipole–dipole correlations occur (Böttcher, 1973).

Short range interactions between dipoles are considered by the Kirkwood–Fröhlich (Eq. (1.6)), which was introduced by Kirkwood (Kirkwood, 1939) and further developed by Fröhlich (Fröhlich, 1958). It can be seen as a generalization of the Onsager equation, taking into account the correlation factor g to model short range forces.

$$\frac{(\varepsilon - \varepsilon_\infty)(2\varepsilon + \varepsilon_\infty)}{\varepsilon(\varepsilon_\infty+2)^2} = \frac{N_A}{9\varepsilon_0 kT}\frac{\rho}{M_r}\mu_g^2 g \tag{1.6}$$

where ε_∞ is dielectric constant characteristic for induced polarization, measured at a frequency low enough that both atomic and electronic polarization are the same as in the static field and high enough so that the permanent dipoles can no longer follow the field; g, correlation factor.

The correlation factor g is a measure of intermolecular correlations, considering one dipole surrounded by its z next neighbours:

$$g = 1 + z\langle \cos \phi_{ij} \rangle \tag{1.7}$$

$\langle \cos \phi_{ij} \rangle$ is average of the cosine of the angle between the two neighbouring molecules i and j.

So we find for a parallel alignment of molecules, i.e. $\langle \cos \phi_{ij} \rangle = 1$, $g > 1$, and for an antiparallel alignment, i.e. $\langle \cos \phi_{ij} \rangle = -1$, $g < 1$.

Values for ε_∞ are not easily obtained experimentally with high frequency electric fields. Thus, ε_∞ is in general replaced by the square of the refractive index n, making use of the Maxwell relation (Maxwell, 1892):

$$\varepsilon = n^2 \tag{1.8}$$

The Kirkwood–Fröhlich (Eq. (1.6)) is only valid for polar molecules. The value of g is ambiguous, as $g = 1$ stands either for disorder or equal amounts of parallel and antiparallel aligned molecules outweighing each other. For associating compounds, the usage of n_D^2 instead of ε_∞ is problematic, as e.g. for water at 293 K: $n_D^2 = 1.7$ and $\varepsilon_\infty \approx 4.5$ (Craig, 1995).

1.1.2. The Clausius–Mossotti and Debye equations

The Clausius–Mossotti relation (Eq. (1.14)) for nonpolar molecules is based on the so-called Lorentz approach. It considers a single molecule at the center of a virtual cavity with the shape of a homogeneously polarized sphere. The molecules surrounding the sphere are treated as a continuum with the macroscopic properties of the dielectric (Lorentz, 1909). The field E_{local} acting on the molecule is

$$E_{\text{local}} = E_i + E - E_{\text{sph}} \tag{1.9}$$

where E_i, internal electric field, caused by interactions with other induced dipoles in the sphere; E, external electric field, produced by the applied voltage; E_{sph}, electric field caused by the induced dipoles outside the sphere, leading to charges on the surface of the sphere.

In an ideal gas, E_{sph} and E_i are zero. In liquids, neighbouring molecules show a polarising effect leading to charges on the sphere's surface, resulting in

$$E_{\text{sph}} = -\frac{P}{3\varepsilon_0} \tag{1.10}$$

By combining Eqs. (1.9) and (1.10), and substituting $(\varepsilon - 1)\varepsilon_0 E$ for P (see Eq. (1.4)), we obtain for the local field E_{local} in nonpolar compounds the expression

$$E_{\text{local}} = E_L = \frac{\varepsilon + 2}{3}E, \tag{1.11}$$

where, E_L = Lorentz field under the condition that $E_i \approx 0$. This is the case for gas, for liquids with randomly distributed molecules and for an isotropic material which does not exhibit a preferred axis (e.g. for a cubic crystal). The value for E_i can be different from zero in the case of those liquids, which do not show random distribution of molecules but possess a crystal-like order with a preferred axis. Thus, it can be imagined that clusters of water have an internal field $E_i \neq 0$.

