Solvents and solvent selection for chromatography

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Solvent Polarity

- General qualitative understanding
- No universal definition
  - Capacity of a solvent to enter into all possible intermolecular interactions
  - Solvents ability to participate in interactions of a dipole type
- Numerous single-property scales
  - Dielectric constant
  - Reichardt's solvatochromic absorption scale

Solvent Polarity

- Scales in use are unfit for purpose
  - No single reference compound or bulk physical property that is uniquely polar
  - Each scale measures some specific characteristic of the selected probe or physical property
  - Scales set up to measure polarity are internally inconsistent
  - No reason to prefer one scale over another

Separation Science Approach

- Semi-empirical scales that classify solvents according to their:
  - Solvent Strength
  - Solvent Selectivity

Solvent Strength

Single parameter estimate of a solvent's ability to cause migration in a chromatographic system

- Not a fundamental solvent property since it depends on the system
- Determined by experiment

Solvent selectivity

- The parameter that distinguished the ability of a solvent to provide separation as well as migration
  - Determined by the solvent's capability to enter into specific intermolecular interactions
    - Dispersion
    - Orientation
    - Induction
    - Hydrogen bonding

Methods for solvent selectivity characterization

- ## Solubility parameters
  - No general agreement on how to calculate partial polar solubility parameters
- ## Solvent triangle classification
  - Each intermolecular interaction associated with a single prototypical solute
- ## Solvatochromic parameters
  - Considers only the polar interactions of a solvent and not its cohesive energy

Solvent Selectivity Triangle

Selection of prototypical solutes

- Nitromethane   dipole-type interactions
- Ethanol   hydrogen-bond base
- Dioxane   hydrogen-bond acid

Solvents classified based on their interactions

(gas-liquid partition coefficients) with the three prototypical solutes

Solvent Selectivity Triangle

Partition coefficients semi-empirically corrected

- Solute size differences
- Polarizability differences
- Differences in dispersion interactions
- Adjusted so that the n-alkanes are the zero point for each interaction

Solvent selectivity triangle

A.R. Johnson, M.F. Vitha, J. Chromatogr. A 1218 (2011) 556-586
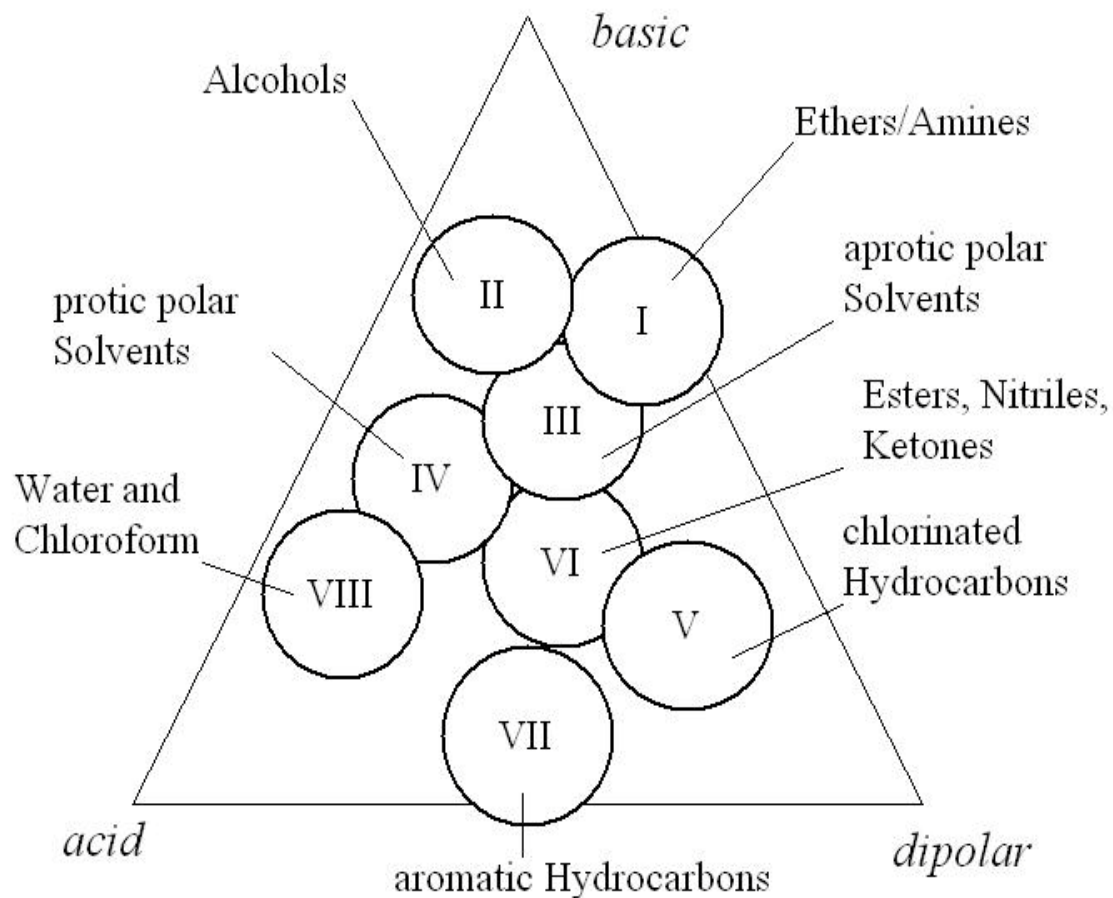
Prototypical Solutes

**Polar solutes with a single dominant intermolecular interaction are virtually unknown**

All solutes that are hydrogen bonding are simultaneously dipolar

| Ethanol	Nitromethane	Dioxane
$S = 0.42$	$S = 0.95$	$S = 0.75$
$A = 0.37$	$A = 0.06$	$A = 0$
$B = 0.38$	$B = 0.31$	$B = 0.64$

Solvatochromic Selectivity Triangle

- Spectroscopic measurement of solvent effects on absorption bands for select solutes

- Each parameter is an average for several solutes and roughly independent of solute identity

  - π^* = dipolarity/polarizability
    - Normalized to DMSO = 1
  - α = hydrogen-bond acidity
    - Normalized to methanol = 1
  - β = hydrogen-bond basicity
    - Normalized to hexamethylphosphoramide = 1

Solvatochromic Selectivity Triangle
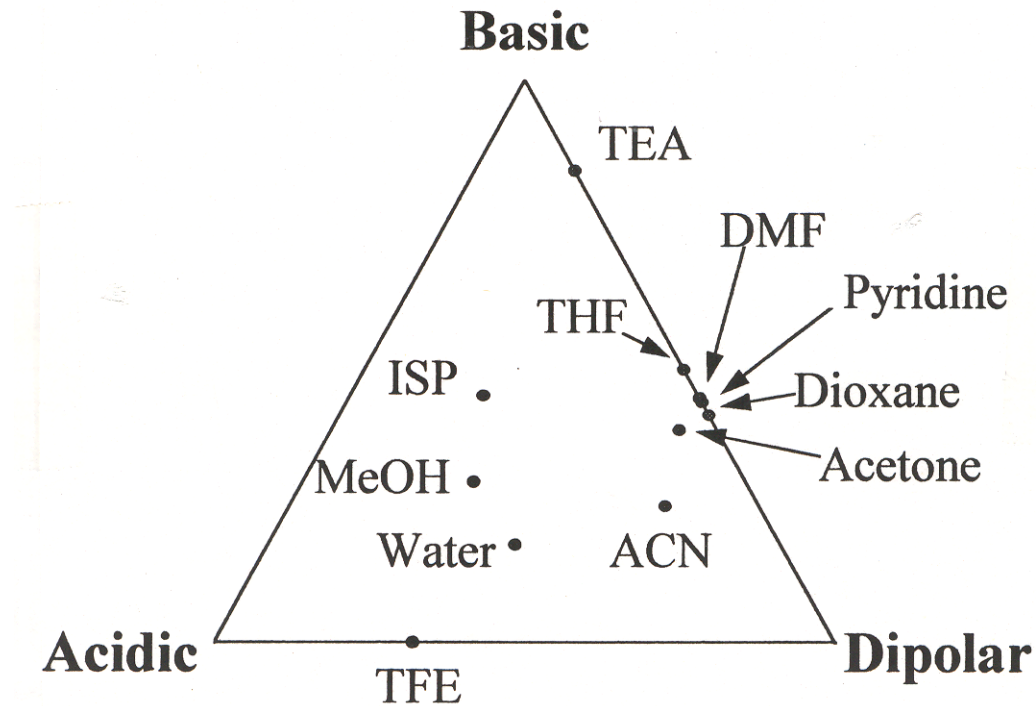
Solvation Parameter Model

