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Solvation of polymers as model for solvent effect investigation: proposition of a novel polarity scale[☆]

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Abstract—A precise understanding of the polymer solvation effect has been considered crucial to many modern methods, but its dependence on the polarity of the medium is still not entirely established. To more thoroughly address this issue, the swelling degrees of polymers with a great variety of structures, taken as solute-models, were measured and correlated with the polarity of ca. 30 solvent systems. Relevant for any resin-supported methods, a characteristic solvation behavior of each class of polymeric material was detected. Moreover by interpreting the relationship between the large set of solute–solvent interaction data and the most solvent properties known so far, the sum of solvent electron acceptor (AN) and donor (DN) numbers, at a 1:1 proportion was suggested as an alternative and more accurate empirical solvent polarity scale. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Although initial reports dealing with the influence of solvent in a determined interaction with solute molecules have been documented since the XIX century,[1] the acceptance of a single solvent polarity scale as the most appropriate for interpreting any solvent effect has not been achieved yet. Although the exact definition of solvent polarity is still elusive, it seems reasonable to consider that this property is related to the overall solvation capability of solvent, encompassing all possible nonspecific and specific intermolecular interactions with solute ions or molecules.[2] For decades, a great amount of experiments has allowed the proposition of some empirical polarity scales, most of them derived from experiments where single solute-models are used to probe (spectrophotometrically, thermodinamically, kinetically, etc) the interaction with solvents of different polarities. A collection of excellent reviews is available regarding the solvent effect and polarity issues.[2,3]

Differing conceptually from all those previous experiments, we have initiated[4] an alternative solvent effect investigation, studying not only a single solute-molecule but instead, a set of cross-linked polymers with a great variety of characteristics. In this approach the solvation properties of these polymers, estimated by the swelling measurements of beads in solvents with different polarities, are correlated with various existing solvent polarity scales. Experimentally, this relationship is examined in a contour solvation curve where swelling degree versus solvent polarity values are plotted. The most accurate polarity parameter will be that one which reveals the best fit (less dispersion) in this curve regardless of the type of resin.

The swelling degrees of some model resins attaching peptide sequences in ca. 30 solvent systems which encompass broadly the polarity scale have been previously determined[4] through microscopic measurement of dry and swollen bead sizes. As the solvation of peptide-resin might be influenced by the electrophilic and nucleophilic moieties of a peptide bond, namely N–H and C=O groups, respectively, we also attempted in that study, the correlation of peptide-resin solvation with the simple sum of both Gutmann's acidic, electrophilic (AN) and basic, nucleophilic (DN) numbers[5] of each solvent. The AN number represents the dimensionless number expressing the acceptor property of a given solvent and is based on the solvent-dependent ^{31}P NMR chemical shifts of

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[☆] See ref. 44.

Keywords: polymer; resin; polarity; peptide; solvent.

Abbreviations: BHAR, benzhydrylamine-resin; Boc, *tert*-butyloxycarbonyl; Bu, *tert*-butyl; Bzl, benzyl; CD, circular dichroism; DCM, dichloromethane; DIEA, diisopropylethylamine; DMF, *N*,*N*′-dimethylformamide; DMSO, dimethylsulfoxide; EPR, electron paramagnetic resonance; EtOH, ethanol; HOBt, 1-hydroxybenzotriazole; Fmoc, 9-fluorenylmethyloxycarbonyl; HPLC, high-performance liquid chromatography; IR, infrared; MeOH, methanol; NMP, *N*-methylpiperidinone; NMR, nuclear magnetic resonance; PEG, poly(ethylene glycol); PS–DVB, copolymer of styrene and divinylbenzene; TBTU, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; TEA, triethylamine; TFA, trifluoroacetic acid; TFE, trifluoroethanol; TOAC, 2,2,6,6-tetramethypiperidine-*N*-oxyl-4-amino-4-carboxylic acid.

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Table 1. Solvent parameters[2,5,10,23]

Entry	Solvent	(AN+DN)	ε	$E_T(30)$ (kcal/mol)w	δ (cal/mL)$^{1/2}$	π^*	α	β	$(\alpha+\beta)$	$(\pi^*+\alpha+\beta)$
1	Toluene	3.4	2.4	33.0	8.90	0.54	0.00	0.11	0.11	0.65
2	DCM	21.4	8.9	40.7	9.70	0.82	0.13	0.10	0.23	1.05
3	Chloroform	27.1	4.7	39.1	9.30	0.58	0.20	0.10	0.30	0.88
4	NMP	40.6	33.0	42.2	11.30	0.92	0.00	0.77	0.77	1.69
5	DMF	42.6	36.7	43.8	12.10	0.88	0.00	0.69	0.69	1.57
6	DMSO	49.1	46.7	45.1	12.00	1.00	0.00	0.76	0.76	1.76
7	TFE	53.5	26.7	54.1	11.90	0.73	1.51	0.00	1.51	2.24
8	EtOH	69.1	24.3	51.9	12.70	0.54	0.86	0.75	1.61	2.15
9	MeOH	71.3	32.6	55.4	14.50	0.60	0.98	0.66	1.64	2.24
10	Formamide	63.8	109.5	55.8	19.20	0.97	0.71	0.48	1.19	2.16
11	50% TFE/Toluene	28.5	14.6	43.6	10.40	0.63	0.78	0.06	0.84	1.47
12	20% TFE/DCM	27.5	12.5	43.4	10.10	0.80	0.41	0.08	0.49	1.29
13	50% TFE/DCM	37.5	17.8	47.4	10.80	0.78	0.82	0.05	0.87	1.65
14	80% TFE/DCM	47.4	23.1	51.4	11.50	0.75	1.23	0.02	1.25	2.00
15	20% DMSO/NMP	42.3	35.7	42.8	11.40	0.94	0.00	0.77	0.77	1.71
16	50% DMSO/THF	38.6	27.1	41.3	10.60	0.79	0.00	0.66	0.66	1.45
17	65% NMP/THF	36.1	24.1	40.5	10.50	0.80	0.00	0.69	0.69	1.49
18	50% DCM/DMF	32.0	22.8	42.3	10.90	0.85	0.07	0.40	0.47	1.32
19	50% DCM/DMSO	35.3	27.8	42.9	10.90	0.91	0.07	0.43	0.50	1.41
20	50% MeOH/DMSO	60.2	39.7	50.3	13.30	0.80	0.49	0.71	1.20	2.00
21	50% TFE/DMF	48.1	31.7	49.0	12.00	0.80	0.76	0.35	1.11	1.91
22	50% TFE/DMSO	51.3	36.7	49.6	12.00	0.87	0.76	0.38	1.14	2.01
23	10% TEA[a]/DCM	25.1	8.3	39.8	9.20	0.75	0.12	0.16	0.28	1.03
24	10% TEA[a]/DMF	44.5	33.3	42.6	11.20	0.80	0.00	0.69	0.69	1.49
25	10% TEA[a]/DMSO	50.4	42.3	43.8	11.10	0.91	0.00	0.76	0.76	1.67
26	20% PIP[a]/DCM	25.1	8.3	39.7	10.00	0.72	0.10	0.29	0.39	1.11
27	20% PIP[a]/DMF	42.1	30.5	42.1	11.90	0.76	0.00	0.76	0.76	1.52
28	20% PIP[a]/DMSO	47.2	38.5	43.2	11.80	0.88	0.00	0.82	0.82	1.70

[a] See Table 2 for values of TEA and PIP solvent parameters.

triethylphosphine oxide. Conversely, DN represents the solvent electron donor character and is correlated with the molar enthalpy value for the reaction of the donor solvent with $SbCl_5$ as a reference solute acceptor.

