From Modeling Separations to Estimation of Biopartitioning Properties: Use of the Solvation Parameter Model in Thin-Layer Chromatography

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Solvation Parameter Model

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

System Constant	Solute Descriptor	Interaction
v	V	Cavity formation Dispersion
e	E	Electron lone pair
s	S	Dipole-type
a	A	Solvent HBB-solute HBA
b	B	Solvent HBA-solute HBB

Solute Descriptors

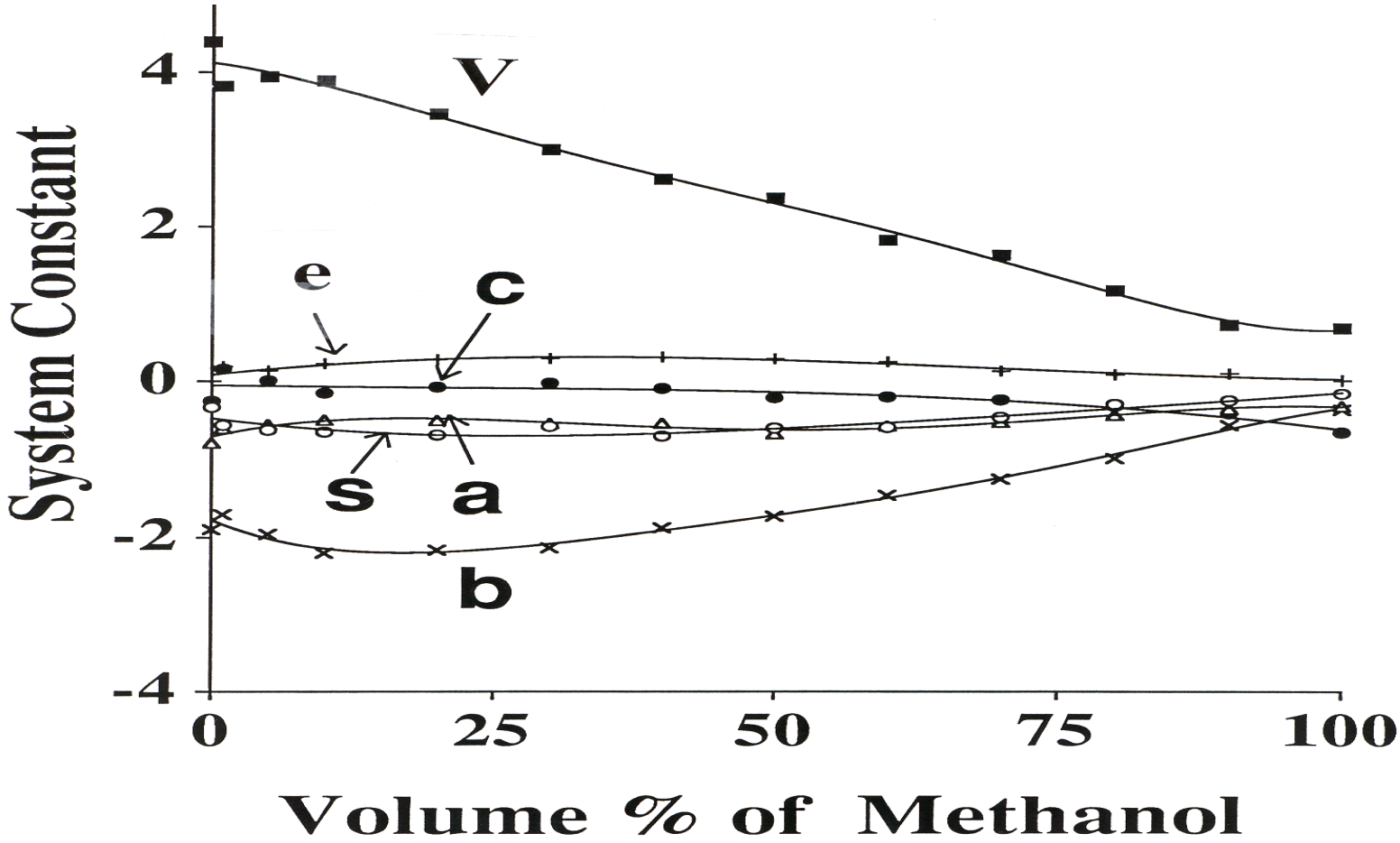
- V is McGowan's Characteristic Volume
- E is the excess molar refraction
- S is the solute dipolarity/polarizability
- A is the effective solute hydrogen-bond acidity
- B is the effective solute hydrogen-bond basicity