Cavity Formation $\longrightarrow$ Reorganization $\longrightarrow$ Solute-Solvent Interactions
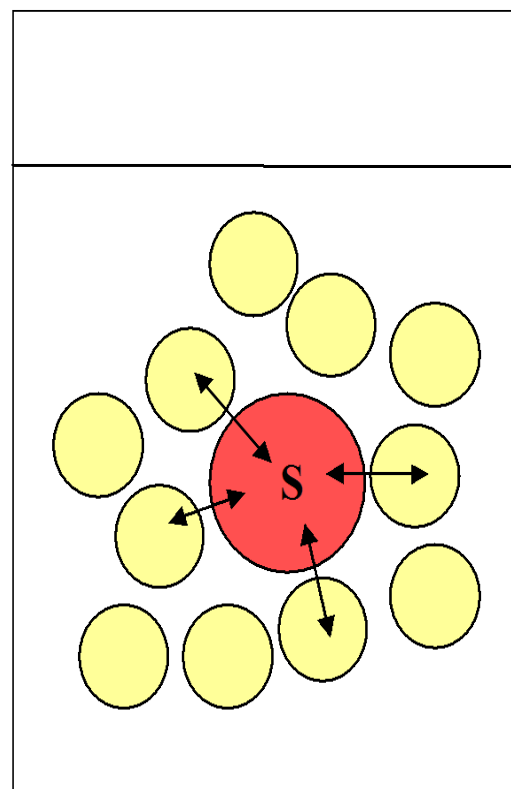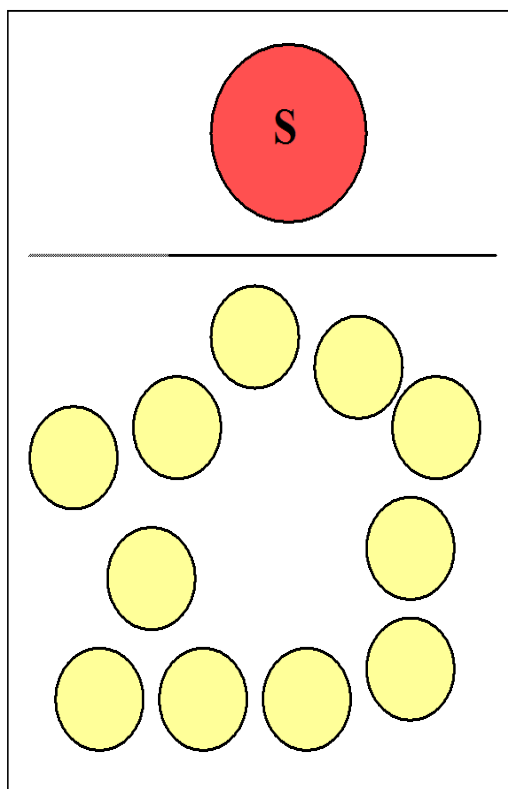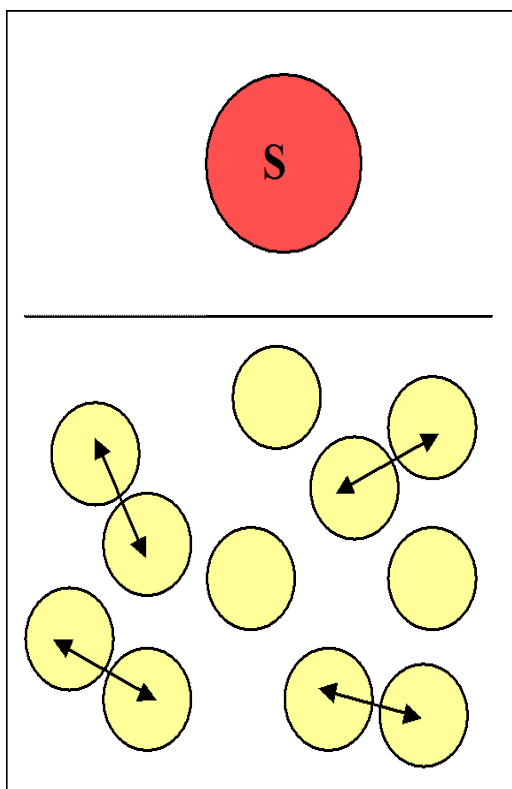
Solvation Parameter Model

Contains a term to accommodate cavity formation

(differences in cohesive energy of solvents)

Assigns general properties to solutes based on their capability for simultaneous multiple interactions

- Dispersion
- Dipole-type (orientation and induction)
- Hydrogen bonding (donor and acceptor properties)

Solvation Parameter Model

System constants relating to properties of the solvent

$$SP = c + e.E + a.A + b.B + s.S + l.L$$

Descriptors relating to solute properties

SP = free energy related property

Solute descriptors

- V is McGowan's Characteristic Volume
- E is the excess molar refraction
- S is the solute dipolarity/polarizability
- A is the effective solute hydrogen-bond acidity
- B is the effective solute hydrogen-bond basicity
- L is the gas-liquid partition coefficient at 25°C with hexadecane as a solvent

C.F. Poole, S.N. Atapattu, S.K. Poole, A.K. Bell, Anal. Chim. Acta 652 (2009) 32-53.

Solvation Parameter Model

System Constant	Solute Descriptor	Free Energy Contribution
l	**L**	*Ease of cavity formation* (solvent-solvent interactions) *Dispersion interactions* (solute-solvent interactions)
e	**E**	*Electron lone pair interactions*
s	**S**	*Dipole-type interactions*
a	**A**	*Solvent hydrogen-bond base-solute hydrogen-bond acid interactions*
b	**B**	*Solvent hydrogen-bond acid-solute hydrogen-bond base interactions*

Solvent Properties

Transfer of solutes from the gas phase to a solvent is defined by 5 system constants

- The system constants are independent of solute identity

- System constants are calculated from the experimental properties of a number of varied compounds

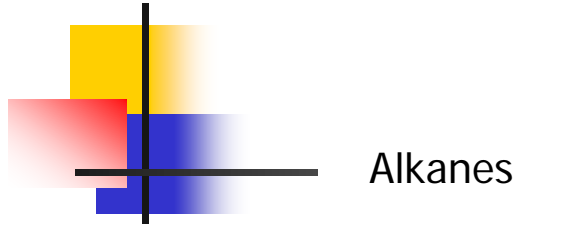- Data requirements established by statistical parameters

Solvent Properties

Solvent	System constants				
	e	*s*	*a*	*b*	*l*
N-Heptane	-0.16	0	0	0	0.98
Chloroform	-0.59	1.26	0.28	1.37	0.98
Acetone	-0.39	1.73	3.06	0	0.87
Methanol	-0.22	1.17	3.70	1.43	0.77
Trifluoroethanol	-0.61	1.46	1.90	4.46	0.63
Water	0.82	2.74	3.90	4.81	-0.21

Dendrogram using Average Linkage (Between Groups)

