Solvent and stationary phase selectivity in enantioselective SFC

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CHIRAL TECHNOLOGIES, INC

Immobilized Polysaccharides

Stable **:** To all normal phase, polar & reversed phase solvents – just like other HPLC columns

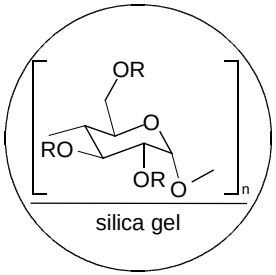
Stable **:** An extended range of allowed co-solvents – THF, MTBE, Ethyl Acetate, Methylene Chloride, Chloroform … enhances the probability of success

Stable **:** Wide range of compatible solvents allows best sample dissolution solvent – important for preparative work

Stable **:** New Chiral Selectors previously not accessible due to solubility in the mobile phase – eg CHIRALPAK® IC

Immobilised CSP

CHIRALPAK IA



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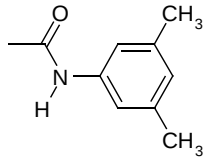

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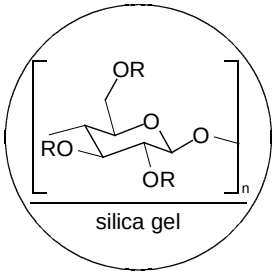

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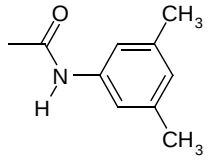

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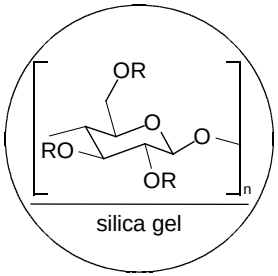

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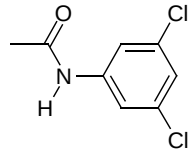


IMMOBILIZED

Solvent Selectivity

Basis of solvent selectivity

- Snyder –
  - Polarity Index (P')
  - Proton acceptor (x_e)
  - Proton donor (x_d)
  - Dipole (x_n)
- *Derived from GC retention of test solutes using the solvents as stationary phases*
- *Is this relevant for the diastereroisomeric chiral polymer – enantiomer complex?*

Solvent selectivity in HPLC

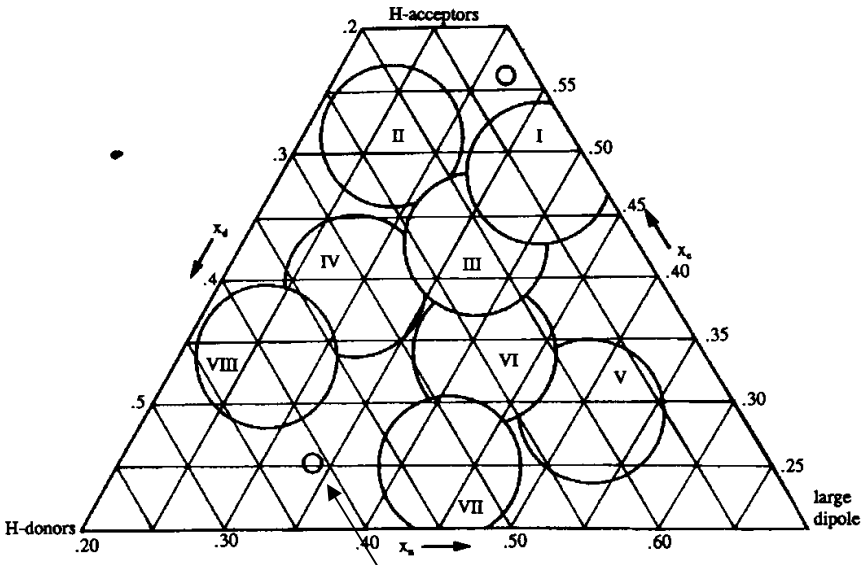


Figure 4.6 Selectivity triangle for HPLC solvents.

chloroform

Selectivity Groups:

I : ethers
II : alcohols
III : THF, sulphoxides
IV : glycols, AcOH
V : dichloromethane
VI : nitriles, esters & ketones
VII : aromatics
VIII : water

Hexane is assumed to be neutral – but what about CO_2?

Mobile Phases

Solvent	Group
Methyl *tert*-butyl ether*	(I)
Methanol	(II)
2-Propanol	(II)
Tetrahydrofuran*	(III)
Dichloromethane*	(V)
Acetonitrile*	(VI)
Methyl acetate* (ethyl acetate)	(VI)
Chloroform*	(VII/VIII)

** Modified if necessary with 0 -20 % methanol or ethanol to adjust solvent strength.*

Solutes

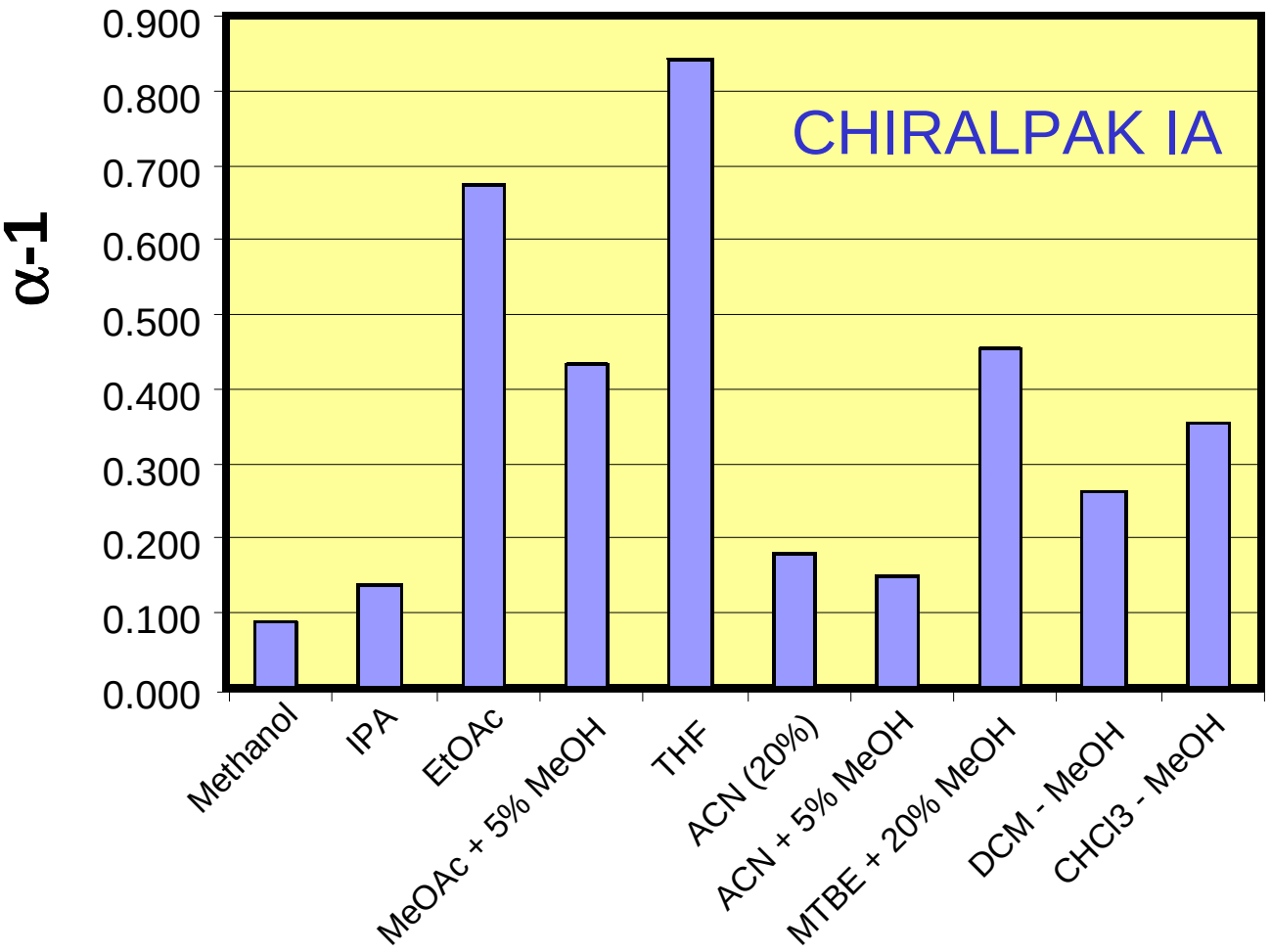
- 39 samples

2-Acetyl-1-tetralone
4-Amino-2-chlorodiphenylacetonitrile
Aminoglutethimide
Benzoin ethyl ether
1-Benzoyl-2-t-Butyl-3-methyl-4-imidazolidinone
Benzyl-2-hydroxy-3-phenylpropionate
2,3-O-Benzylidenethreitol
4-Benzoyloxy-2-azetidinone
1-(Benzyloxycarbonyl)-2-tButyl-3-methyl-4-imidazolidinone
2-Bromo-1-indanol
2-Bromomethyl-1,4-benzodioxane
Chlormezanone
Devrinol
1,5-Dimethyl-4-phenyl-2-imidazolidinone
EEDQ
γ-(4-Fluorophenyl)-γ-butyrolactone
6-Fluoro-1,2,3,4-tetrahydro-2-methylquinoline
GFS (aka Guaifenesin)
Hydrobenzoin
5-(4-Hydroxyphenyl)-5-phenylhydantoin
1-Indanol
Mephenesin
Methocarbamol
2-Methyl-1-Indanone
3-Methyl-1-Indanone
α-Methyl-α-phenylsuccinimide
1-methyl-2-tetralone
2-Methyl-1-Tetralone
Metolachlor
Naringenin
Pantolactone
Pantothenol
Phenoxybenzamine
2-Phenylbutyrophenone
1-Phenylethyl-3,5-dinitrobenzoate
1-Phenyl-1-propanol
1,2,3,4-Tetrahydro-1-naphthol
Trimebutine
Warfarin

