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Potential and limitations of quantitative NMR in pharmaceutical analysis

Bernd W.K.Diehl

Limitations

„Before an analyst uses the method of his college, he will use its toothbrush”

Oder/or

“Was der Bauer nicht kennt, frisst er nicht”

Potential

NMR gives ***molar amounts***

NMR is an ***Ab Initio Method***

0,05 % up to 100% Linearity and Dynamic

Selectivity by choosing the nuclei

Potential

NMR gives ***molar amounts***

NMR is an ***Ab Initio Method***

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Selectivity by choosing the nuclei

NMR is the most powerful detector

Compared to other indirect detection systems

IR, UV, DAD, FID, LSD,

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Methods

- Internal standard
- Twofold analysis using different internal standards
- Standard addition
- External calibration
- External standard

SAMPLE PREPARATION!

- Concentration
- Solvent variation
- Derivatisation
- Temperature

Further upcoming methods (no comments in this presentation):

- HPLC/NMR Coupling
- Solid State NMR

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Applications

- Definition of standards
  NMR as a tool to create primary standards. Ab initio determination
- Identity test for re-import
  Comparison of active parts and formulation aids
- Complex mixtures
  Simultaneous analysis of drugs, by-products, formulation aids and solvents
  Derivatisation, Validation
- Phytopharmaceuticals
  Aloe Vera, Lecithin, Fatty oils …..
- Polymers, Biopolymers
  Polysaccharide, Chondroitin sulfate, Heparin, modified starch, Peptides,
  Formulation aids, PEG, PVP, silicone …
- Heteronuclear NMR

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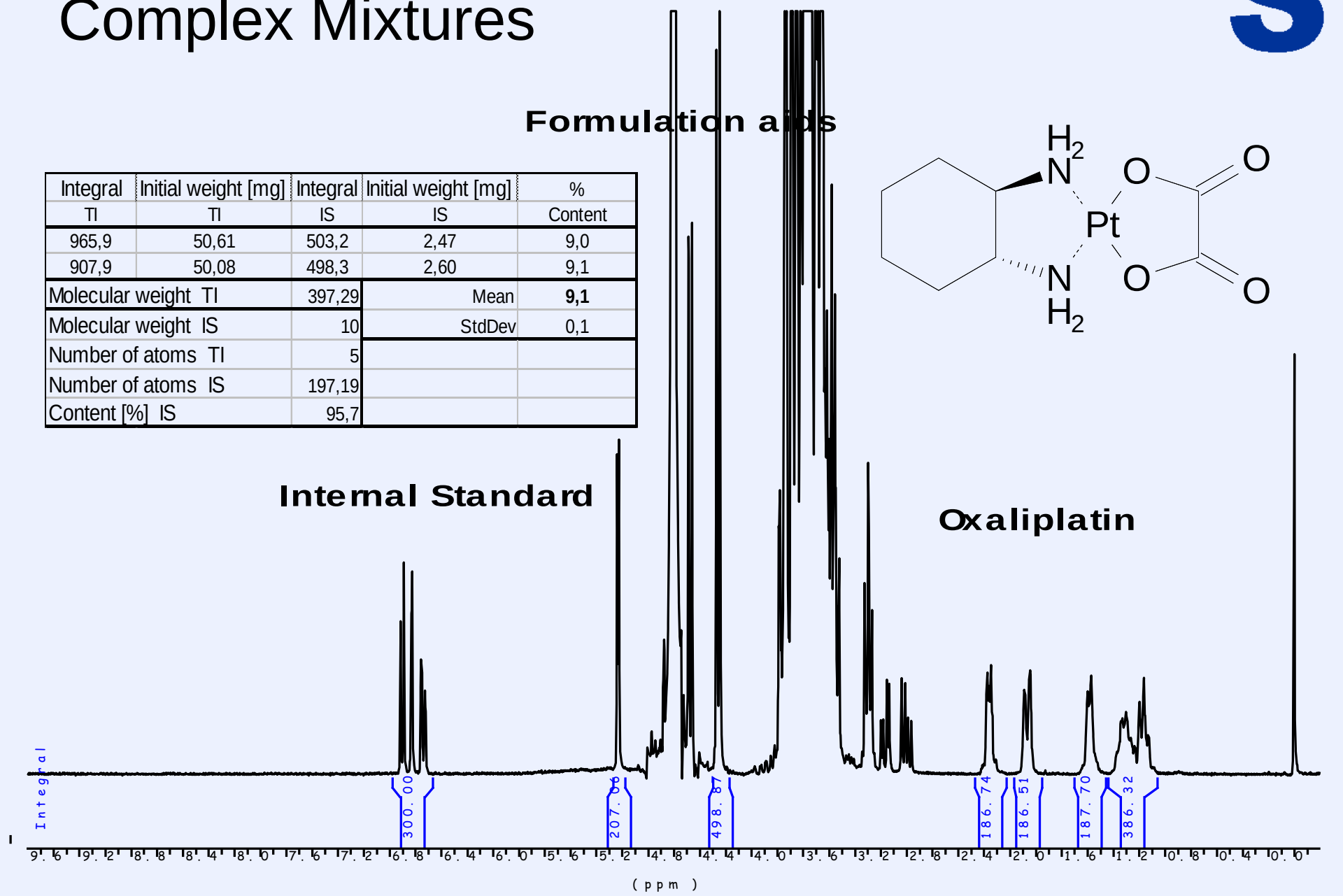
Complex Mixtures

Integral TI	Initial weight [mg] TI	Integral IS	Initial weight [mg] IS	% Content
965,9	50,61	503,2	2,47	9,0
907,9	50,08	498,3	2,60	9,1
Molecular weight TI		397,29	Mean	**9,1**
Molecular weight IS		10	StdDev	0,1
Number of atoms TI		5		
Number of atoms IS		197,19		
Content [%] IS		95,7		



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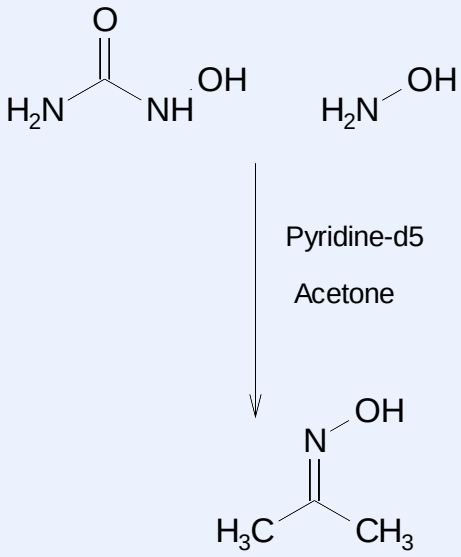
Derivatisation



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Validation

Reproducibility

Test	Integral P	In. weight [mg] P	Integral IS	In. weight [mg] IS	mMol IS	mMol P	[mg] P	% detected	% In. weight
R1	8,7	100,24	200,0	5,77	0,038	0,003	0,110	0,11	0,14
R2	9,2	99,99	200,0	5,08	0,034	0,003	0,103	0,10	0,16
R3	9,7	101,09	200,0	5,81	0,039	0,004	0,124	0,12	0,15
R4	13,1	101,28	200,0	5,53	0,037	0,005	0,159	0,16	0,15
R5	13,4	101,22	200,0	5,91	0,039	0,005	0,174	0,17	0,17
R6	10,6	101,15	200,0	5,94	0,040	0,004	0,138	0,14	0,15
R7 (L3)	12,7	100,40	200,0	5,27	0,035	0,004	0,147	0,15	0,15