The initial results with the tested amphoteric (AN+DN) solvent term were promising, as it showed better correlation with the swelling degree of peptide-resins than the dielectric constant (ε) or even the Dimroth–Reichardt's $E_T(30)$ polarity parameter[6] which is one of the most widely accepted in chemistry. This latter solvent scale is based on the measured transition energy (kcal/mol) for the longest wavelength of the absorption band of the model solute pyridinium *N*-phenoxide betaine dye.

As a function of these preliminarily findings, the main focus of the present study is on the development of a more complete investigation regarding the suitability of the (AN+DN) parameter as an alternative and more accurate polarity scale. Thus, a great amount of polarity parameters and also of model polymeric materials was carefully selected to further develop the present correlation approach. In regard to the examined solvent properties, besides the ε and $E_T(30)$ scales, Hildebrand's solubility parameter δ,[7] which has been to date the parameter of choice to correlate with the polymer solvation,[8] was also investigated. It represents the measure of the (cohesive) energy required to separate solvent molecules from one another as a consequence of the need for accommodating solute molecules.

In addition to these examples of 'one-parameter' scales, (ε, $E_T(30)$ and δ), there are still others which suggest the combination of two or more solvent properties simultaneously to better unravel solvent effect in a generic sense. The introduced (AN+DN) term is therefore representative of the so-called 'two-parameter' theory.[9] In analogy, we also included in the present report the classical Kamlet–Taft's α, β and π^* parameters.[10] The first two terms are related to the electrophilic (hydrogen donor) and nucleophilic (hydrogen acceptor) properties of the solvent and are obtained from studies of a set of solute–solvent interactions.[2,10] Their values correspond to the average energy of the longest wavelength absorption peaks of the solute in the solvent molecules and transformed into a dimensionless scale which ranges from 0 to 1. Otherwise, the π^* parameter was proposed by the same authors suggesting that it may reflect the polarity/polarizability properties of the solvent.

Thus, paralleling the (AN+DN) scale to be evaluated, the sum of the α and β properties was also tested including or not the π^* parameter. Therefore the $(\alpha+\beta)$ and the $(\pi^*+\alpha+\beta)$ additive terms constitute together with ε, $E_T(30)$ and δ terms, the set of solvent properties to be compared with the (AN+DN) scale in their correlation with the swelling characteristics of polymers. The latter $(\pi^*+\alpha+\beta)$ summation term is representative of the 'multi-parameter' theory[11] and has often been applied to interpret many types of solute–solvent interactions.[2,3,10] For the sake of simplicity the coefficients for each components of the $(\alpha+\beta)$ or of the $(\pi^*+\alpha+\beta)$ expressions will be considered as being 1 in this study. Otherwise, following a previous report,[4] the (AN+DN) parameter will be tested comparatively in 1:1; 2:1 and 1:2 proportions between its two components.

Table 2. Solvent parameters[2,5,10,23]

Solvent	AN	DN	ε	$E_T(30)$ (kcal/mol)	δ (cal/mL)$^{1/2}$	π^*	α	β	$\alpha+\beta$	$\pi^*+\alpha+\beta$
n-Hexane	0	0	1.9	31.0	7.30	−0.04	0	0	0	−0.04
n-Heptane	0	0	–	31.1	7.40	−0.08	0	0	0	−0.08
Toluene	3.3	0.1	2.4	33.0	8.90	0.54	0	0.11	0.11	0.65
Benzene	8.2	0.1	2.3	34.3	9.20	0.59	0	0.10	0.10	0.69
Carbon tetrachloride	8.6	0	2.2	32.4	8.60	0.28	0	0.10	0.10	0.38
1,1-Dichloroethane	16.2	0	10.0	39.4	–	0.48	0.1	0.10	0.20	0.68
1,2-Dichloroethane	16.7	0	10.1	41.3	9.90	0.81	0	0.10	0.10	0.91
Nitrobenzene	14.8	4.4	34.8	41.2	10.00	1.01	0	0.30	0.30	1.31
Dichloroethylenecarbonate	16.7	3.2	10.1	41.9	–	–	–	–	–	–
DCM	20.4	1.0	8.9	40.7	9.70	0.82	0.13	0.10	0.23	1.05
Diethyl ether	3.9	19.2	4.2	34.5	7.40	0.27	0	0.47	0.47	0.74
Nitromethane	20.5	2.7	36.7	46.3	12.70	0.85	0.22	0.06	0.28	1.13
1,4-Dioxane	10.3	14.3	2.2	36.0	10.00	0.55	0	0.37	0.37	0.92
Ethyl acetate	9.3	17.1	6.0	38.1	9.00	0.55	0	0.45	0.45	1.00
Methyl acetate	10.7	16.3	6.7	38.9	–	0.60	0	0.42	0.42	1.02
Chloroform	23.1	4.0	4.7	39.1	9.30	0.58	0.20	0.10	0.30	0.88
Benzonitrile	15.5	11.9	25.2	41.5	8.40	0.90	0	0.37	0.37	1.27
Tetrahydrofuran (THF)	8.0	20.0	7.5	37.4	9.10	0.58	0	0.55	0.55	1.13
Acetone	12.5	17.0	20.7	42.2	9.60	0.71	0.08	0.43	0.51	1.22
Dimethoxyethane	10.2	20.0	7.2	38.2	8.30	0.53	0	0.41	0.41	0.94
Acetonitrile	18.9	14.1	36.0	45.6	11.90	0.75	0.19	0.40	0.59	1.34
Propylene CO_3	18.3	15.1	65	46.6	–	0.83	0	0.40	0.40	1.23
Tributylphosphate	9.9	23.7	7.9	39.6	–	0.65	0	0.80	0.80	1.45
Sulfolane	19.2	14.8	43.3	44.0	–	0.98	0	0.39	0.39	1.37
Tetramethylene sulfone	19.2	14.8	–	44.0	–	–	–	–	–	–
4-Butyrolactone	17.3	18.0	12.6	44.3	–	0.87	0	0.49	0.49	1.36
Tetramethylurea	9.2	29.6	23.4	41.0	–	0.83	0	0.80	0.80	1.63
Trimethylphosphate	16.3	23.0	20.6	43.6	–	0.72	0	0.77	0.77	1.49
Piperidine (PIP)	0	40.0	5.8	35.5	11.10	0.30	0	1.04	1.04	1.34
NMP	13.3	27.3	33.0	42.2	11.30	0.92	0	0.77	0.77	1.69
Dimethylacetamide	13.6	27.8	37.8	42.9	10.80	0.88	0	0.76	0.76	1.74
DMF	16.0	26.6	36.7	43.8	12.10	0.88	0	0.69	0.69	1.57
Diethylacetamide	13.6	32.2	–	41.4	–	0.84	0	0.78	0.78	1.72
Pyridine	14.2	33.1	12.3	40.5	10.70	0.87	0	0.64	0.64	1.51
DMSO	19.3	29.8	46.7	45.1	12.00	1.00	0	0.76	0.76	1.76
Hexamethylphosphoramide	10.6	38.8	29.6	40.9	10.50	0.87	0	1.05	1.05	1.92
TFE	53.5	0.0	26.7	54.1	11.90	0.73	1.51	0	1.51	2.24
2-Phenylethanol	33.8	23.0	–	49.5	–	0.88	0.64	0.61	1.25	2.13
N-Methylformamide	32.1	27.0	182.4	54.1	16.10	0.90	0.62	0.80	1.42	2.32
Diethylamine	9.4	50.0	3.6	35.4	8.00	0.24	0.03	0.70	0.73	0.97
Benzyl alcohol	36.8	23.0	–	50.4	12.1	0.98	0.60	0.52	1.12	2.10
Ethylamine	4.8	55.5	6.2	–	–	–	–	–	–	–
Triethylamine (TEA)	1.4	61.0	2.4	33.3	7.40	0.14	0	0.71	0.71	0.85
Formamide	39.8	24.0	109.5	55.8	19.20	0.97	0.71	0.48	1.19	2.16
t-Butanol	27.1	38.0	12.5	43.7	10.50	0.41	0.42	0.93	1.35	1.76
1-Butanol	36.8	29.0	17.5	49.7	11.60	0.47	0.84	0.84	1.68	2.15
EtOH	37.1	32.0	24.3	51.9	12.70	0.54	0.86	0.75	1.61	2.15
2-Propanol	33.5	36.0	18.3	48.4	11.40	0.48	0.76	0.84	1.60	2.08
MeOH	41.3	30.0	32.6	55.4	14.50	0.60	0.98	0.66	1.64	2.24
Water	54.8	18.0	78.4	62.8	23.40	1.09	1.17	0.47	1.64	2.73
Acetic acid	52.9	20.0	6.2	51.7	10.10	0.64	1.12	0.45	1.57	2.21
Diaminoethane	20.9	55.0	–	42.0	–	0.47	0.13	1.43	1.56	2.03
Ethylenodiamine	20.9	55.0	12.9	–	12.30	–	–	–	–	–
Formic acid	83.6	19.0	57.9	57.7	12.1	0.65	1.23	0.38	1.61	2.26
Trifluoroacetic acid (TFA)	105	0	8.2	–	10.60	0.50	–	–	–	–
Trifluoromethane sulfonic acid	129.1	0	–	–	–	–	–	–	–	–