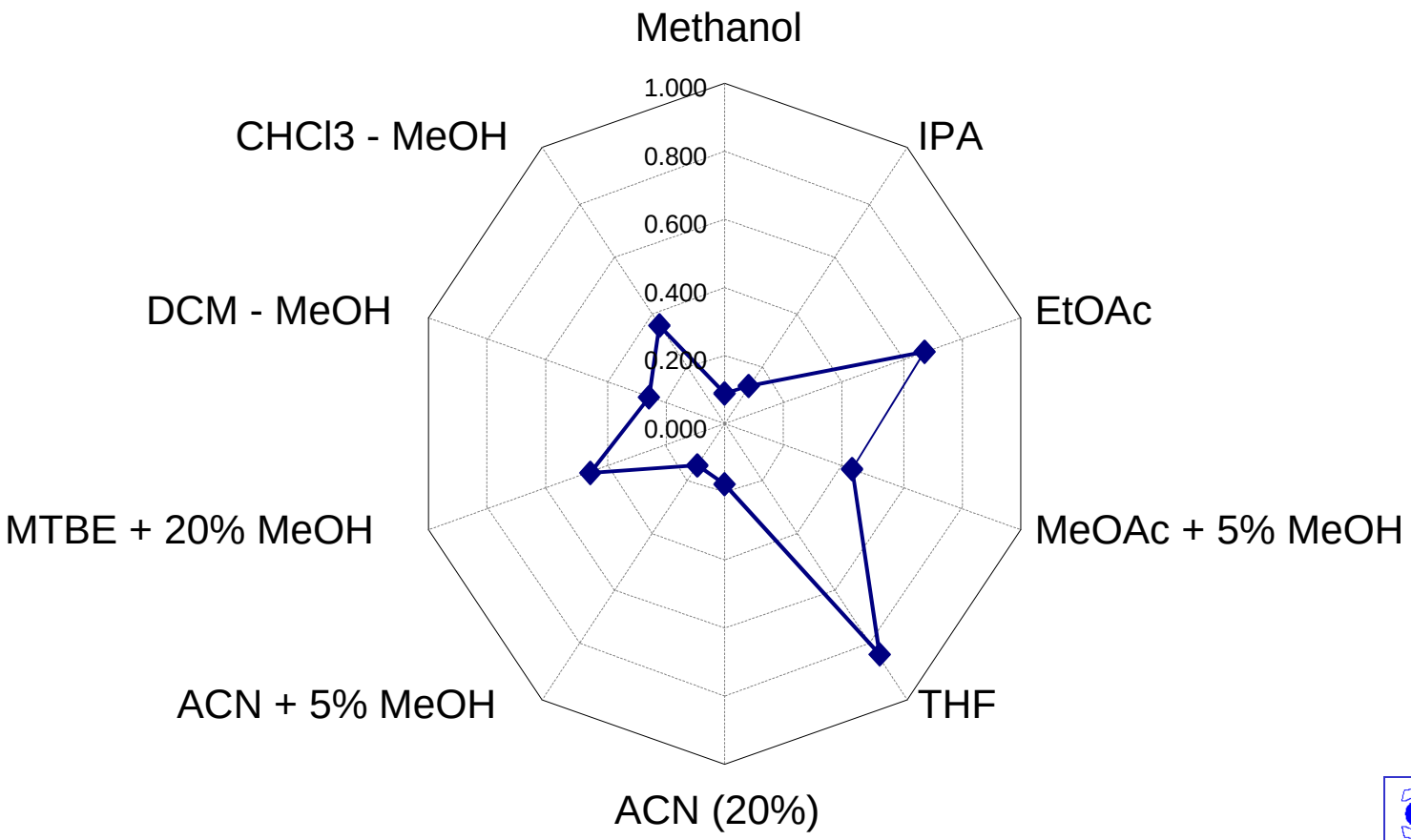
Selectivity Measurement

- Where there is no separation, selectivity = 1
  - ($a = k'_2/k'_1$)
- A more sensitive metric is (a-1), which is zero for no separation
  - Disadvantage – it looks a small number, even for good separations!

Benzoin Ethyl Ether

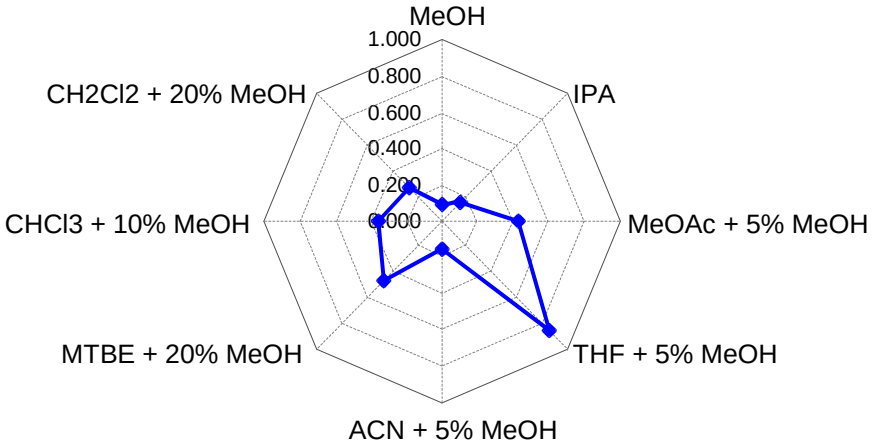


“Radar” graph


Methanol
IPA
EtOAc
MeOAc + 5% MeOH
THF
ACN (20%)
ACN + 5% MeOH
MTBE + 20% MeOH
DCM - MeOH
CHCl3 - MeOH
1.000
0.800
0.600
0.400
0.200
0.000

Benzoin Ethyl Ether

CHIRALPAK IA



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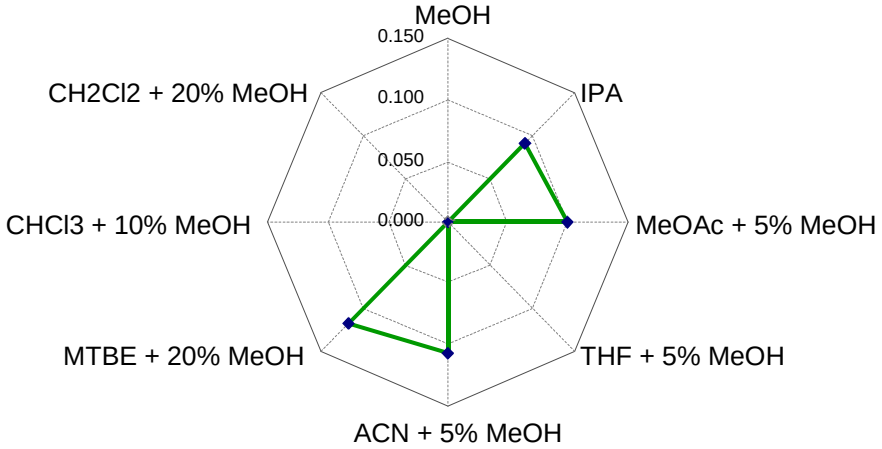

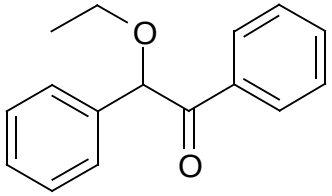

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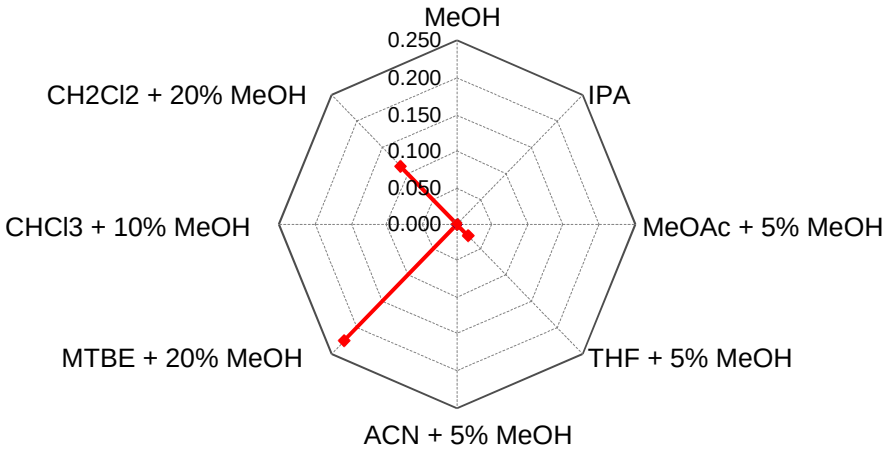
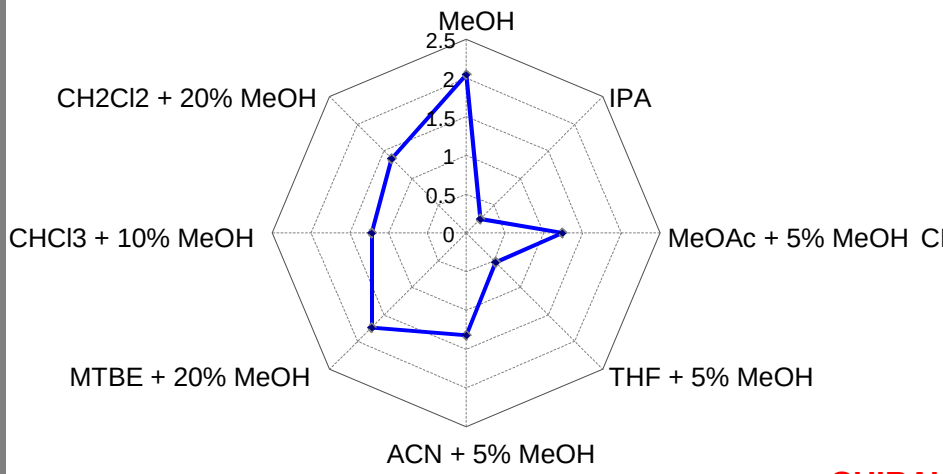