According to Clausius (Clausius, 1879) and Mossotti (Mossotti, 1847) we obtain for nonpolar molecules of constant polarizability

$$P = \kappa\mu_i = \kappa\alpha E_L \tag{1.12}$$

$$P_M = \frac{N_A\rho}{M_r}\mu_i = \frac{N_A\rho}{M_r}\alpha E_L \tag{1.13}$$

where P, polarization, dipole density (C m^{-2}); κ, molecules per volume; μ_I, induced dipole moment; α, polarizability (C m^2 V^{-1}); P_M, molar polarization (C mol^{-1})

Combining Eqs. (1.4) and (1.12), and replacing E_L with Eq. (1.11) we obtain the Clausius–Mossotti equation for nonpolar molecules

$$\frac{\varepsilon-1}{\varepsilon+2} = \frac{\kappa}{3\varepsilon_0}\alpha \tag{1.14}$$

or, by combining Eq. (1.4) with Eq. (1.13) instead of Eq. (1.12)

$$\frac{\varepsilon-1}{\varepsilon+2}\frac{M_r}{\rho} = \frac{N_A}{3\varepsilon_0}\alpha \tag{1.15}$$

The Clausius–Mossotti equation was extended to polar molecules by Debye (1912):

$$\frac{\varepsilon-1}{\varepsilon+2}\frac{M_r}{\rho} = \frac{N_A}{3\varepsilon_0}\left(\alpha + \frac{\mu_g^2}{3kT}\right) \tag{1.16}$$

The Debye equation (Eq. (1.16)) is only valid for gas under low pressure and highly diluted solutions of polar molecules in nonpolar solvents, where dipole–dipole interactions can be neglected.

An excellent survey of the theoretical background outlined in Section 1.1 can be found in the book of Böttcher (1973).

1.2. The modified Debye equation according to Leuenberger

In order to apply the Debye equation, which describes well polar molecules in the gas phase, to the liquid state, we will reintroduce the internal electric field E_i (see Eq. (1.9)).

Replacing E_{sph} in Eq. (1.9) with Eq. (1.10) and introducing the resulting expression for E_L into Eq. (1.12), dividing it by E, we obtain

$$\frac{P}{E} = \kappa\alpha\left[\frac{E_i}{E} + 1 + \frac{P}{E}\frac{1}{3\varepsilon_0}\right] \tag{1.17}$$

Eq. (1.4) is divided by E and the resulting equation is substituted for (P/E) in Eq. (1.17). Multiplication by 3 and rearrangement leads to

$$\frac{\varepsilon-1}{3E_i/E + (\varepsilon+2)} = \frac{\kappa}{3\varepsilon_0}\alpha \tag{1.18}$$

In the case of $(E_i/E) = 0$, Eq. (1.18) is reduced to the Clausius–Mossotti equation (Eq. (1.14)).

Extending Eq. (1.18) to molecules with a permanent dipole (see Eq. (1.16)), the modified Debye equation according to Leuenberger (Eq. (1.19)) results:

$$\frac{\varepsilon-1}{3E_i/E + (\varepsilon+2)}\frac{M_r}{\rho} = \frac{N_A}{3\varepsilon_0}\left(\alpha + \frac{\mu_g^2}{3kT}\right) \tag{1.19}$$

The term (E_i/E) will be used in the following for the description of molecular interactions in pure solvents. It has to be mentioned that it is not necessary to know the exact value of the external field E, as (E_i/E) can be determined directly. It will be compared with the corresponding values of the Kirkwood–Fröhlich factor g (see Section 1.1.1) and of the solubility parameter δ.

2. Materials and methods

2.1. Solvents

The following pure solvents were studied in the temperature range of 290.7–343.2 K:

- water;
- ethanol, 1-propanol, 1,2-propanediol, and glycerol, being polar, hydrogen-bonding compounds completely miscible with water;
- benzylalcohol, a polar and hydrogen-bonding substance only partially miscible with water;
- chlorobenzene, a polar substance, not miscible with water;
- 1,4-dioxane, symmetric and, therefore, nonpolar, fully miscible with water, due to the capacity of forming hydrogen bonds;

- benzene, a nonpolar solvent, not miscible with water.

Bidistilled water was freshly prepared by means of a Fontavapor 285 (Büchi AG CH-Flawil). The organic solvents of high purity were acquired commercially from Fluka Chemie GmbH CH-Buchs [chlorobenzene (art. no. 235070), 1,4-dioxane (art. no. 42512), 1,2-propanol (art. no. 82090), 1,2-propanediol (art. no. 82280), glycerol (art. no. 49770)] and Siegfried AG CH-Zofingen [benzene (art. no. 113520), benzylalcohol (art. no. 104505), ethanol (art. no. 214100)].

Physical properties of the solvents studied are presented in Table 1.

2.2. Experimental setup

For dielectric measurements the liquids were brought into a double-walled cylinder condensator connected to a precision LCR meter (HP 4284A, Agilent Technologies Inc. USA-Palo Alto, CA) by means of a test fixture (HP 16047C). The measurements were made at 100 kHz with a voltage of 1.00 V. The temperature was kept at the required value (± 0.1 K) with a thermostat (Thermomix UB and Frigomix U-1, B. Braun Biotech International GmbH D-Melsungen).