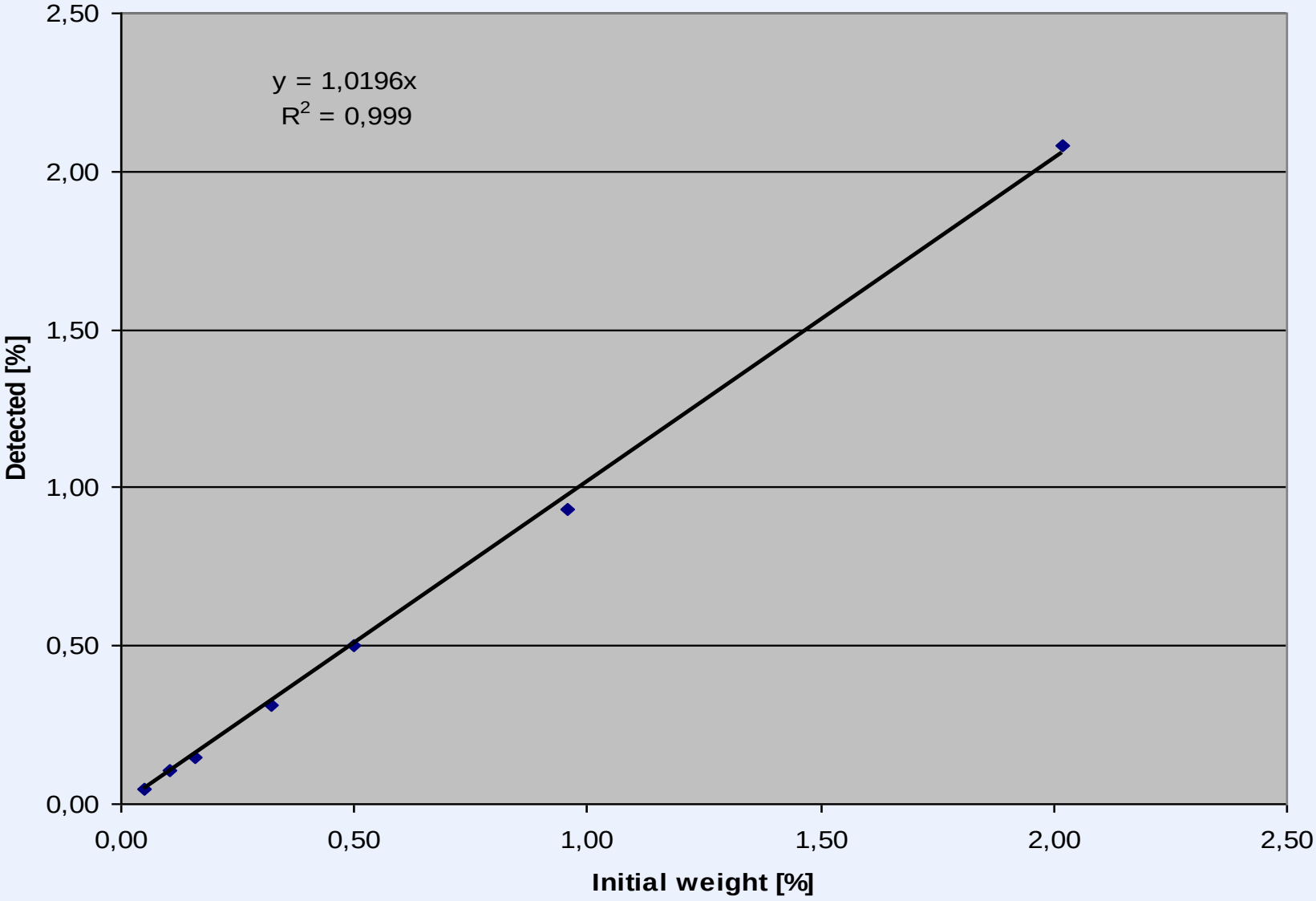
	Molecular weight P		33,03				Mean	0,14	0,15
	Molecular weight IS		150,22				Recovery	88,1	
	Number H (P)		3				StdDev	0,02	
	Number H (IS)		6				StdDev %	17,2	
	Content IS (%)		99,9						

Linearity

Test	Integral P	In. weight [mg] P	Integral IS	In. weight [mg] IS	mMol IS	mMol P	[mg] P	% detected	% In. weight
L1	4,1	108,10	200,0	5,60	0,037	0,002	0,051	0,05	0,05
L2	9,1	101,76	200,0	5,45	0,036	0,003	0,109	0,11	0,11
L3	12,7	100,40	200,0	5,27	0,035	0,004	0,147	0,15	0,16
L4	23,7	100,02	200,0	5,97	0,040	0,009	0,310	0,31	0,32
L5	47,9	105,20	200,0	5,01	0,033	0,016	0,527	0,50	0,50
L6	85,8	107,18	200,0	5,29	0,035	0,030	0,997	0,93	0,96
L7	165,1	101,77	200,0	5,85	0,039	0,064	2,121	2,08	2,02

	Molecular weight P		33,03						
	Molecular weight IS		150,22				Recovery	98,2	
	Number H (P)		3				StdDev	3,6	
	Number H (IS)		6						
	Content IS (%)		99,9						

Linearity


y = 1,0196x
R2 = 0,999
2,50
2,00
1,50
1,00
0,50
0,00
Detected [%]
0,00
0,50
1,00
1,50
2,00
2,50
Initial weight [%]

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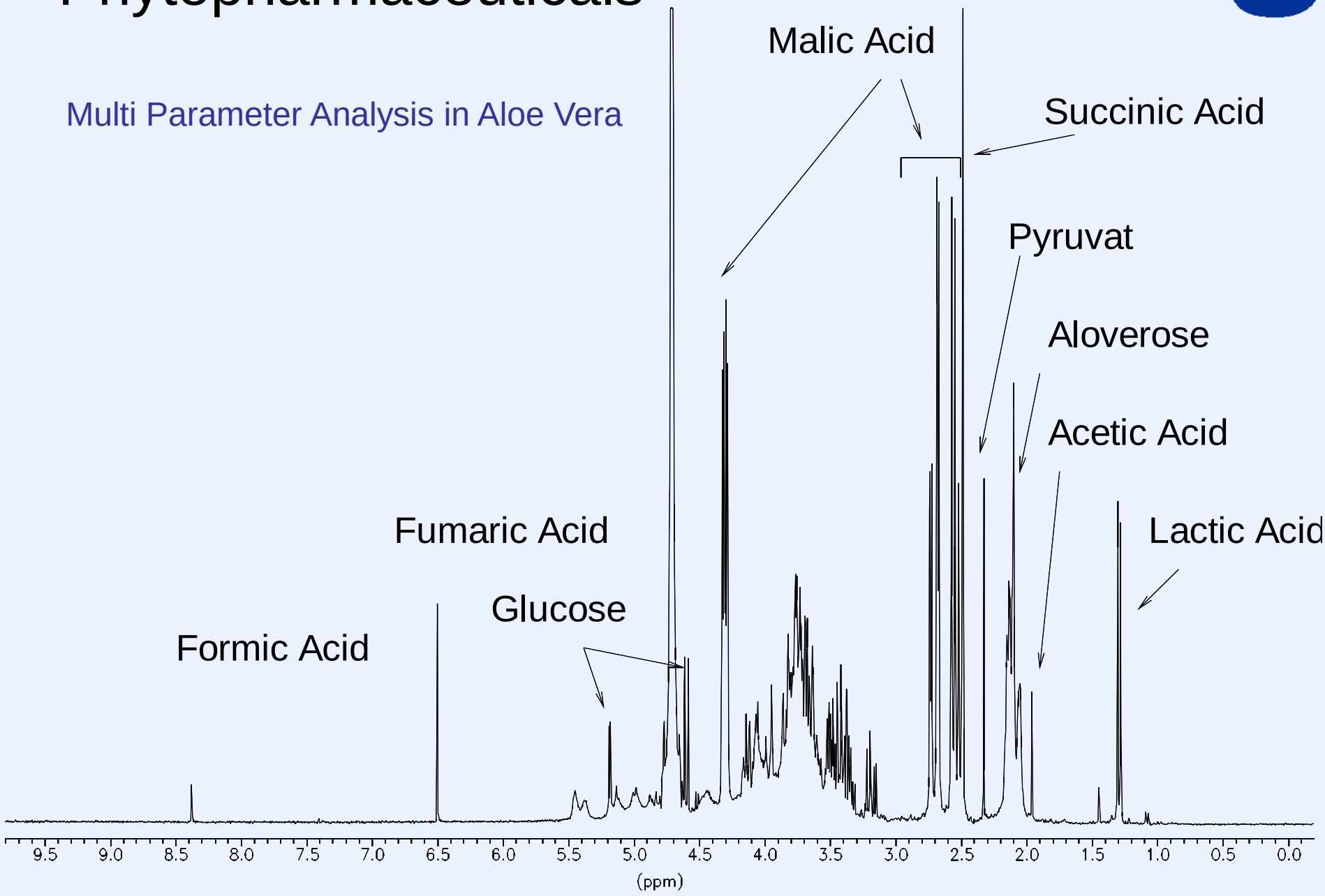
Phytopharmaceuticals