Rescaled Distance Cluster Combine
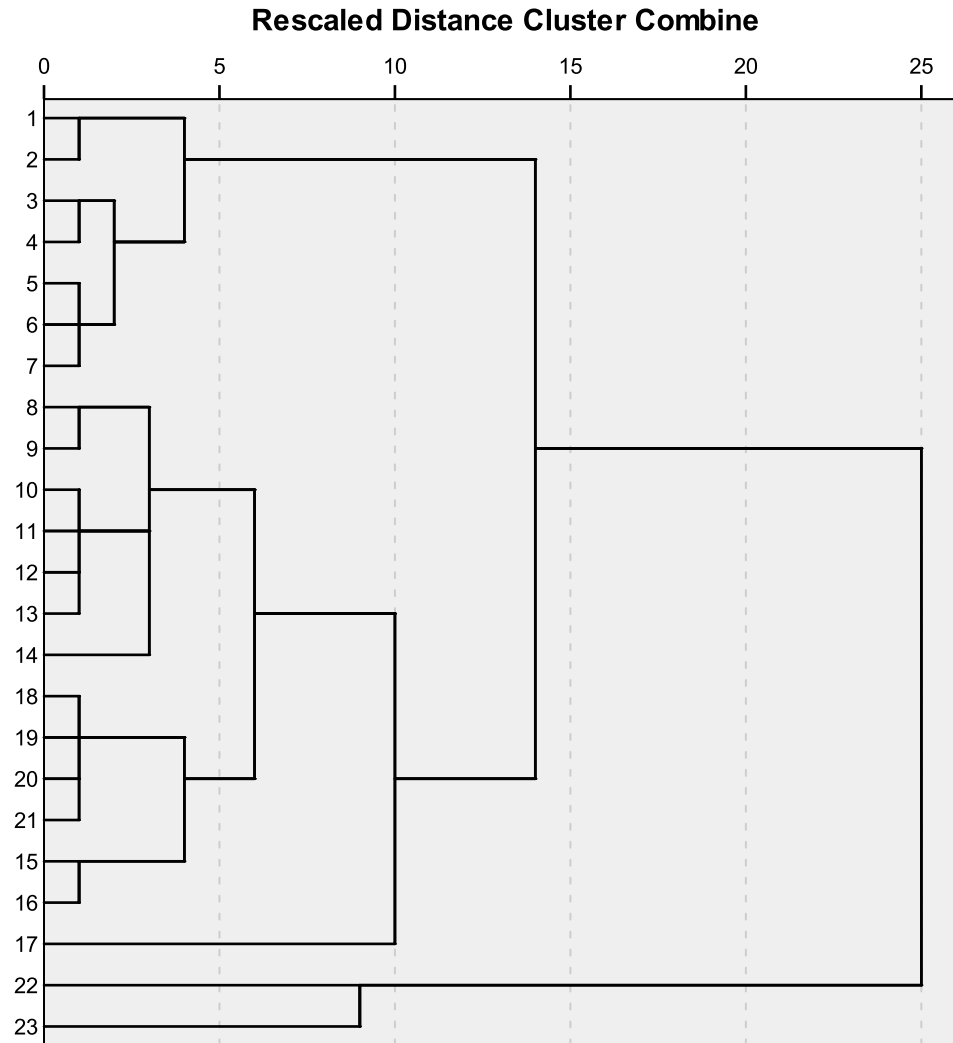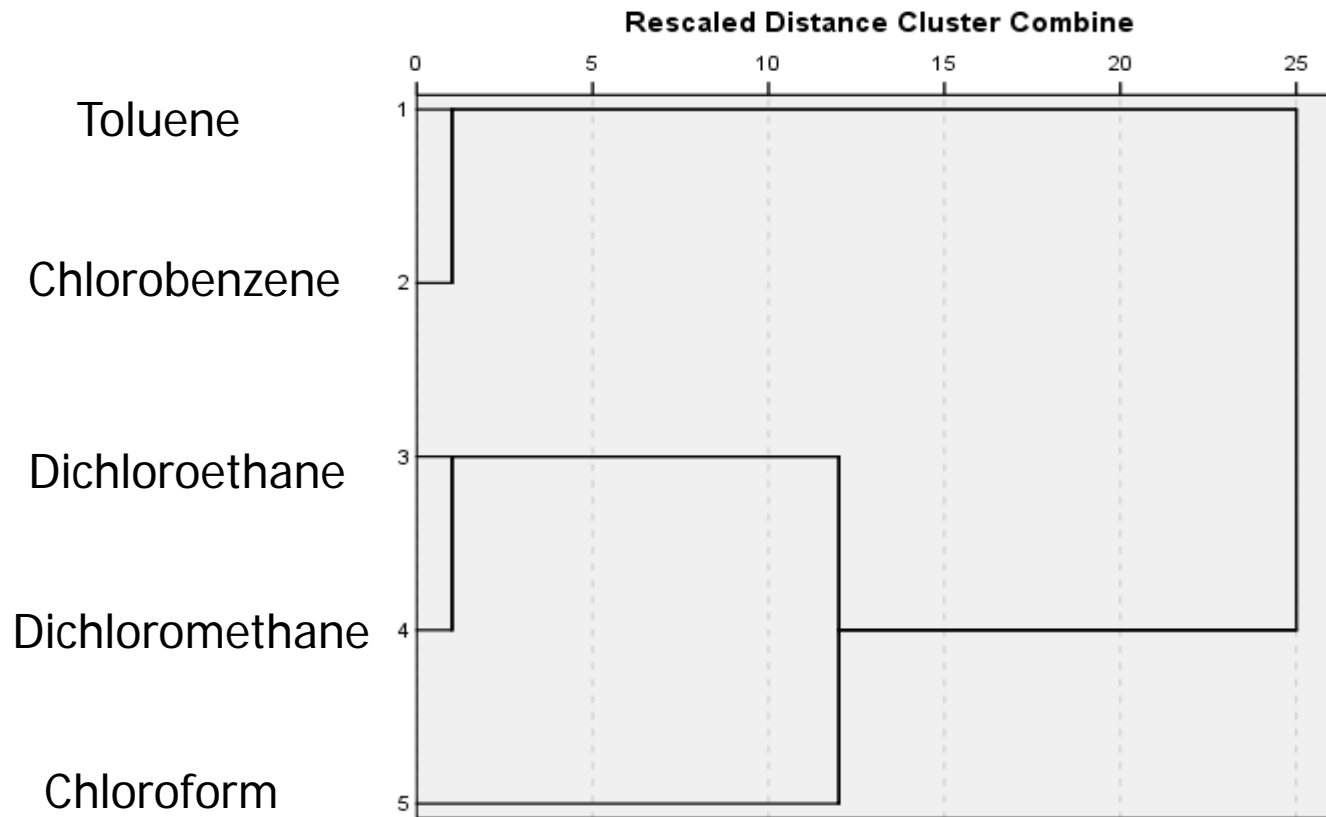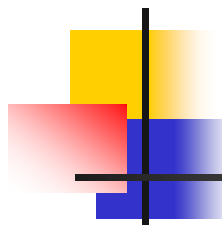
Group 2

Dendrogram using Average Linkage (Between Groups)

Dendrogram using Average Linkage (Between Groups)

Rescaled Distance Cluster Combine

	e	s	a	b	l
	-0.39	1.73	3.06	0	0.87
	-0.35	1.32	2.89	0	0.92

Methyl *t*-Butyl Ether

Diethyl Ether

Acetone

Ethyl Acetate

Acetonitrile

Propylene Carbonate
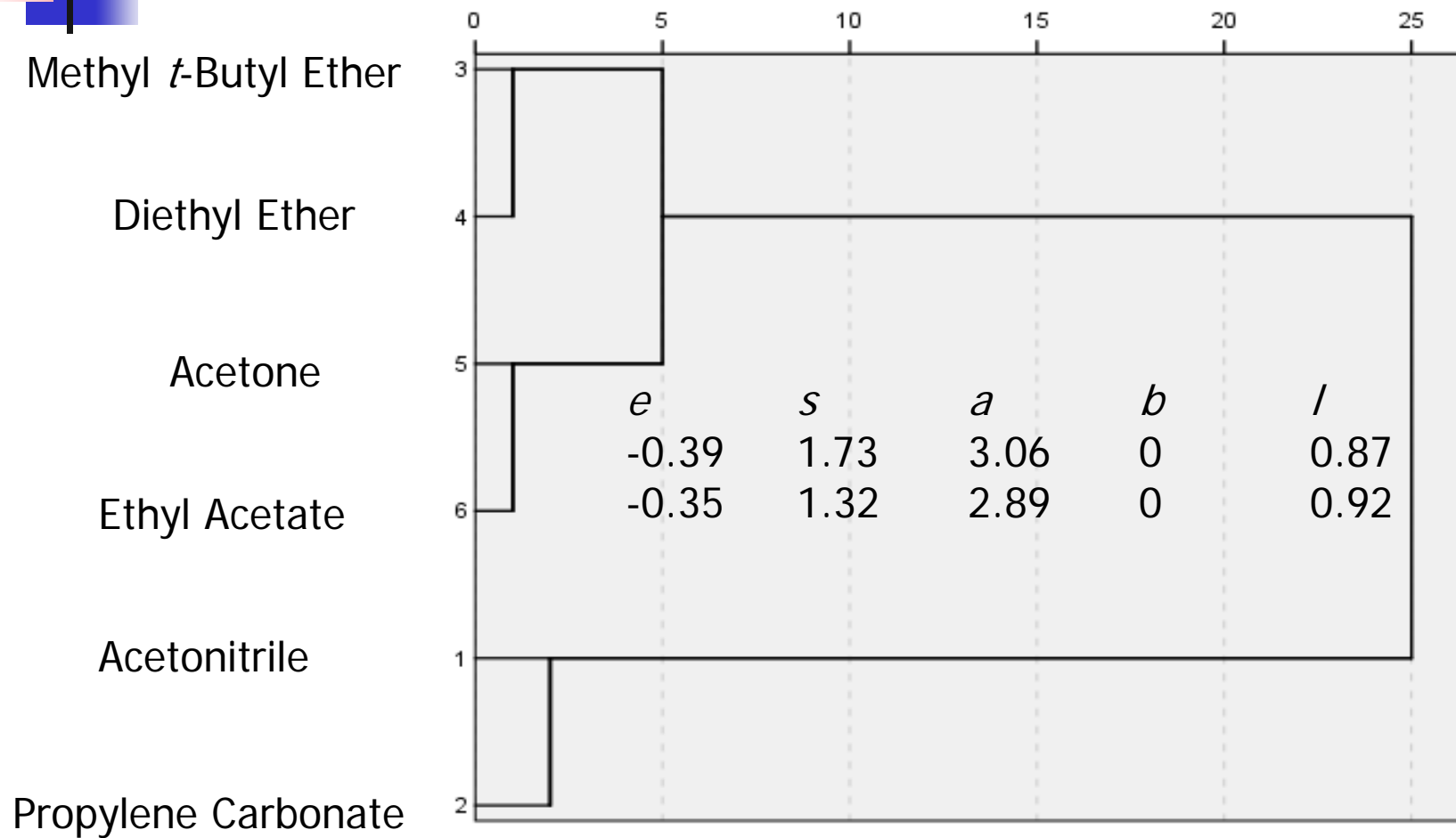
n-Alcohols

Dendrogram using Average Linkage (Between Groups)