Free Energy Related Property

- For TLC this is the R_M Value
- For GC and LC this is log K or log k
- For condensed phase distribution systems this is log K
- For gas to condensed phase systems this is Log L

$$R_M = \log (1 - R_F) / R_F$$

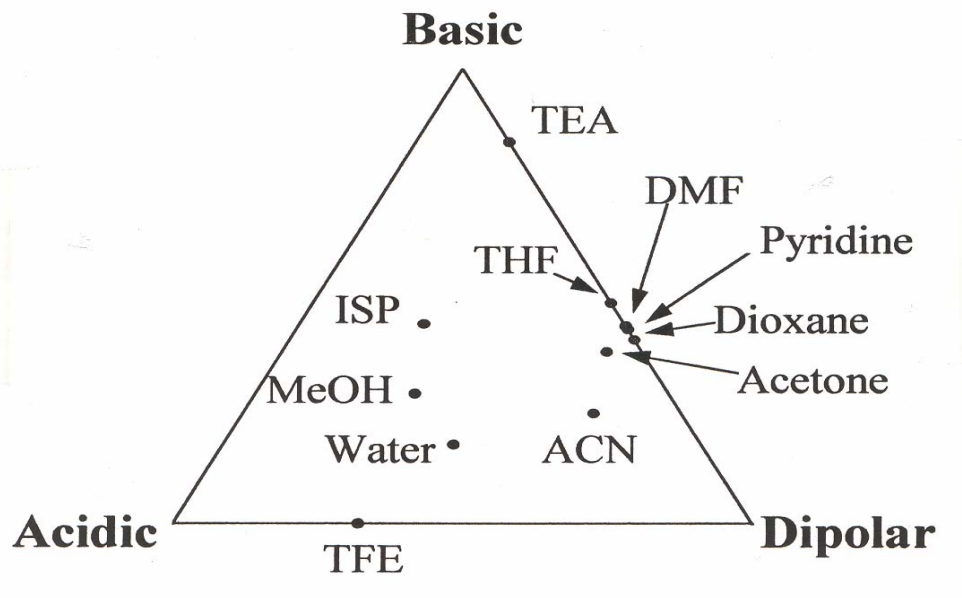
System Map


System Constant
4
2
0
-2
-4
V
e
c
s
a
b
0
25
50
75
100
Volume % of Methanol

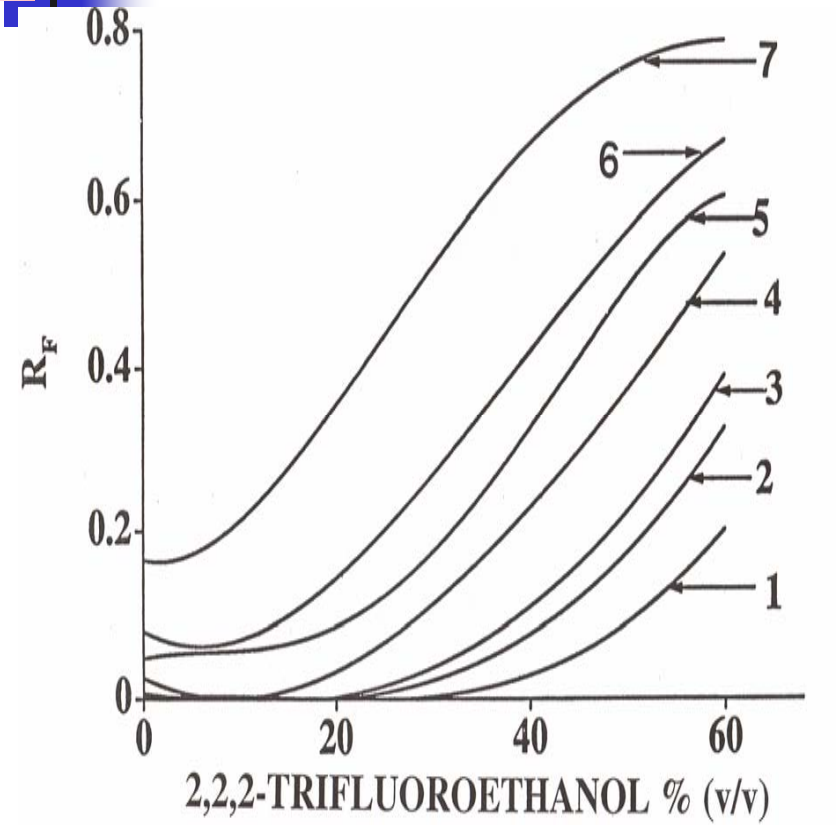
System Maps

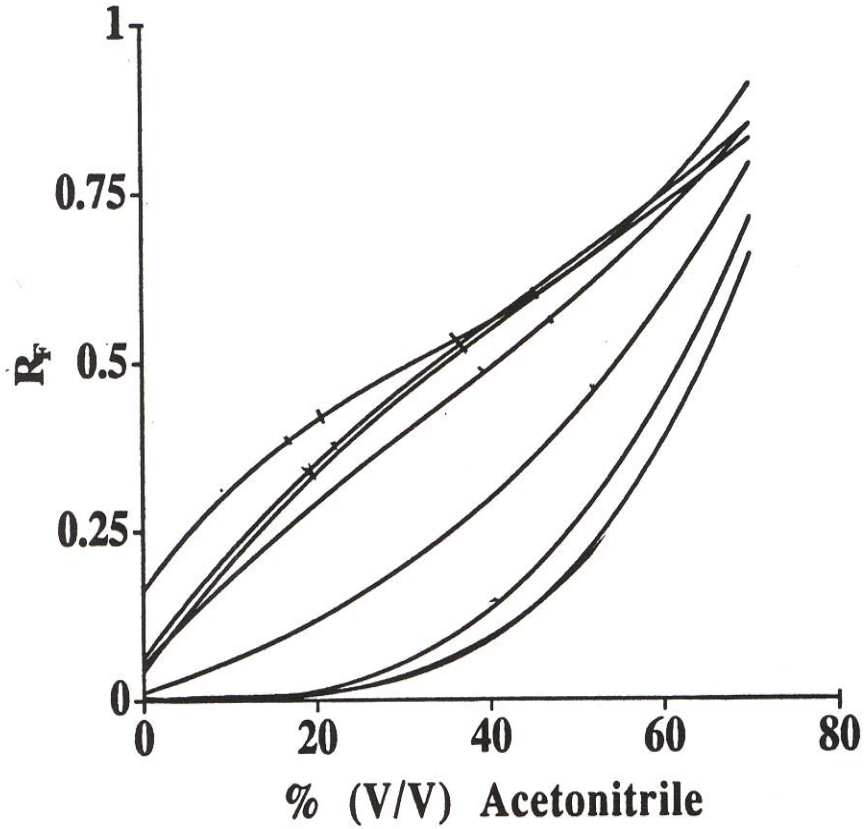
Solvent
Methanol
2-Propanol
Trifluoroethanol
Acetonitrile
Tetrahydrofuran
Acetone
Dimethylformamide
Pyridine