Multi Parameter Analysis in Aloe Vera



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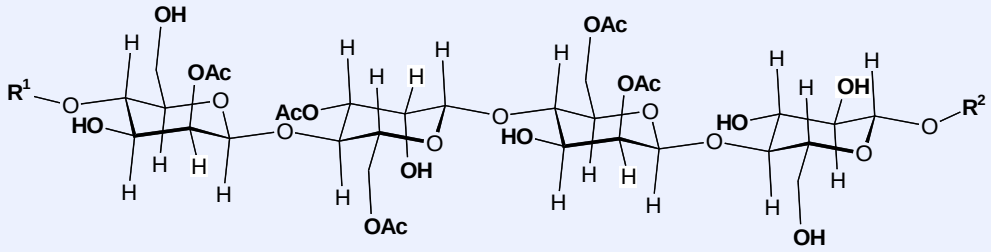
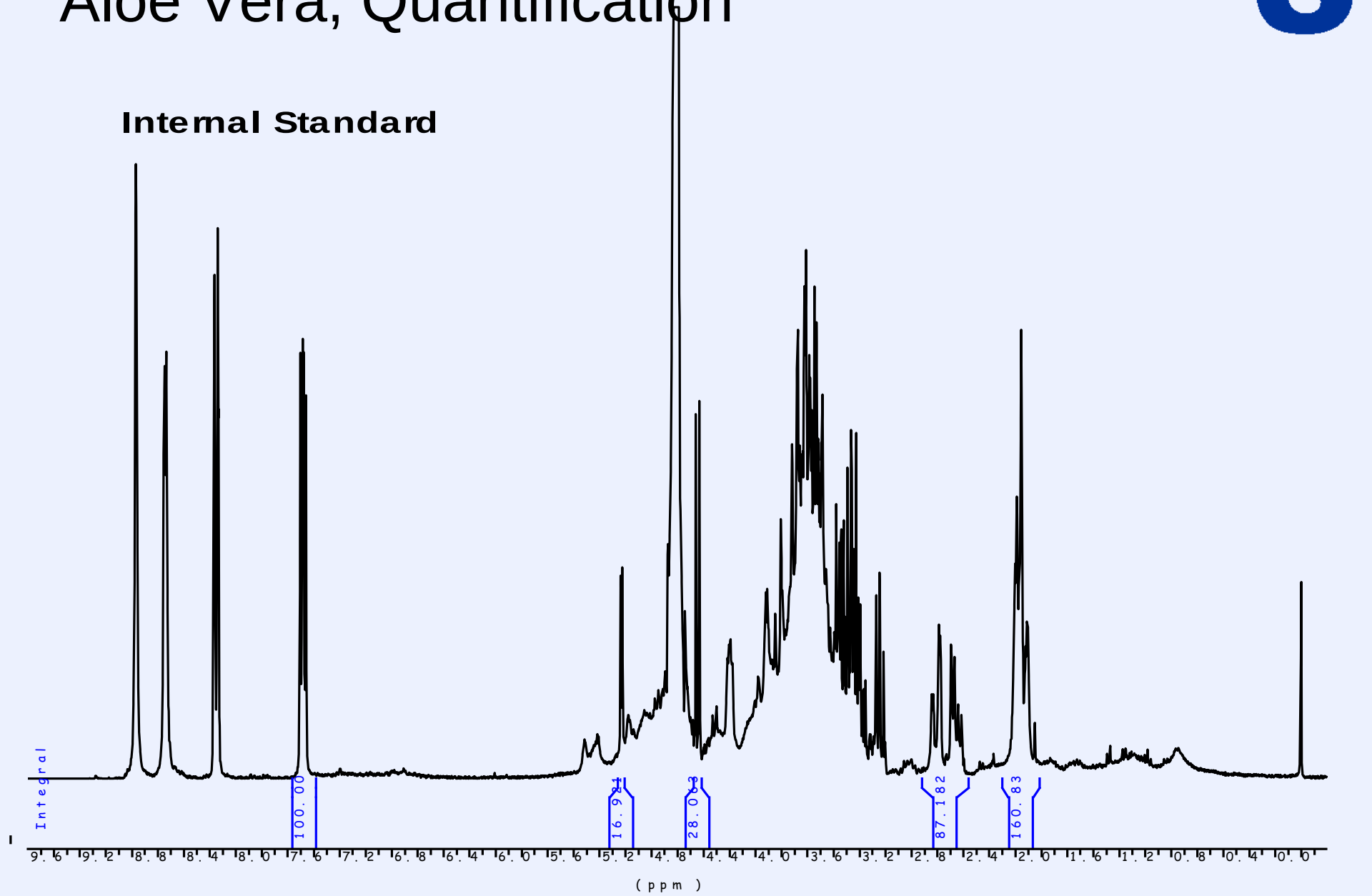
Aloverose