2,3-O-Benzylidenethreitol

CHIRALPAK IA



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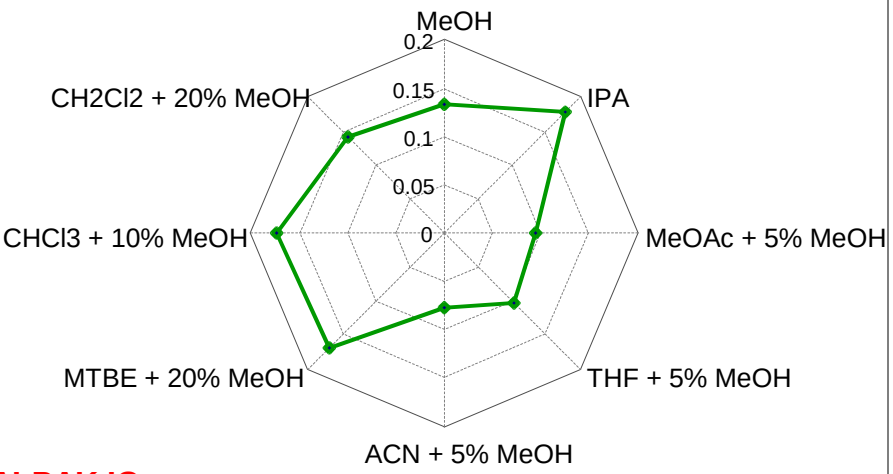

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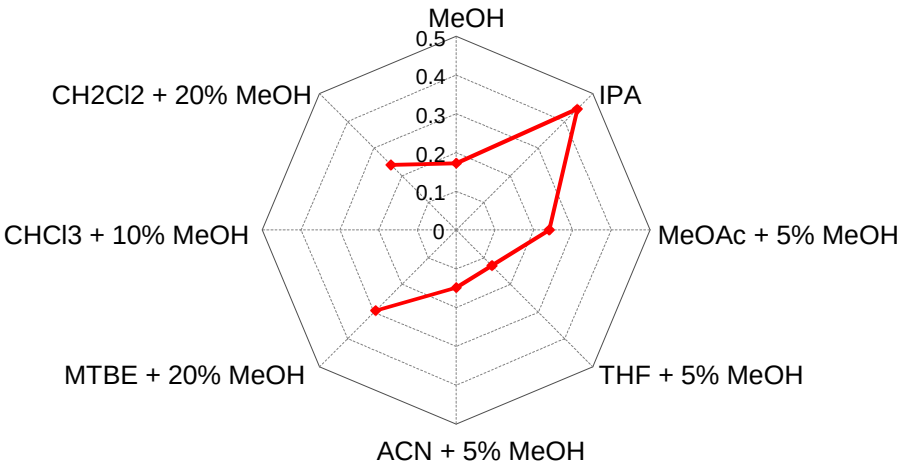
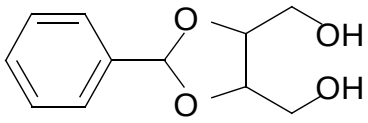
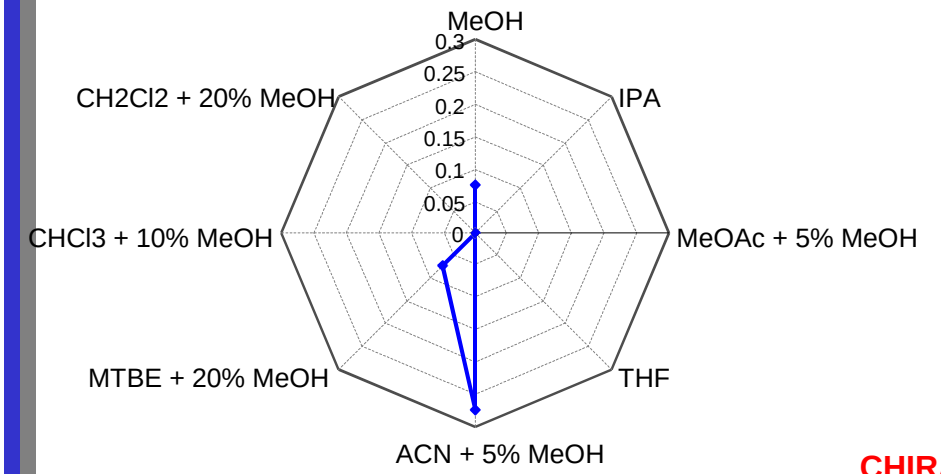




Devrinol

CHIRALPAK IA



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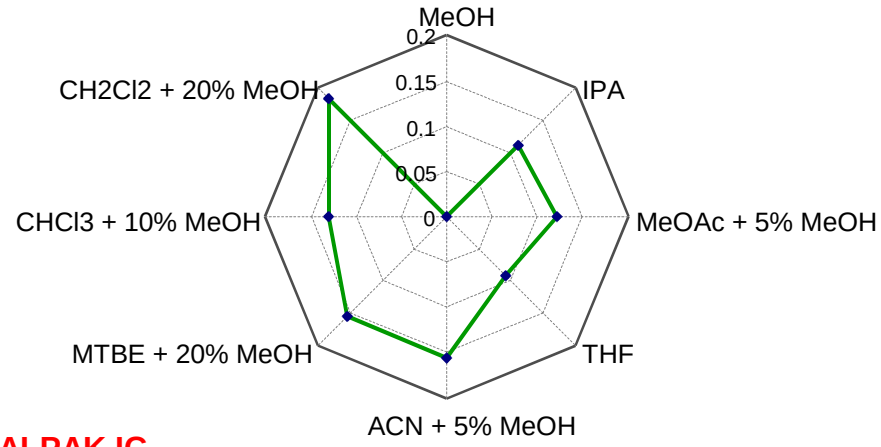

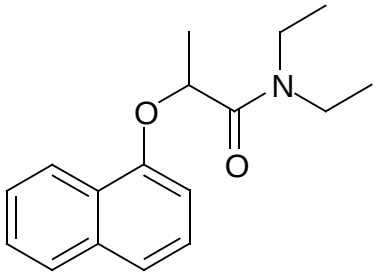

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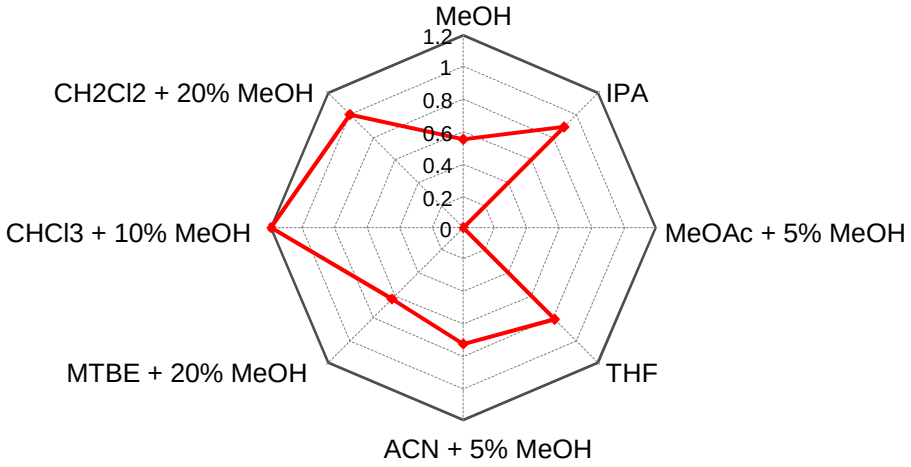
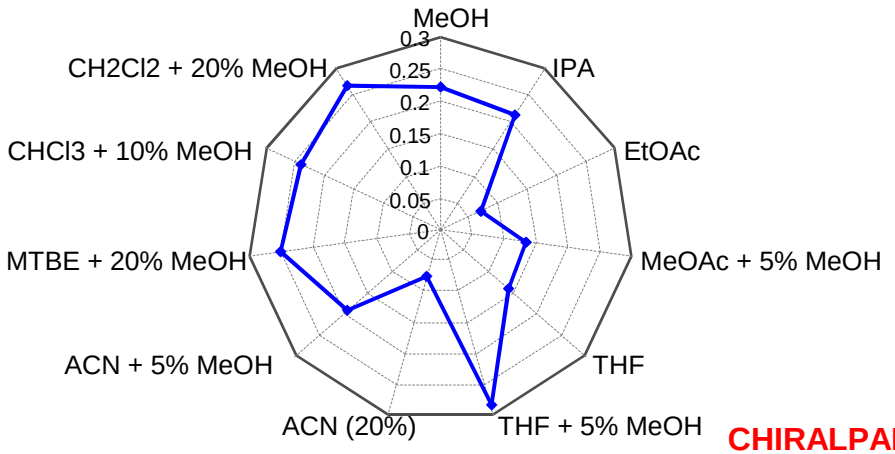