Density measurements were made using a vibrating-tube densimeter (DMA 58, Anton Paar AG A-Graz) (± 0.01 K). Refractive indices n_D were measured by means of a Abbé refractometer (AR8, A. Krüss Optronic GmbH D-Hamburg) (± 0.1 K).

The dipole moments μ_g used for calculations are literature values for the gas phase (CRC Handbook of Chemistry and Physics, 1997). For nonvolatile compounds, they can also be determined by measuring highly diluted solutions in nonpolar solvents (Hedestrand, 1929).

2.3. Calculations

2.3.1. Calculation of correlation factor g of the Kirkwood–Fröhlich equation

In case of polar compounds, the values of g were calculated according to Eq. (1.6). For nonpolar compounds, the Kirkwood–Fröhlich equation cannot be used as g diverges for $\mu_g = 0$.

For ε_∞, the dielectric constant characteristic for induced polarization, the square of the refractive index at $\lambda = 589.3$ nm was used (see Eq. (1.8)).

2.3.2. Calculation of (E_i/E) of the modified Debye equation according to Leuenberger (E_i/E) was calculated according to Eq. (1.19).

As the external electric field E varies in a cylinder condensator as a function of the radius r (Frauenfelder and Huber, 1967), it does not make sense to calculate E and to estimate E_i.

The values for the polarizability α were calculated using the Lorentz–Lorenz equation (Lorentz, 1880; Lorenz, 1880)

Table 1
Physical properties of the solvents studied at $T = 298.2$ K (Riddick and Bunger, 1970; Barton, 1991; CRC Handbook of Chemistry and Physics, 1997)

Solvent	μ_g (C m)	Solubility parameter $[(\mathrm{J\ m^{-3}})^{0.5}]$				ρ (kg m^{-3})	Miscibility with water
		δ	δ_d	δ_p	δ_h		
Benzene	0.00×10^{-30}	18.6×10^3	18.4×10^3	0.0×10^3	2.0×10^3	0.874×10^3	Not misc.
Benzylalcohol	5.70×10^{-30}	23.8×10^3	18.4×10^3	6.3×10^3	13.7×10^3	1.041×10^3	Partially misc.
Chlorobenzene	5.64×10^{-30}	19.6×10^3	19.0×10^3	4.3×10^3	2.0×10^3	1.106×10^3	Not misc.
1,4-dioxane	0.00×10^{-30}	20.5×10^3	19.0×10^3	1.8×10^3	7.4×10^3	1.028×10^3	Fully misc.
Ethanol	5.64×10^{-30}	26.5×10^3	15.8×10^3	8.8×10^3	19.4×10^3	0.785×10^3	Fully misc.
Glycerol	8.67×10^{-30}	36.1×10^3	17.4×10^3	12.1×10^3	29.3×10^3	1.261×10^3 at 293.2 K	Fully misc.
1,2-propanediol	7.34×10^{-30}	30.2×10^3	16.8×10^3	9.4×10^3	23.3×10^3	1.033×10^3	Fully misc.
1-propanol	5.60×10^{-30}	24.5×10^3	16.0×10^3	6.8×10^3	17.4×10^3	0.800×10^3	Fully misc.
Water	6.17×10^{-30}	47.8×10^3	15.6×10^3	16.0×10^3	42.3×10^3	0.997×10^3	–

Table 2
The values of the correlation factor g of the Kirkwood–Fröhlich (Eq. (1.6)) and of (E_i/E) of the modified Debye equation according to Leuenberger (Eq. (1.19)) for pure solvents