Rescaled Distance Cluster Combine

	e	s	a	b	l
	-0.22	1.17	3.70	1.43	0.77
	-0.21	0.79	3.64	1.31	0.85
	-0.19	0.65	4.02	1.04	0.87
	-0.20	0.56	3.58	0.70	0.94

Methanol 1

Ethanol 2

Propan-1-ol 3

Octan-1-ol 4
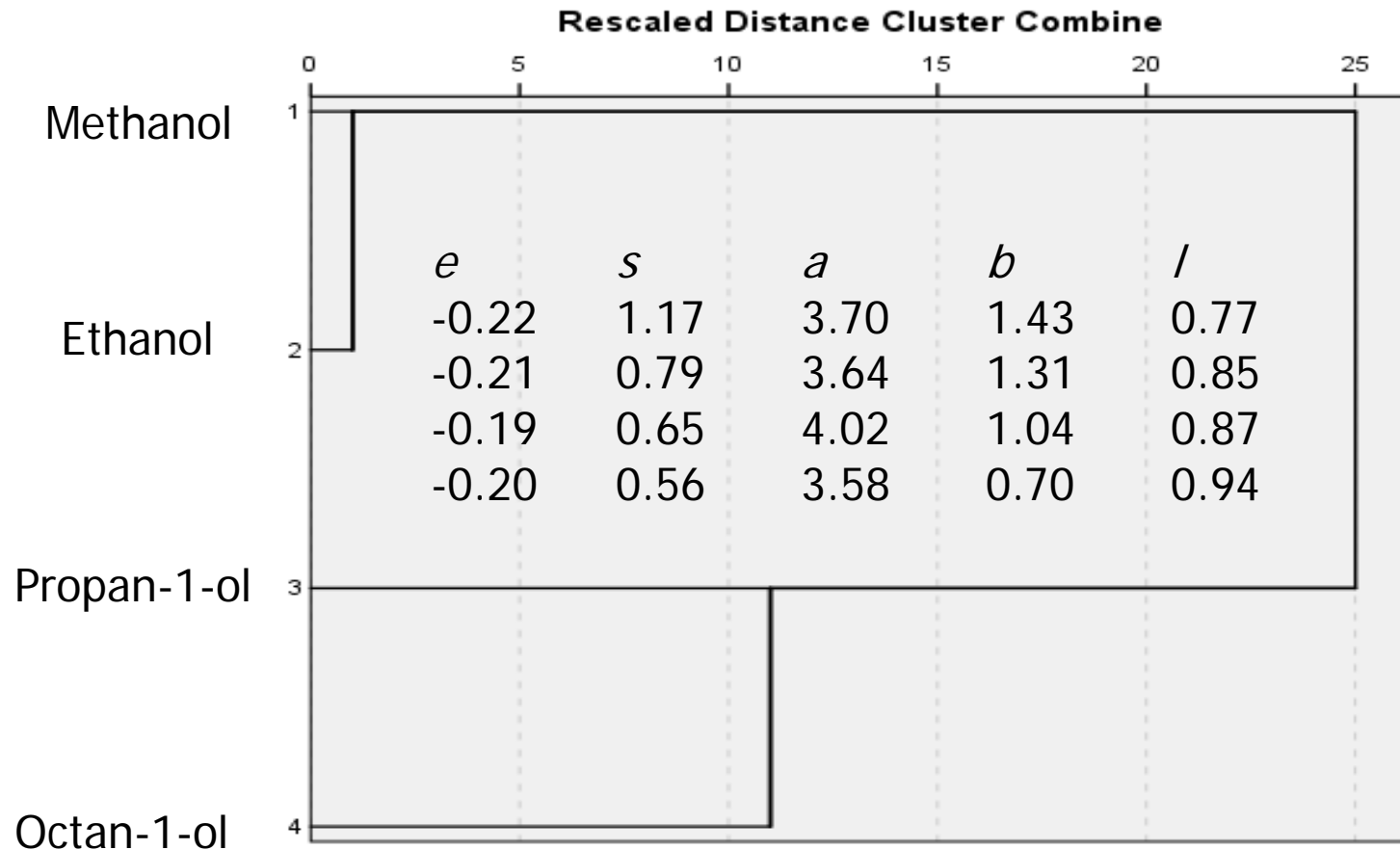
Solvents behaving independently

Dendrogram using Average Linkage (Between Groups)

Rescaled Distance Cluster Combine
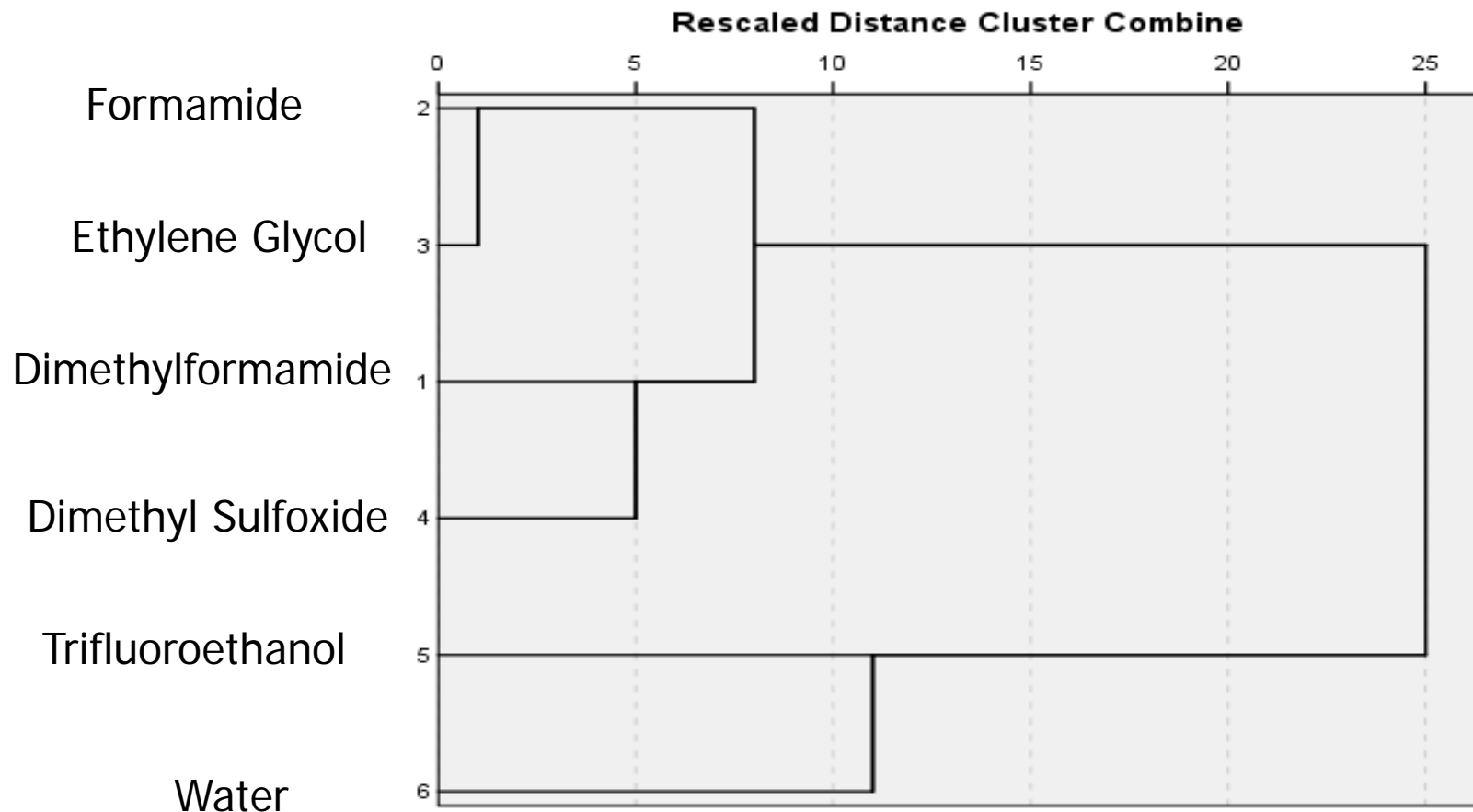
Solvents behaving independently