Global

CHIRALPAK IA



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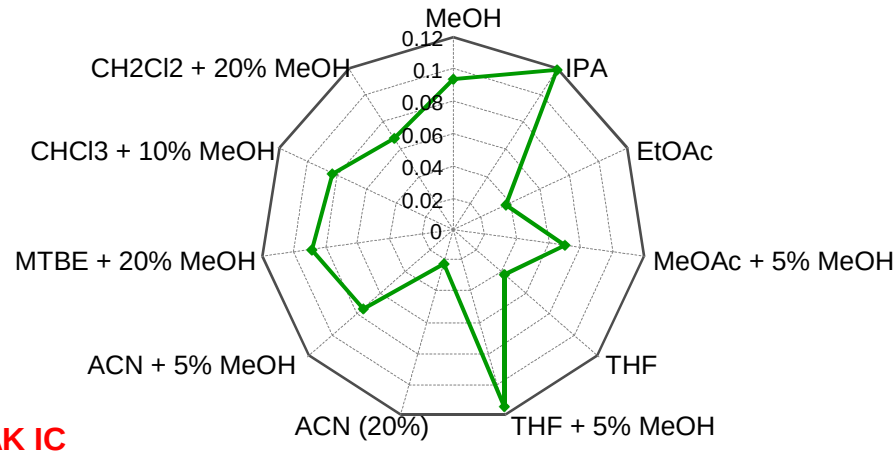

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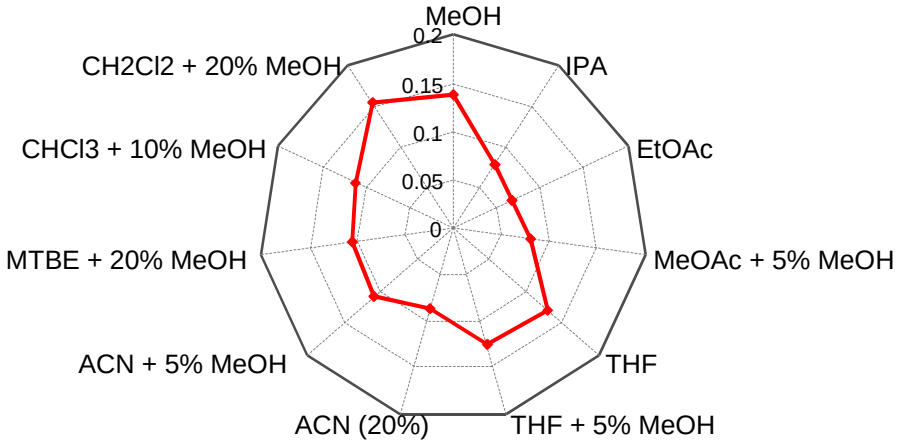
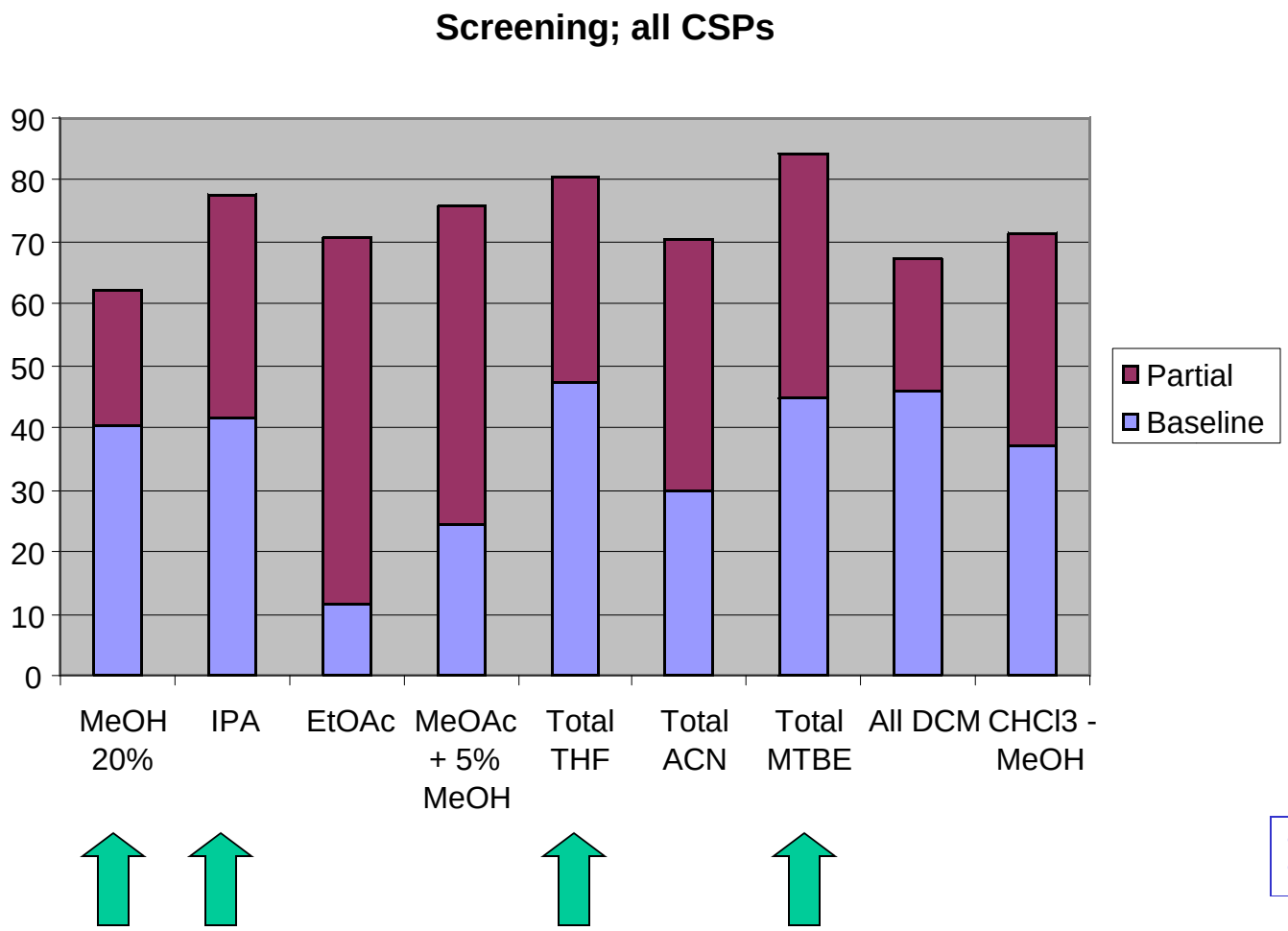


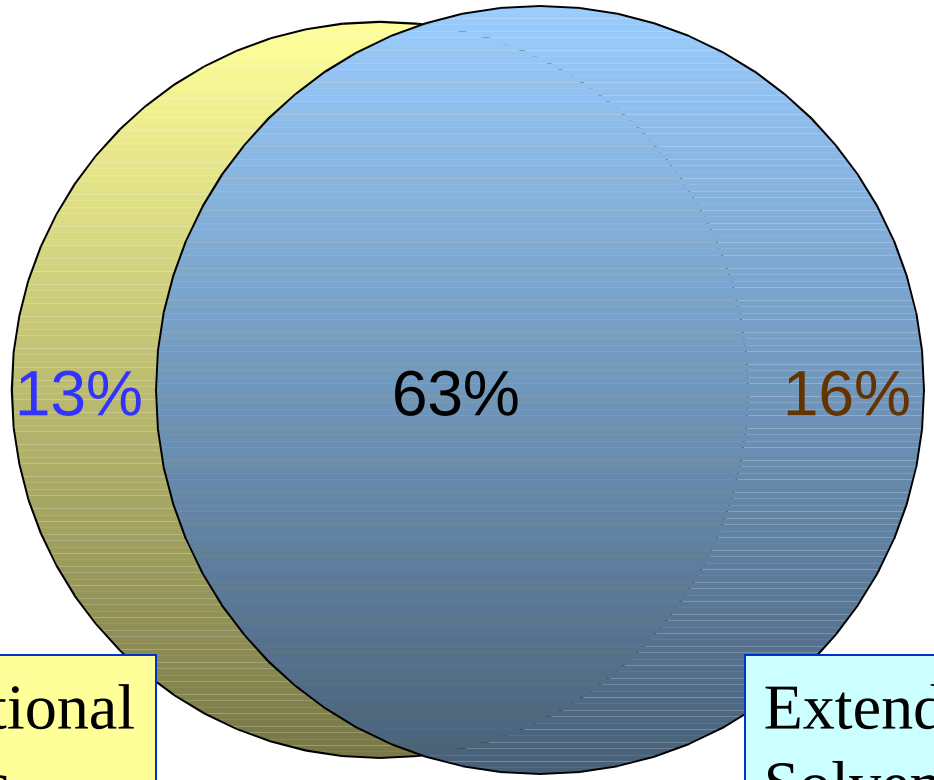
Success Rates - Solvents



Do we need extended range solvents?