Aloe Vera, Quantification



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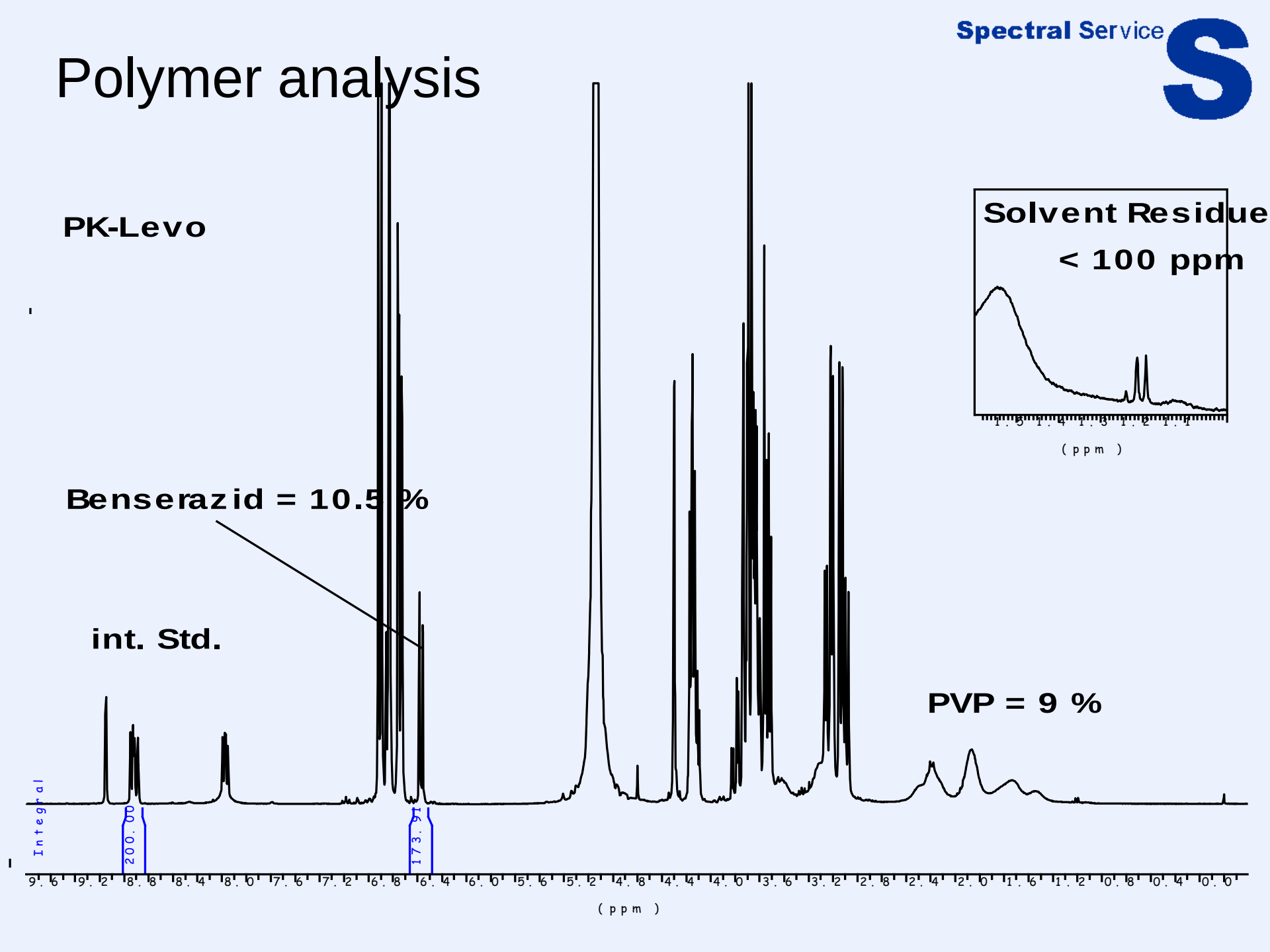
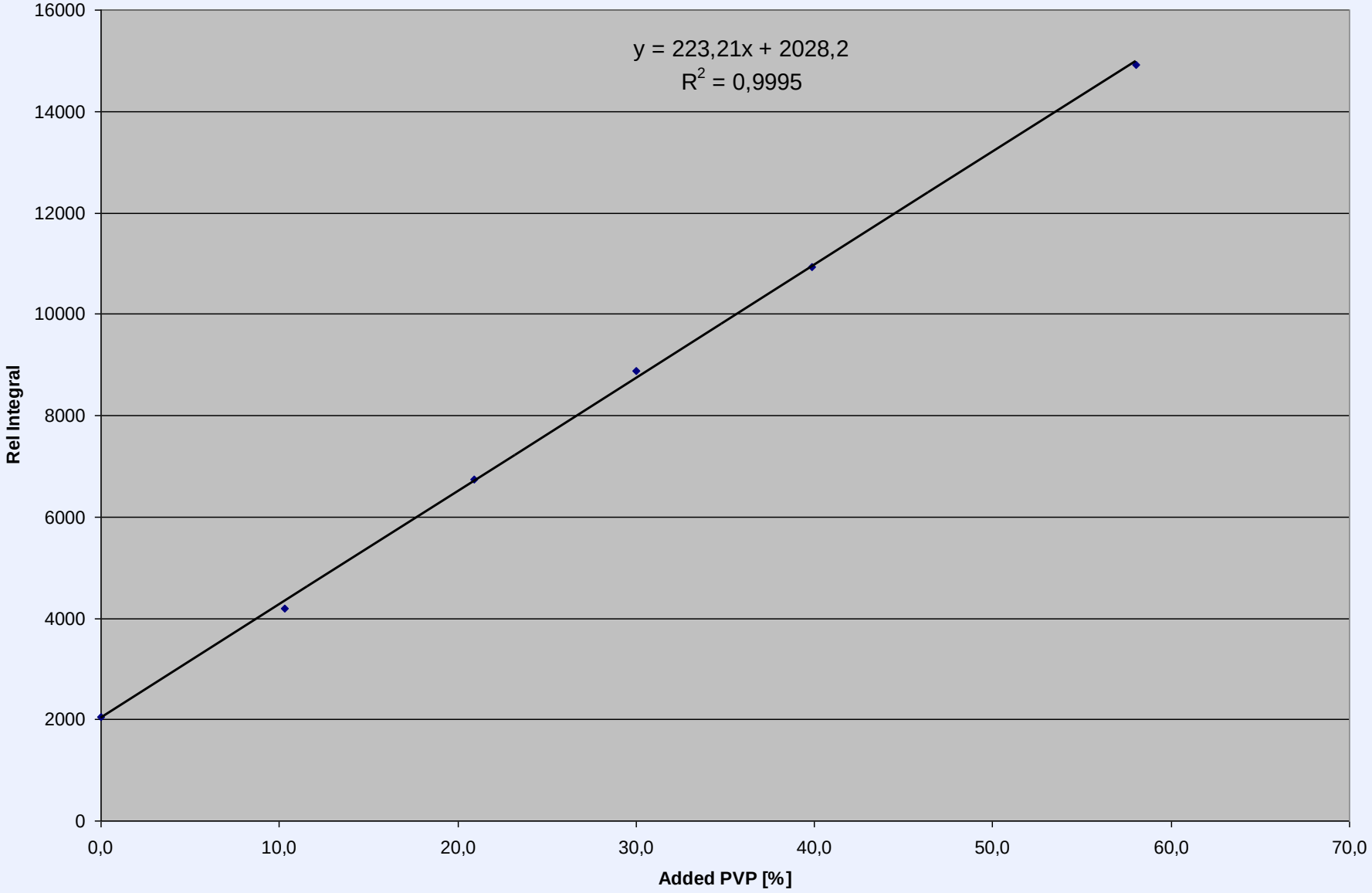
Polymer analysis