Solvent	System constants				
	e	s	a	b	l
Dimethylformamide	-0.87	2.11	3.77	0	1.01
Formamide	0.31	2.29	4.13	1.93	0.44
Ethylene Glycol	0.13	1.66	4.46	2.36	0.57
Dimethyl sulfoxide	0.13	2.81	5.47	0	0.73
Trifluoroethanol	-0.61	1.46	1.90	4.46	0.63
Water	0.82	2.74	3.90	4.81	-0.21

Solvent selection for method development in thin-layer chromatography

- n-Heptane
- Toluene
- Dichloromethane
- Chloroform
- Methyl *t*-Butyl Ether
- Acetone
- Acetonitrile

- Methanol
- Propan-1-ol
- Formamide
- Dimethylformamide
- Trifluoroethanol
- Water

Strength Adjusting Solvent

- **Normal-Phase Chromatography**
  - Weak and Moderately Polar Compounds
    - n-Heptane
  - Polar Compounds
    - Strongest solvent that fails to migrate sample
    - Facilitates incorporation of solvents immiscible with n-Heptane
- **Reversed-Phase Chromatography**
  - Always water

Solvent Strength Parameter ε°

- Solvent strength of a pure solvent can be defined by ε° for any adsorbent

- Free energy of adsorption of the solvent per unit surface area with pentane assigned as the zero reference

- Organization of solvents in ascending order of ε° is known as an eluotropic series

Inorganic Oxides

- Solvent strength parameter for silica gel

$$\varepsilon^\circ = -0.264V + 0.199S + 0.384A + 0.355B + 0.272$$

- Can be used to estimate ε° values to about 0.04 units for solvents lacking experimental values
- Silica gel retains solutes primarily through hydrogen-bonding and to a lesser extent dipole-type interactions

Inorganic Oxides

- Solvent strength parameter for alumina

$$\varepsilon° = -0.226V + 0.359S + 0.938A + 0.475B + 0.230$$

- Significantly more hydrogen-bond basic and dipolar/polarizable than silica gel
- Less hydrogen-bond acidic than silica gel

S. K. Poole and C. F. Poole, Chromatographia 53 (2001) S-162-166

Eluotropic series for silica gel

Solvent	ε°	Solvent	ε°
n-Heptane	-0.02	Formamide	0.55
Toluene	0.22	Propan-1-ol	0.60
Chloroform	0.26	Trifluoroethanol	0.62
Methyl t-butyl ether	0.29	Methanol	0.70
Dichloromethane	0.30	Water	0.72
Acetonitrile	0.52		
Acetone	0.53	each CH_2 = -0.05	
Dimethylformamide	0.51		

Solvent Selection for Normal-Phase Chromatography

SELECTION OF THE SUITABLE SOLVENTS

I   II   III   IV   V   VI   VII   VIII
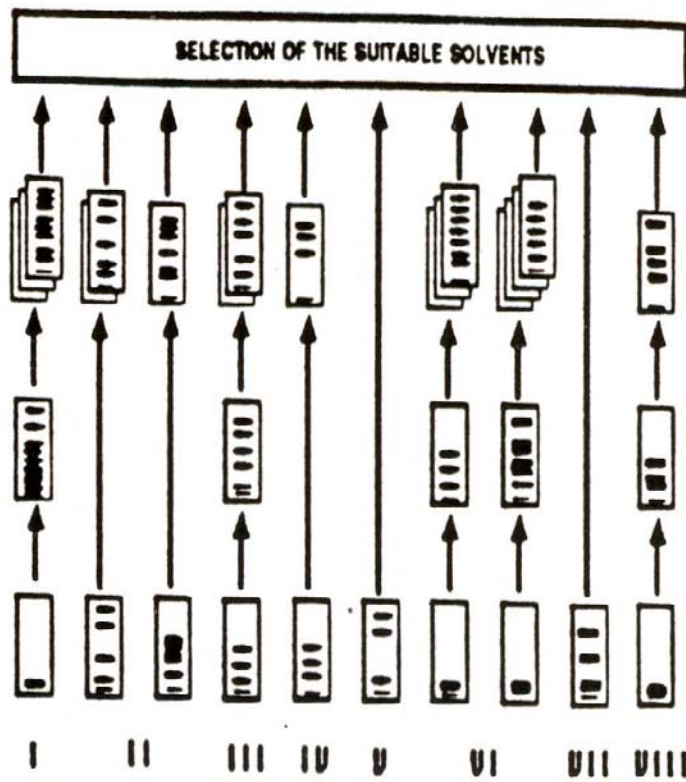
PRISMA MODEL

