

Direct Analysis Under Ambient
Conditions without Sample
Preparation:
**“Instant Gratification” for Small
Molecule Analysis**

Robert B. Cody
JEOL USA, Inc.

With (more than) a little help from my friends...

- **James A. Laramee**
 - EAI Corporation
- **Michael Nilles**
 - Geo-Centers
- **H. Dupont Durst**
 - Edgewood Chemical and Biological Center
- **Zhanpin Wu**
 - JEOL USA, Inc.
- **Doug Simmons**
 - IonSense



What is DART™?

- DART is a new non-contact surface sampling technique for mass spectrometry or ion mobility spectrometry at atmospheric pressure under ambient conditions.
- Think of it as an “open-air direct probe” or “EZ-Pass for mass spectrometry”
- DART can be used to analyze gases, liquid, solids and materials on surfaces.

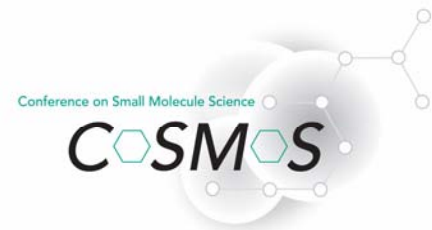
DART Status

- Developed by J. Laramee and R. Cody at JEOL USA, Inc. from 2001-2003. Patents filed.
- Announced and commercially available in 2005.
 - PittCon Editors' Gold Award
 - R&D 100 Award, 2005
- Licensed to IonSensetm Inc.

No chromatography?

Often, if...

- Simple DART mass spectrum reduces background
- DART is sensitive to target and not to interferences
- We can rely on high resolution and/or MS/MS for specificity
- Different compounds don't desorb in the same instant. "Distillation"



Let's begin with a demonstration...

[DART demo.mov](#)

Direct Analysis in Real Time

The AccuTOF-DART

JEOL USA

IonSense

Video download available on-line at:

http://www.jeolusa.com/ms/msprods/accutof_dart.html

DART applications:

- Drugs (medicinal, herbal, illicit, counterfeit)
- Metabolites (see also WP046)
- Explosives
- Synthetic organics and organometallics
- Chemical Warfare Agents (CWA)
- Foods and beverages
- Pesticides
- Toxic industrial materials
- Packaging and polymers (volatiles, dyes plasticizers, and pyrolysis)
- Plus...GC/MS, LC/MS

TOF Analyzer

- DART is interfaced to a JEOL AccuTOFtm time-of-flight mass spectrometer
- High resolution and exact mass measurements provide selectivity
- Exact masses and accurate isotopic abundances permit identification of unknowns
- Fast data acquisition for high throughput

The Mass Spectrometer

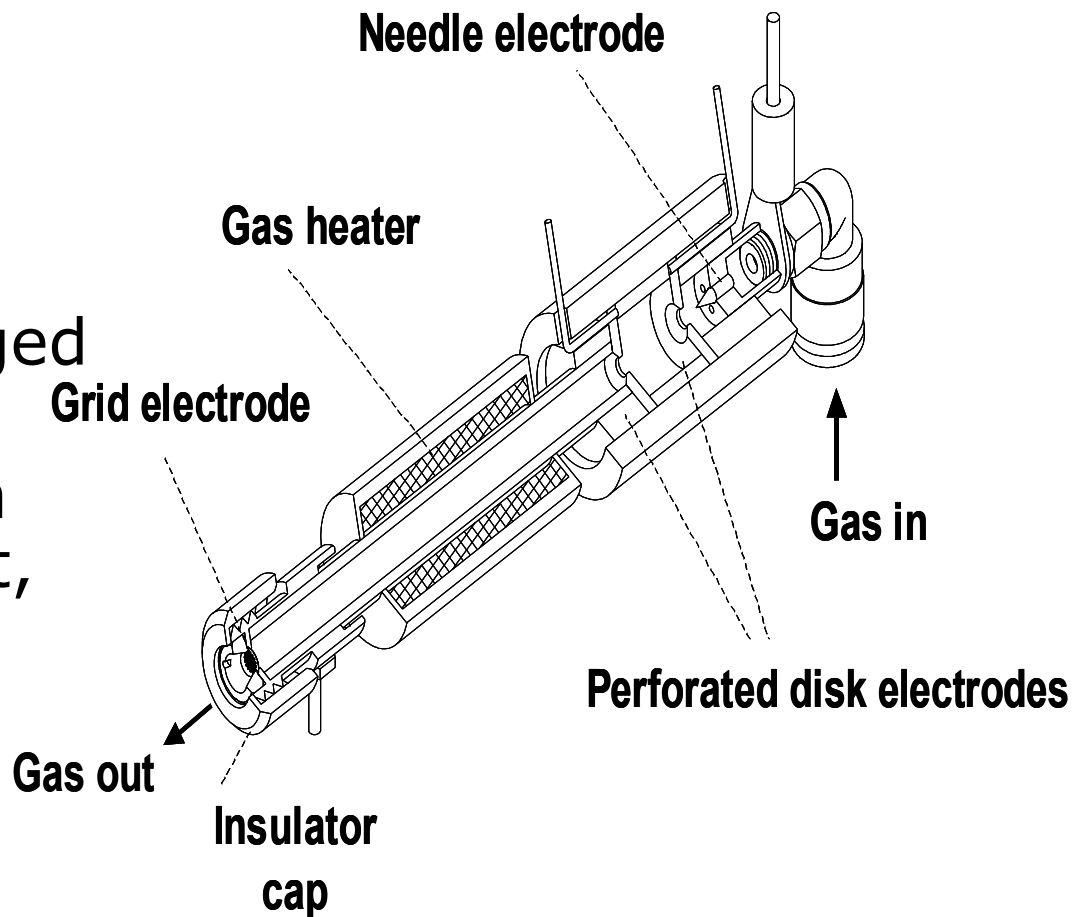
Configured for LC/MS



With DART Ion Source

DART Schematic

- Gas flows through DART
- Electrical discharge creates a plasma
- Lenses remove charged particles
- Grid prevents ion-ion recombination at exit, and other functions
- No exposed high voltages
- Operated at ambient pressure in open air



DART Ionization

Penning ionization

Sample ionized directly by energy transfer from metastables (M^*)

Proton transfer

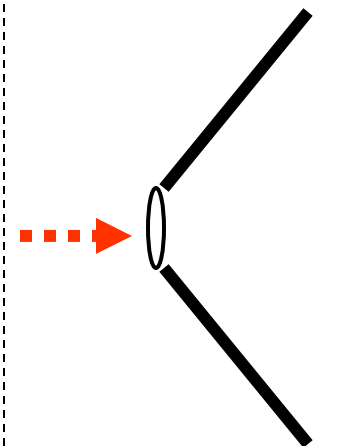
1. He^* ionizes atmospheric water
2. Ionized water clusters transfer proton to sample

Electron capture

1. Penning electrons rapidly thermalized
2. Oxygen captures electrons
3. O_2^- ionizes sample

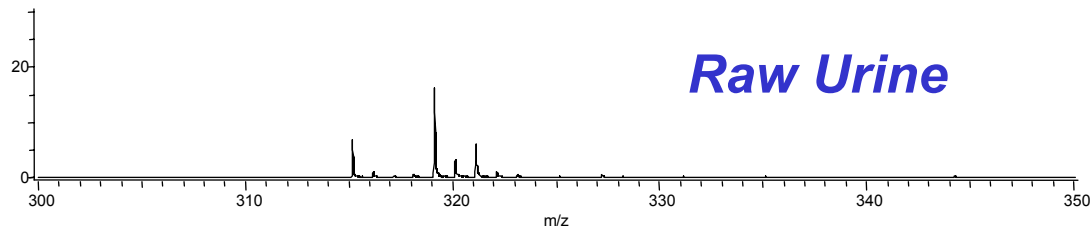
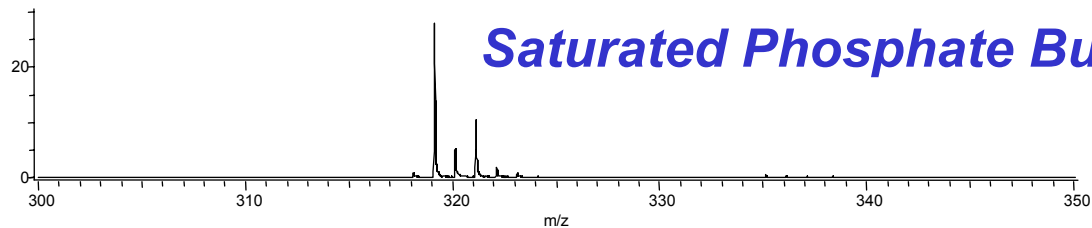
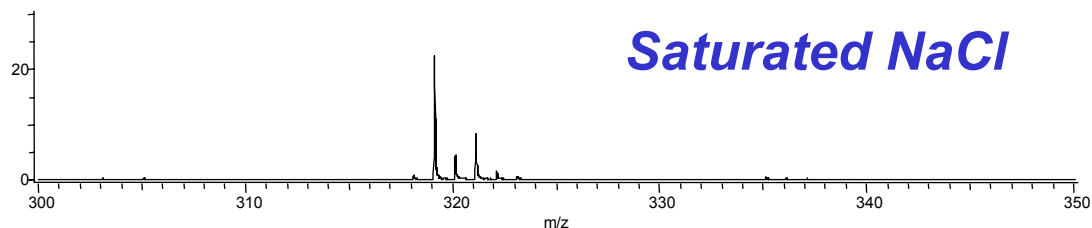
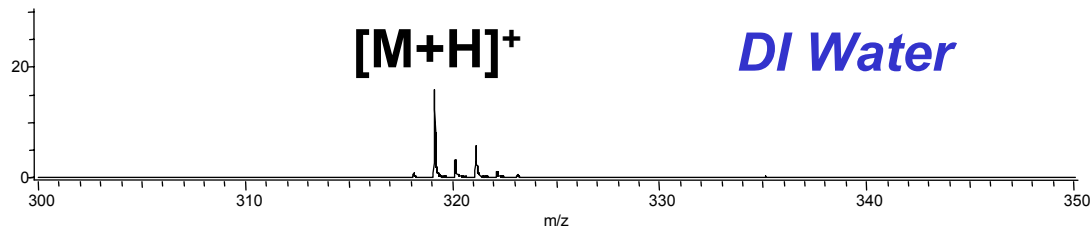