None

8%



MeOH
IPA
MeCN

THF
MeOAc
MTBE
CH_2Cl_2
$CHCl_3$

Conventional Solvents

Extended Solvents

Best separations

- MTBE : 14%
- Methanol : 9%
- 2-Propanol : 23%
- THF : 17%
- Dichloromethane : 9%
- Acetonitrile : 9%
- (M)ethyl acetate* : 11%
- Chloroform* : 9%

** Low UV transmission at short wavelengths*

Group correlation

If the solvent selectivity groups mean anything, then there should be correlation between ACN and (m)ethyl acetate and between methanol and 2-propanol

% 2nd best						
$CHCl_3$	1	2	3	5	6	
Best						
1	-	20	0	20	60	0
2	18	9	9	9	18	18
3	17	33	-	0	50	0
5	33	0	0	-	0	67
6	0	0	57		43	0
$CHCl_3$	67	0	0	33	0	-

Screening recommendations

Initial screening:

Co-Solvent	% in CO2
THF	25
20% MeOH in MTBE	25
Methanol	20
2-Propanol	20

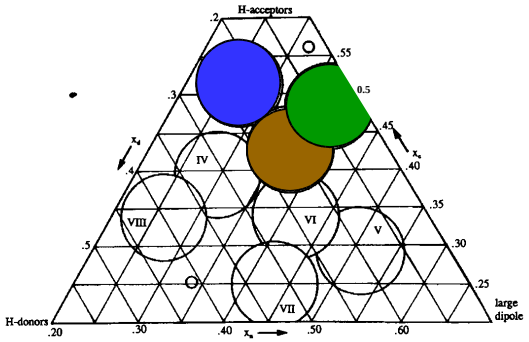


Figure 4.6 Selectivity triangle for HPLC solvents.

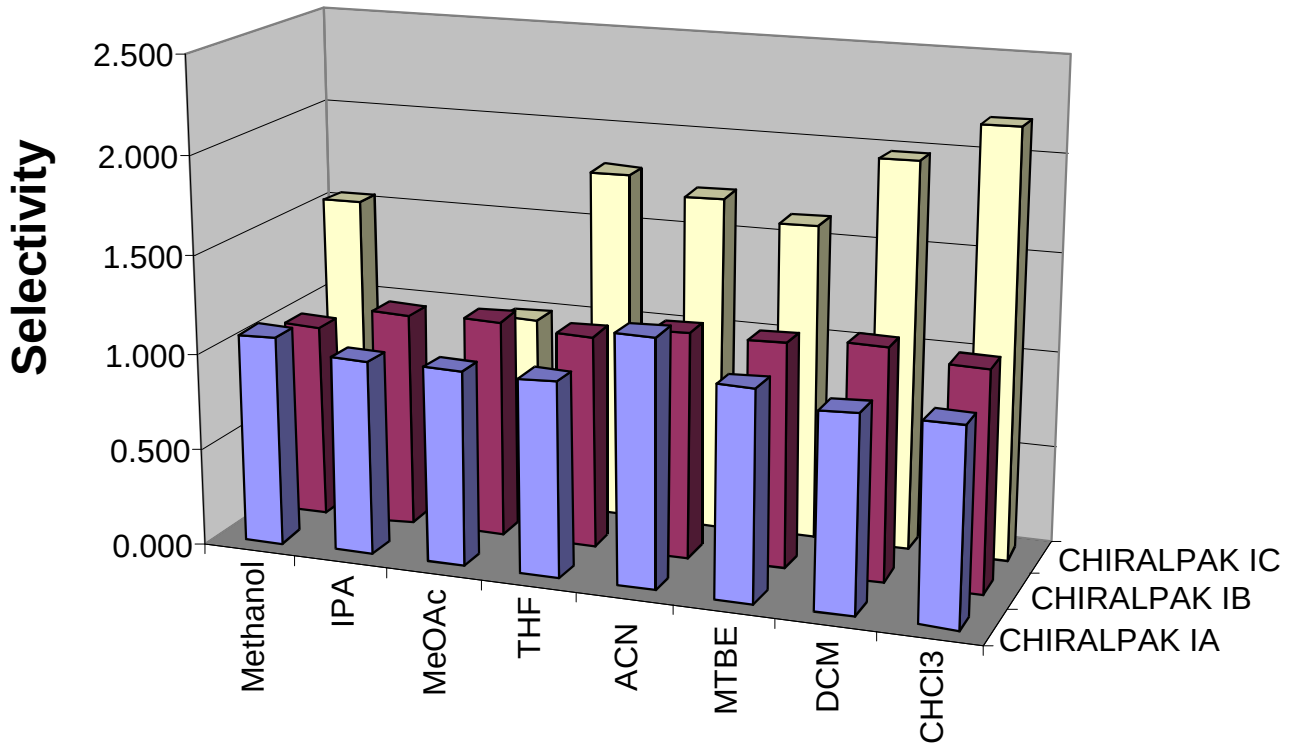
Mobile Phase strength to be adjusted depending on solute retention.

These solvents give selectivity > 1 for all solutes separated

Stationary Phase Selectivity

Immobilized CSP

Devrinol

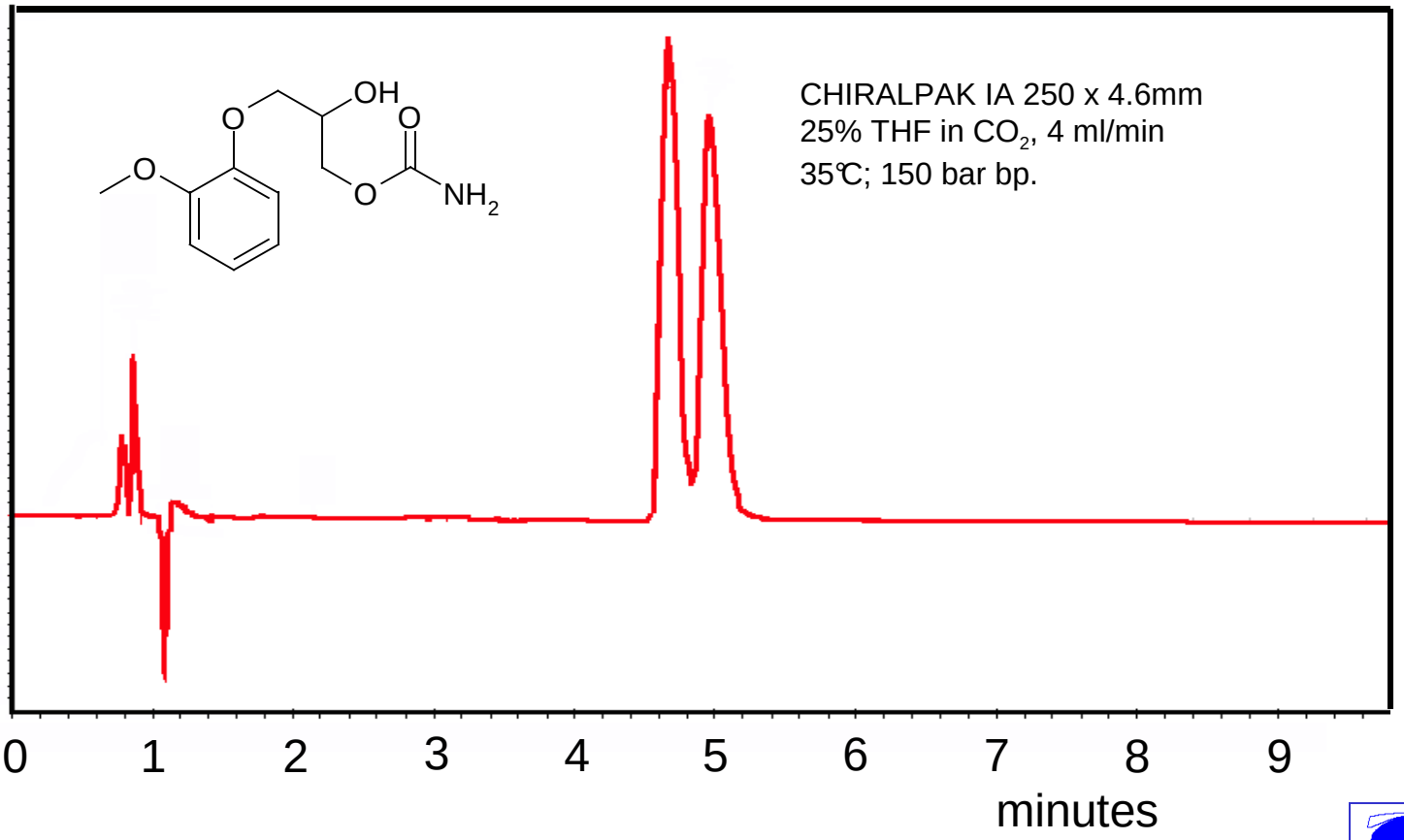

Selectivity
2.500
2.000
1.500
1.000
0.500
0.000
Methanol
IPA
MeOAc
THF
ACN
MTBE
DCM
CHCl3
CHIRALPAK IC
CHIRALPAK IB
CHIRALPAK IA

Success CSP

	Full	Partial	Success
CHIRALPAK IA	44.7	36.8	81.6
CHIRALPAK IB	21.1	44.7	65.8
CHIRALPAK IC	47.4	34.2	81.6
Global	60.5	31.6	92.1