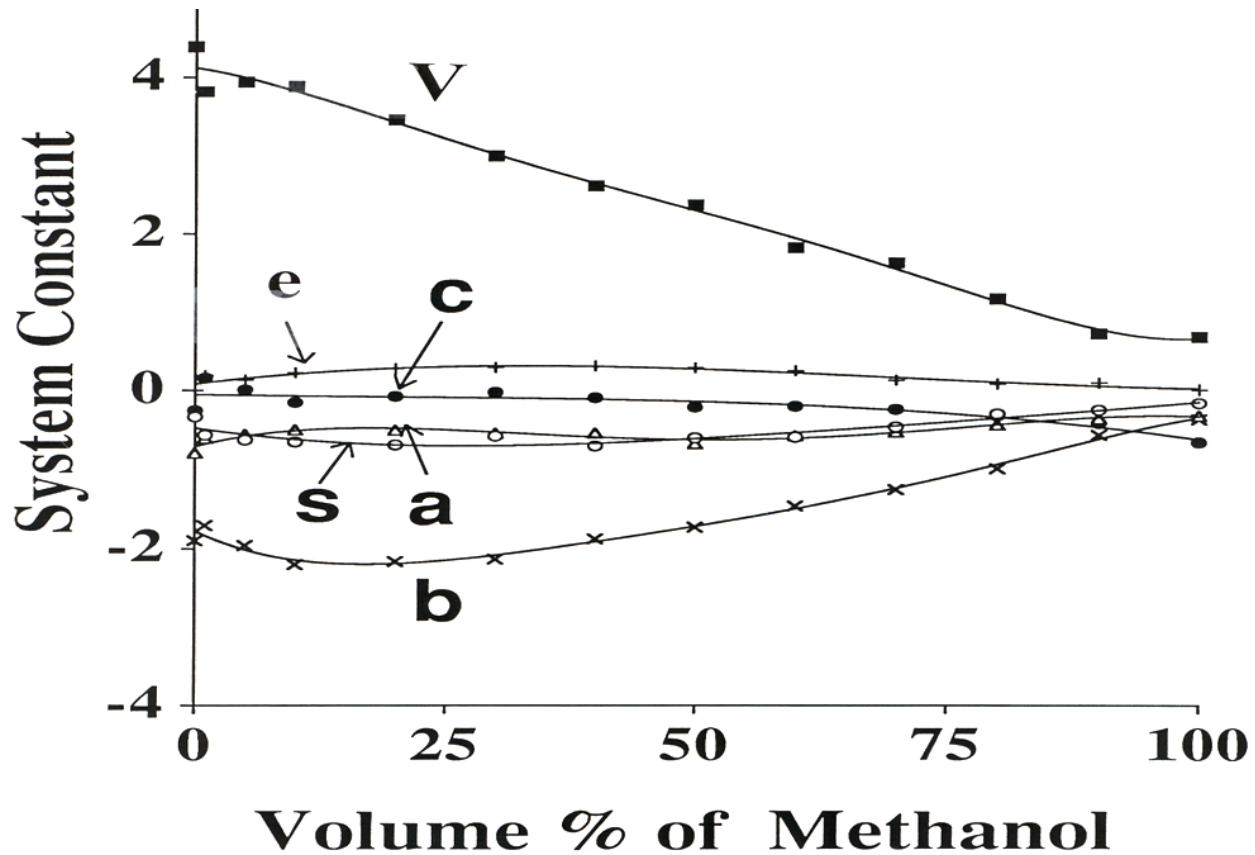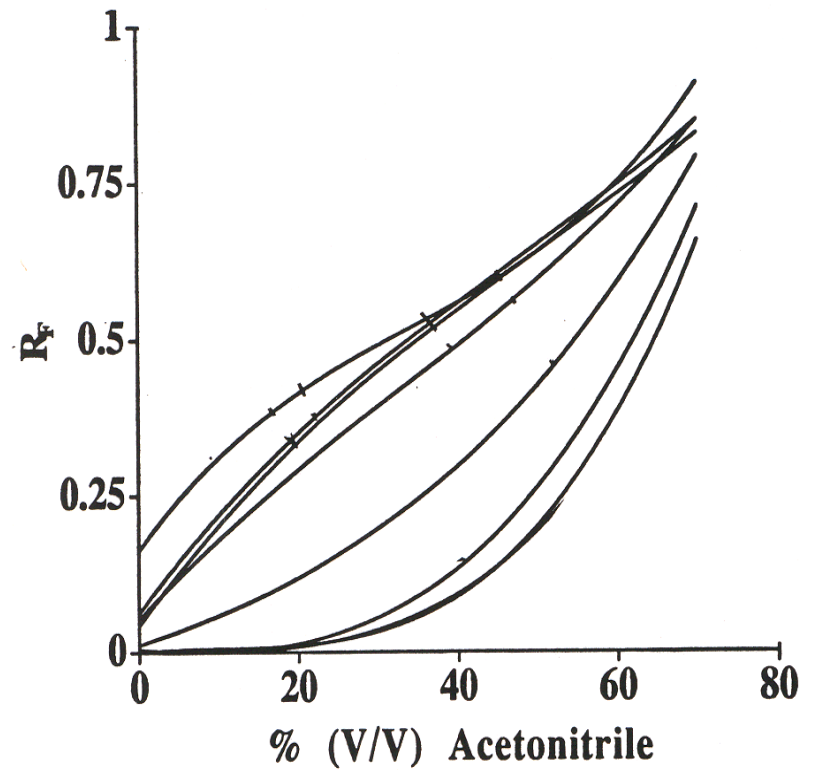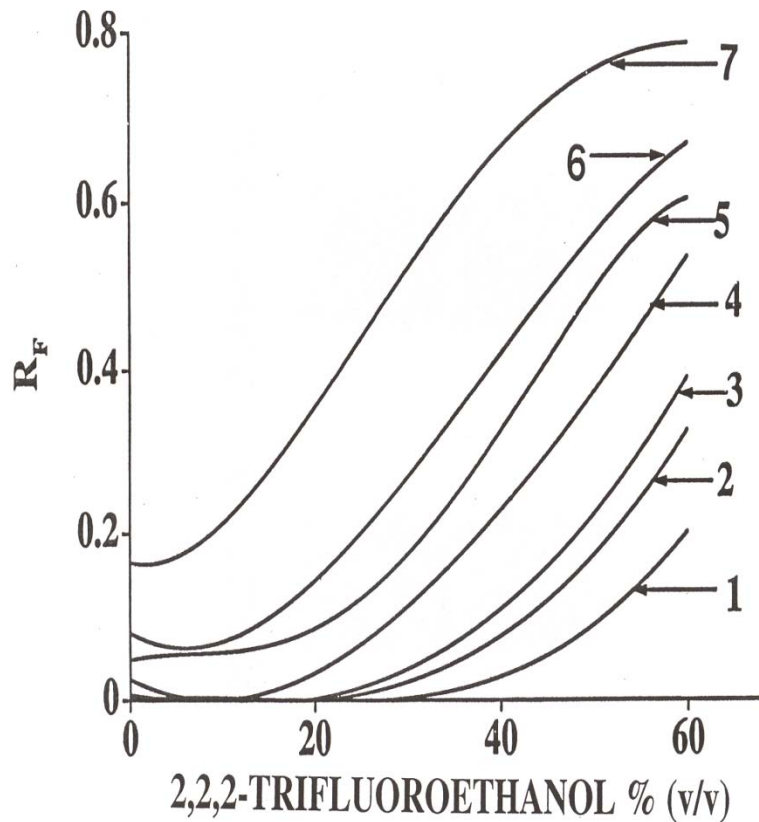**Screen solvents from different selectivity groups**

Optimize selected solvents

System Maps used to Model Reversed-Phase Separations

Solvent Selection for Reversed-Phase Chromatography

Solvation parameter model

Gas → Condensed Phase

$$SP = c + eE + sS + aA + bB + lL$$

Condensed Phase → Condensed Phase

$$SP = c + eE + sS + aA + bB + vV$$

$$SP = \text{free energy related property}$$

Totally organic biphasic systems

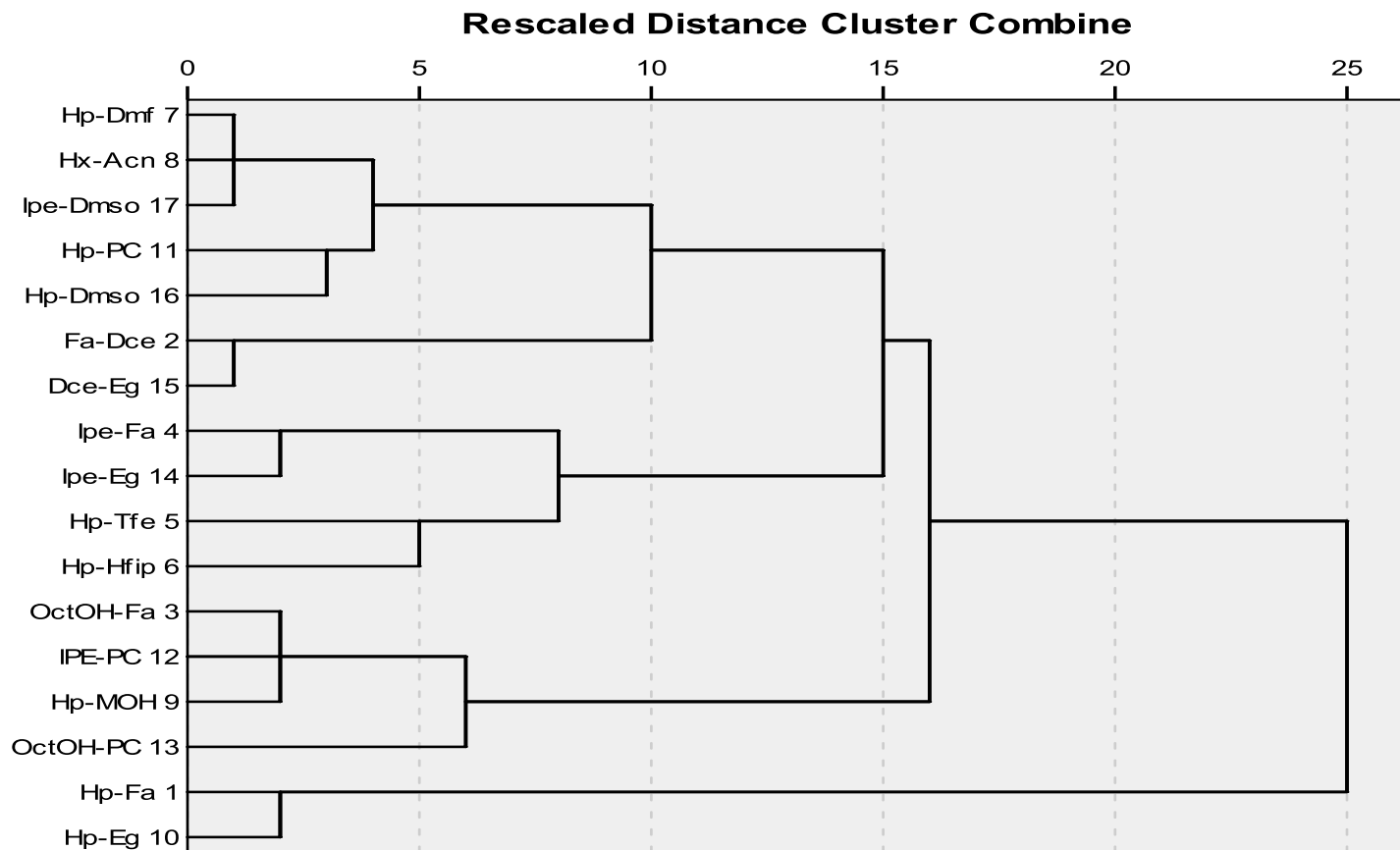|	Heptane	Isopentyl Ether	Dichloro-ethane	Octanol
Acetonitrile	IM	M	M	M
Propylene carbonate	IM	IM	M	IM
Formamide	IM	IM	IM	IM
Dimethylformamide	IM	IM	M	M
Dimethyl sulfoxide	IM	IM	M	M
Methanol	IM	M	M	M
Ethylene glycol	IM	IM	IM	M
Trifluoroethanol	IM	M	M	M