Solvent		Temperature (K)							
		290.7	298.2	305.7	313.2	320.7	328.2	335.7	343.2
Benzene	(E_i/E)	−0.03	−0.04	−0.05	−0.06	−0.05	−0.05	−0.08	−0.08
	g	–	–	–	–	–	–	–	–
Benzylalcohol	(E_i/E)	−0.64	−0.57	−0.50	−0.45	−0.41	−0.37	−0.34	−0.31
	g	2.23	2.15	2.07	1.99	1.91	1.83	1.75	1.69
Chlorobenzene	(E_i/E)	−0.84	−0.81	−0.77	−0.74	−0.71	−0.68	−0.65	−0.65
	g	0.77	0.76	0.76	0.75	0.75	0.74	0.74	0.73
1,4-dioxane	(E_i/E)	0.17	0.17	0.17	0.17	0.17	0.17	0.18	0.18
	g	–	–	–	–	–	–	–	–
Ethanol	(E_i/E)	−2.73	−2.45	−2.20	−1.96	−1.73	−1.54	−1.36	−1.20
	g	3.27	3.20	3.13	3.06	2.92	2.82	2.71	2.58
Glycerol	(E_i/E)	−8.96	−8.55	−8.13	−7.64	−7.20	−6.80	−6.40	−6.07
	g	2.56	2.55	2.54	2.49	2.45	2.41	2.36	2.33
1,2-propanediol	(E_i/E)	−4.82	−4.50	−4.18	−3.87	−3.65	−3.35	−3.11	−2.89
	g	2.56	2.53	2.48	2.42	2.42	2.32	2.28	2.23
1-propanol	(E_i/E)	−1.26	−1.08	−0.91	−0.76	−0.63	−0.51	−0.41	−0.34
	g	3.40	3.32	3.23	3.14	3.04	2.93	2.82	2.69
Water	(E_i/E)	−21.62	−20.66	−19.68	−18.61	−17.80	−16.84	−16.00	−15.32
	g	2.87	2.83	2.79	2.73	2.70	2.64	2.59	2.56

Note that g can only be calculated for polar compounds, non-applicability of Eq. (1.6) Indicated by a dash (–).

$$\frac{n^2-1}{n^2+2}\,\frac{M_r}{\rho}=\frac{N_A}{3\varepsilon_0}\alpha \tag{2.1}$$

which gave excellent results compared with literature data (Riddick and Bunger, 1970) both for polar and nonpolar compounds.

3. Results

3.1. Calculation of *g*-values according to the Kirkwood–Fröhlich equation

The results for the temperature range 290.7–343.2 *K* are reported in Table 2 and Fig. 1.

For the solvents studied the following groups can be distinguished according to their g values:

- g not calculable [Eq. (1.6) not applicable for nonpolar solvents (benzene; 1,4-dioxane)];
- $g < 1$, independent of temperature (chlorobenzene);
- $g > 1$, temperature dependent (glycerol, 1,2-propanediol, water);
- $g > 1$, strongly temperature dependent (benzylalcohol, ethanol, 1-propanol).

3.2. Calculation of (E_i/E)-values according to the modified Debye equation

The results for the examined temperature interval of 290.7–343.2 *K* are presented in Table 2.

The following four groups of solvents can be distinguished according to their (E_i/E) values:

- strongly temperature dependent, highly negative (water, ethanol, 1-propanol, 1,2-propanediol, glycerol);
- temperature dependent, negative (chlorobenzene, benzylalcohol);
- independent of temperature, $(E_i/E)\approx 0$ (benzene);
- independent of temperature, (E_i/E) slightly positive (1,4-dioxane).

The linear relationship

$$\frac{E_i}{E}=m\frac{1}{T}+b \tag{3.1}$$

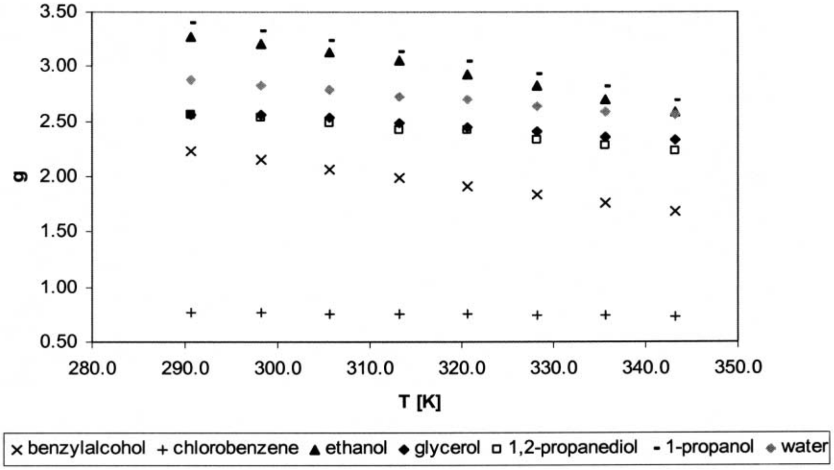

Fig. 1. The correlation factor g of the Kirkwood–Fröhlich equation of pure polar liquids in the temperature range of 290.7–343.2 K.

can be found for the investigated temperature range, the values for the slope m, the constant b, and the squared correlation coefficient R^2 are reported in Table 3.