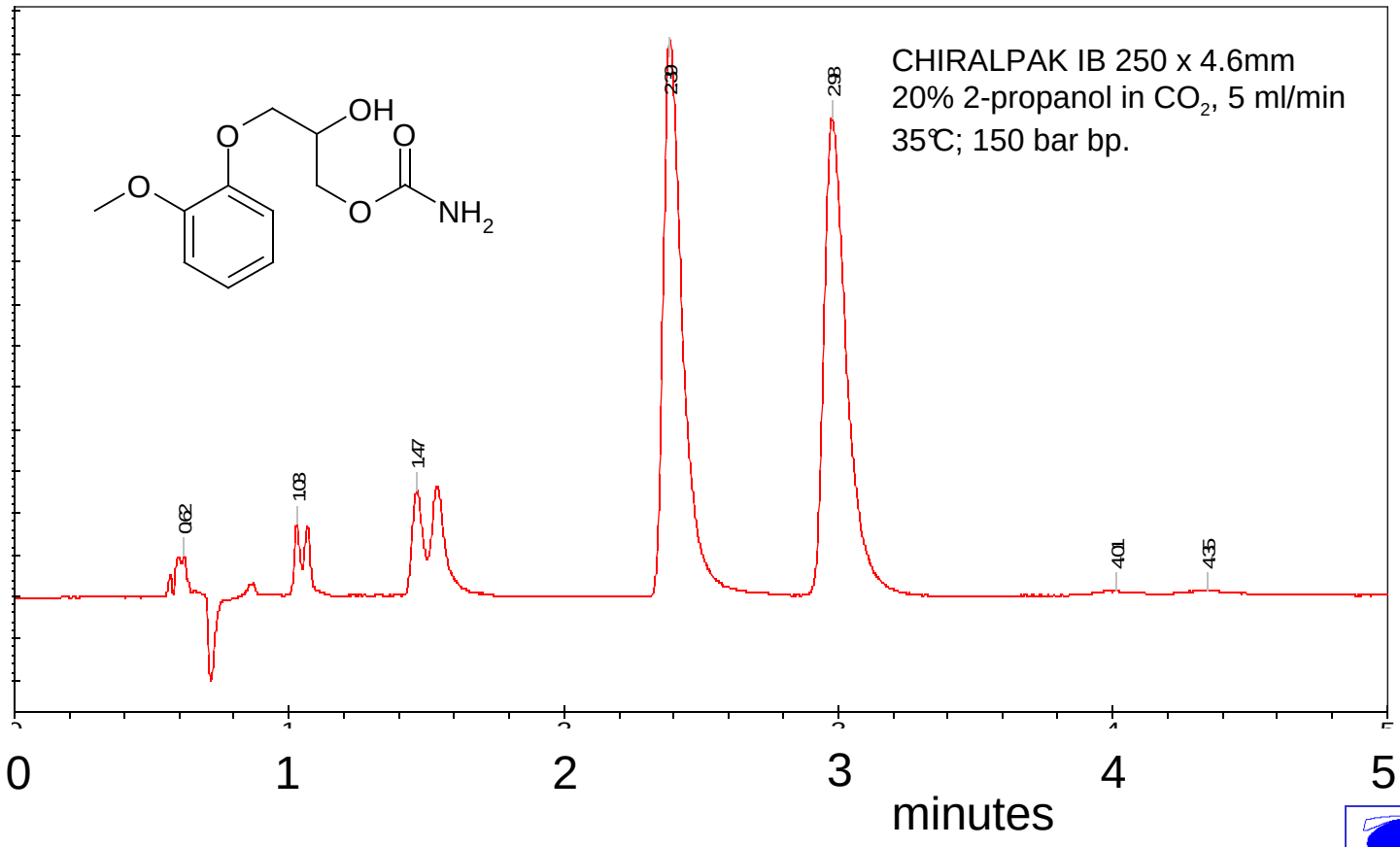
All solvents

CHIRALPAK IA



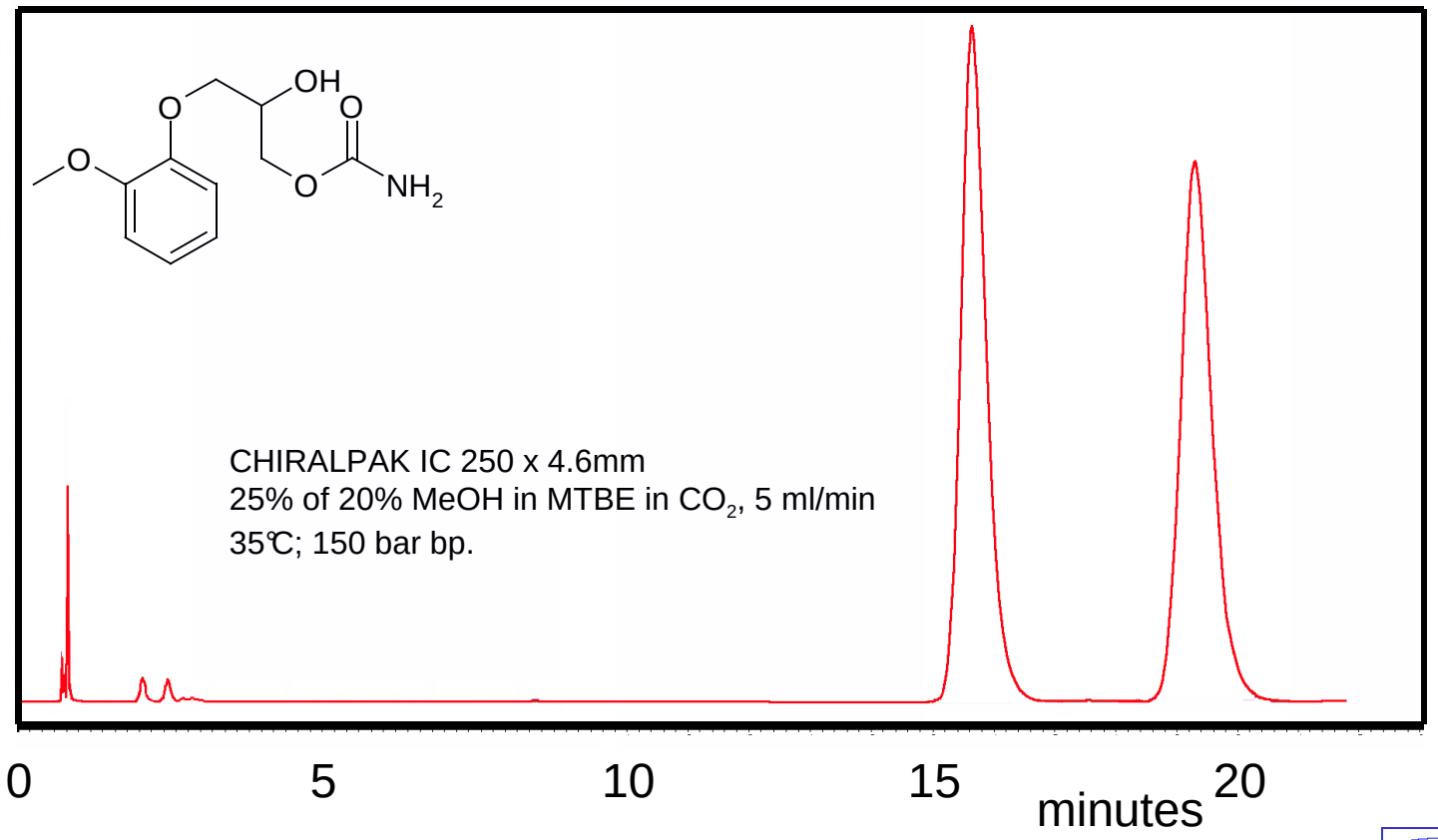
Methocarbamol

CHIRALPAK IB



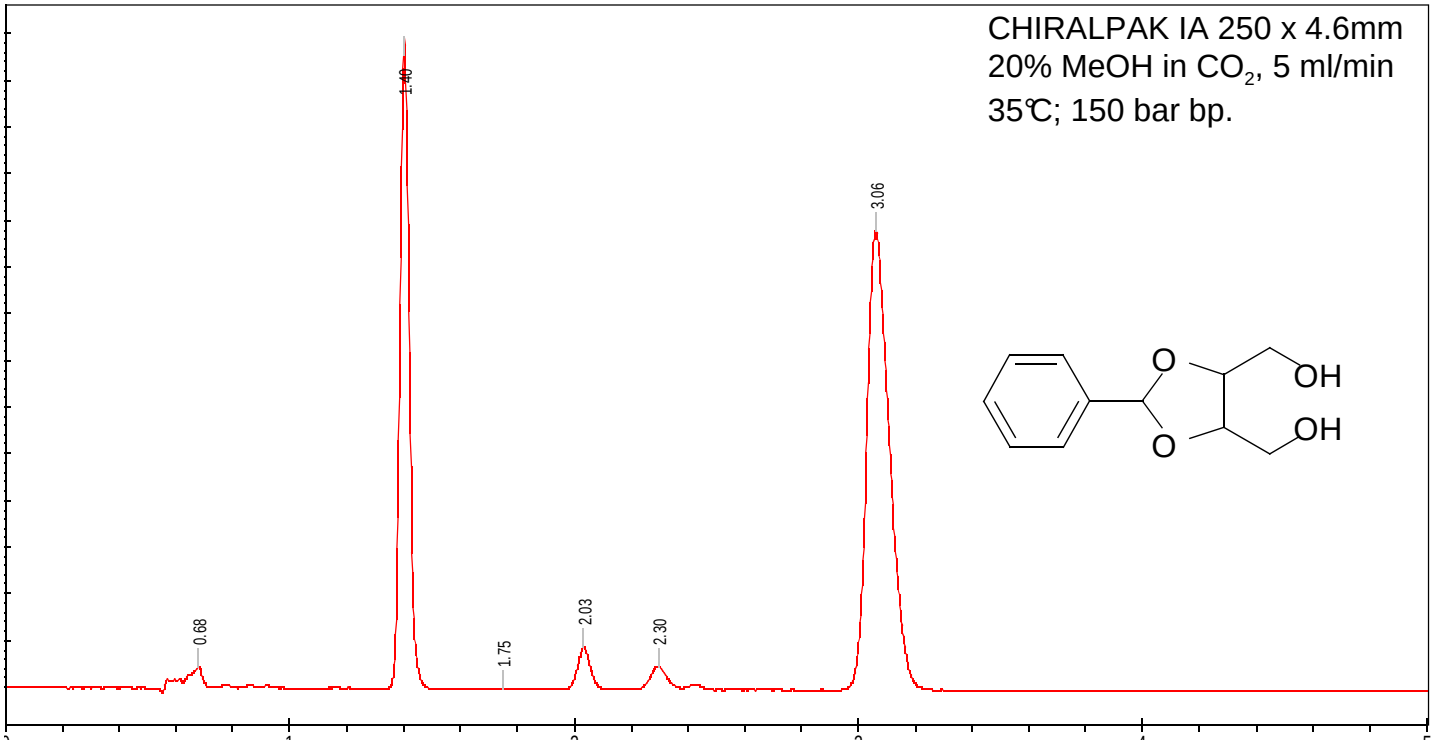
Methocarbamol

CHIRALPAK IC



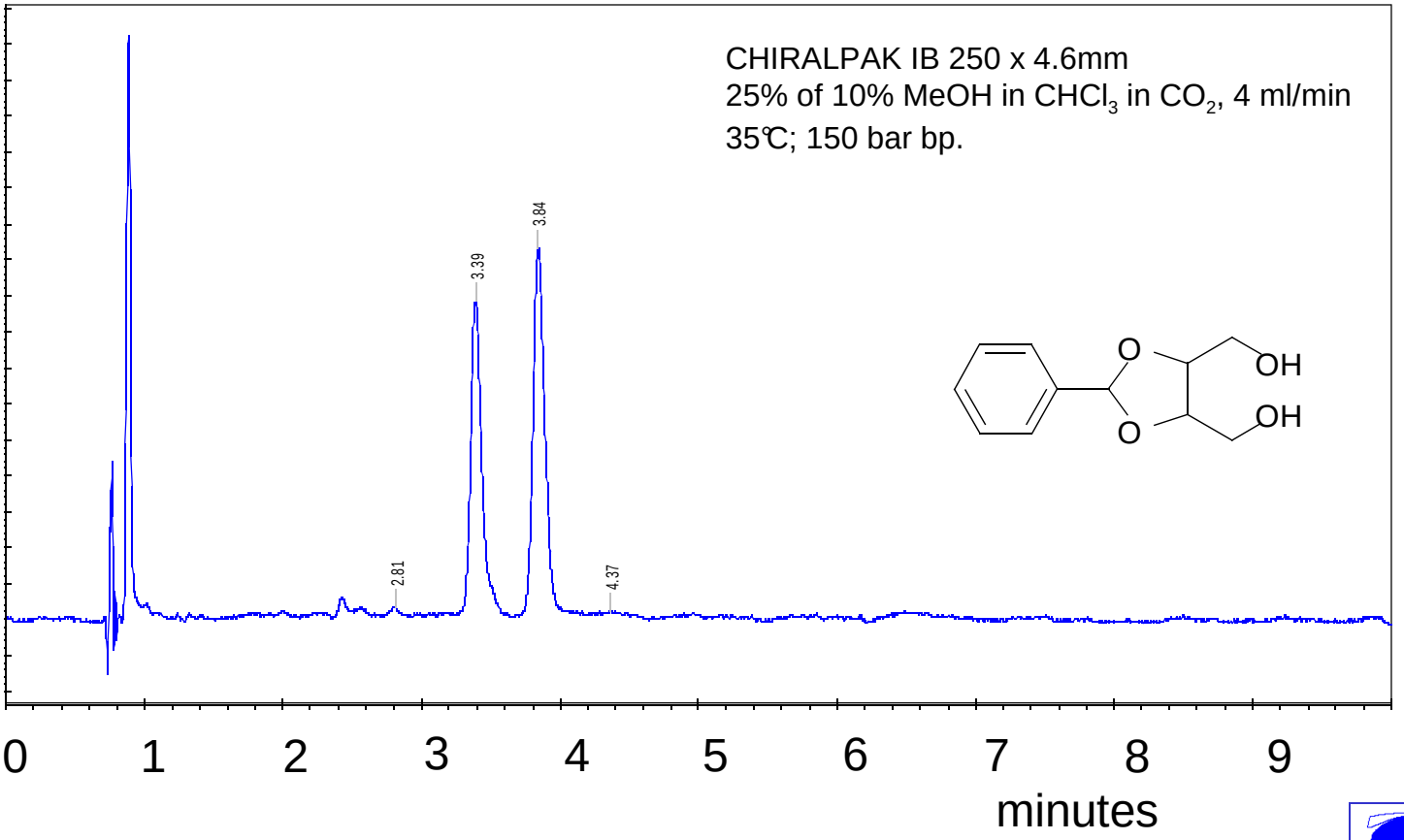
Methocarbamol

CHIRALPAK IA



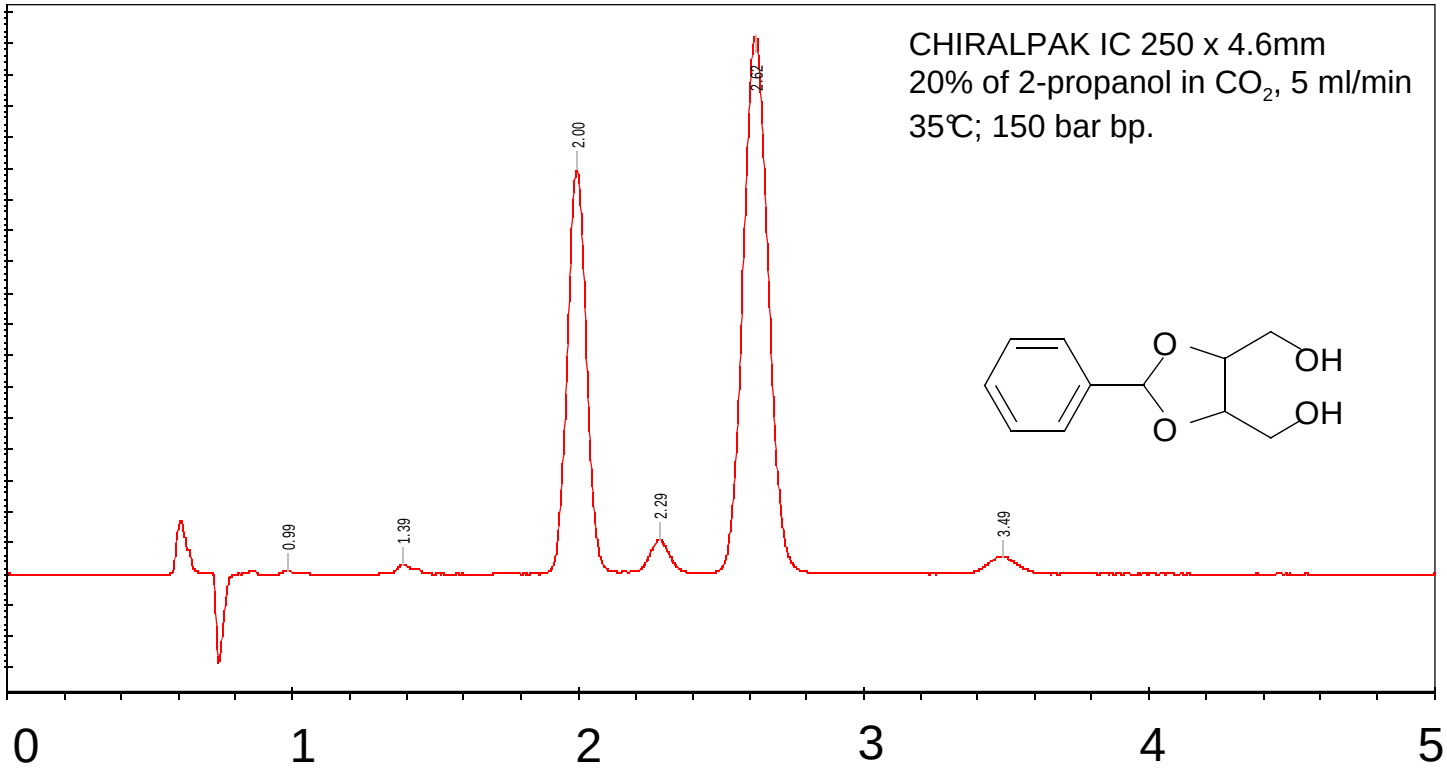
2,3-O-Benzylidinethreitol

CHIRALPAK IB



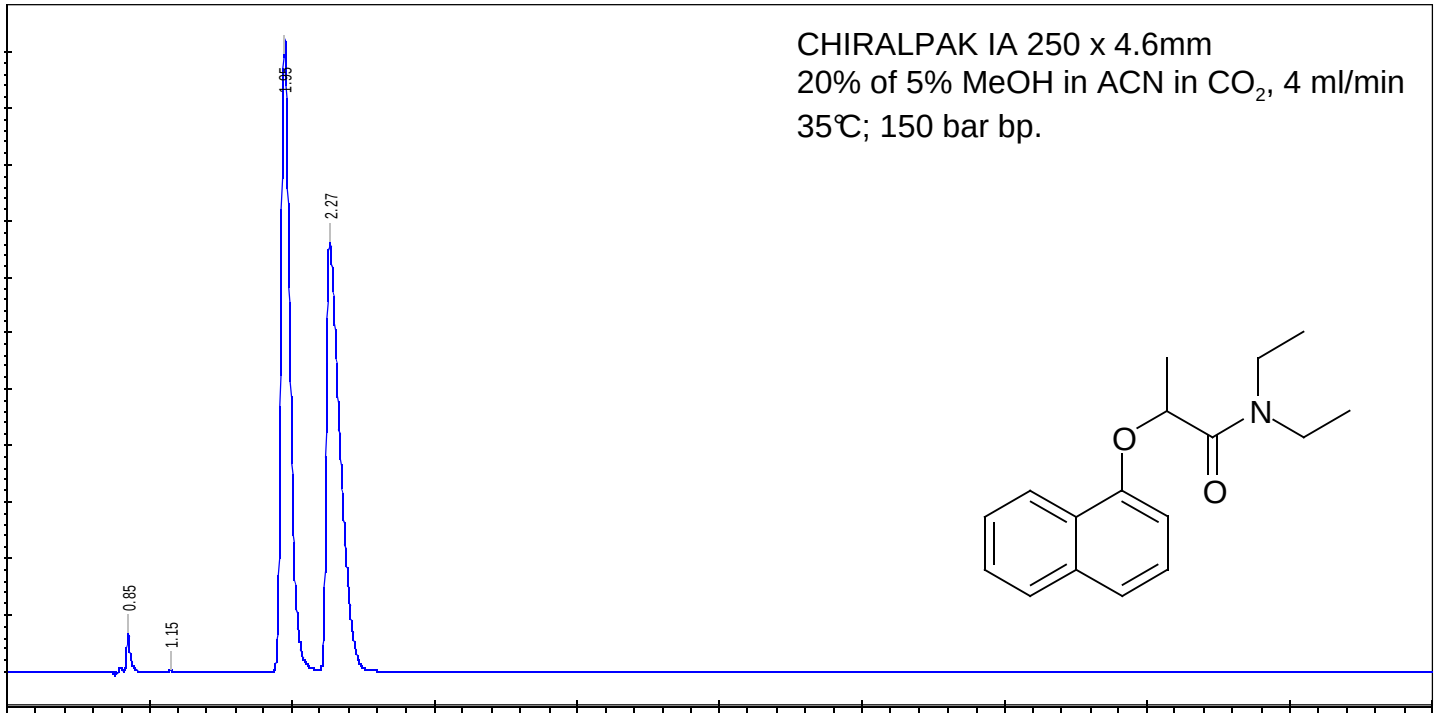
2,3-O-Benzylidinethreitol

CHIRALPAK IC