M = miscible and IM = low mutual solubility

Biphasic systems formed with heptane

Counter Solvent	System constants				
	e	s	a	b	v
Acetonitrile	0.35	-1.44	-1.61	-0.87	0.67
Methanol	0.19	-0.69	-1.10	-0.95	0.62
Ethylene glycol	0.09	-1.55	-3.78	-1.55	2.13
Formamide	0.56	-2.24	-3.25	-1.61	2.39
Dimethylformamide	0.04	-1.39	-2.16	-0.59	0.49
Dimethyl sulfoxide	0	-1.78	-3.09	-1.17	1.18
Propylene carbonate	0.45	-2.09	-2.65	-0.43	0.81
Trifluoroethanol	0.88	-1.56	-1.31	-2.93	1.30
Water	0.67	-2.06	-3.32	-4.73	4.54

Totally organic biphasic systems

Dendrogram using Average Linkage (Between Groups)

Rescaled Distance Cluster Combine

Aqueous biphasic systems

Dendrogram using Average Linkage (Between Groups)

Rescaled Distance Cluster Combine

T. Karunasekara, C.F. Poole, J. Planar Chromatogr. 25 (2012) 190-199.
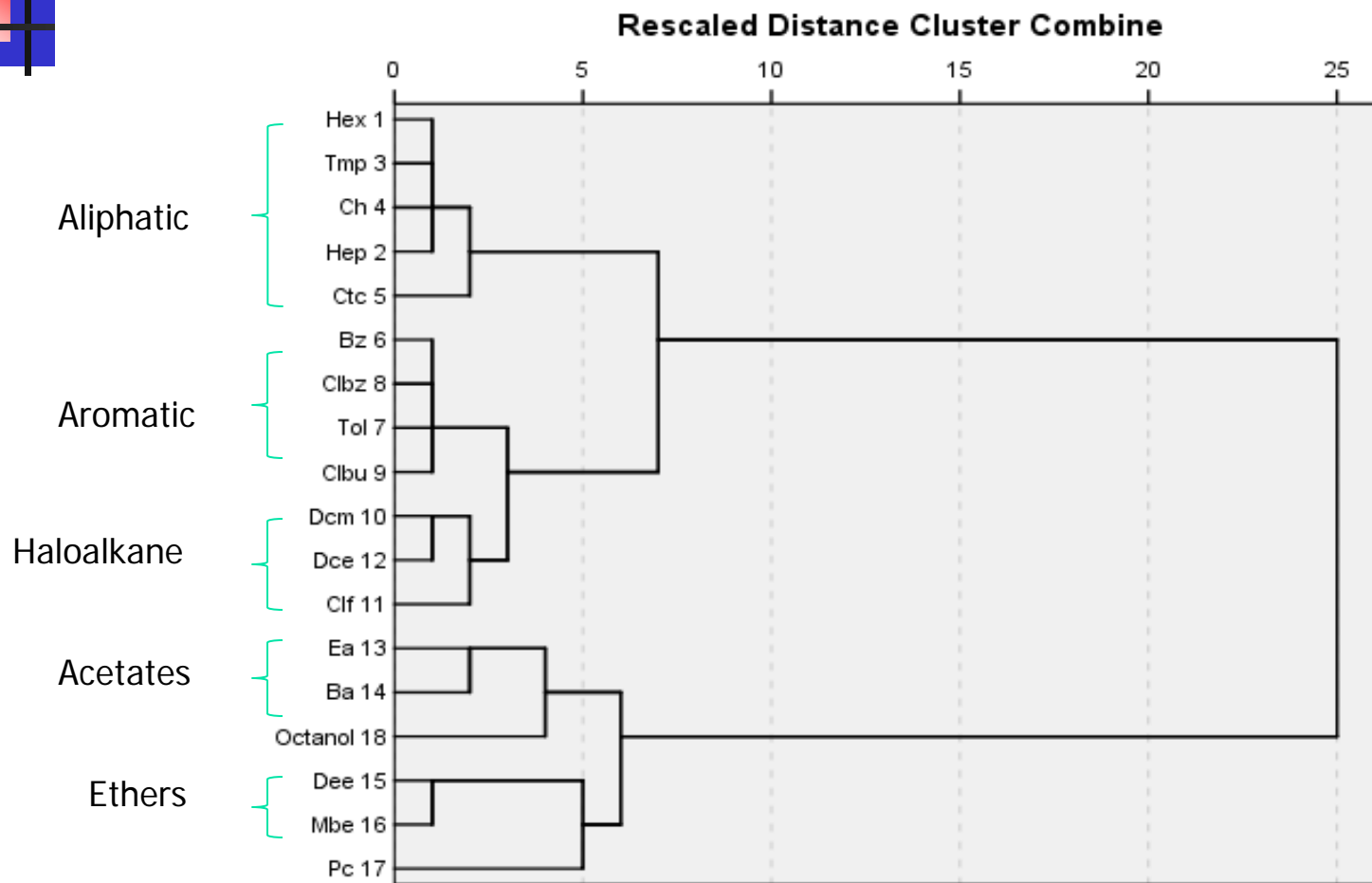
Variation of the system constants

Totally organic biphasic systems

$v < 2$

$b < 2$

Aqueous biphasic systems

$v > 4$

$b > 4$
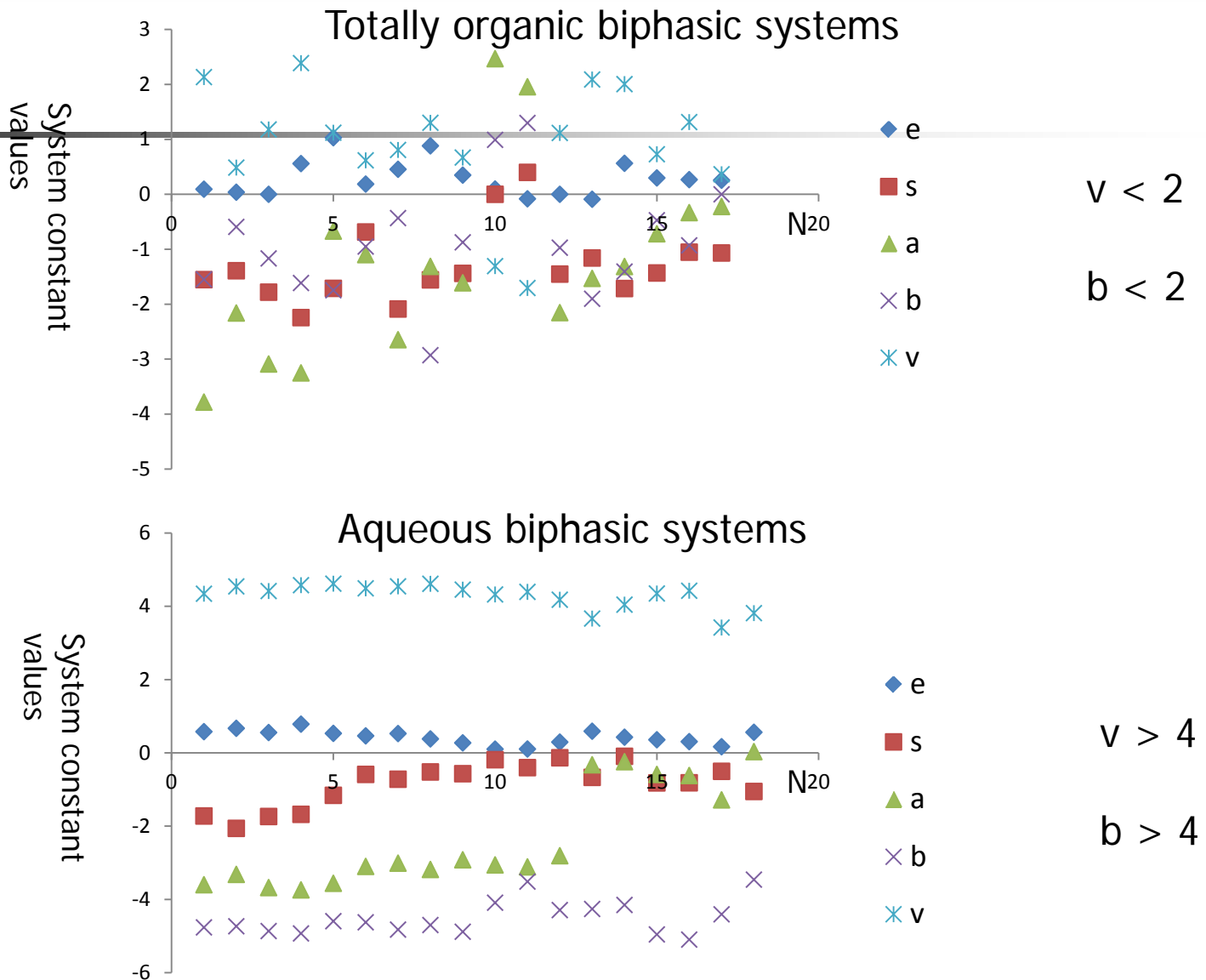
Biphasic systems including water
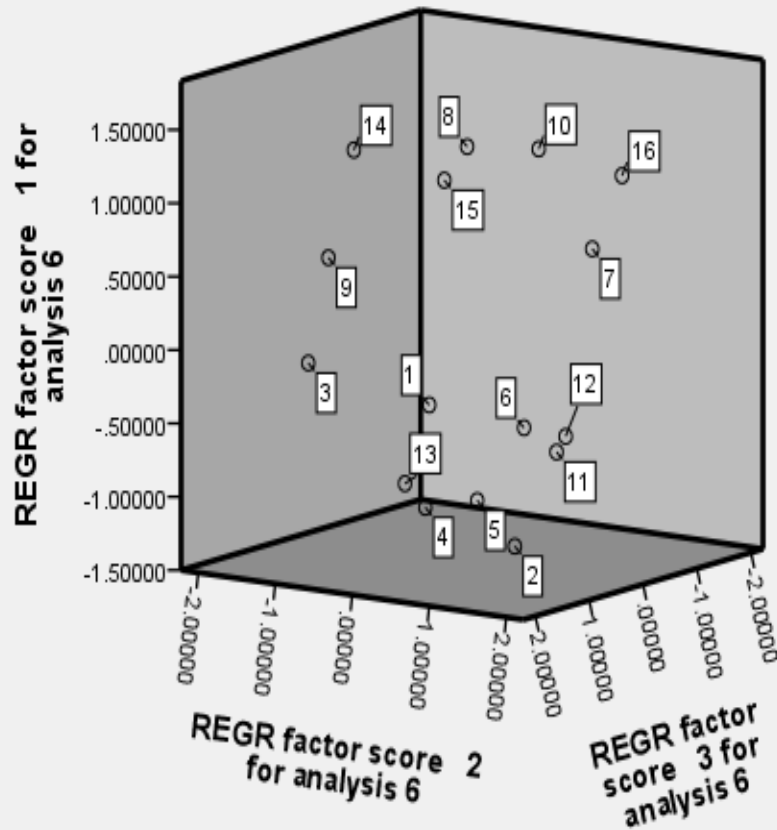
1 = Heptane-Formamide