DART Source



MS API Interface

Contamination Resistance



Chlorpromazine
[M+H]⁺

*No alkali metal
cation adducts*

*No multiple
charging*

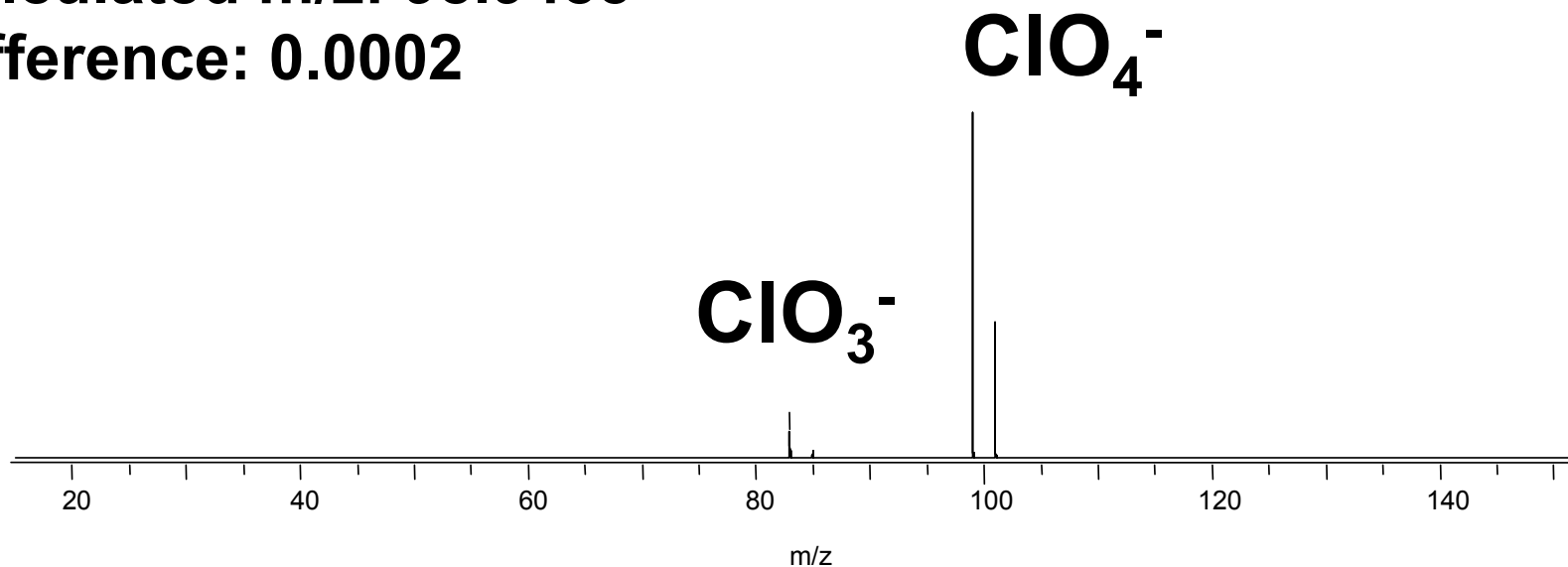
*No apparent
suppression*

An inorganic explosive with no significant vapor pressure: Sodium Perchlorate

Measured m/z (ClO_4^-): 98.9487

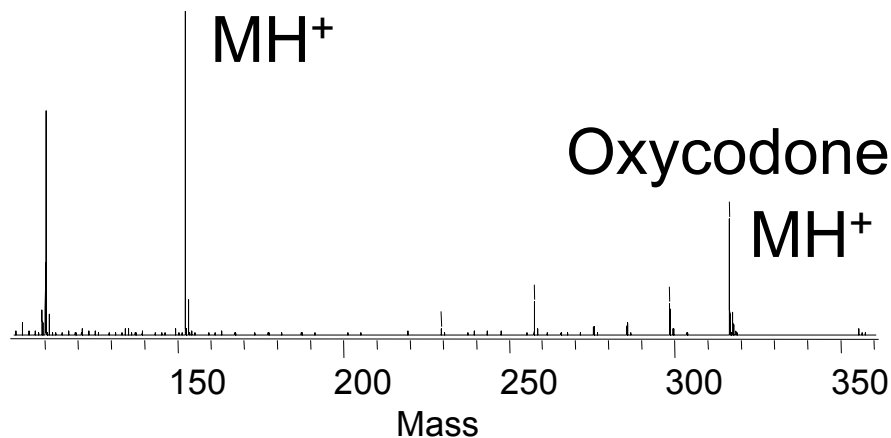
Calculated m/z : 98.9485

Difference: 0.0002

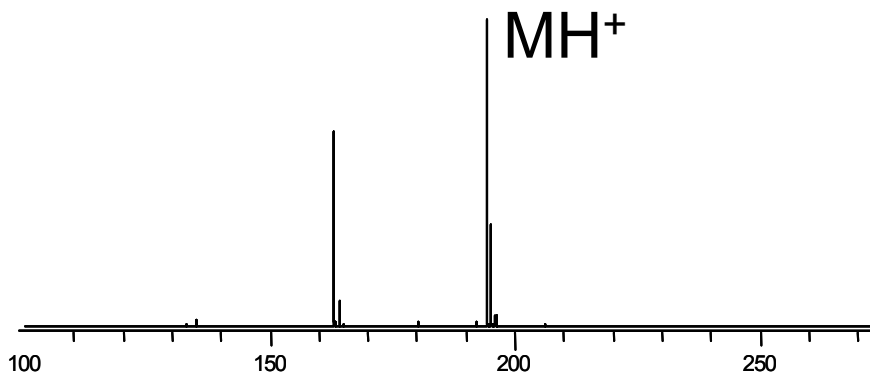


Direct Detection of Drugs in Pill Form

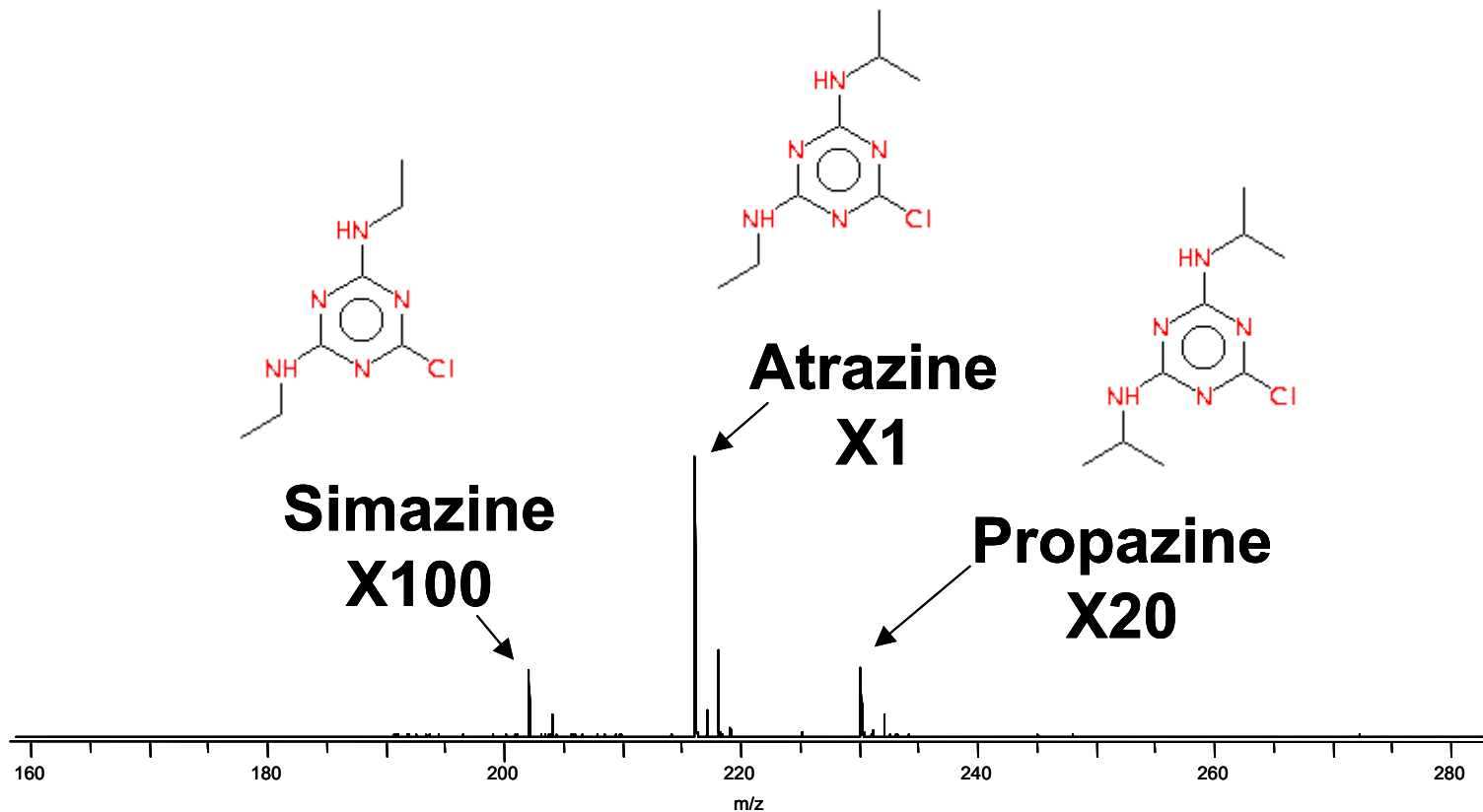
Acetaminophen



“Ecstasy” (MDMA)