As complement to this designed effort in searching for a novel and more suitable solvent polarity scale, the present investigation also further aimed at better understanding the factors that may govern the complex polymer solvation phenomenon. The large amount of swelling data to be here obtained would certainly be of value for the improvement, not only of the solid phase peptide synthesis[12] itself, but also for other polymer-supported methodologies such as the widely applied solid phase organic synthesis procedure[13] often in association with the unique combinatorial chemistry experimental strategy.[14] Needless to say, the fundamental aspect of all these experimental approaches lies in the fact that they all depend markedly on the efficiency of the solvation property of polymeric materials chosen as the solid support for their applications. In this context, it seems imperative that the selection of the model resins for the present study must be made judiciously. Thus, the set of cross-linked resins to be investigated in this report comprises a large amount of polymeric materials with different characteristics including their overall polarity, ionic form and the amount and type of backbone-attached ligands.

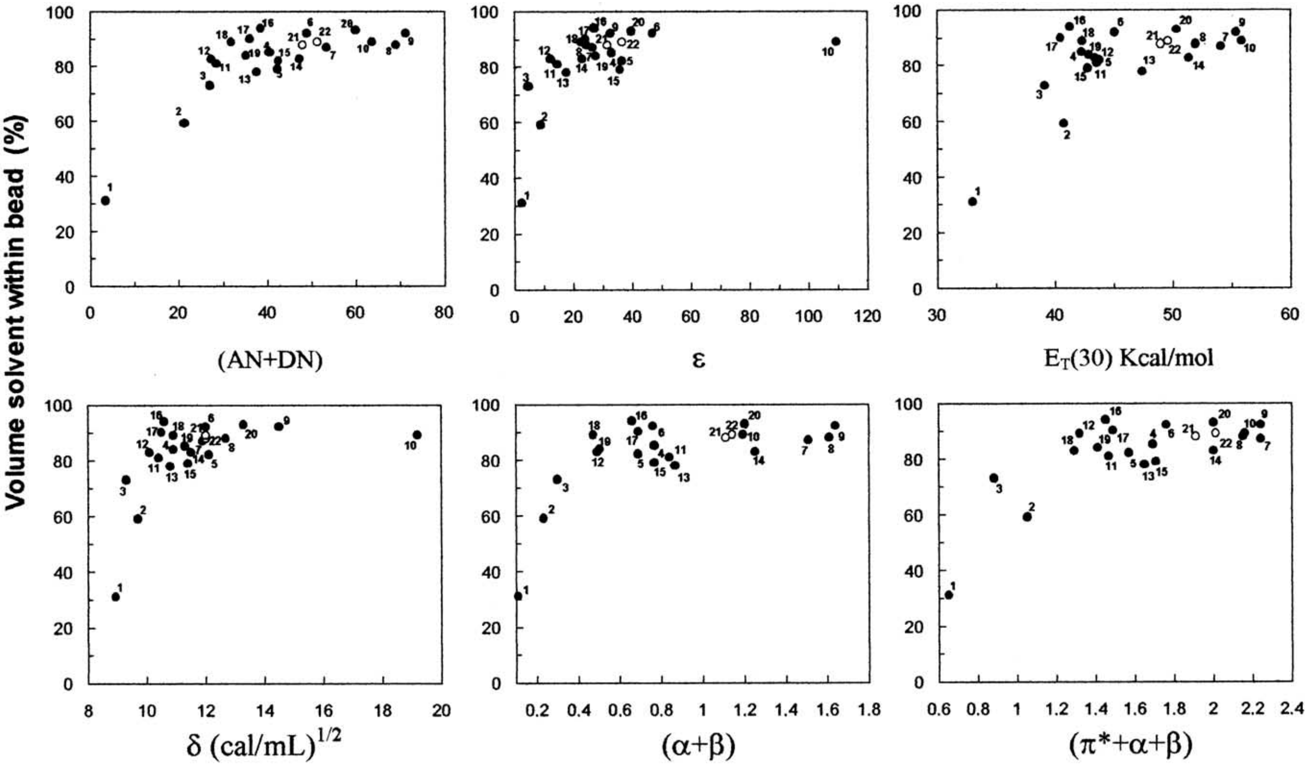

Figure 1. Swelling of resin (**1**), BHAR–NH_3^+, 2.4 mmol/g as a function of solvent (AN+DN), ε, $E_T(30)$, δ, $(\alpha+\beta)$ and $(\pi^* + \alpha + \beta)$ values.

2. Results

The polymers selected for the present study are: resin (**1**), a very highly positively charged benzhydrylamine-resin (BHAR–NH_3^+, 2.4 mmol ammonium group/g), a phenylmethylamine group-containing copolymer of styrene and 1% divinylbenzene (PS-DVB), synthesized according to an earlier report;[15] resin (**2**): the hydrophobic PS–DVB copolymer alone; resins (**3**) [Bu(DADP)$_4$–BHAR] and (**4**) [(NANP)$_4$–BHAR], the 1.4 mmol/g BHAR resin attaching either the (DADP)$_4$ sequence protected at Asp-side chains with the *tert*-butyl (Bu) groups or the unprotected and more polar (NANP)$_4$ segment, respectively, and both with a very high (about 70%, g/g) peptide-content. Resin (**5**) is an aminoalkyl-cross-linked polymer[16] composed predominantly of polydimethylacrylamide matrix (SPAR-50, 0.6 mmol/g, from Advanced ChemTech Inc.) and that significantly differs from the others by containing an entirely hydrophilic network. Resin (**6**) is also a representative of a polystyrene-based copolymer but containing 2% of a polar cross-linking function (tetraethyleneglycol diacrylate) replacing the traditional divinylbenzene group. This resin, namely PS–TTEGDA, was synthesized according to a previous report[17] and contains 0.7 mmol/g of amine functions in deprotonated form. Lastly, resin (**7**) is a 1% chloromethylated-PS–DVB but grafting poly-(ethyleneglycol) (PEG) group[18] which increases the hydrophilicity of the polymer backbone. The PEG group may be derived to introduce amine groups in the polymer structure and the commercial presently studied resin contains 0.3 mmol/g amine groups [(TentaGel-SNH_2) or (TG)-resin], from Advanced ChemTech Inc.