3.3. Comparison of results: modified Debye model and Kirkwood–Fröhlich approach

No algebraic connection between the modified Debye equation according to Leuenberger (Eq. (1.19)) and the Kirkwood–Fröhlich equation (Eq. (1.6)) can be made, as they are based on different assumptions concerning the examined microstructure of the liquid. Thus, for $T = 298.2$ K, (E_i/E) was plotted against g in order to explore if an empirical relation could be found (Fig. 2).

3.4. Comparison of results: modified Debye model and solubility parameter

For the examined pure solvents, an empirical linear relationship between the absolute values of the slopes m of $(E_i/E)f(1/T)$ (see Eq. (3.1)) and the corresponding values of ε at 298.2 K could be found:

$$|m| = 158\varepsilon - 837, \ R^2 = 0.985 \tag{3.2}$$

Paruta et al. (1962) established an empirical equation

$$\delta = 0.45\varepsilon + 15.3 \tag{3.3}$$

which links the solubility parameter δ (MPa$^{0.5}$) with the relative permittivity ε. Thus, it is possible to establish as well an empirical equation between δ and $|m|$ (see Fig. 3):

$$\delta = 2.4|m| + 20\ 348; \ R^2 = 0.971 \tag{3.4}$$

Table 3
The linear regression of (E_i/E) versus $(1/T)$ (see Table 2)

Solvent	$(E_i/E) = m(1/T) + b$; squared correlation coefficient R^2		
	m	b	R^2
Benzene	85.2	−0.33	0.783
Benzylalcohol	−620.4	1.52	0.985
Chlorobenzene	−386.6	0.49	0.988
1,4-dioxane	−19.0	0.23	0.759
Ethanol	−2918.9	7.34	0.998
Glycerol	−5606.7	10.28	0.999
1,2-propanediol	−3670.9	7.82	0.999
1-propanol	−1770.5	4.87	0.993
Water	−121 73.86	20.21	0.999

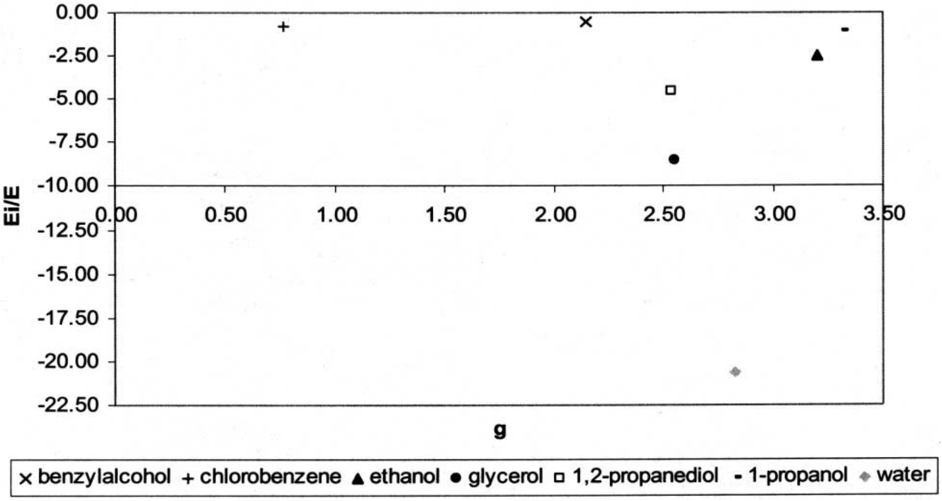

Fig. 2. The comparison of (E_i/E) of the modified Debye equation according to Leuenberger with the correlation factor g of the Kirkwood–Fröhlich equation ($T = 298.2$ K).

4. Discussion

4.1. Calculation of g-values according to the Kirkwood–Fröhlich equation

All examined liquids except chlorobenzene show a g value > 1, which means a parallel alignment of the molecules is favoured, and a marked temperature dependence of g, with raising temperature the value of g decreases, i.e. the high order of a structured liquid is broken up.