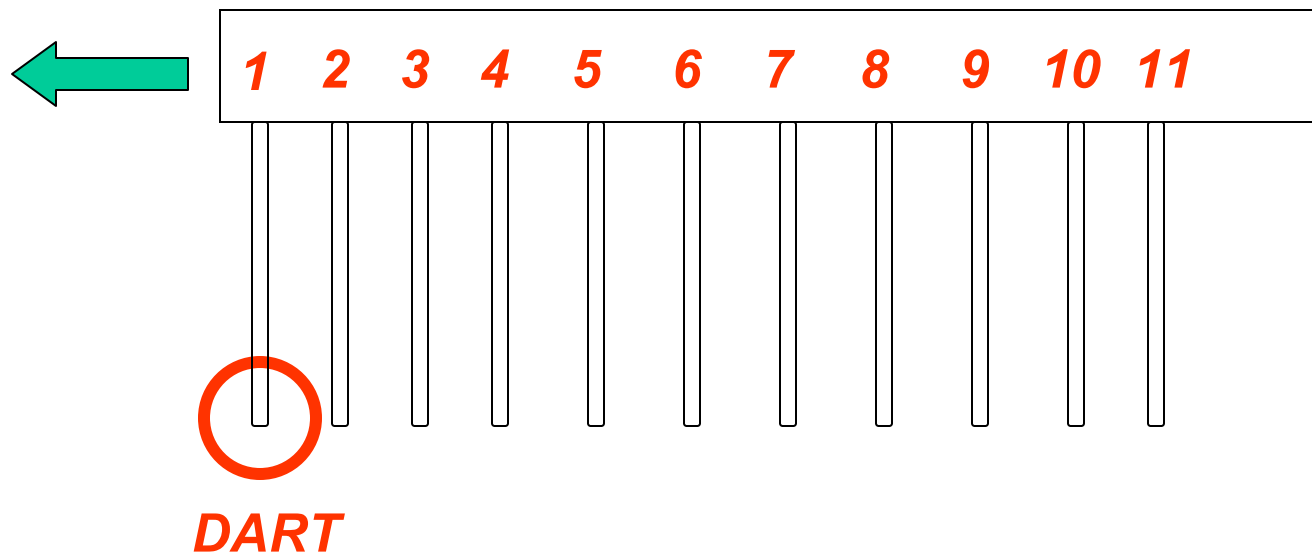


Trace impurities: 0.2% simazine in atrazine



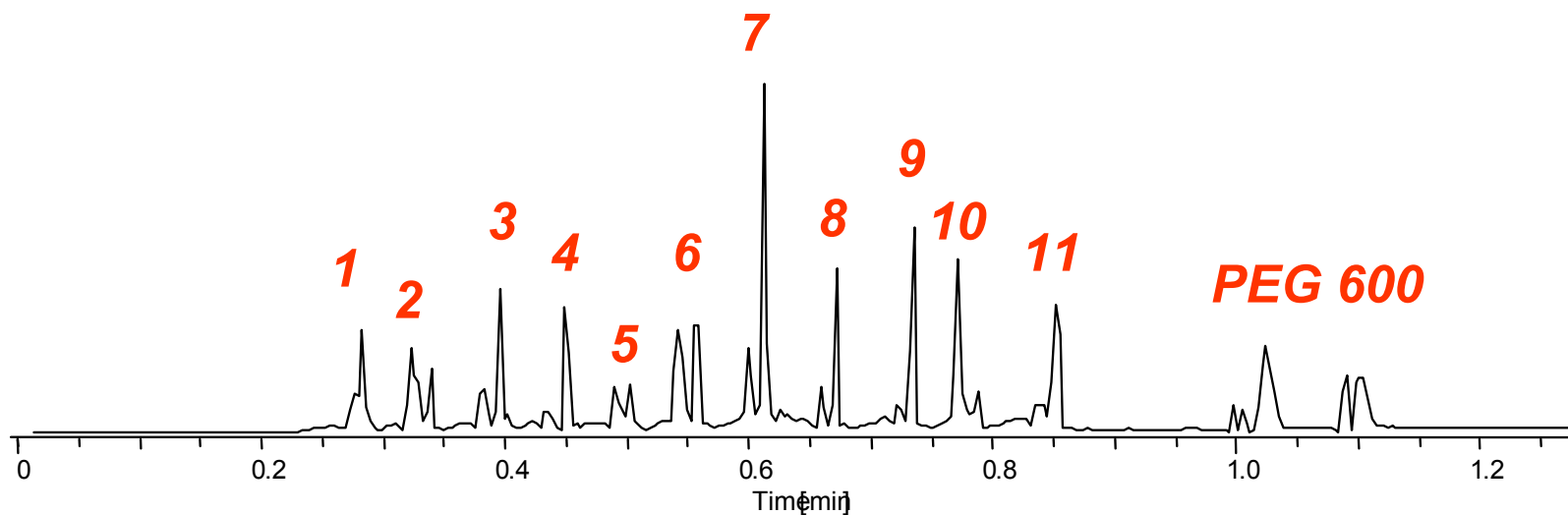
5 second analysis: all *m/z* differ by < 2mmu
from calculated values

Experiment



- Samples deposited on melting point tubes
- Pass tubes quickly through DART source
- Acquire 5-10 spectra per second
- Post-calibration with PEG 600 on filter paper

TIC for high-throughput trial

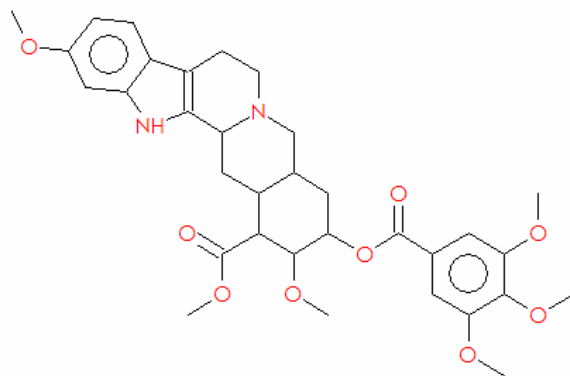
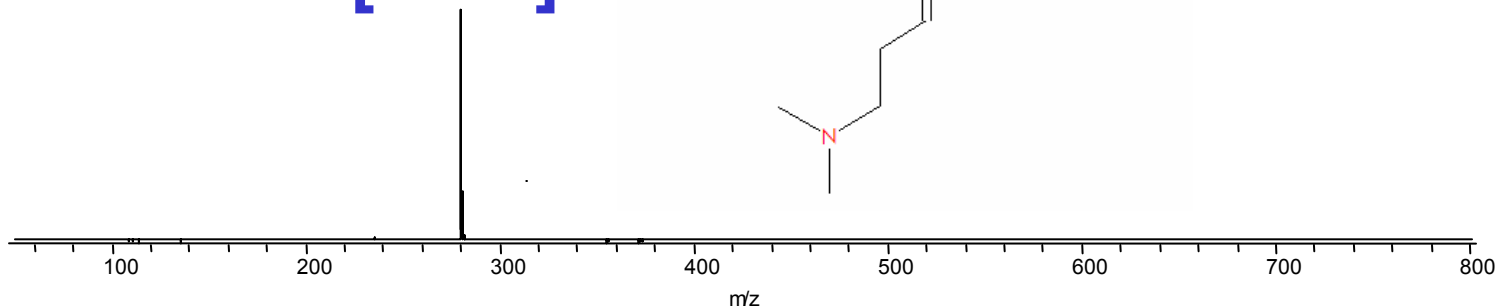
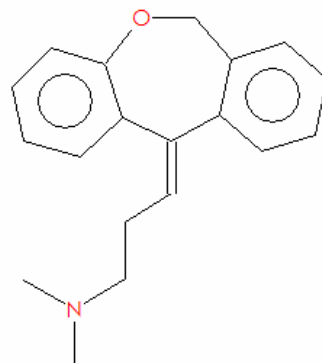