Stationary Phase
Octadecylsiloxane
Cyanopropylsiloxane
Diol (few systems)

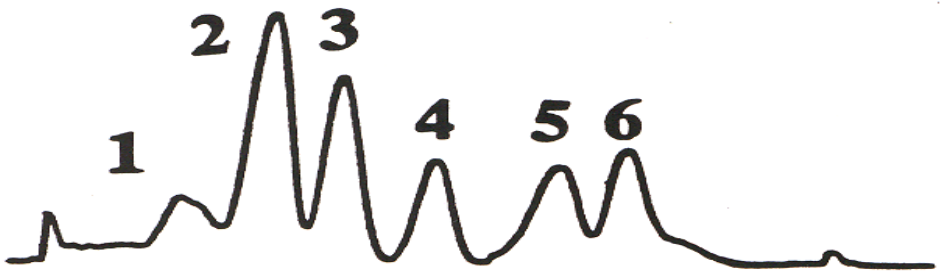


Retention Maps





Separation of Analgesics



	R_F Values	
	Predicted	Experimental
2,2,2-trifluoroethanol-water (3:7)		
Ibuprofen	0.06	0.06 ± 0.01
Naproxen	0.09	0.12 ± 0.03
Phenacetin	0.20	0.19 ± 0.02
Caffeine	0.30	0.30 ± 0.01
Asprin	0.40	0.46 ± 0.05
Acetaminophen	0.64	0.63 ± 0.01

Separation of Phenols

Mobile Phase	Predicted ΔR_F		
70% Methanol	0.16	0.21	0.21
50% Trifluoroethanol	0.16	0.16	0.17
50% Dimethylformamide	0.13	0.24	0.20
50% Acetonitrile	0.12	0.21	0.20