The investigated solvents can be divided into the following groups:

- Chlorobenzene ($\mu_g = 5.64 \times 10^{-30}$ C m), showing an antiparallel arrangement with a practically temperature independent g-value < 1 ($g_{298.2\ K} = 0.76$; $\Delta g_{290.7-343.2\ K} = 0.04$). Chlorobenzene is not able to form hydrogen bonds and is not miscible with water.
- Benzylalcohol ($\mu_g = 5.70 \times 10^{-30}$ C m), a benzene ring being a prominent part of its structure in analogy to chlorobenzene, but showing a distinct parallel alignment ($g_{298.2\ K} = 2.15$). With the rise of the temperature, g is reduced and the parallel alignment becomes less pronounced ($\Delta g_{290.7-343.2\ K} = 0.54$).Benzylalcohol can form hydrogen bonds and is partially miscible with water.
- Glycerol and 1,2-propanediol ($\mu_g = 8.67 \times 10^{-30}$ and 7.34×10^{-30} C m, respectively) show both a more distinct parallel alignment than benzylalcohol ($g_{298.2\ K} = 2.55$ and 2.53, respectively). However, the parallel arrangement is less sensitive to a temperature increase ($\Delta g_{290.7-343.2K} = 0.23$ and 0.33, respectively). This effect may be due to stronger dipole–dipole interaction compared with benzylalcohol.Water ($\mu_g = 6.17 \times 10^{-30}$ C m) shows slightly higher values for g ($g_{298.2\ K} = 2.83$) with a similar temperature sensitivity ($\Delta g_{290.7-343.2K} = 0.31$) compared with the investigated polyols.These solvents build three-dimensional networks through the formation of hydrogen bonds, probably favouring neither a strongly parallel nor antiparallel alignment due to the fully flexible hydroxy groups. The application of an external electric field E induces a certain parallel or antiparallel alignment in the direction of the applied field.All three solvents are able to form hydrogen bonds and glycerol and 1,2-propanediol are fully miscible with water.
- 1-propanol ($\mu_g = 5.60 \times 10^{-30}$ C m) and ethanol ($\mu_g = 5.64 \times 10^{-30}$ C m) show the highest g-values ($g_{298.2\ K} = 3.32$ and 3.20, respectively) with an important temperature dependency ($\Delta g_{290.7-343.2\ K} = 0.71$ and 0.69, respectively).

Both solvents show a stronger parallel alignment than the earlier solvents, this can be due to the linear structure of the molecules. 1-propanol shows a slightly higher value for *g* than ethanol (3.40 and 3.27, respectively). This could be caused by the longer nonpolar group of 1-propanol favouring a parallel alignment, as this allows both a separate grouping of nonpolar and polar structures and a dense packing.Both solvents are able to form hydrogen bonds and are fully miscible with water.

It is interesting to compare chlorobenzene with benzylalcohol, both molecules having similar dipole moments in the gas phase ($\mu_g = 5.64 \times 10^{-30}$ and 5.70×10^{-30} C m, respectively). They possess a similar structure: a voluminous nonpolar benzene ring to which a strongly electronegative atom is attached, either solely or as a part of an atom group; this leads to a polarisation of the molecule. Contrary to benzylalcohol, chlorobenzene does not form hydrogen bonds. The rigidity and the electronegative properties of chlorobenzene (a bulky, positive polarized benzene group with a negative polarized chloride atom attached to it) can be assumed to be the reason for the favouring of an antiparallel alignment of molecules. For the—due to the CH_2-group—flexible benzylalcohol, the hydrogen bonding capacity allows for parallel and antiparallel alignment in an alternate order of positive and negative charged atoms. Parallel alignment may be favoured because it should allow a denser packing. The reason for no marked temperature dependence of the *g*-values of chlorobenzene (see Fig. 1) could lie in the fact that through its electronegative and steric properties and due to its rigidity there are not many possible favourable arrangements, so a temperature rise leads primarily to an expansion of the liquid which may even facilitate antiparallel alignment. It can be concluded that there is a strong dipole–dipole interaction keeping the antiparallel alignment, which does not seem to be broken up by the rise of the temperature. However, it has to be kept in mind that the *g*-values are close to 1, the antiparallel alignment, therefore, not being very distinct.

4.2. Calculation of (E_i/E)-values according to the modified Debye equation

For the examined temperature range good correlations of (E_i/E) with ($1/T$) were obtained for all polar compounds, with squared correlation coefficients $R^2 \geq 0.985$. For the nonpolar benzene and 1,4-dioxane, the correlations are not as good, with values of $R^2 = 0.783$ and 0.759, respectively. This