PVP, Standard Addition



Hetero Nuclear NMR

^{31}P NMR and ^{19}F NMR

Selectivity, e.g. only phospholipids give signals, triglycerides not

No chromatographic separation needed

Chemical Shift instead of RT

^{13}C Satellites are useful “internal” standards for calibration

^{13}C NMR

Analysis of complex mixtures in neat liquid

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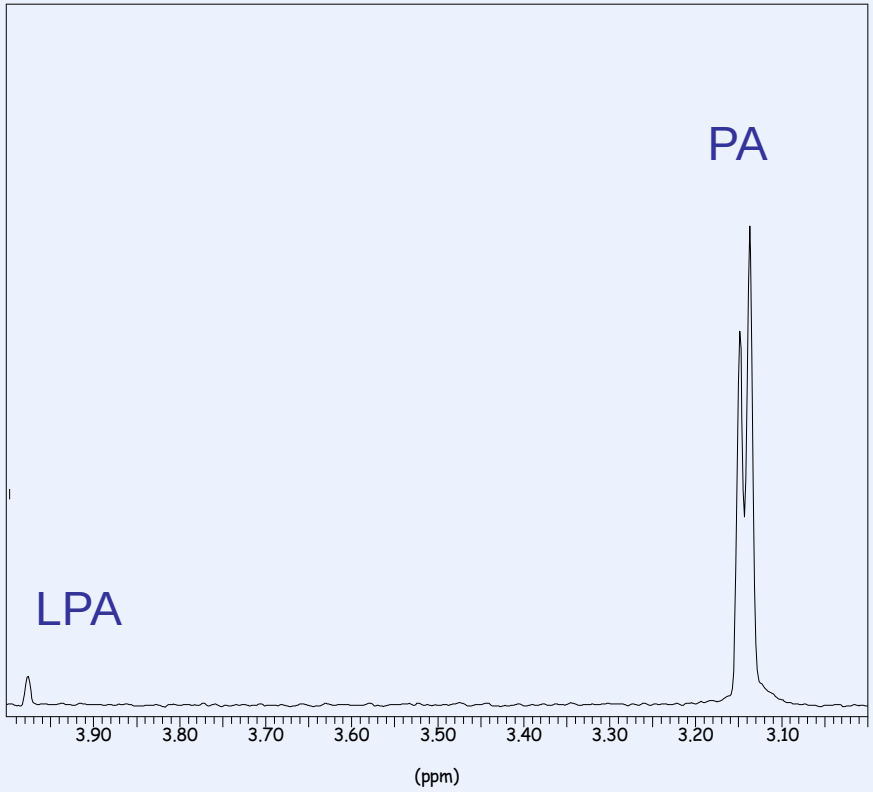
^{31}P-NMR of Soy Lecithin



^{19}F-NMR of Fluazinam

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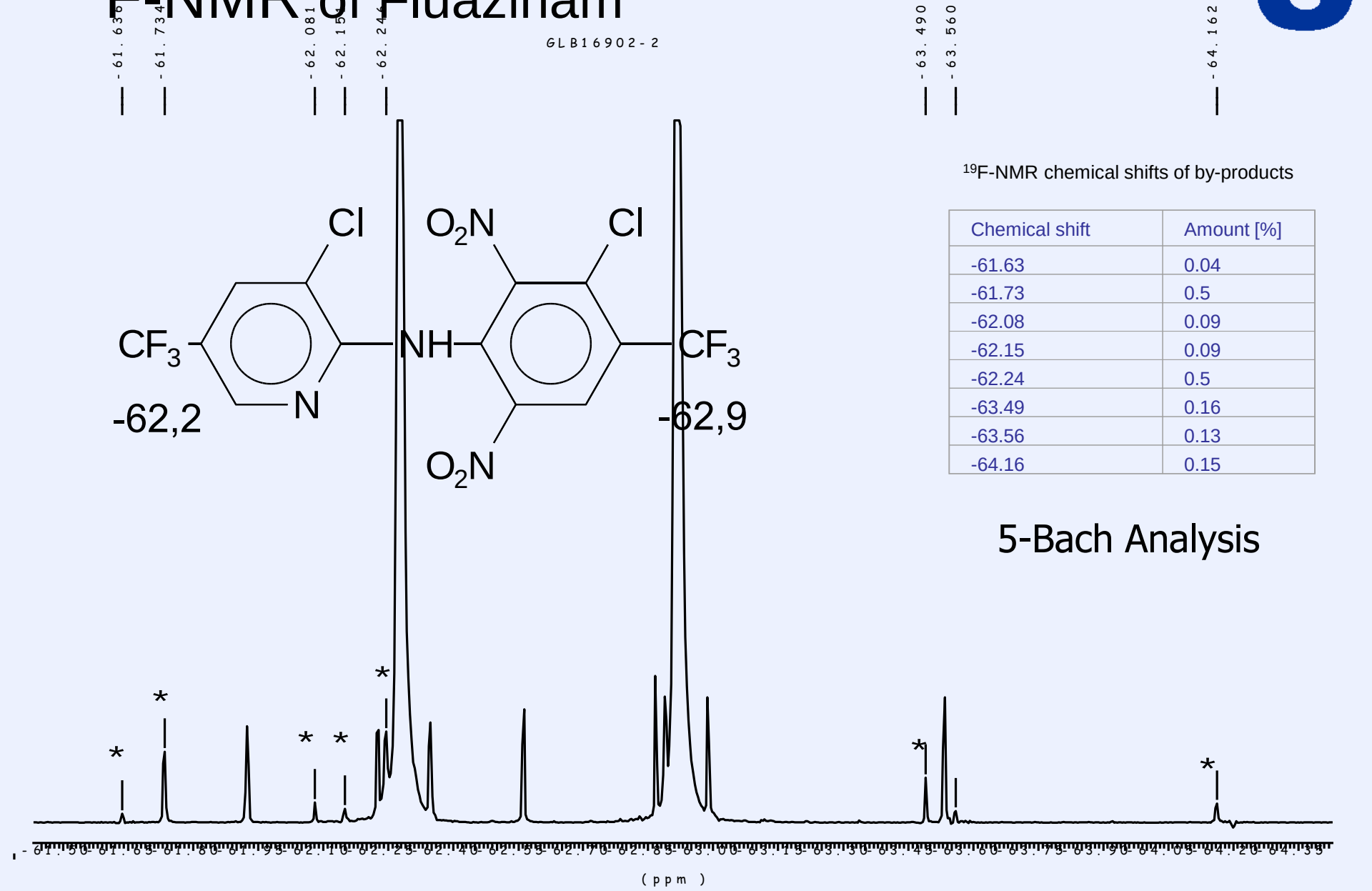

^{19}F-NMR chemical shifts of by-products

Chemical shift	Amount [%]
-61.63	0.04
-61.73	0.5
-62.08	0.09
-62.15	0.09
-62.24	0.5
-63.49	0.16
-63.56	0.13
-64.16	0.15