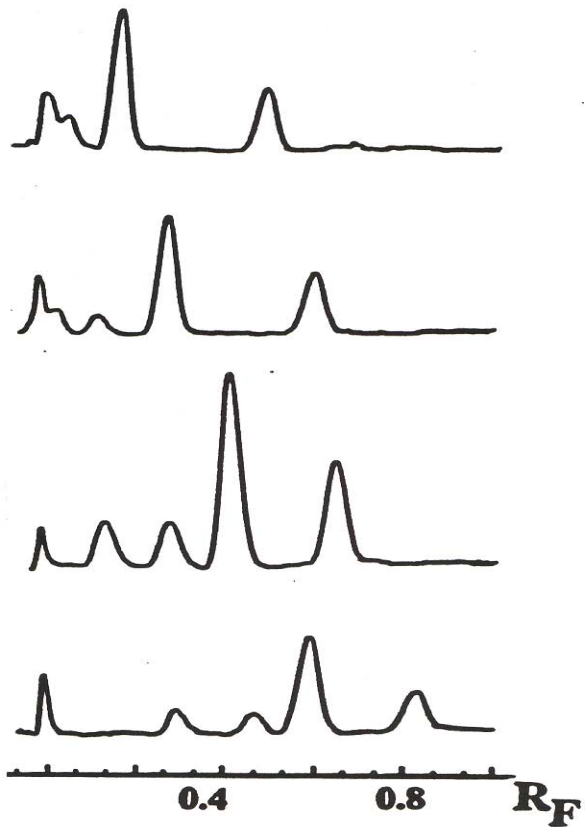
Stationary Phase: Cyanopropylsiloxane

Sample: Pentachlorophenol, 2,4,6-Trichlorophenol, 4-Nitrophenol, and Catechol

Separation of Phenols

Confirmation of Predictions with Solvent Ranked First

Methanol	R_F			
40 %	0.01	0.05	0.18	0.49 (exp)
	0.01	0.05	0.16	0.46 (pred)
50 %	0.03	0.11	0.26	0.59
	0.02	0.08	0.23	0.55
60 %	0.12	0.26	0.41	0.69
	0.07	0.18	0.39	0.65
70 %	**0.28**	**0.45**	**0.58**	**0.82**
	0.22	**0.38**	**0.59**	**0.79**



Calculation of Solute Descriptors

Compound = Ephedrine

V = 1.4385 SD = 0.083

E = 0.920 N = 12

S = 0.65 *Solver used to solve simultaneous set of*

A = 0.20 *equations by changing descriptor values*

B = 1.24 *to minimize* ΔR_M

$\Delta R_M = R_M$ observed – R_M predicted

System	v	e	s	a	b	c	$(\Delta R_M)^2$
1	2.21	0	-0.17	-0.33	-1.24	-0.82	0.012
2	1.52	0.41	0	0	-1.92	-0.57	0.058
3	etc.						

Surrogate Models

Similarity of sorption properties is established by comparison of the capacity of the system for all solute-solvent interactions measured and defined in the same way

- **Emulation**
  - ⇒**The system constants should be (nearly) identical**

- **Correlation**
  - ⇒**The ratio of the system constants (usually normalized by division by *v*) should be the same (or nearly the same) for both processes**

$$\log K_2 = p \log K_1 + q$$

Lipophilicity

	v	e/v	s/v	a/v	b/v
Log P_{OW}	3.81	0.15	-0.28	0.01	-0.91
60% DMF	0.80	0.26	-0.18	0	-0.84
20% ISP	2.84	0	-0.06	-0.12	-0.74
20% Pyridine	1.97	0	-0.15	0	-0.80

Stationary Phase RP-18WF

Best model is 30-60% Dimethylformamide

No Good TLC Models for Lipophilicity

SYSTEM CONSTANTS DATABASES

Biopartitioning

- Intestinal Absorption
- Blood-Brain Distribution
- Water-Skin Distribution
- Soil-Water Distribution
- Plant Cuticle Matrix-Water Distribution
- Non-Specific Toxicity to Fish and Bacteria
- Nasal Pungency
- Eye Irritation

Search for Correlation Models

There are no useful models in the TLC system constants database for

Intestinal Absorption

Blood-Brain Distribution

Soil-Water Distribution

Plant Cuticle Matrix-Water Distribution

Search for Correlation Models

There are suitable models in the TLC database to estimate non-specific toxicity

Fathead Minnow

Gupy

Tadpole

Tetrahymena pyriformis (Tetratox test)