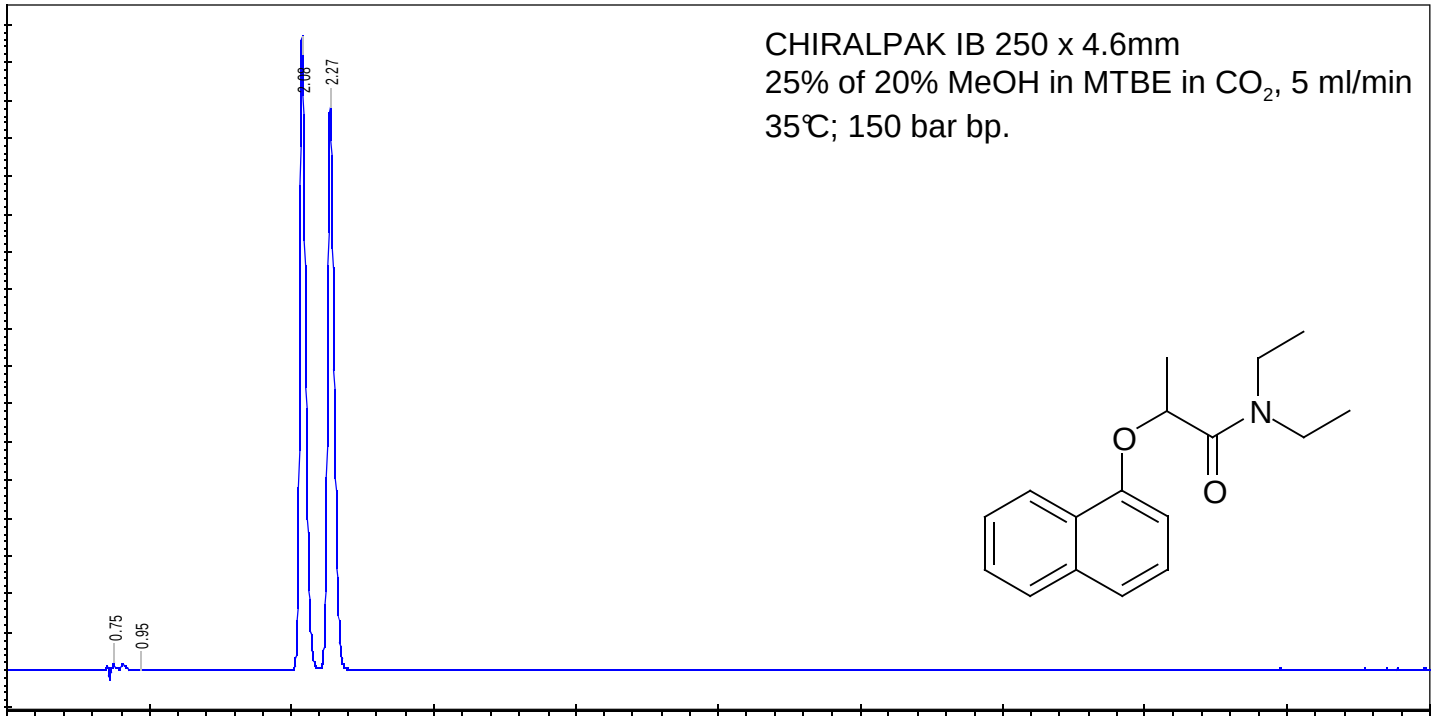
2,3-O-Benzylidinethreitol

CHIRALPAK IA



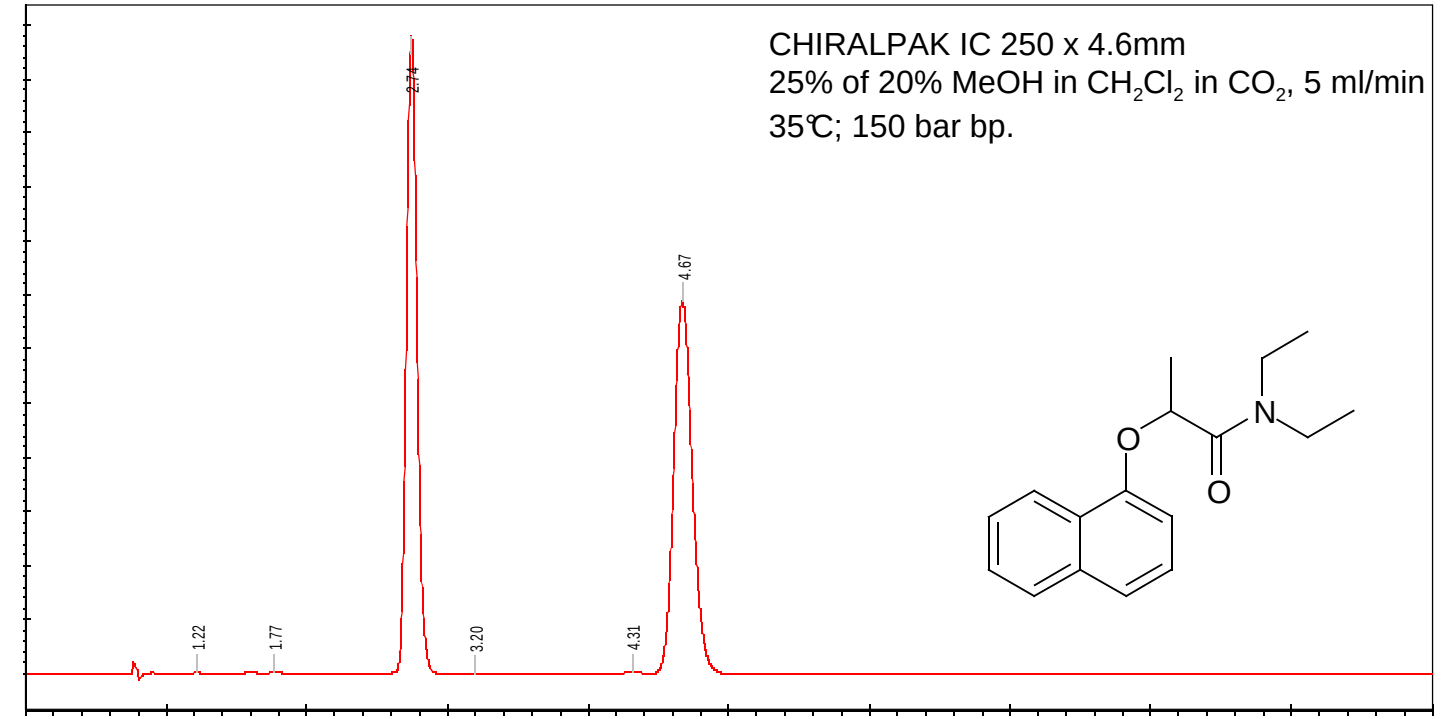
Devrinol

CHIRALPAK IB



Devrinol

CHIRALPAK IC



Devrinol

% CSP Success (SFC)

Best selectivity:

CHIRALPAK IA : 46%
CHIRALPAK IB : 10%
CHIRALPAK IC : 33%

All separations (Partial + full; 39 solutes)

Conclusions

- The sample set used comprised 39 compounds; enough for initial guidelines. 92% were separated ($\alpha > 1$)
- Selectivity can be enhanced – and in some cases separations achieved – by the use of “extended range” solvents and immobilized CSPs.
- Four co-solvents are recommended for initial screening:
  - THF
  - MTBE + MeOH
  - Methanol
  - 2-propanol
- Other solvents can be used to improve selectivity if needed aStill other solvent options are available; these are to be investigated.
- Simple solvent selectivity theory does not apply to chiral SFC