2 = Formamide-Dichloroethane

3 = Octanol-Formamide

4 = Isopentyl ether-Formamide

5 = Heptane-Trifluoroethanol

6 = Heptane-Dimethylformamide

7 = Heptane-Acetonitrile

8 = Heptane-Methanol

9 = Heptane-Ethylene glycol

10 = Chloroform-Water

11 = Cyclohexane-Water

12 = Octanol-Water

13 = Toluene-Water

14 = Di-n-Butyl ether-Water

15 = Heptane-Water

16 = Dichloroethane-water

Dimethyl sulfoxide

- As a useful industrial solvent it has many applications in synthesis ,spectroscopy and chemical engineering processes

- Has an ability to dissolve both polar and non polar compounds

- Miscible with many organic solvents as well as water

- Has a wide range of medical uses

- Selectively extract polycyclic aromatic hydrocarbons

- Generally considered as a non hydrogen bond acid…???

Biphasic systems with Heptane

Counter solvent	System constants				
	e	s	a	b	v
Propylene carbonate	0.45	-2.09	-2.65	-0.43	0.81
Dimethylformamide	0.04	-1.39	-2.16	-0.59	0.49
Acetonitrile	0.35	-1.44	-1.61	-0.87	0.67
Dimethyl sulfoxide	0	-1.78	-3.09	-1.17	1.18
Ethylene glycol	0.09	-1.55	-3.78	-1.55	2.13
Formamide	0.56	-2.24	-3.25	-1.61	2.39
Trifluoroethanol	0.88	-1.56	-1.31	-2.93	1.30
Water	0.67	-2.06	-3.32	-4.73	4.54

*T. Karunasekara, C.F. Poole, J. Chromatogr. A **1218** (2011) 4525-4536.*

Effect of Water on the Acidity of DMSO

Partition with thoroughly dried DMSO (0.005% water)
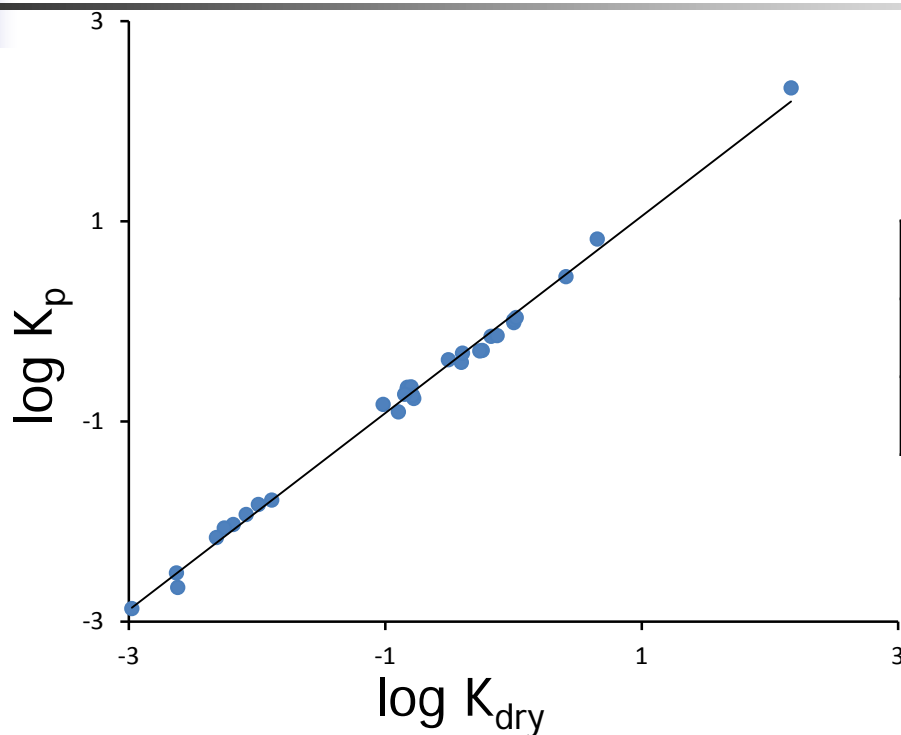
95% CI	Upper	Lower
Slope	1.020	0.988
Intercept	0.030	-0.016

$r^2 = 0.9981$
$SE = 0.048$
$F = 15394$
$n = 30$

$\log K_{dry} = -\ 0.39\ -\ 1.49\ S\ -\ 2.72\ A\ -\ 1.37\ B\ +\ 1.60\ V$

*T. Karunasekara, C.F. Poole, J. Chromatogr. A **1218** (2011) 4525-4536.*

Selective Extraction Using DMSO

- Extracts polycyclic aromatic compounds from hydrocarbon-like solvents

- Log Kp = 0.289-1.781S-3.088A-1.167B+1.180V

- Moderately cohesive(v=1.180)

  - Acts as a barrier for low polarity compounds

- Reasonable capacity for polar interactions

  - Provides the driving force for transfer of polycyclic aromatic compounds to DMSO

    (s=-1.781 a=-3.088 b=-1.167)

*T. Karunasekara, C.F. Poole, J. Chromatogr. A **1218** (2011) 4525-4536.*

Dimethyl sulfoxide-Heptane

Compound	Contribution to the partition coefficient (log K_p)				
	sS	aA	bB	vV	Estimated (K_p)
Anthracene	2.317	0	0.303	-1.716	4.12
Fluoranthene	2.639	0	0.323	-1.870	6.35
Pyrene	2.627	0	0.334	-1.870	6.33
Naphthalene	1.606	0	0.225	-1.280	1.83
1-Acetonaphthone	2.486	0	0.644	-1.632	16.2
1-Nitronaphthalene	2.629	0	0.338	-1.489	15.5
1-Naphthol	2.007	2.338	0.384	-1.350	1230
Bicyclohexyl	0.534	0	0	-1.867	0.024
Phenylcyclohexyl	1.058	0	0.082	-1.715	0.140

e = 0 for the heptane-dimethyl sulfoxide system