0.58 min

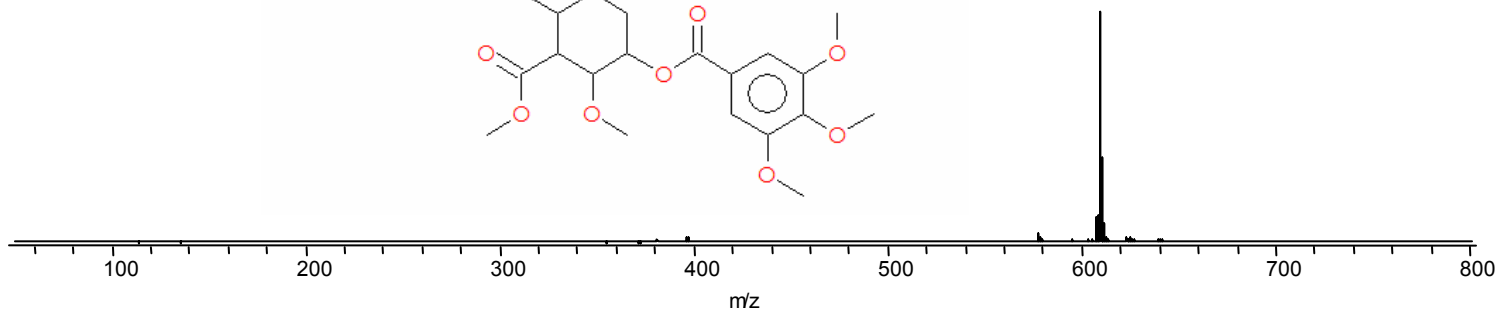
~3 seconds per compound

Example mass spectra

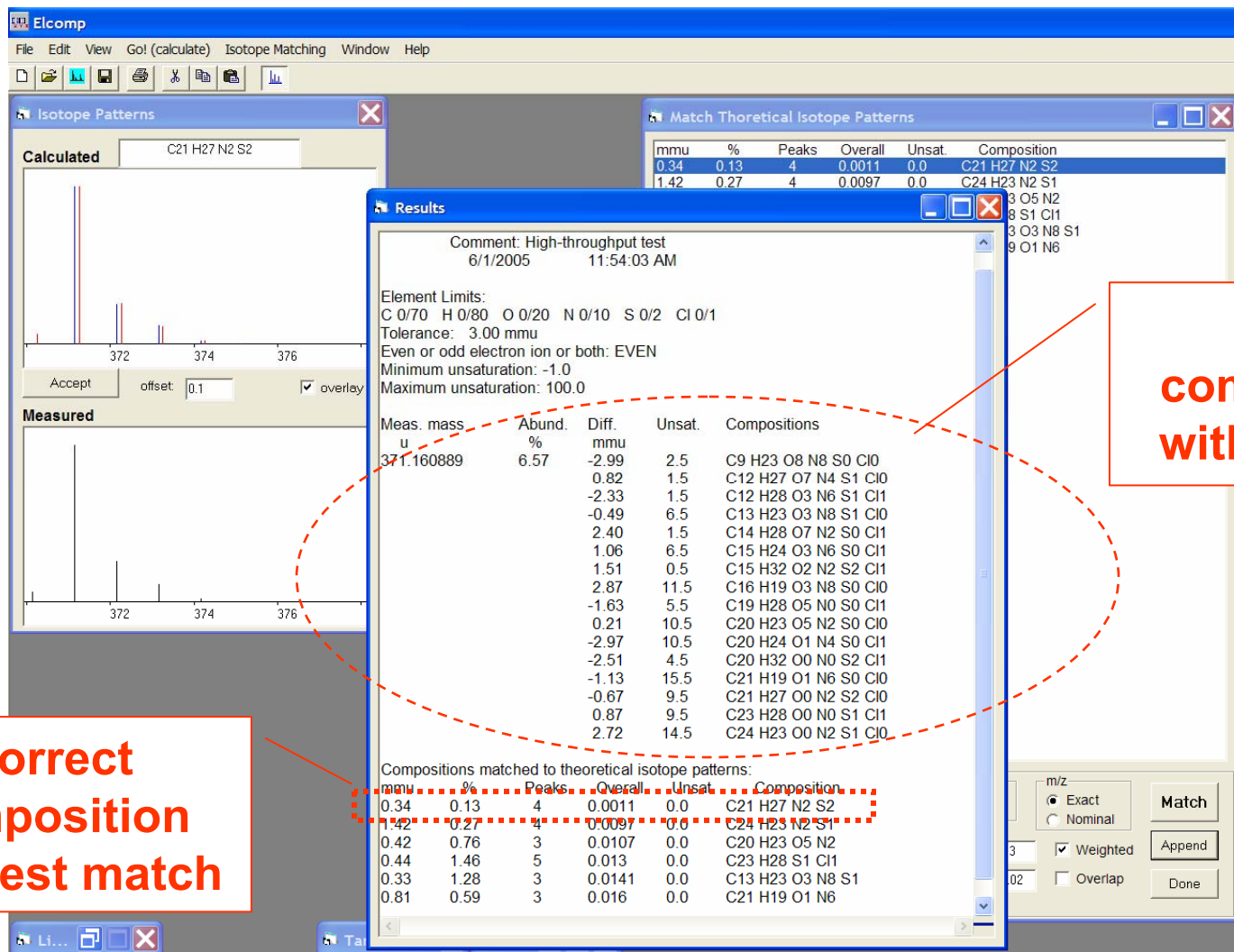
Doxepin
[M+H]⁺



Reserpine
[M+H]⁺



Automated isotope matching software



The screenshot shows the Elcomp software interface with several windows open:

- Isotope Patterns:** Shows calculated and measured mass spectra for C₂₁H₂₇N₂S₂. The x-axis represents m/z with markers at 372, 374, and 376.
- Match Theoretical Isotope Patterns:** A table listing theoretical compositions and their match statistics.
- Results:** A detailed window showing search parameters and a list of potential compositions.

Match Theoretical Isotope Patterns Table:

mmu	%	Peaks	Overall	Unsat.	Composition
0.34	0.13	4	0.0011	0.0	C ₂₁ H ₂₇ N ₂ S ₂
1.42	0.27	4	0.0097	0.0	C ₂₄ H ₂₃ N ₂ S ₁

Results Window Content:

Comment: High-throughput test
6/1/2005 11:54:03 AM

Element Limits:
C 0/70 H 0/80 O 0/20 N 0/10 S 0/2 Cl 0/1
Tolerance: 3.00 mmu
Even or odd electron ion or both: EVEN
Minimum unsaturation: -1.0
Maximum unsaturation: 100.0

Meas. mass	Abund.	Diff.	Unsat.	Compositions
u	%	mmu		
371.160889	6.57	-2.99	2.5	C ₉ H ₂₃ O ₈ N ₈ S ₀ Cl ₀
		0.82	1.5	C ₁₂ H ₂₇ O ₇ N ₄ S ₁ Cl ₀
		-2.33	1.5	C ₁₂ H ₂₈ O ₃ N ₆ S ₁ Cl ₁
		-0.49	6.5	C ₁₃ H ₂₃ O ₃ N ₈ S ₁ Cl ₀
		2.40	1.5	C ₁₄ H ₂₈ O ₇ N ₂ S ₀ Cl ₁
		1.06	6.5	C ₁₅ H ₂₄ O ₃ N ₆ S ₀ Cl ₁
		1.51	0.5	C ₁₅ H ₃₂ O ₂ N ₂ S ₂ Cl ₁
		2.87	11.5	C ₁₆ H ₁₉ O ₃ N ₈ S ₀ Cl ₀
		-1.63	5.5	C ₁₉ H ₂₈ O ₅ N ₀ S ₀ Cl ₁
		0.21	10.5	C ₂₀ H ₂₃ O ₅ N ₂ S ₀ Cl ₀
		-2.97	10.5	C ₂₀ H ₂₄ O ₁ N ₄ S ₀ Cl ₁
		-2.51	4.5	C ₂₀ H ₃₂ O ₀ N ₀ S ₂ Cl ₁
		-1.13	15.5	C ₂₁ H ₁₉ O ₁ N ₆ S ₀ Cl ₀
		-0.67	9.5	C ₂₁ H ₂₇ O ₀ N ₂ S ₂ Cl ₀
		0.87	9.5	C ₂₃ H ₂₈ O ₀ N ₀ S ₁ Cl ₁
		2.72	14.5	C ₂₄ H ₂₃ O ₀ N ₂ S ₁ Cl ₀

Compositions matched to theoretical isotope patterns:

mmu	%	Peaks	Overall	Unsat.	Composition
0.34	0.13	4	0.0011	0.0	C ₂₁ H ₂₇ N ₂ S ₂
1.42	0.27	4	0.0097	0.0	C ₂₄ H ₂₃ N ₂ S ₁
0.42	0.76	3	0.0107	0.0	C ₂₀ H ₂₃ O ₅ N ₂
0.44	1.46	5	0.013	0.0	C ₂₃ H ₂₈ S ₁ Cl ₁
0.33	1.28	3	0.0141	0.0	C ₁₃ H ₂₃ O ₃ N ₈ S ₁
0.81	0.59	3	0.016	0.0	C ₂₁ H ₁₉ O ₁ N ₆

16 compositions within 0.003 u

Correct composition has best match

Elemental Compositions

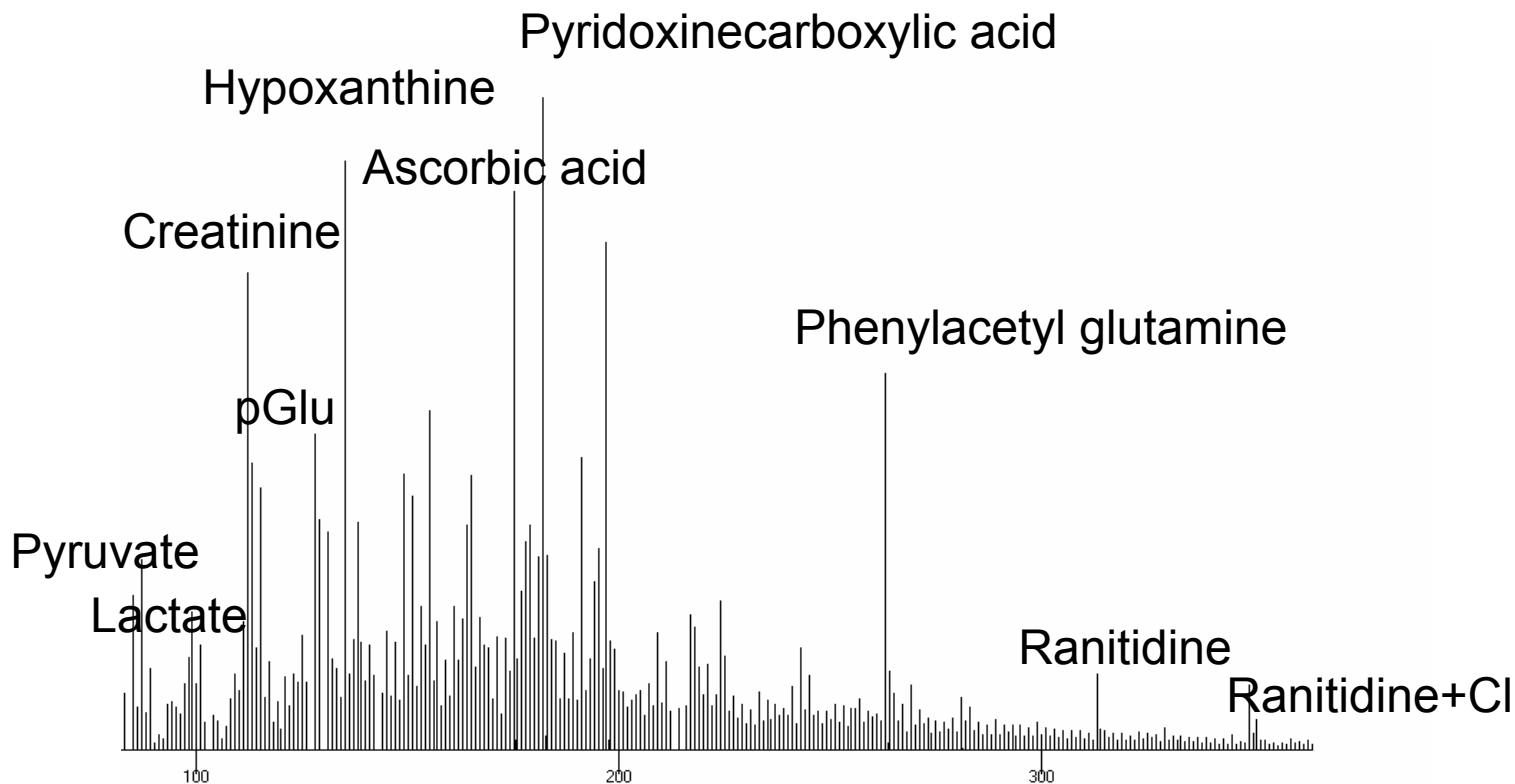
Limits: C 0/70 H 0/80 O 0/20 N 0/10 S 0/2 Cl 0/1