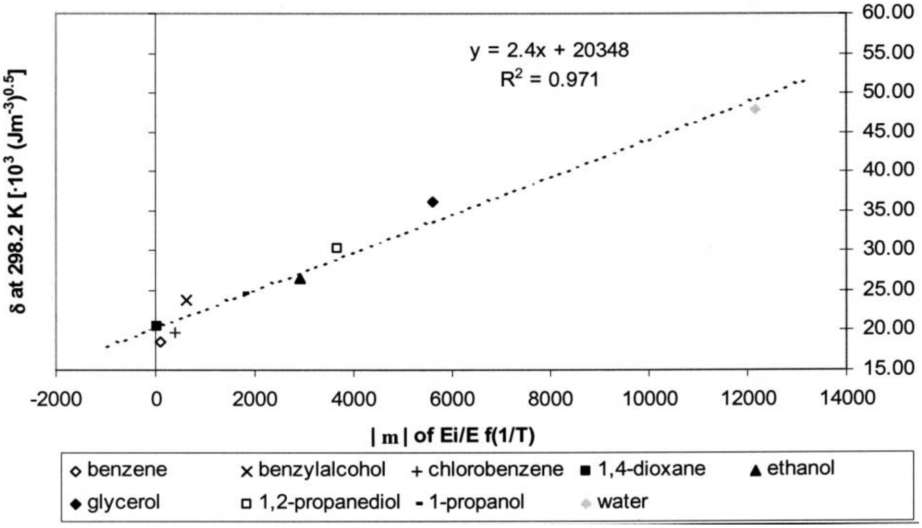

Fig. 3. A linear relationship can be established between the solubility parameter and the absolute value for the slope *m* of (E_i/E)$f(1/T)$.

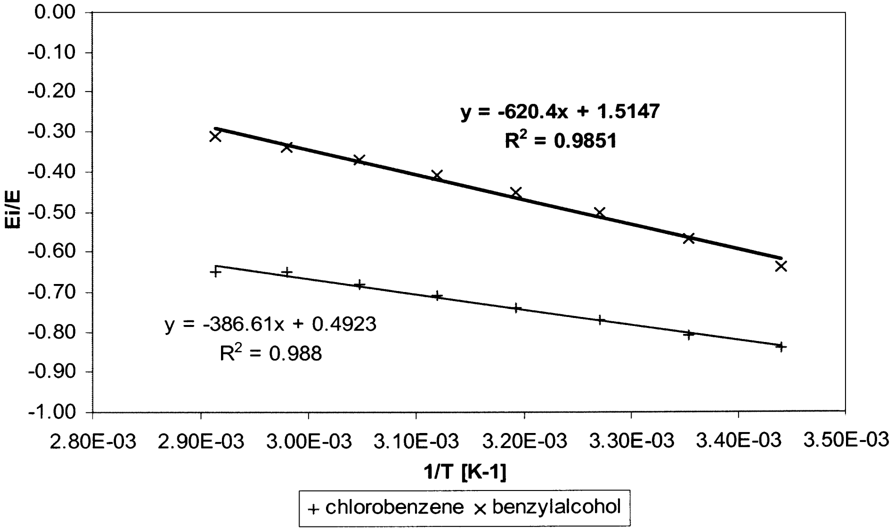

Fig. 4. (E_i/E)-values of chlorobenzene and benzylalcohol versus the reciprocal temperature. Both compounds have a very similar structure and dipole moment (see Table 1).

can be explained by the fact that the direction of dipoles in the electric field, dipole–dipole interactions and hydrogen bonds are strongly temperature dependent, contrary to molecular interactions of nonpolar molecules, which show only slight dependence on temperature, due to the induced dipole moments (Böttcher, 1973). Therefore, (E_i/E) can be seen as a sensitive parameter for dipole–dipole interactions and hydrogen bonds, those intermolecular forces, which are of particular interest as regards the description of the polar pharmaceutical solvents.

Comparing chlorobenzene and benzylalcohol, both molecules possessing similar dipole moments and structures (see Section 4.1), the sensitivity of (E_i/E)-values of benzylalcohol towards change in temperature is nearly a factor 2 higher than that of chlorobenzene (see Table 3 and Fig. 4). This can be explained by the fact that hydrogen bonds, which are formed by benzylalcohol, are more influenced by a temperature increase than the dipole–dipole interactions of benzylalcohol and chlorobenzene. For the investigated temperature range, the (E_i/E)-values of chlorobenzene are found to be larger than those of benzylalcohol, suggesting stronger close interaction forces. These, at first look somewhat surprising findings, may be explained by hydrogen bonds in benzylalcohol being partially broken at $T = 290.7–343.2$ K.