The list of 28 single and mixed solvents that were used in the present study, most of them applied in different steps of the solid phase peptide synthesis,[12] together with the corresponding values of the six solvent polarity parameters are shown in Table 1. In addition the more complete Table 2 lists the values of solvent properties for 57 single solvents. The supplementary information section contains the set of measured swelling degrees of the seven resins determined in a microscope. The percentage of swollen bead volume occupied by the solvent ranged from a minimum of 7% (resin **4**, toluene) to a maximum of 94% (resin **1**, DMSO/THF). Similarly to that applied for the study of other empirical solvent properties[8,19] and following a previous study,[4] the equation below was used for the determination of values of solvent parameter for mixed solvents. In this equation, x_1 and x_2 are the solvent parameters for the two components of the mixture, and ϕ_1 and ϕ_2 are the corresponding volume fractions.

$$X_{1+2} = \phi_1 x_1 + \phi_2 x_2 \qquad (1)$$

Figs. 1–3 show, as representative examples, the solvation profiles for resins **1–3** [(BHAR–NH_3^+, PS–DVB and Bu(DADP)$_4$–BHAR, respectively], when their swelling data are correlated with (AN+DN), ε, $E_T(30)$, δ, $(\alpha+\beta)$ and $(\alpha+\beta+\pi^*)$ values. Irrespective of the resins examined the best correlation occurs with the solvent (AN+DN) term (Figs. 1(A), 2(A) and 3(A), respectively) than with other parameters. The also amphoteric $(\alpha+\beta)$ scale seems to follow, with a slightly poorer correlation, the good relationship observed when the (AN+DN) number is used. This

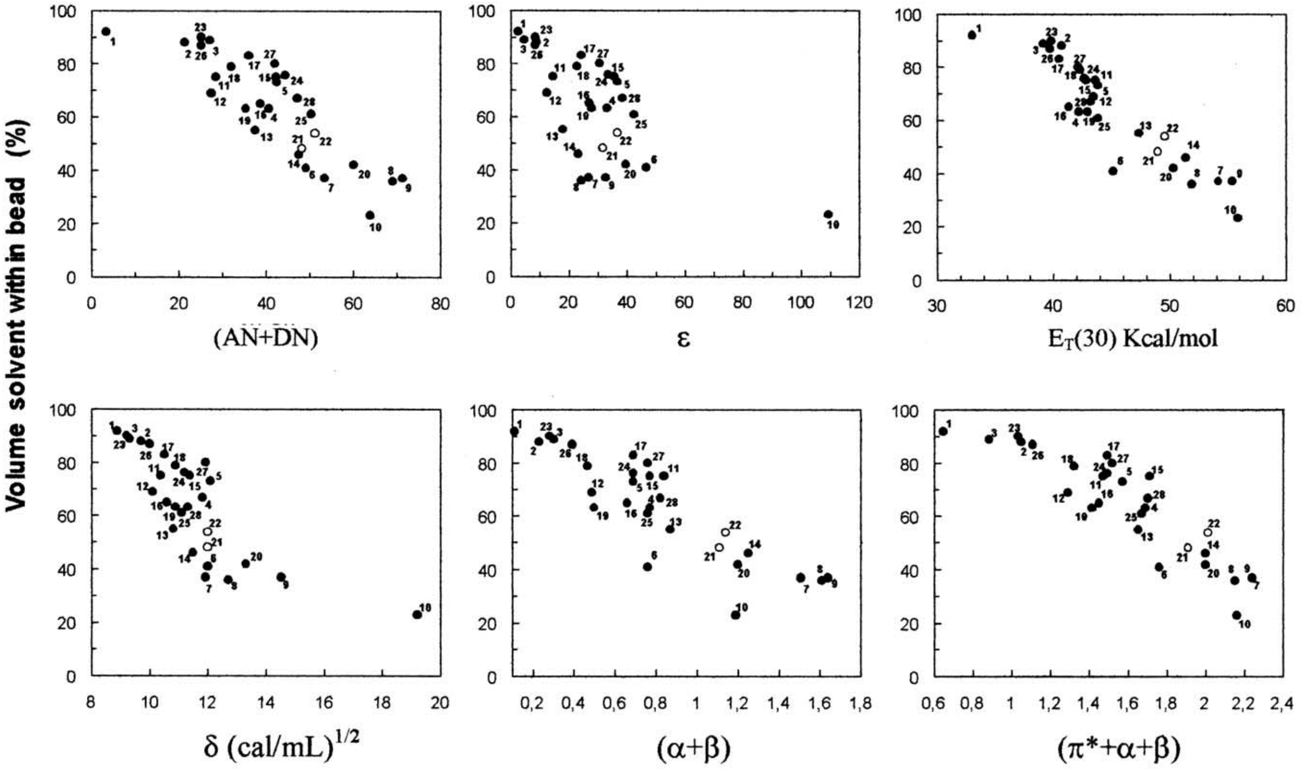

Figure 2. Swelling of resin (**2**), PS–DVB as a function of solvent (AN+DN), ε, $E_T(30)$, δ, $(\alpha+\beta)$ and $(\pi^*+\alpha+\beta)$ values.

trend is also observed in resins **4**–**7** and the corresponding four contoured solvation curves are collectively shown in Fig. 4. The complementary figures which reveal less accurate relationships between swelling data and other polarity parameters for resins **4**–**7** are included in the supplementary information section.