Tolerance: 3mmu, even-electron ions

<u>Compound</u>	<u>Composition</u>	<u>Calculated m/z</u>	<u>#Comps</u>	<u>Rank</u>
Phenolphthalein	C20H15O4	319.097035	18	1
Promazine	C17H21N2S	285.142544	11	1
Quinine	C20H25N2O2	325.191603	8	1
Nortriptylene	C19H22N	264.175224	5	1
Thioridazine	C21H27N2S2	371.161565	16	1
Chlorpromazine	C17H20N2SCI	319.103572	18	1
Doxepin	C19H22NO	280.170139	5	1
Hydrocortisone	C21H31O5	363.21715	9	1
Reserpine	C33H41N2O9	609.281208	30	1
Caffeine	C8H11N4O2	195.088201	7	1
Erythromycin	C37H68NO13	734.469069	22	1

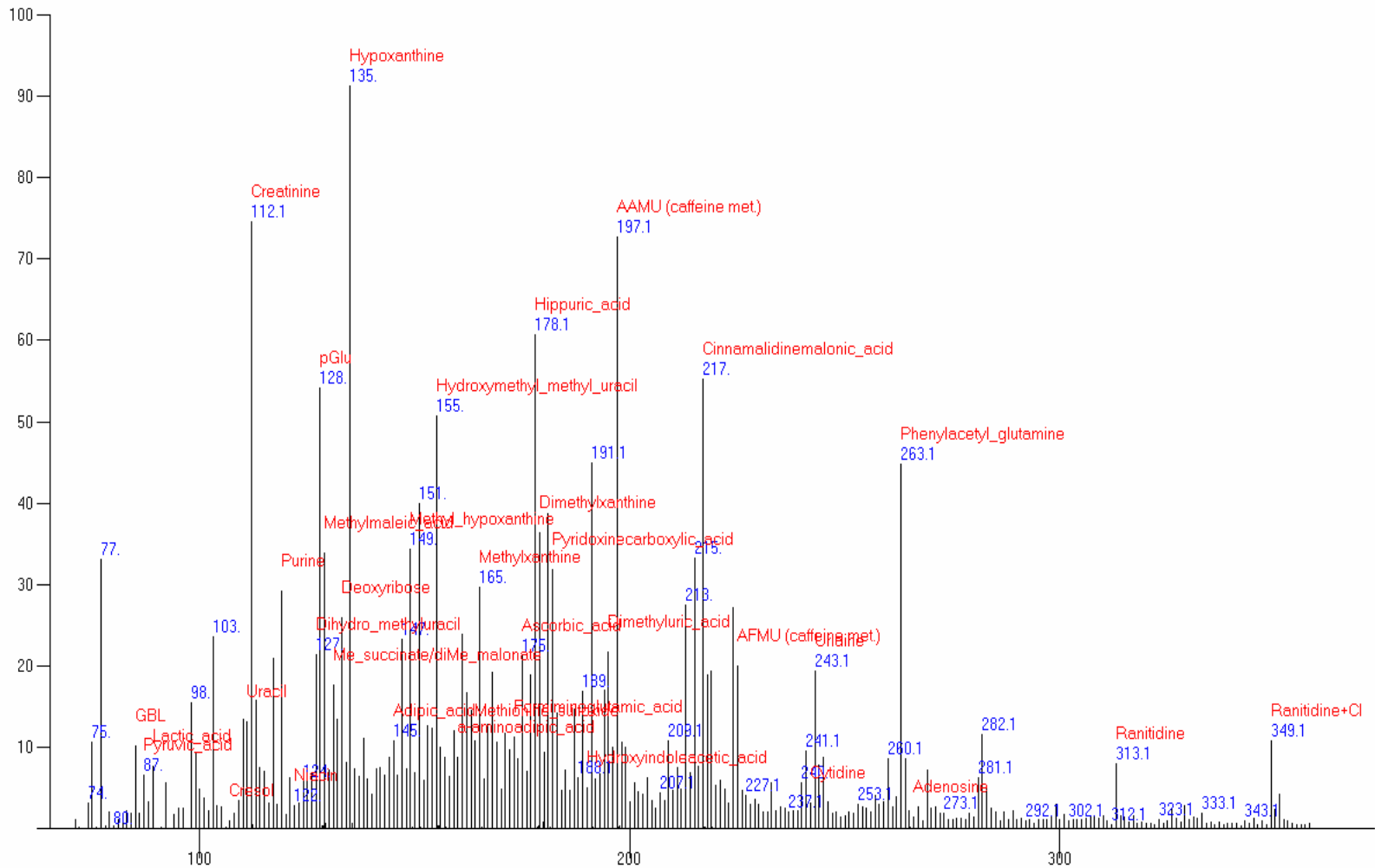
All compositions correctly identified, r.m.s. error = 2.2 ppm

Urine



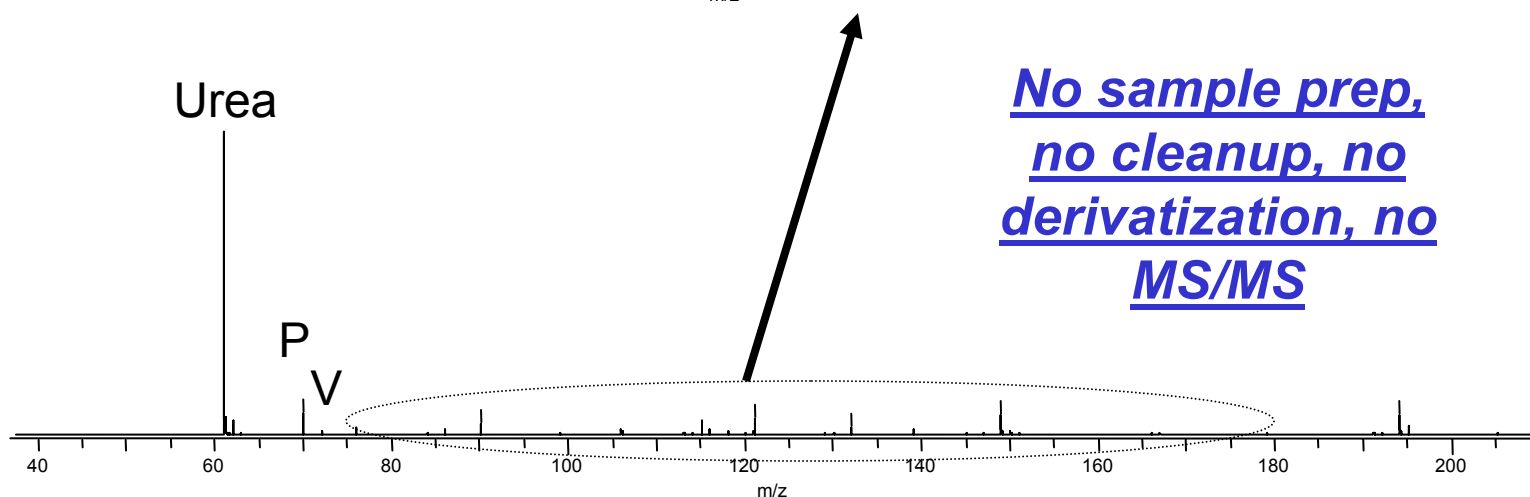
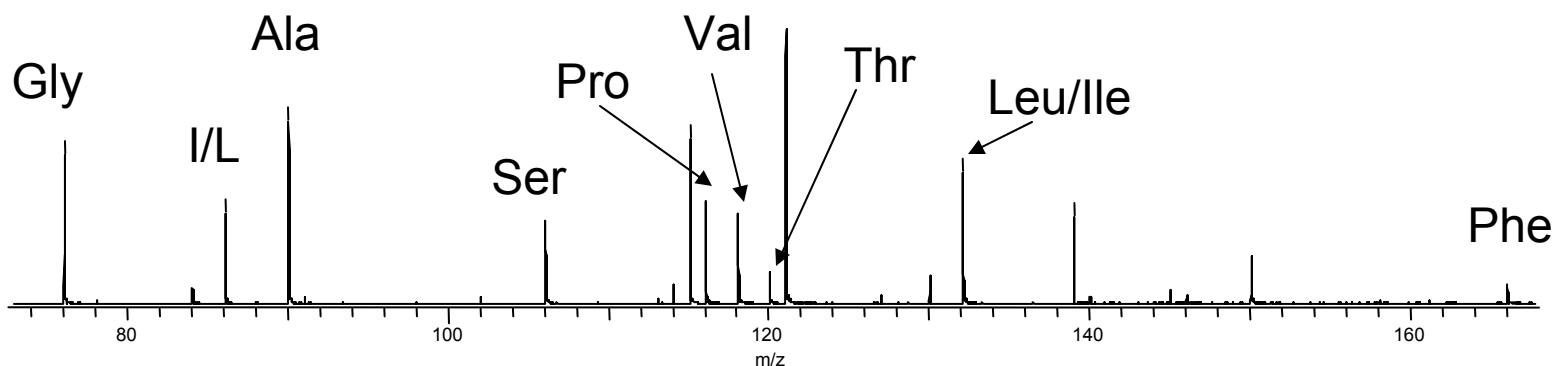
Computer Analysis of Spectrum

Rel. Abund.



m/z

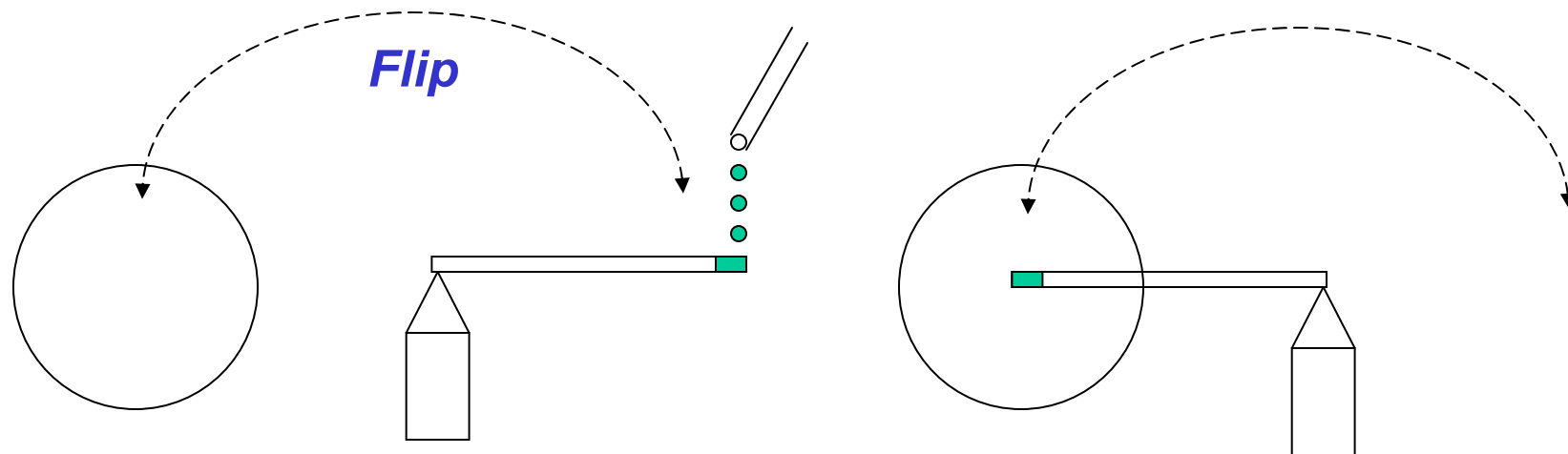
Blood droplet: Amino Acids (Positive Ions)



No sample prep,
no cleanup, no
derivatization, no
MS/MS

Is this useful? I don't know...maybe?