It is interesting to compare the values of chlorobenzene and ethanol, molecules possessing very different structures but the same dipole moment in the gas phase ($\mu_g = 5.64 \times 10^{-30}$). In the case of chlorobenzene, a polar substance which is not miscible with water, (E_i/E) is only slightly negative showing a relatively weak temperature dependence, while ethanol, which is polar and shows hydrogen-bonding, has strongly negative values which are highly temperature-dependent (Fig. 5). The relatively low (E_i/E)-values measured (e.g. -0.81 at $T = 298.2$ K) support also the antiparallel alignment of the molecules found through the values for g (see Section 4.1). Due to the antiparallel alignment the superposition of counteracting dipole fields leads only to a weak residual internal field E_i. This resulting internal field E_i is a factor 20 higher than the electric field E_i in the case of the nonpolar benzene (see Table 2).

The fact that chlorobenzene and ethanol can be so clearly distinguished by their (E_i/E)-values, leads to the conclusion that the modified Debye equation according to Leuenberger is a powerful tool for the description of polar interactions in liquids.

4.3. Comparison of results: modified Debye model and Kirkwood–Fröhlich approach

No correlation was found between (E_i/E) and g (Fig. 2). This can be explained by (E_i/E) and g describing two different properties of a liquid system: (E_i/E) appears to be a parameter for the extent of close range molecular polar and hydrogen-bond interactions and g describes the arrangement of molecules, the preference for either parallel or nonparallel alignment.

4.4. Comparison of results: modified Debye model and solubility parameter at 298.2 K

The fact that a correlation can be established between the solubility parameter δ and the slope $|m|$ of Eq. (3.2) means that the solubility parameter δ can be determined by using Eq. (3.4). This has the advantage that $|m|$ is more accessible through experiments, especially for non-volatile compounds (e.g. polymers).

However, one has to be cautious with empirical linear relationships such as $\delta(\varepsilon)$ and $\delta(|m|)$ (see Eqs. (3.3) and (3.4)). The following critical remark needs to be made: the slope m is a temperature independent value, while δ clearly is dependent on temperature. The quantitative description of $\delta(T)$ for pure liquids though has not been very successful yet, especially for hydrogen bonding liquids (Hansen and Beerbower 1971; Barton, 1991).

4.5. Conclusions

The examinations showed that the modified Debye equation according to Leuenberger, which describes both polar, hydrogen bonding molecules and nonpolar compounds in the gaseous and liquid state, could prove a useful tool to describe intermolecular forces, especially in polar, hydrogen bonding liquids.

The slope $|m|$ of the linear regression of (E_i/E) versus ($1/T$) can be correlated with the solubility parameter δ. Thus, it is possible to calculate in a consistent way δ of polar liquids with hydrogen bonding capacity.

It was also shown that no correlations exist between (E_i/E) and the correlation factor g of the Kirkwood-Fröhlich equation. Both describe different properties of the liquid: (E_i/E) can be seen as a measure for close range molecular interactions, which are dominated by the contributions of the strong hydrogen bonds. On the other hand,

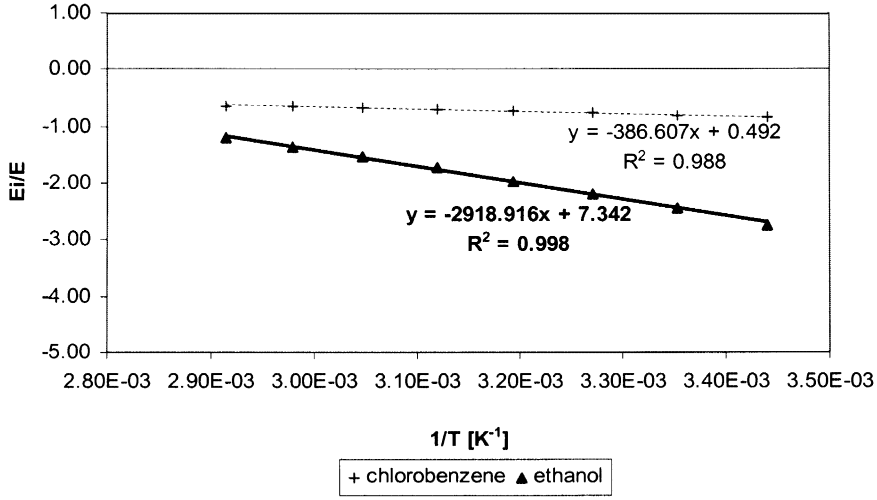

Fig. 5. (E_i/E)-values of chlorobenzene and ethanol versus the reciprocal temperature. The dipole moment in the gas phase of both compounds is $\mu_g = 5.64 \times 10^{-30}$ C m.

g describes the molecules' preference for either parallel or nonparallel alignment, which allows some interpretation concerning the degree of order in the liquid.

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