The proportion between AN and DN numbers was also

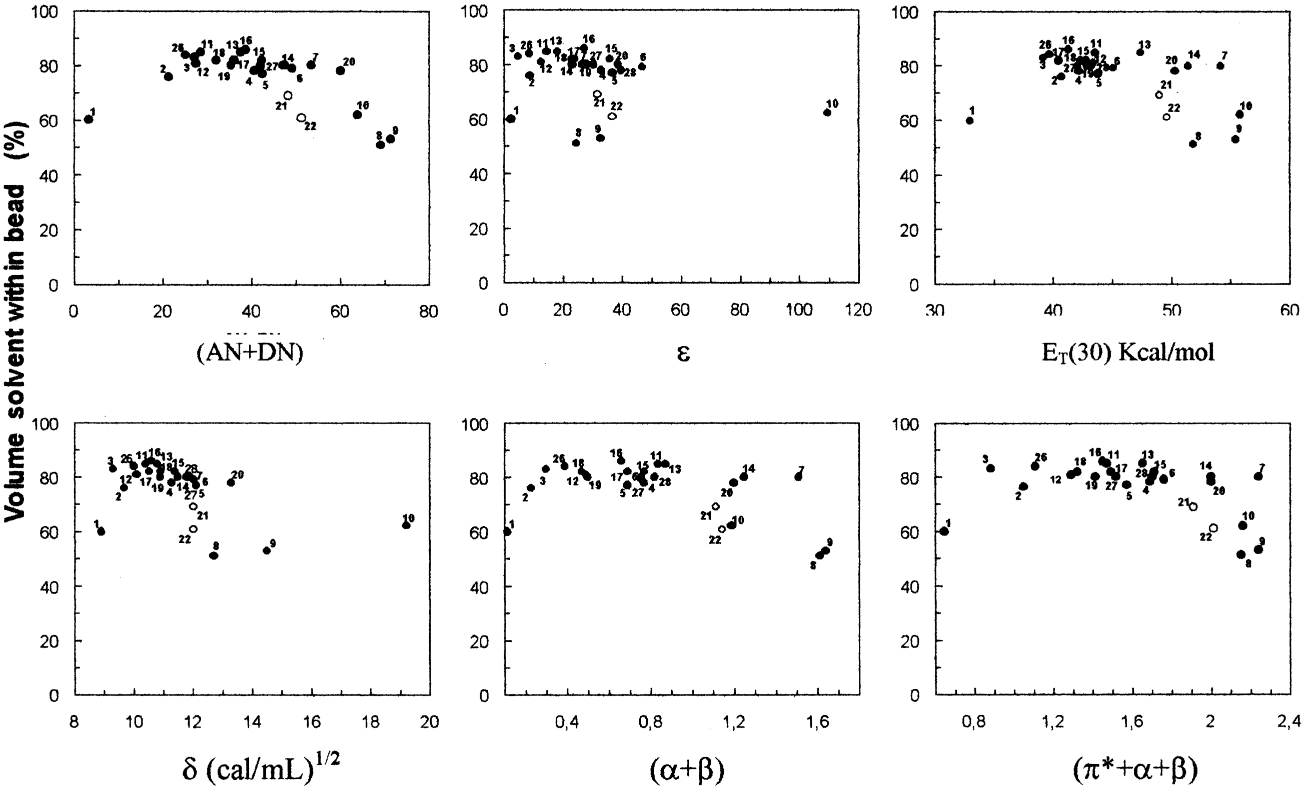

Figure 3. Swelling of resin (**3**), Bu(DADP)$_4$–BHAR, 1.4 mmol/g as a function of solvent (AN+DN), ε, $E_T(30)$, δ, $(\alpha+\beta)$ and $(\pi^*+\alpha+\beta)$ values.

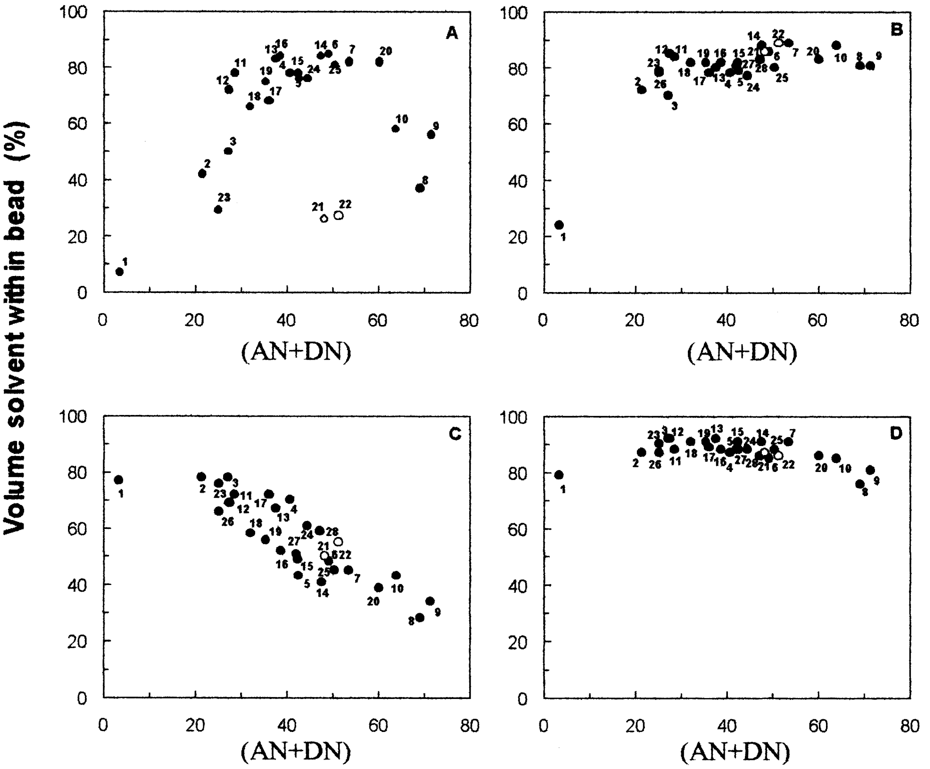

Figure 4. Swelling of resins (**4**), (NANP)$_4$–BHAR, 1.4 mmol/g (A), (**5**), SPAR-50, 0.6 mmol/g (B), (**6**), PS–TTEGDA, 0.7 mmol/g (C) and (**7**), TG, 0.3 mmol/g (D) as a function of solvent (AN+DN) values.

varied (2:1 and 1:2) but as previously observed with some peptide-resins,[4] the correlations of all resins (**1**–**7**) with swelling data in these two proportions were weaker than that observed when in the practical 1:1 proportion (comparative figures in the supplementary information section). Finally, by analyzing the set of swelling versus polarity parameter values, the mixed solvents 21 and 22 (TFE/DMF and TFE/DMSO), represented by open circles, deviate from the average solvation curve only with (NANP)$_4$–BHAR (resin **4**, Fig. 4(A)) and to a much lesser extent with Bu(DADP)$_4$–BHAR (resin **3**, Fig. 3). Lower swelling degrees than those predicted by their polarity values are observed. This effect which occurs only with this type of mixed solvents was already described[4] and therefore will be further discussed in terms of their heterogeneous composition.

As a second but also relevant goal of the present investigation, a clear difference in the solvation of each resins is observed depending on their structural characteristics (Figs. 1–4). The following maximum solvation regions in terms of the (AN+DN) values are detected for each resin: lower than 20 for the apolar PS–DVB and PS–TTEGDA (resins **2** and **6**, respectively); above 40–50 for the polar BHAR–NH$_3^+$ and SPAR-50 (resins **1** and **5**, respectively). An intermediary position is occupied by Bu(DADP)$_4$–BHAR (resin **3**) and (NANP)$_4$–BHAR (resin **4**), which display enhanced solvation in solvent systems characterized by (AN+DN) polarity values centered near 40 (Fig. 3) and 50 (Fig. 4(A)), respectively. Interestingly, a different swelling behavior (Fig. 4(D)) was observed with the TG-resin (resin **7**). This PEG-grafted polymer may be included in the intermediary position in terms of polarity as its maximum solvation region occurs near 40. However differing from all others, this resin does not display a significant decrease in swelling regardless of the polarity value of the solvent system. The measured minimum swelling values are as high as 80% and thus, it is the only polymer which presents an excellent solvation irrespective of the polarity of the medium.