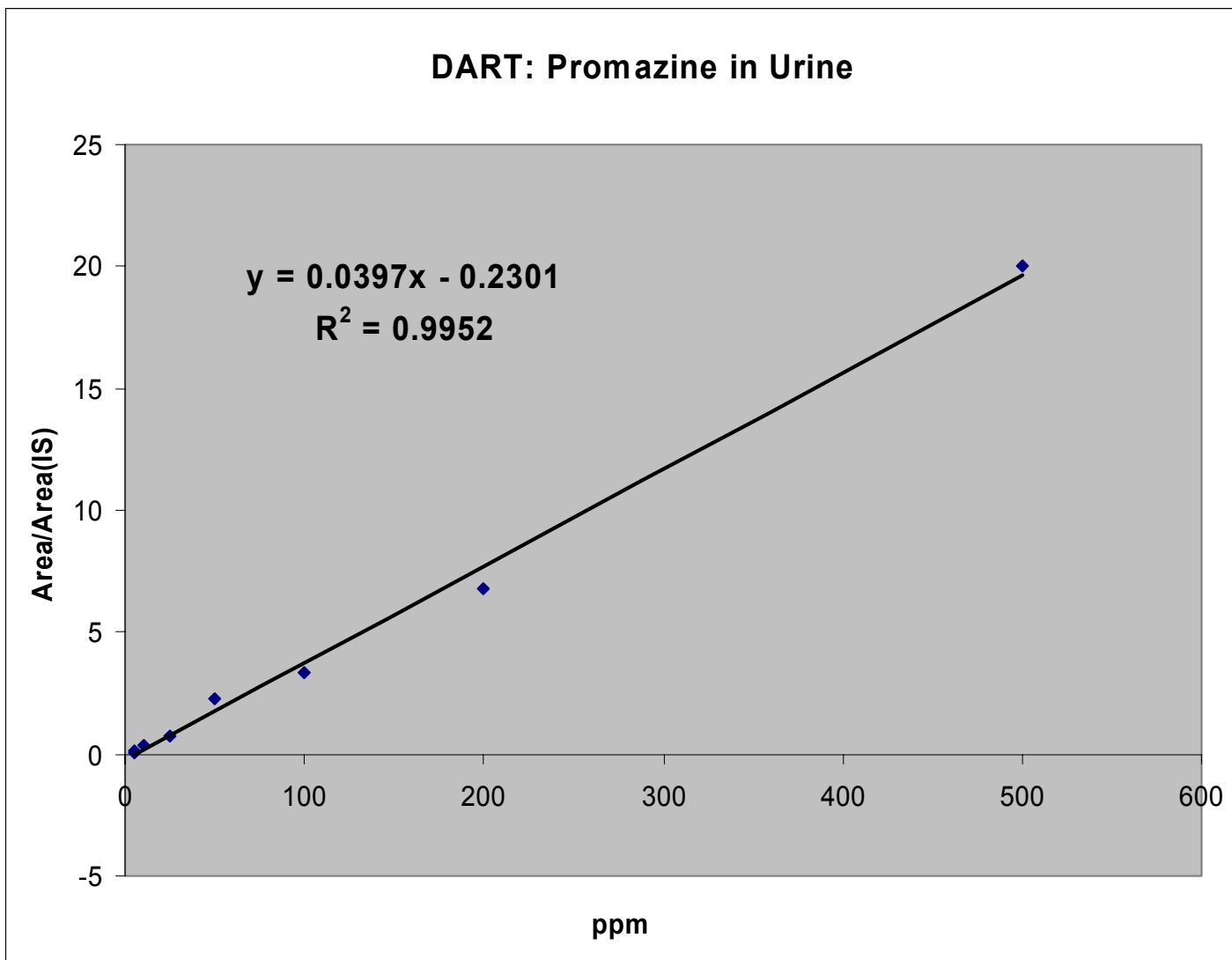
Drugs in Urine and Plasma



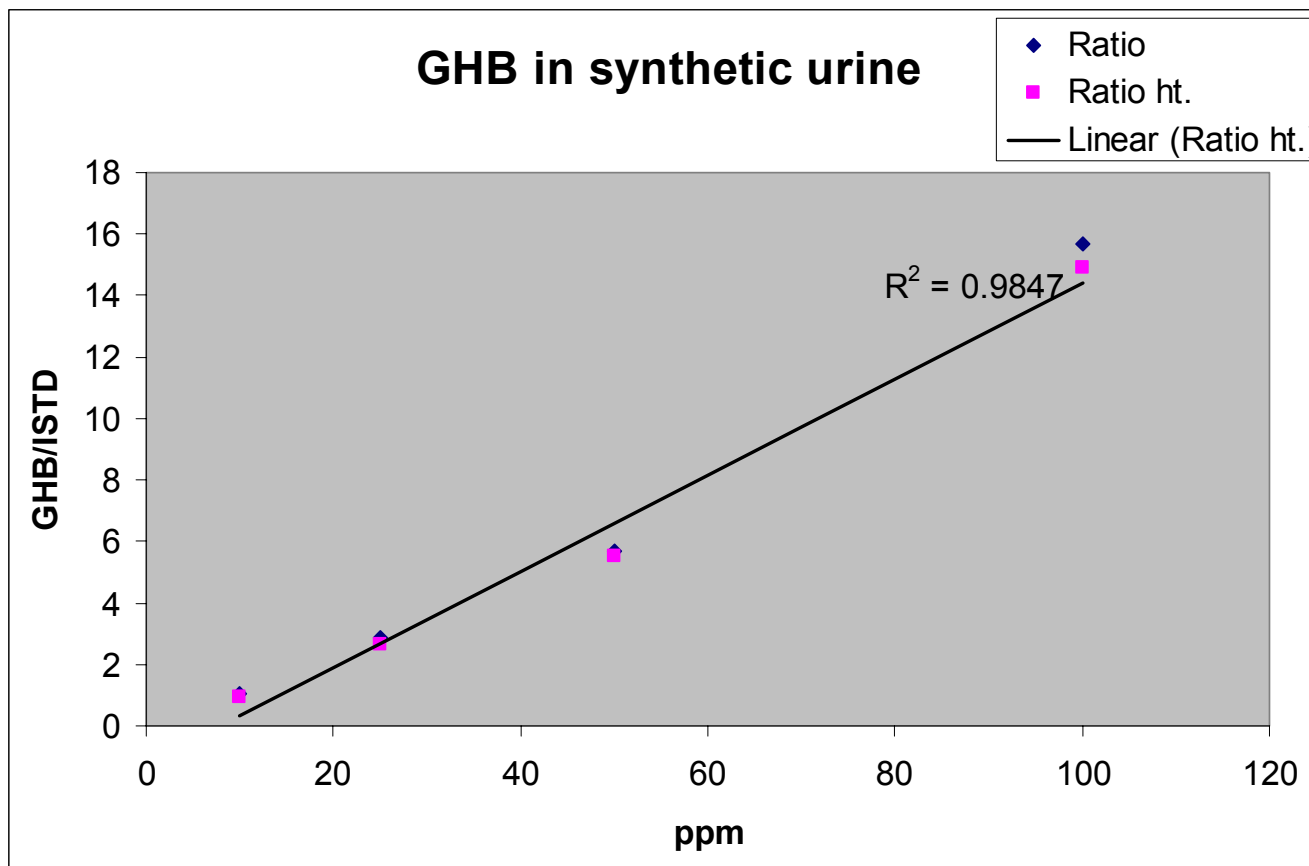
- Pipette a few microliters onto glass rod
- Swing into position
- See spectrum within seconds
- Remove, rinse, repeat

Promazine in Urine

Chlorpromazine internal standard



Gamma Hydroxybutyrate (GHB) in Urine (Deuterated I.S.)



**Thanks to Eshwar Jagerdeo and Roman Karas,
FBI Laboratory, Quantico VA**

Chromatography -- Yes!

No single technique will do everything.