5-Bach Analysis

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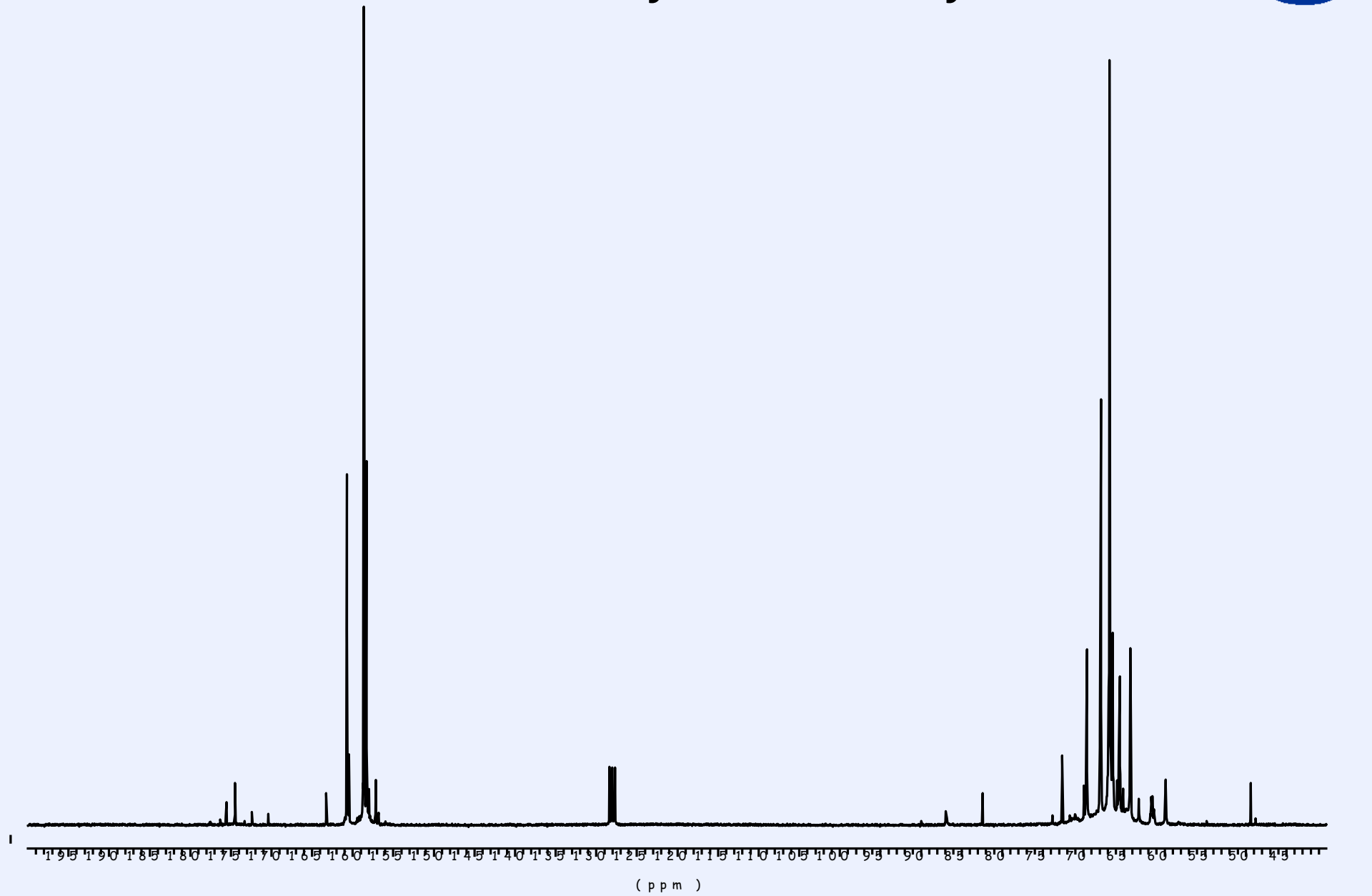
^{13}C-NMR of Formaldehyde Donor Systems