3. Discussion

3.1. The applied resin solvation versus solvent polarity approach

The differentiated approach herein applied for simultaneously examining resin solvation process and validity of different polarity parameters was first based on the well known statement that polymers display maximum swelling in solvents with polarity similar to their polymeric backbone. This finding was for instance, verified when the Hildebrand' δ parameter was applied for correlating swelling of different types of polymeric materials.[8] It means that the exact profile of the contoured solvation curve showing the relationship between swelling and polarity values will always depend on the physico-chemical characteristic of each polymer. As observed in all the figures of the present work and that will be further discussed in more details, those more hydrophobic or hydrophilic resins will have their maximum solvation regions in these figures shifted to the left or right sides of the polarity scale corresponding to the more apolar or polar regions, respectively. Alternatively a maximum solvation region located in the middle of this scale may be also observed when in the

Table 3. The (AN+DN) solvent scale

Solvent	(AN+DN)	Solvent	(AN+DN)
n-Hexane	0	*N*-Methyl-pyrrolidinone (NMP)	40.6
n-Heptane	0	Dimethylacetamide	41.4
Toluene	3.4	*N*,*N*-Dimethylformamide (DMF)	42.6
Benzene	8.3	Diethylacetamide	45.8
Carbon tetrachloride	8.6	Pyridine	47.3
1,1-Dichloroethane	16.2	Dimethylsulfoxide (DMSO)	49.1
1,2-Dichloroethane	16.7	Hexamethylphosphoramide	49.4
Nitrobenzene	19.2	Hexamethylphosphoramide	49.4
Dichloroethylenecarbonate	19.9	1,1,1-Trifluoroethanol (TFE)	53.5
Dichloromethane (DCM)	21.4	2-Phenylethanol	56.8
Diethyl ether	23.1	*N*-Methylformamide	59.1
Nitromethane	23.2	Diethylamine	59.4
Dioxane	24.6	Benzyl alcohol	59.8
Ethyl acetate	26.4	Ethylamine	60.3
Methyl acetate	27.0	Triethylamine (TEA)	62.4
Chloroform	27.1	Formamide	63.8
Benzonitrile	27.4	*t*-Butanol	65.1
Tetrahydrofuran (THF)	28.0	1-Butanol	65.8
Acetone	29.5	Ethanol (EtOH)	69.1
Dimethoxyethane	30.2	2-Propanol	69.5
Acetonitrile	33.0	Methanol (MeOH)	71.3
Propylene CO_3	33.4	Water	72.8
Tributylphosphate	33.6	Acetic acid	72.9
Sulfolane	34.0	Diaminoethane	75.9
Tetramethylene sulfone	34.0	Ethylenodiamine	75.9
4-Butyrolactone	35.3	Formic acid	102.6
Tetramethylurea	38.8	Trifluoroacetic acid (TFA)	105.0
Trimethylphosphate	39.3	Trifluoromethane sulfonic acid	129.1
Piperidine (PIP)	40.0		

case of resins containing intermediary polarity characteristic. Accordingly, Figs. 1–4 of the present report (and all those of supplementary information section) show examples of each of this type of solvation behavior.

This heterogeneity in terms of figures when swelling and polarity values are both correlated, regardless of the resin or of the solvent parameter selected, strongly evinces that the determination of a single linear or non-linear regression equation, with its corresponding correlation coefficient applicable for this complex relationship is not yet achieved and awaiting for a more complete investigation. One possibility to further clarify this complex problem may involve the simultaneous use of a variety of solvent parameters in a single equation (multi-parameter theory[11]). To date, only a report[20] has suggested a linear relationship between the swelling degree of a polyurethaneimide-type resin with the $E_T(30)$ solvent parameter.[20] However the restriction of this approach only to few types of solvents that did not encompass entirely the polarity scale as done in the present work, hampered the visualization of a possible maximum solvation region for this type of polymer.

Taken together and despite this impossibility in determining any type of correlation coefficient for the swelling versus polarity values, the main assumption stated in this work is that, by examining visually the degree of dispersion of the large amount of data of the solvation curves, one can judiciously select the solvent property that seems to be the most appropriate for scaling polarity. Certainly this parameter will be that one which has displayed lesser dispersion (best fit) of data thoroughly all these correlation curves as a consequence of its higher sensitivity and accuracy towards resin–solvent interaction effect. To better validate this effort, the set of resins investigated in this report comprised deliberately ionic and neutral polymers, those containing entirely hydrophilic or hydrophobic backbones, and also those with a mixed character given by the attachment of chemical groups or peptide chains, containing different polarities and amounts spread in their matrices. In our view this was basically the simple but valid criteria herein applied for interpreting the polymer solvation phenomenon and the potential of the alternative (AN+DN) polarity scale, comparatively to those already existing in the literature.

3.2. The (AN+DN) solvent term

In an excellent review[21] regarding physicochemical properties of polymers for solid phase organic synthesis, the authors have suggested a more complete evaluation of the preliminarily proposed (AN+DN) solvent term mainly in comparison with the traditional Hildebrand's δ parameter. In our view, the large amount of presently accumulated data correlating the swelling behavior of a total of eleven types of polymers (four from a previous study[4]),[‡] most with known solvent properties, confirmed that the (AN+DN) term might be considered a novel empirical polarity scale. Of great relevance is the fact that it was unequivocally proven that this scale is more adequate to probe solvation of any type of polymers in comparison with the δ parameter. The better accuracy of the (AN+DN) term, when

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[‡] As the correlation between swelling of BHAR–NH_2 (1.4 mmol/g), Bz(DADP)$_4$–BHAR (70% peptide-content), ING–BHAR (6 and 47%) resins with (AN+DN), in 2:1, 1:1, 2:1 proportions, and with ε and $E_T(30)$ terms were already described,[4] the lacking correlation data of these resins with additional δ, $(\alpha+\beta)$ and $(\pi^*+\alpha+\beta)$ solvent parameters are now included in supplementary information section of this work.

Table 4. Binary correlations of solvent parameters

X/Y	(AN+DN)
ε	$(\mathrm{AN}+\mathrm{DN})=36.59+0.23\varepsilon$, $r=0.2994/n=49$
$E_\mathrm{T}(30)$	$(\mathrm{AN}+\mathrm{DN})=-58.09+2.29E_\mathrm{T}(30)$, $r=0.7374/n=52$
δ	$(\mathrm{AN}+\mathrm{DN})=-2.29+4.19\delta$, $r=0.4961/n=41$
π^*	$(\mathrm{AN}+\mathrm{DN})=32.14+15.25\ \pi^*$, $r=0.1709/n=51$
$(\alpha+\beta)$	$(\mathrm{AN}+\mathrm{DN})=10.38+39.92\ (\alpha+\beta)$, $r=0.9251/n=50$
$(\pi^*+\alpha+\beta)$	$(\mathrm{AN}+\mathrm{DN})=-2.99+30.76\ (\pi^*+\alpha+\beta)$ $r=0.8607/n=50$

r=correlation coefficient of linear regression; n=number of solvents.

its components are, in 1:1 and not in other proportions, was also demonstrated regardless of the type of the polymeric material (corresponding figures in the supplementary information section). Table 3 shows the complete (AN+DN) polarity scale containing values of 57 solvents ranging from a minimum of 0 (hexane) to a maximum of near 130 (trifluoromethanosulfonic acid).

As complement, the linear correlations calculated between the (AN+DN) number and other solvent properties examined in this study were calculated and are shown in Table 4. The best correlation of the (AN+DN) scale occurs exactly with those representative of the two-parameter[9] $(\alpha+\beta)$ or multi-parameter[2,11] $(\pi^*+\alpha+\beta)$ solvent effect concepts. In these two cases the calculated correlation coefficients (r) with the (AN+DN) parameter are 0.92 and 0.86, respectively. In agreement with their comparative poorer fits observed in all the swelling versus polarity term plots, the two representatives of the one-parameter solvent effect theory [$E_\mathrm{T}(30)$ and δ] display only fair relationships with the (AN+DN) values (r=0.73 and 0.49, respectively). In addition, much more weak correlations are calculated using the remaining single parameters ε and π^* (r=0.30 and 0.18, respectively).