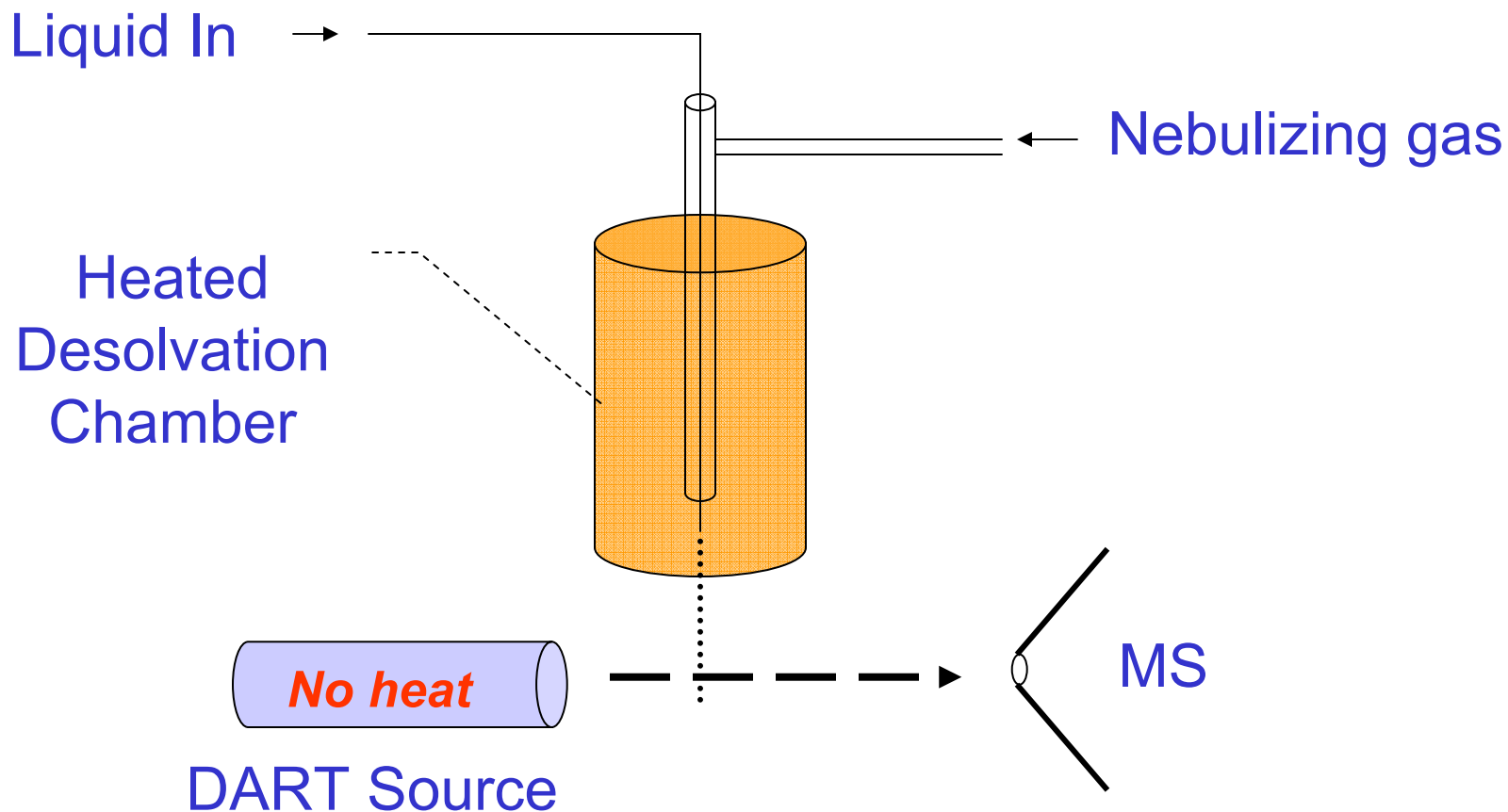
We still need separation techniques for:

- Separation of isomers
- Detection of trace analytes that might be overlooked or hidden by interferences
- “Needle-in-a-haystack” that needs lots of analytical power.
- Retention time as confirming data

Why LC/DART?

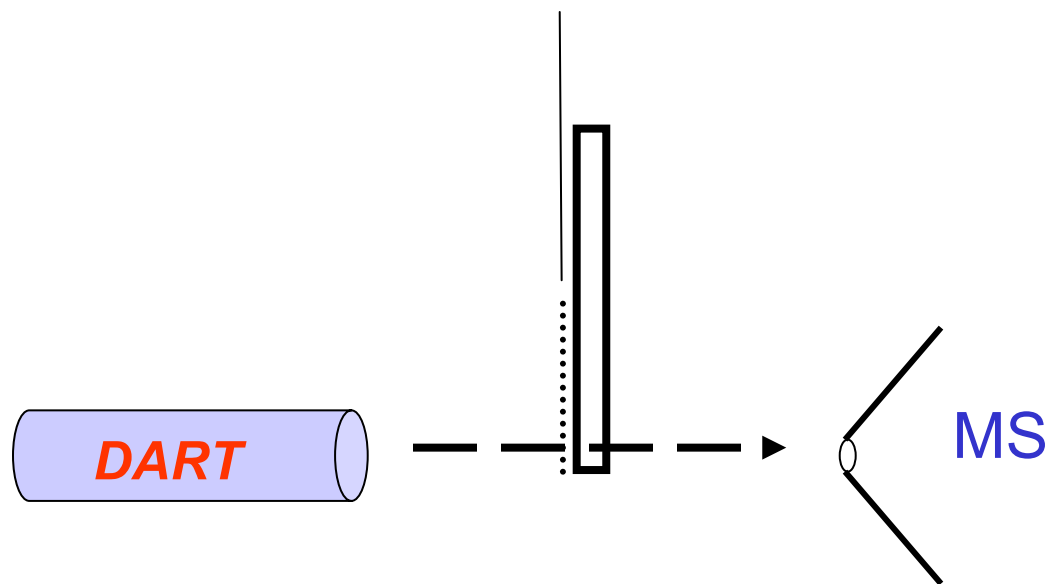
- Wide range of flow rates: few $\mu\text{l}/\text{min}$ to ml/min . Not restricted to high flows like APCI.
- Wider range of target compounds
- Simpler and more predictable spectra
- More resistant to contamination?

Experimental Approach to LC/DART-MS: Use the APCI Source (Corona needle OFF)



Very Low-flow Alternative

Trickle liquid onto support



Or.. "Frit-DART"?