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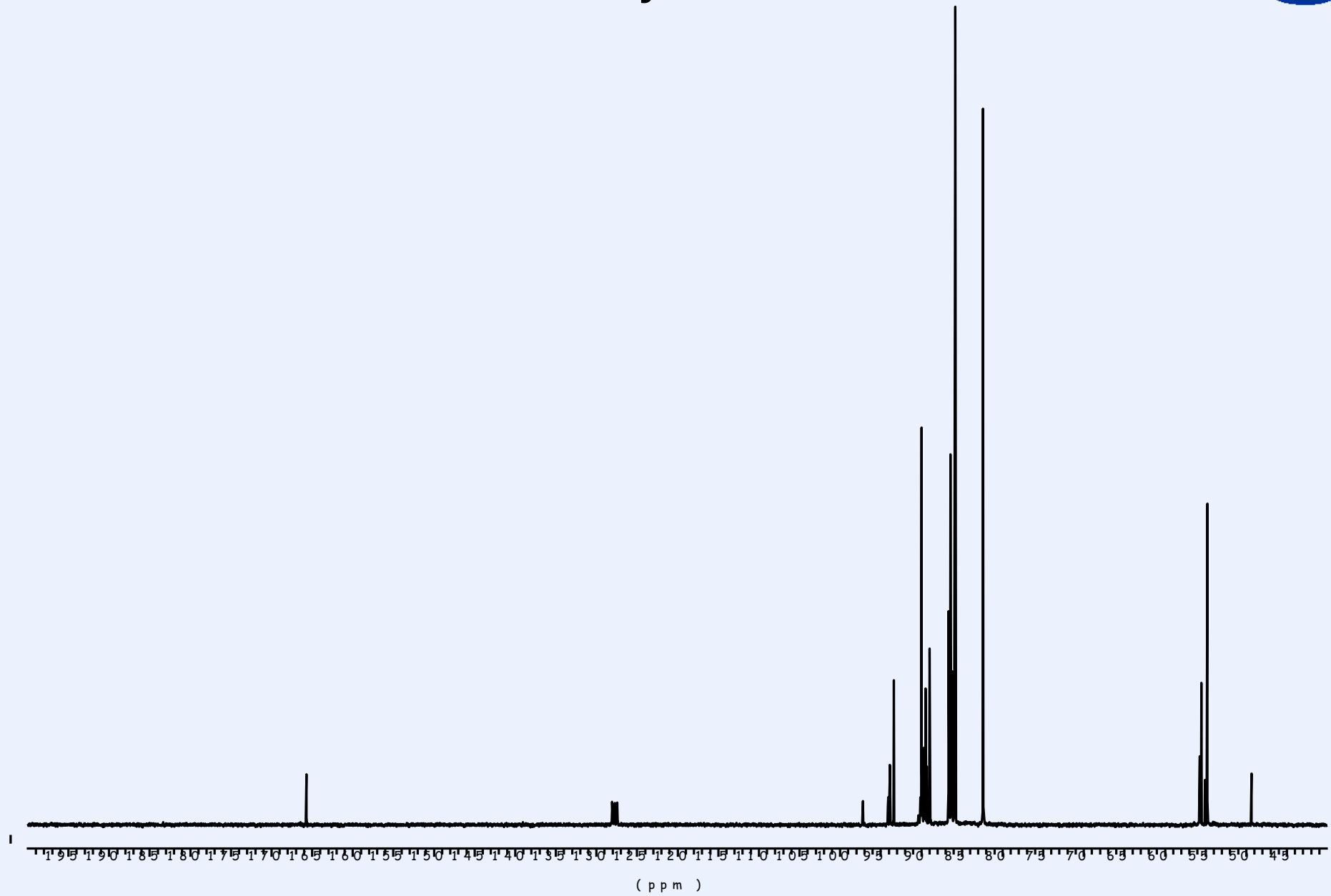
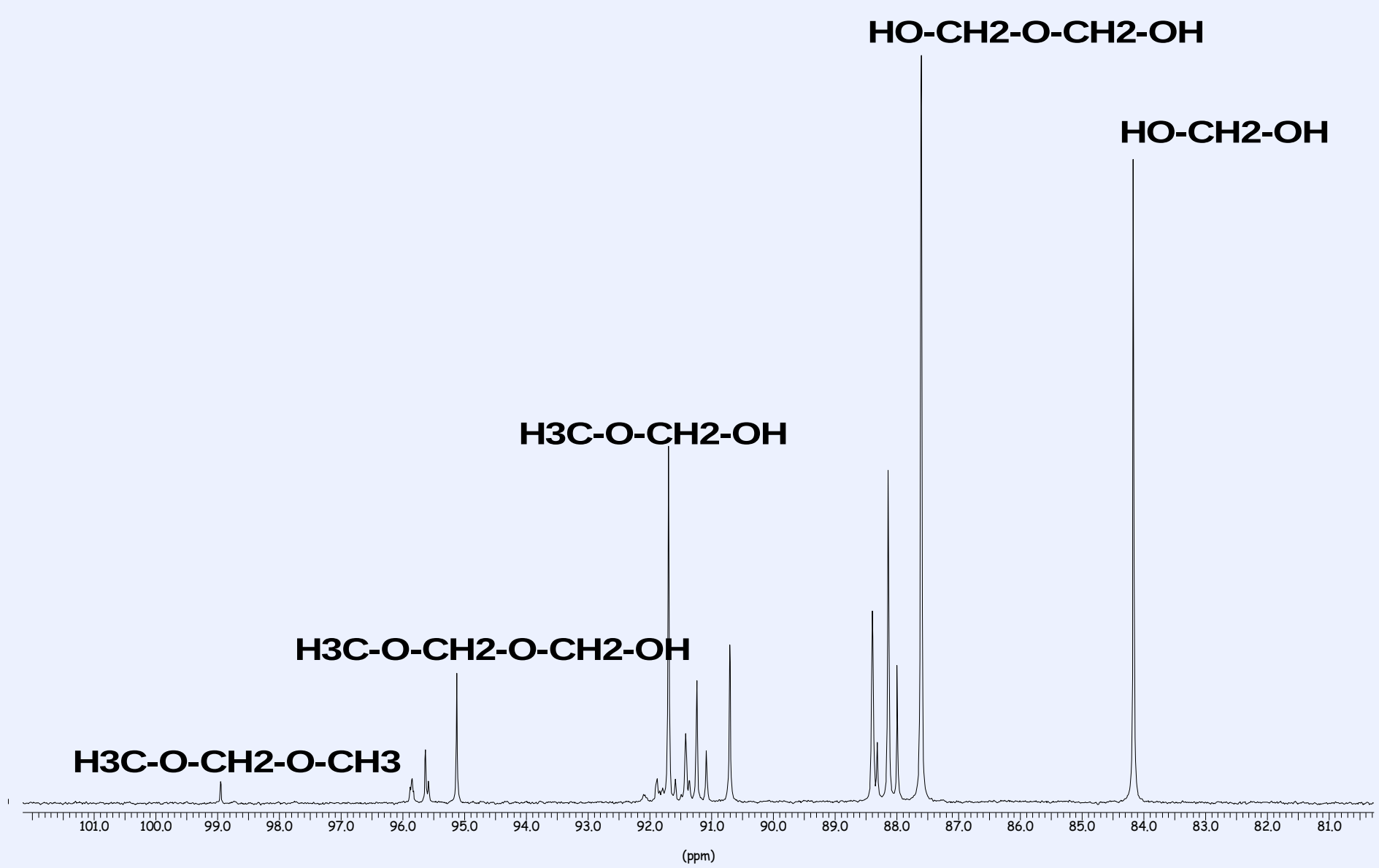
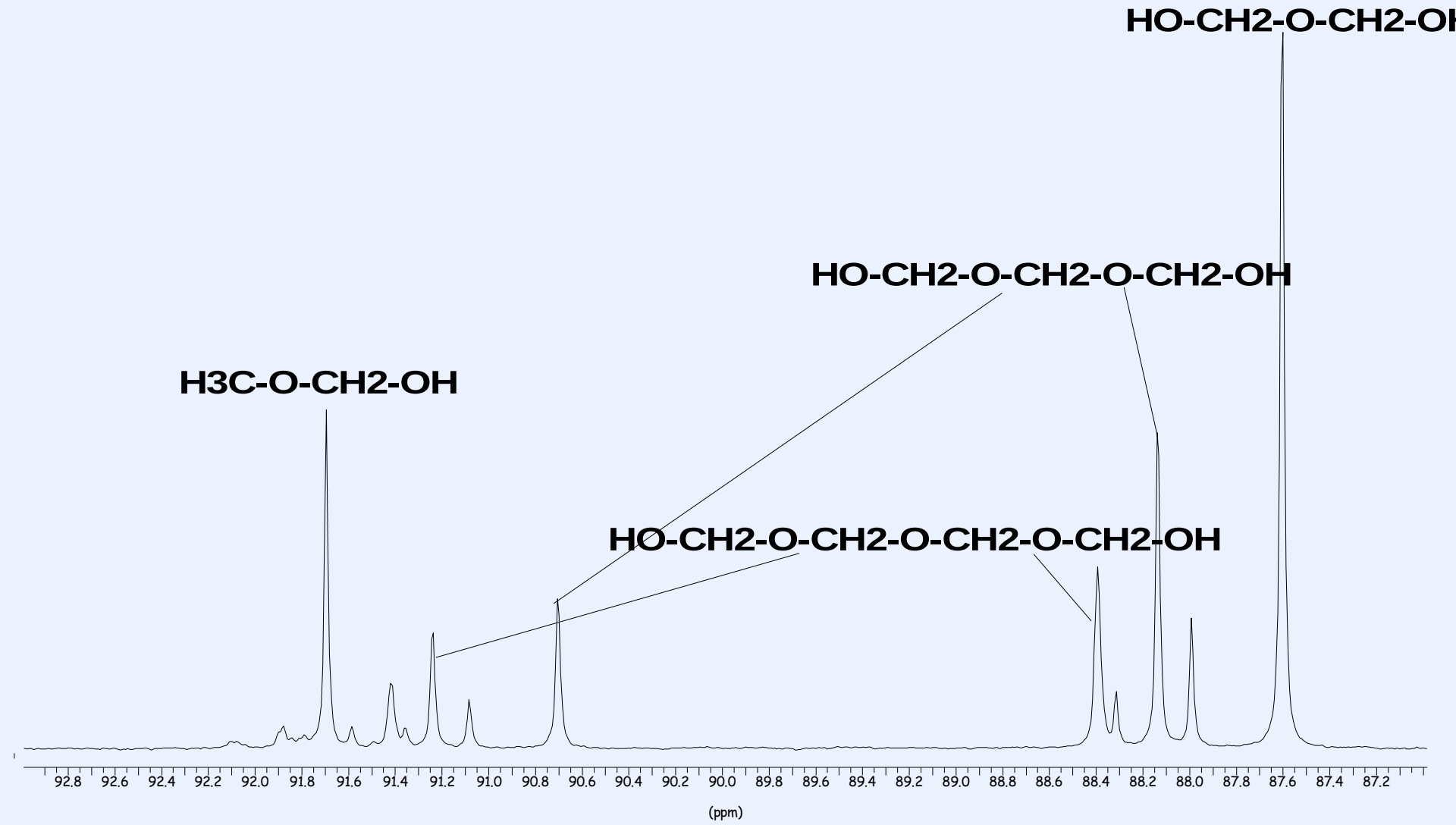
^{13}C-NMR of Formaldehyde