Search for Correlation Models

Fathead Minnow LD_{50}

	v	e/v	s/v	a/v	b/v
Fish	3.39	0.07	0	0.12	-1.08
TLC	1.32	0	0	0.13	-1.00

Stationary Phase RP-18WF

Mobile Phase 10-40% Pyridine

Search for Correlation Models

Microtox Test

	v	e/v	s/v	a/v	b/v
Microtox	2.88	0.22	0	0	-0.87
TLC	2.31	0.17	0	0	-0.87

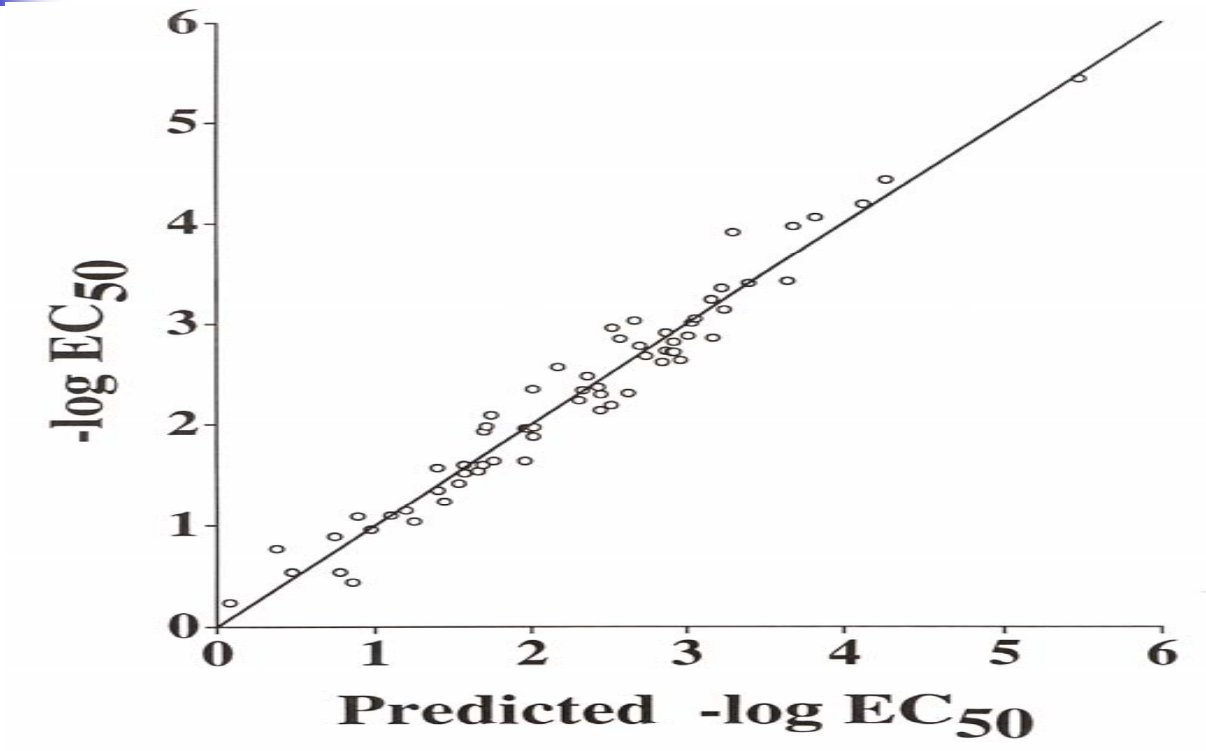
Stationary Phase CN

Mobile Phase 10-35 % 2-Propanol (best)

5-20 % Acetonitrile (good)

10-20 % Methanol (useful)

Non-specific Toxicity: Guppy



Stationary Phase RP-18 WF

Mobile Phase 30% Acetonitrile

Alternative

- Use TLC to estimate solute descriptors for use in any of the biopartitioning models.
- Allows TLC data to be used in a broader sense to estimate biopartitioning properties
- Unlike for correlation models a standard set of TLC systems suffices to estimate correlation models

Inorganic Oxides

Simultaneous contribution of solute and solvent interactions with the adsorbent folded into the R_M value

The heterogeneous energy distribution of sites) and steric requirements (fixed position of sites) conceptually not accommodated by the model

Inorganic Oxides

- The solute term ($\varepsilon^{\circ}A_S$) and solute term (S^*) of the simple competition model can be modeled independently and successfully
- The definitions of S^* and A_S are difficult to reconcile with their predicted properties
- The simple competition model ignores contributions from solute-solvent interactions in the mobile phase

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