Taken together one may state that those polarity scales which consider the solute–solvent interaction in a generic sense as an acid–base process, seem to be the most adequate. Accordingly, after the (AN+DN) scale, improved correlations are observed with the $(\alpha+\beta)$ and the polyfunctional $(\pi^*+\alpha+\beta)$ terms. One possibility to explain the slightly lesser adequacy of both these additive terms may be due to the fact that Kamlet–Taft's parameters are all an average of data from a great amount of solvent effect studies using several types of solute probes. This characteristic can be considered advantageous in some circumstances but may also be regarded as one of their weaknesses.[2]

In respect to other solvent parameters which show a more reduced correlation with the resin solvation data, one can speculate that it is due to the fact that none of them contain the important amphoteric character existing in the (AN+DN) number. A second possibility may lie in the inadequacy of the solute-probe molecule used for their determination as compared with those used for AN and DN scale properties. This might be the case of the Dimroth–Reichardt's $E_\mathrm{T}(30)$ parameter. Of note is also the fair suitability of the Hildebrand's solubility parameter δ. These results might be partially credited to its less rigorous determination method, although some successful examples of good correlation between δ values of the polymer with those of the solvent have been reported.[8,22] In this case, as each resin has a characteristic polarity, its maximum solvation will occur with solvents with similar δ values.

The very weak correlation of the ε property with the swelling property of resins is indicated by the very low (r=0.30) correlation coefficient with the (AN+DN) term. This inadequacy is expected as this macroscopic solvent parameter only reflects the electrostatic interaction between solute and solvent molecules but not how effective is the alignment between both dipoles. Moreover, no other types of interaction are included in this solvent parameter thus precluding its acceptance as a suitable polarity scale.[23]

To explain the better accuracy of the (AN+DN) term to access the solvation property of polymers one can hypothesize that besides its amphoteric character, an additional factor may be involved in the improved suitability of the selected probe molecules for scaling its two components. As stressed, the AN number reflects the electrophilic property of solvents and the triethylphosphine oxide is the probe chosen for its determination. This compound presents the same special and important requirements which can be important for its use as an appropriate probe:[5] (i) the nucleus of the solute molecule is not close to the actual site of interaction (basic oxygen atom); (ii) the model-solute is a very strong base. This characteristic assures a high sensitivity of the phosphorus resonance to solvent change; (iii) the solute–solvent interaction always occurs at a well-defined site, namely, at the oxygen atom; the remaining coordination sites of the phosphorus atom are blocked off by inert alkyl groups.

In the other hand, the measurement of the nucleophilicity of solvents represented by the DN number depends on the $\mathrm{SbCl_5}$ compound as probe model molecule. This solute also seems to be very appropriate as it fulfills the following requirements: (i) irrespective of the donor molecule, the adducts are formed in a 1:1 molar ratio; (ii) $\mathrm{SbCl_5}$ is a very strong acceptor and this allows a reasonable degree of adduct formation even with very weak donors; (iii) the Sb–Cl bonds are difficult to be heterolyzed and ionization equilibrium can be neglected even in the case of interaction with strong donor molecules.

The notion of solvent polarity is often used to choose a solvent or to explain solvent effects. Because solute–solvent interactions depend on the structure of both components, the proposition of a universal solvent polarity scale seems to be very difficult and maybe unattainable. Thus in using the (AN+DN) scale one should always be aware of this inherent weakness. But despite this expected limitation in the search for this perfect polarity scale, the results herein described, based on the study of a set of different polymers combined with the selection of appropriate solvent systems, validate the (AN+DN) term as a novel, dimensionless and accurate polarity term. Obviously how widely applicable and adequate is this scale when other solute–solvent interactions are to be considered, is still an open issue and awaiting further research. In other areas, excepting chemistry (mainly in biology), the traditional but in most cases, inadequate mention of the dielectric constant as the universal polarity scale has been a very common practice for decades. Thus one may hopefully expect that a more practical and acceptable polarity scale might appear for progressively correcting this type of conceptual misunderstanding.

3.3. Solvation property of polymers

To better validate the findings of the present polymer solvation study, some important experimental requirements were previously defined: (i) in addition to the large amount of solvent systems chosen for encompassing as broadly as possible the polarity scale, the set of examined polymers was characterized by their heterogeneity in terms of the type of the solute-models; (ii) before swelling measurements, the home-made resins were sifted in pore metal sieves to reduce the standard deviations of resin diameters as previously published;[4] (iii) the microscopic measurement method[15,24] of resin beads was applied due to its high accuracy and sensitivity; (iv) in the specific case of peptide-resins, the amount, polarity and aggregation tendency of the peptide sequence were altered to monitor the influence of these different factors.

Briefly, the driving force for swelling of cross-linked polymer network is made up of influences by the entropic and enthalpic changes associated with the interaction process between solvent and solute molecules.[8,25] When the sum of these contributions imposes a negative variation on Gibb's free energy values, expansion of the resin network occurs, reflected by the swelling degree values. This effect is therefore dependent on the polymer characteristic itself and mainly on its interaction with the solvent molecule. This implies that in the correlation approach herein applied, each type of polymer should be characterized by a maximum solvation region in a swelling versus solvent polarity plot.

The overall findings of the previous study[4] are in close accordance with this assumption. The different solvation behavior of each resin can be summarized as follows: those containing predominantly a hydrophobic character such as the PS–DB and PS–TTEGDA (or the 6% peptide-content ING–BHAR and the 1.4 mmol/g deprotonated amine group BHAR–NH_2 described earlier[4]), swell better in more apolar solvents characterized by (AN+DN) values lower than 30. This effect is certainly due to the dominant influence of hydrophobic polystyrene matrices of these resins. For polymers such as Bu$(DADP)_4$–BHAR or [Bz$(DADP)_4$–BHAR[4]], they are in an intermediary polarity position due to the contribution of a larger amount of polar C=O and N–H dipole moieties of peptide bonds attached to their structure (near 70% peptide-content in both resins). In this case improved solvation region is shifted to solvents characterized by (AN+DN) values in the 30–40 range.

The class of more polar solutes includes the cationic 2.4 mmol/g BHAR–NH_3^+, the entirely hydrophilic SPAR-50 and the examples of two highly peptide-loaded peptide-resins but attaching either a very polar [$(NANP)_4$–BHAR, 68% peptide-content] or a polar and well-known[26] aggregating (ING–BHAR, 47% peptide-content[4]) sequence, respectively. These polymers display improved solvation in single or mixed solvents characterized by having (AN+DN) values about 50 or higher. Finally the characteristic solvation behavior observed with the PEG-attaching PS-based TG resin (TG), of very common use in peptide synthesis seems to emphasize the relevance of the special characteristic of the polymer backbone. This resin presents optimized solvation in practically all type of solvents with the maximum solvation region in those having (AN+DN) values around 40. But irrespective of the solvent, no swelling degree lower than 80% is observed in the contour solvation curve. As this swelling behavior is not simply expected from its polarity character, one may infer that the TG-resin might be characterized by special physicochemical features given by a well-established copolymerization design.

In this regard a certain degree of structural inhomogeneity is known to occur when the copolymers of styrene and divinylbenzene are prepared.[27] This is basically due to the lack of commercial availability of pure isomers of the latter cross-linking compound and alternative examples of its replacement with other groups have been reported. In addition to the PS–TTEGDA herein examined and which contains tetraethyleneglycol-diacrylate as the cross-linking group[17] there are others such as the JandaJel[28] containing, instead, a 1,4-bis(vinylphenoxy)-butane group. Due to the improved homogeneity some of this class of cross-linked polystyrene resins are already available commercially as is the case of the latter polymer. This structural characteristic has been taken into account, for instance,[21] to compare through spectroscopic experiments, different characteristics of resins with potentiality for application in polymer supported synthesis methodologies.