^{13}C-NMR of Formaldehyde



^{13}C-NMR of Formaldehyde



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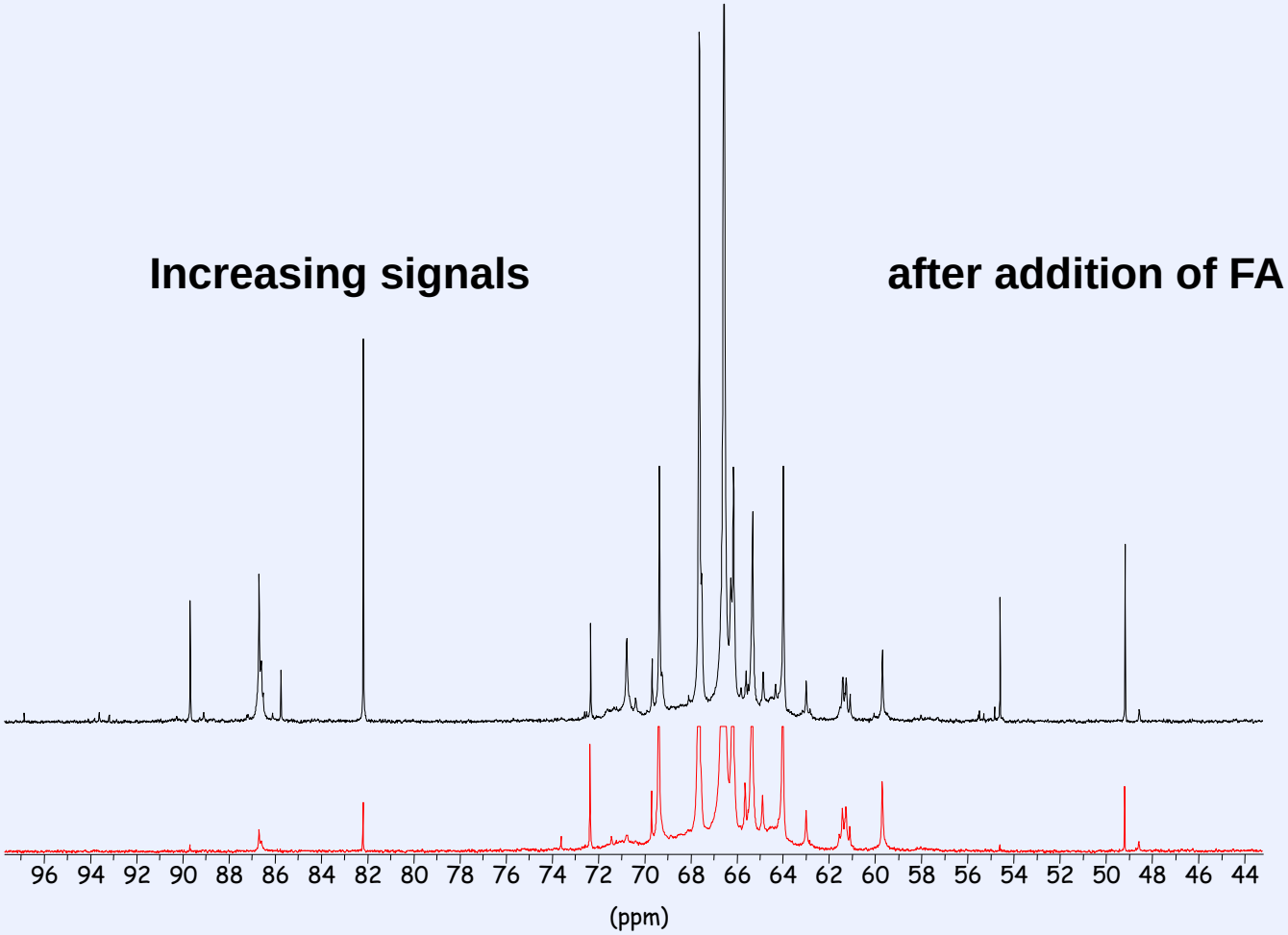
^{13}C-NMR of Formaldehyde Donor System

Increasing signals

after addition of FA solution



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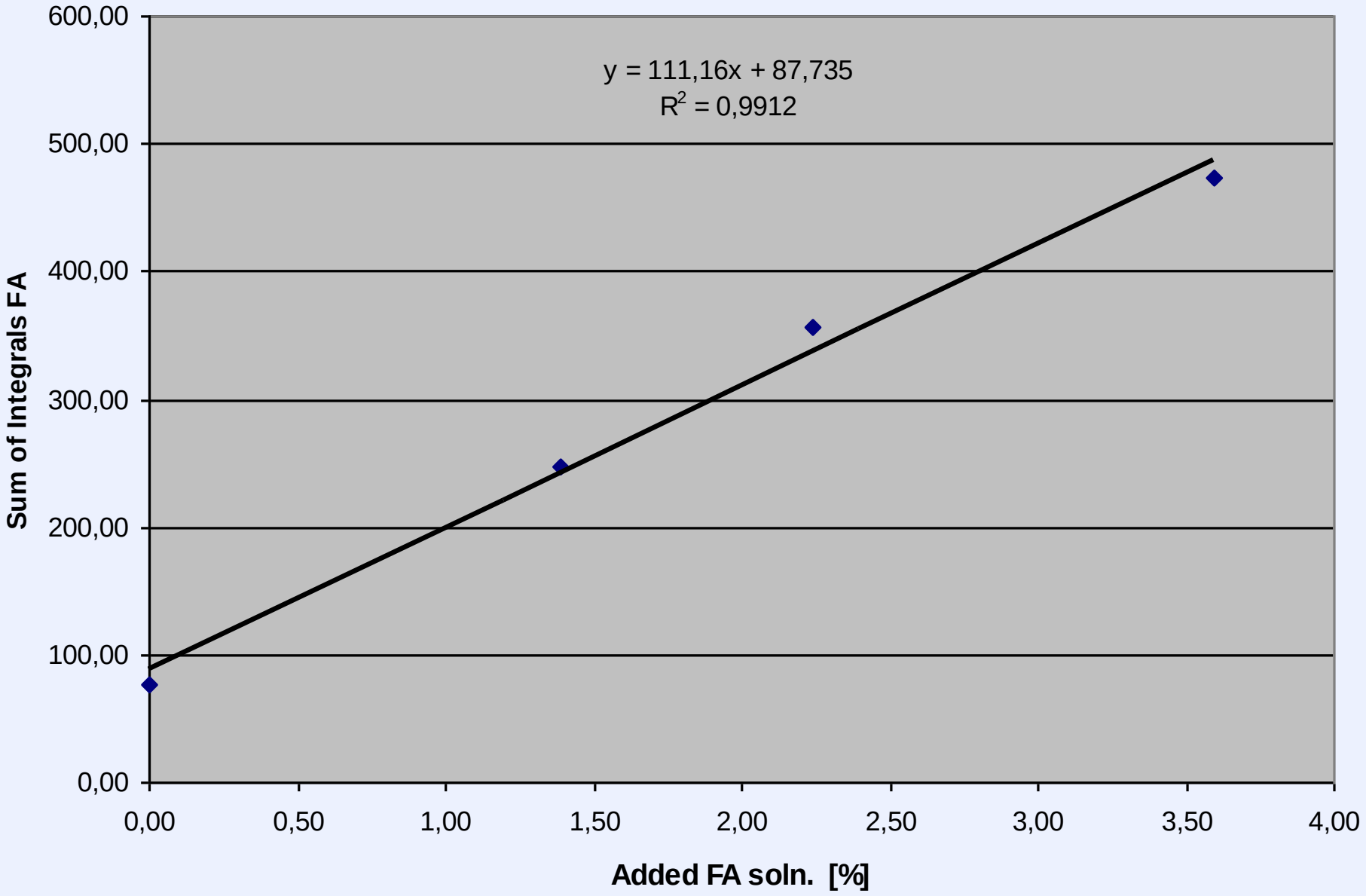
^{13}C-NMR of Formaldehyde Donor System



Conclusion

The potentials of quantitative NMR actually are not conceivable

But, the method must become world wide accepted by the authorities:

USB, DIN, EU guidelines, Pharmacopoeia etc.

Conclusion

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But, the method must become world wide accepted by the authorities:

USB, DIN, EU guidelines, Pharmacopoeia etc.

Furthermore you need:

Fantasy, Imagination and Passion

.... and some hundred MHz

Thanks to:

- Spectral Service Team

- and to your patience