As examples of practical relevance deriving from polymer solvation studies, the enhanced swelling of the cationic 2.4 mmol/g BHAR–NH_3^+ observed in more polar solvents led us promptly to speculate that it might also swell reasonably in aqueous solution. It was further confirmed and this aminated resin, introduced[29] to be used exclusively in organic solvents as the solid support for peptide synthesis, was also employed as an alternative anion exchanger resin in column chromatography for the successful purification of negatively charged biological compounds.[30] Also based upon the measured lack of swelling in apolar solvents, of this highly amine-loaded BHAR (protonated form), we recently have demonstrated[31] the need for modification in the solvent system of the traditional picric acid method[32] for quantification of resin-bound amine groups.

Finally, the mixed solvents (open circles—Figs. 1–4) 21 and 22 (TFE/DMF and TFE/DMSO, respectively) are unique in terms of physicochemical characteristics. They consist of strong electron acceptor (TFE) and strong donor (DMF or DMSO) components (heterogeneous solvent) thus presenting the inherent tendency to self-associate rather than to solvate solute molecules.[33] This implies that their solvation strength is clearly dependent upon the amount of interactions to be disrupted between solute molecules or in the present case, throughout the polymer network. The stronger the association effect inside the bead, the more difficult it is for these two heterogeneous solvent systems to solvate the polymer. In this case a lower solvation degree of resin than that predicted by their polarity values is observed. Accordingly, this shrinking effect of resin beads with solvents 21 and 22 is more clearly seen only in the highly peptide-loaded $(NANP)_4$–BHAR (68%, Fig. 4(A)) which contains a very folded peptide structure[34] or in the aggregating sequence-containing ING–BHAR (47%).[4] To emphasize the relevance of the peptide loading effect, this latter peptide-resin, when attaching a smaller amount of peptide chains (6% peptide content) did not suffer from the shrinking effect in these two heterogeneous solvents.[4] Thus, the comparatively smaller shrinking effect observed with $Bu(DADP)_4$–BHAR (Fig. 3(A)) and $Bz(DADP)_4$–BHAR[4] in solvents 21 and 22 is indicative of a lower tendency of both peptide segments to self-association if compared for instance, with the $(NANP)_4$ sequence (all these resins contain the same peptide loading values).

Of note, this bead shrinking effect does not occur in all other resins, thus indicating the absence of any significant interaction process spread throughout their matrices. We deem the type of contour solvation curve here designed might be therefore a unique and valuable strategy for monitoring and quantifying the degree of aggregation occurring in the polymer network. Moreover an additional advantage in scaling solvent effects with the two-parameter polarity scales, as is the case of the (AN+DN) term, must be reminded. The interpretation for the unusual swelling of polymers towards heterogeneous solvents such as TFE/DMF or TFE/DMSO is not feasible when considering for instance, one-parameter solvent parameters such as δ, ε or $E_T(30)$. These findings make more clear the need for knowing the nature and the effect of the mixed solvent to be used (heterogeneous or homogeneous) for any types of solute–solvent interactions, unfortunately still not usually taken into account, mainly in non-chemistry areas.

The factors which may control resin solvation have been intensively investigated through a great set of experimental strategies in the last decades. The explosive trend in polymer-dependent methodologies has led to the appearance of a large number of alternative resins as well as successful spectroscopic investigations of this phenomenon. Amongst these attempts, relevant data have being collected from NMR,[35] CD,[36] IR[37] and EPR[38] studies. In our case, in complement to the beginning of the mentioned solvation study of resins through microscopic measurements of beads,[4] we have also applied the EPR procedure but innovating as concerns the paramagnetic probe to be used. The paramagnetic amino acid TOAC (2,2,6,6-tetramethylpiperidine-*N*-oxyl-4-amino-4-carboxylic acid)[39] which we have derived for peptide labeling[40] and structure–activity[41] approaches, was also applied to labeling resins and peptide-resins to monitor dynamics of swollen polymer backbones.[42]

All together these efforts seem to be of great value for improving methodologies that depend markedly on the pioneering and revolutionary concept of performing chemical reactions on heterogeneous and insoluble supports, started in the literature almost four decades ago.[43] The set of findings obtained in the present resin solvation–solvent polarity investigation which has encompassed a large amount of different polymeric materials and solvent systems may therefore, in association with those deriving from spectroscopic techniques, provide new insights for optimization of many polymer-dependent chemical or biological methodologies.

4. Experimental

N^α-*tert*-Butyloxycarbonyl (Boc)-β-benzyl- or N^α-9-fluorenylmethyloxycarbonyl (Fmoc)-*tert*-butyl-Asp and other side chain deprotected Boc- or Fmoc-amino acids were purchased from Bachem, Torrance, CA. SPAR-50 and TentaGel-SNH_2 or TG resins were acquired from Advanced ChemTech and PS-DVB copolymer from Bio Rad Laboratories. Batches of BHAR (0.2, 1.4 and 2.4 mmol/g) were synthesized in this laboratory, following earlier reports.[15,29] The PS–TTEGDA resin was synthesized as published elsewhere.[17] Solvents and reagents were purchased from Fluka, Aldrich or Sigma Co. and those used for swelling studies were HPLC grade.

4.1. Peptide synthesis

The peptides were synthesized manually accordingly to the standard Boc[12a,b]- or Fmoc[12c,d]-protocols. In the Boc-chemistry, after the coupling of the C-terminal amino acid to the resin, the successive α-amino group deprotection and neutralization steps were performed in 30% TFA/DCM (30 min) and 10% DIEA/DCM (10 min). Conversely, a single 20 min piperidine/DMF treatment was needed to deprotect and neutralize the amine function of the growing sequence in the Fmoc-strategy. The amino acids were coupled with TBTU in the presence of HOBt and DIEA using DMF or 20% DMSO/NMP as solvent system. After a two-hour coupling time, the qualitative ninhydrin test was performed to estimate the completeness of the reaction. To check the purity of the synthesized peptide sequence attached to the resin cleavage reactions with small aliquots of resin were carried out with the low-high HF procedure (Boc-chemistry) or K[12d] reagent (Fmoc-chemistry). Analytical HPLC (Waters), LC/MS (electrospray)-mass spectrometry (Micromass) and amino acid analysis (Beckman 6300 analyzer) were used to check the homogeneity of each synthesized resin-bound peptide sequences.

4.2. Swelling measurement of beads

Before use in peptide synthesis and/or in microscopic measurement of bead sizes, most resin batches were sized by sifting in porous metal sieves to lower the standard deviations of resin diameters to about 4%. Swelling studies of these narrowly sized populations of beads were performed and published previously.[4] Briefly, 150–200 dry and swollen beads of each resin, allowed to solvate overnight, were spread over a microscope slide and measured directly with an Olympus, model SZ11 microscope coupled with a Image-Pro Plus, 3.0.01.00 version software. Since the sizes in a sample of beads are not normally but log-normally distributed, the central value and the distribution of the particle diameters were estimated by the more accurate geometric mean values and geometric standard deviations. With the exception of the ionized resin **1** and the copolymer PS–DVB (resin **2**), the others were measured with their amino groups in the deprotonated form, obtained by

3×5 min TEA/DCM/DMF (1:4.5:4.5, v/v/v) washings followed by 5×2 min DCM/DMF (1:1, v/v) and 5×2 min DCM washings. Resins were dried in vacuum using an Abderhalden-type apparatus with MeOH reflux.

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