Prototype LC/DART

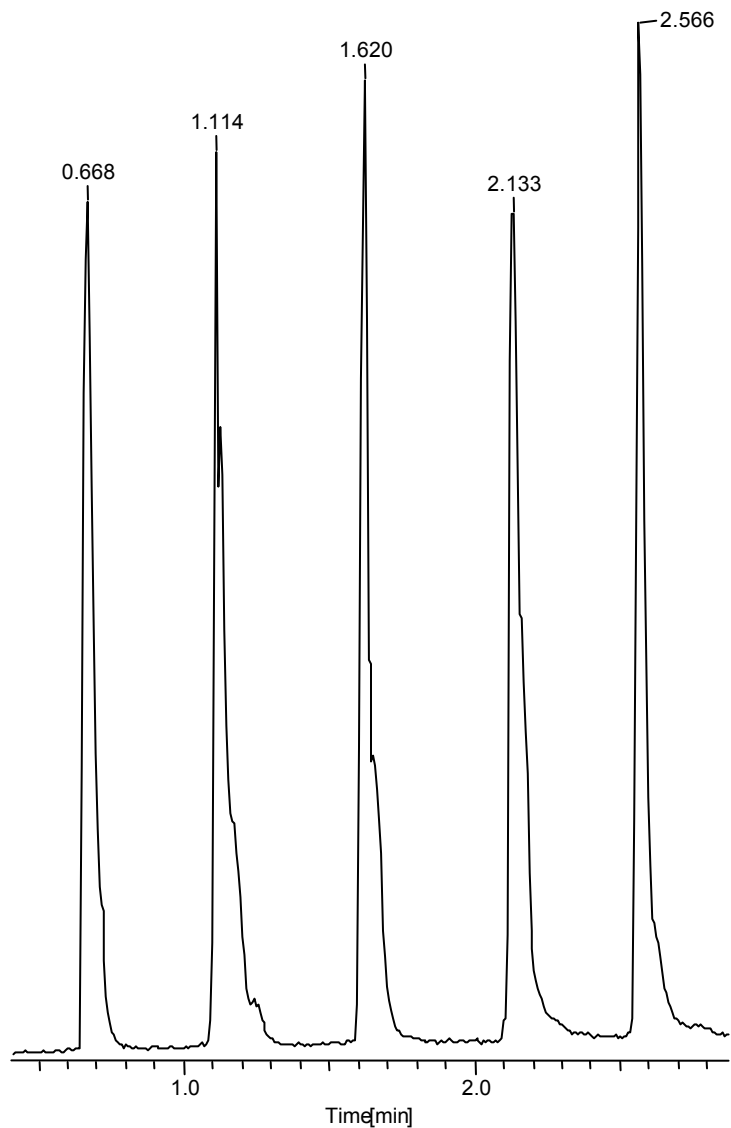


DART Prototype

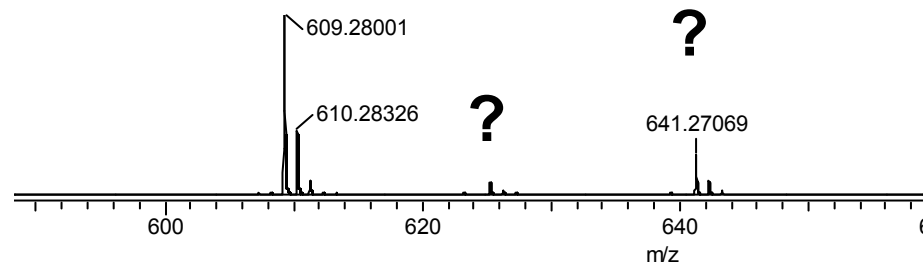


Inserted into APCI Source
Geometry NOT optimized

Manual Flow Injections



Reserpine MH⁺

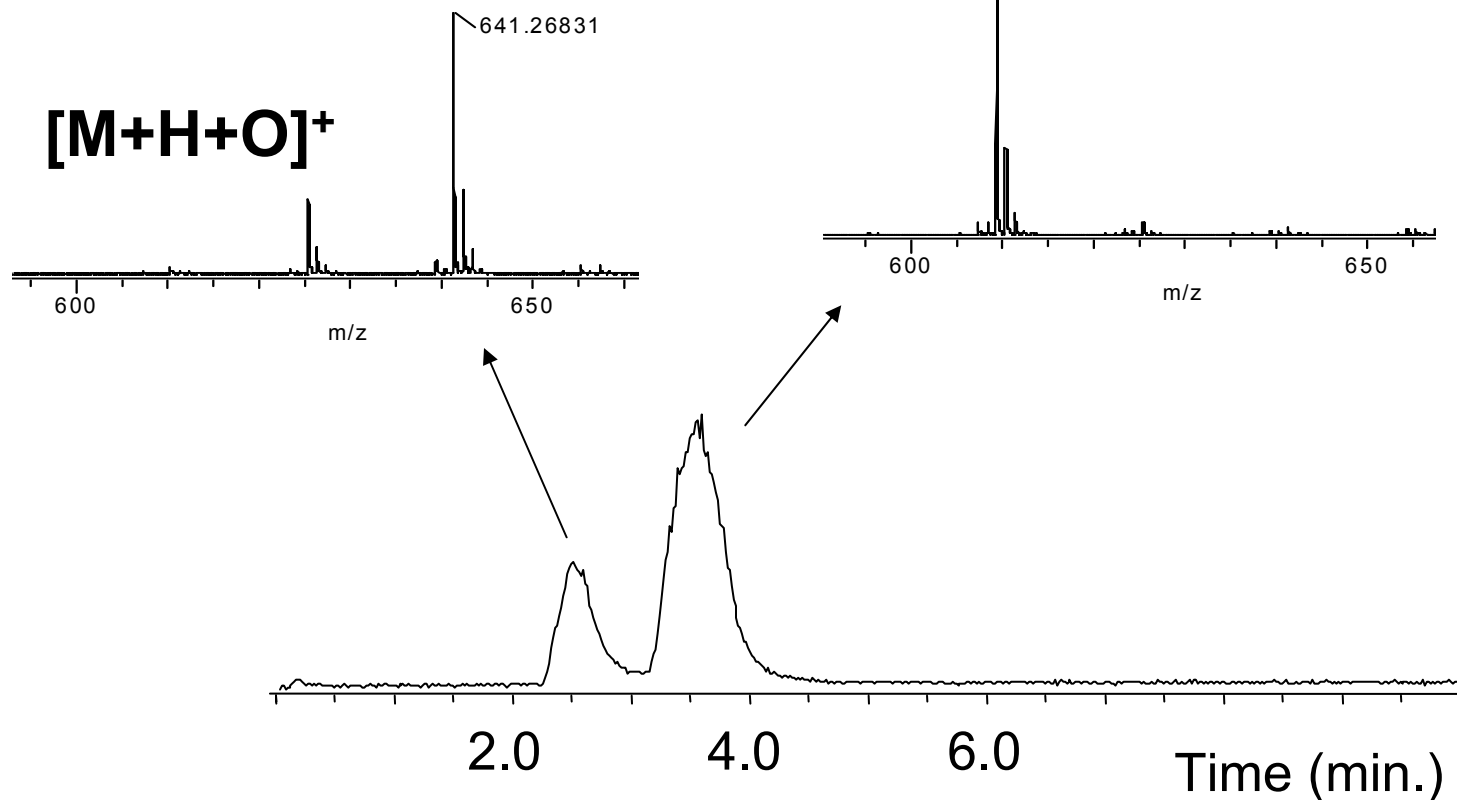


[M+H+O₂]⁺
Real or artifact?

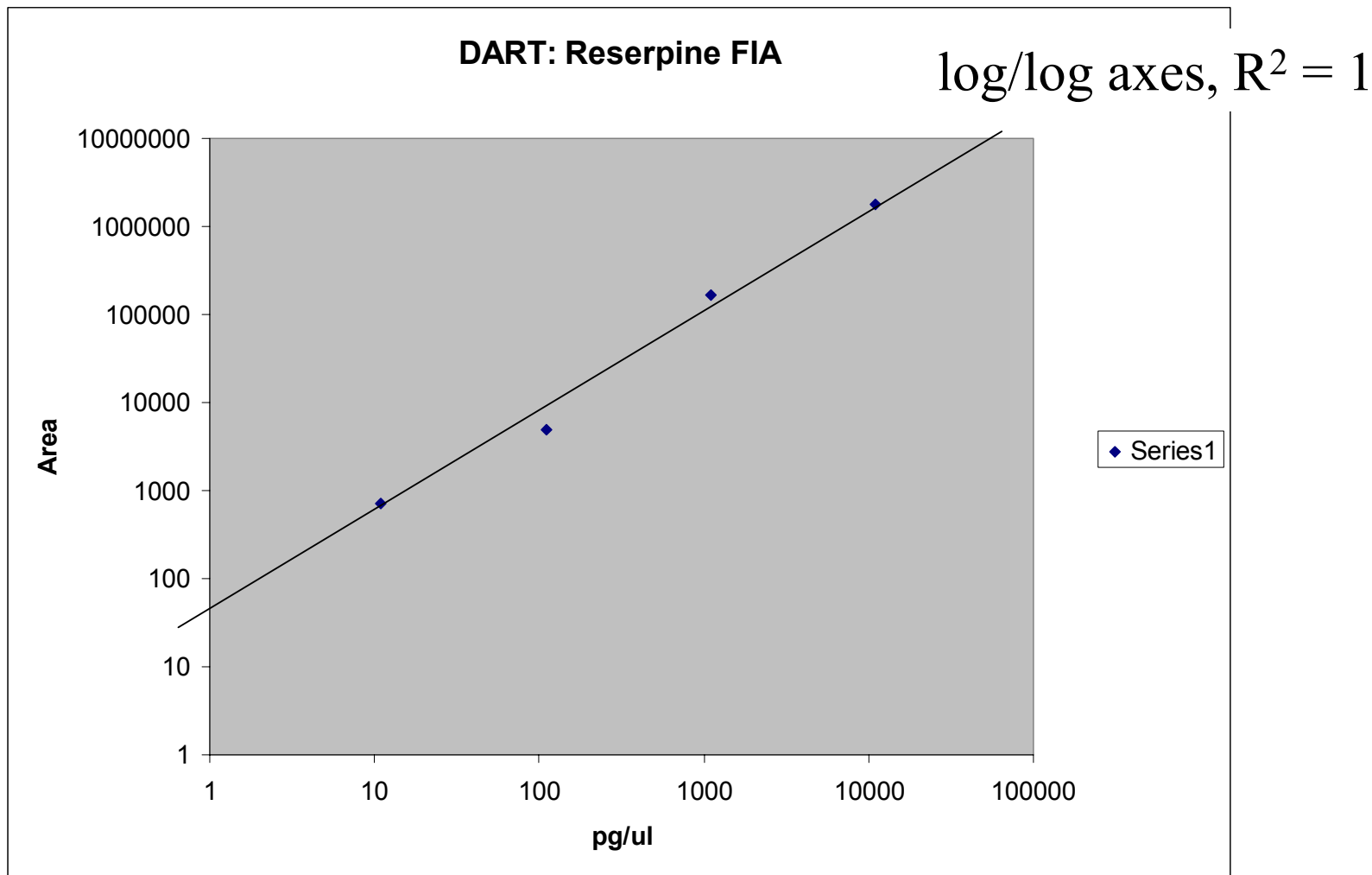
C18 Column, Isocratic (100% CH₃CN)

[M+H+O₂]⁺
Not an artifact

MH⁺



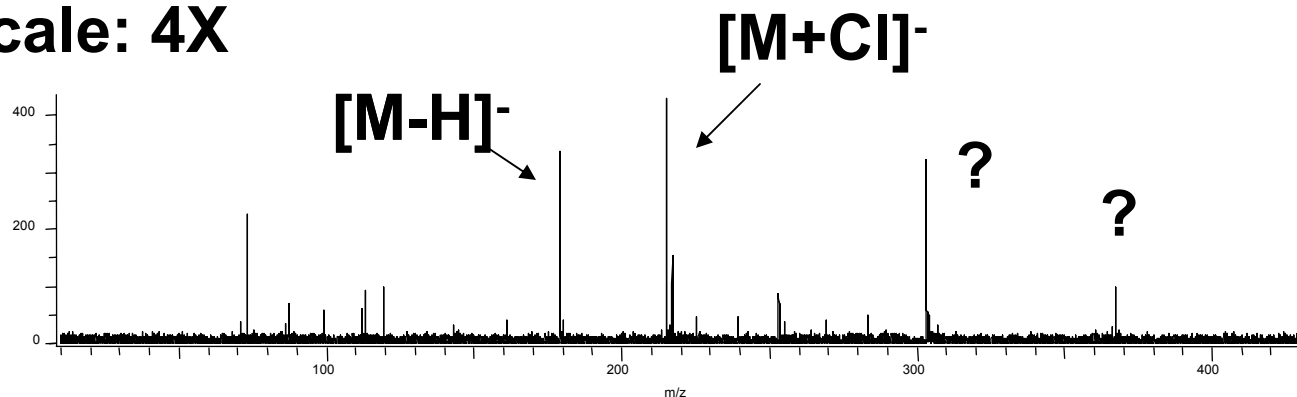
10 pg/ul to 10,000 pg/ul



Glucose, Flow injections

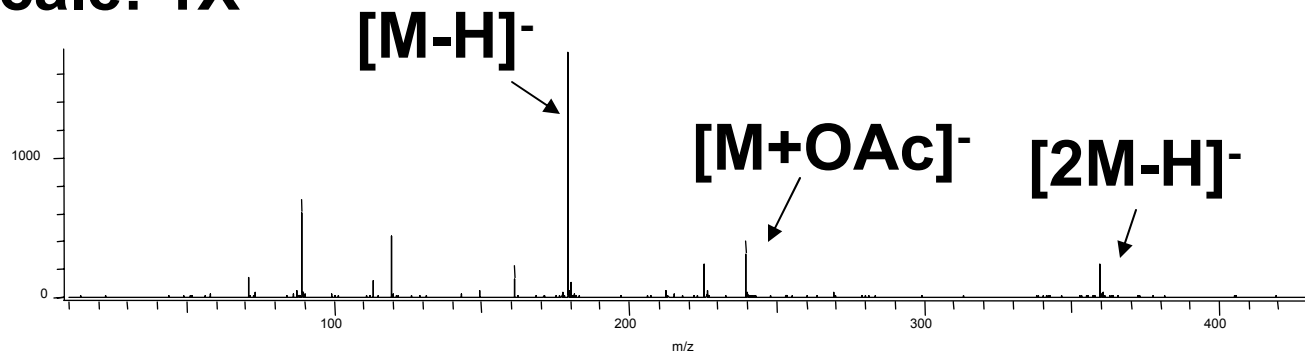
Solvent: H₂O/MeOH/HOAc

Scale: 4X



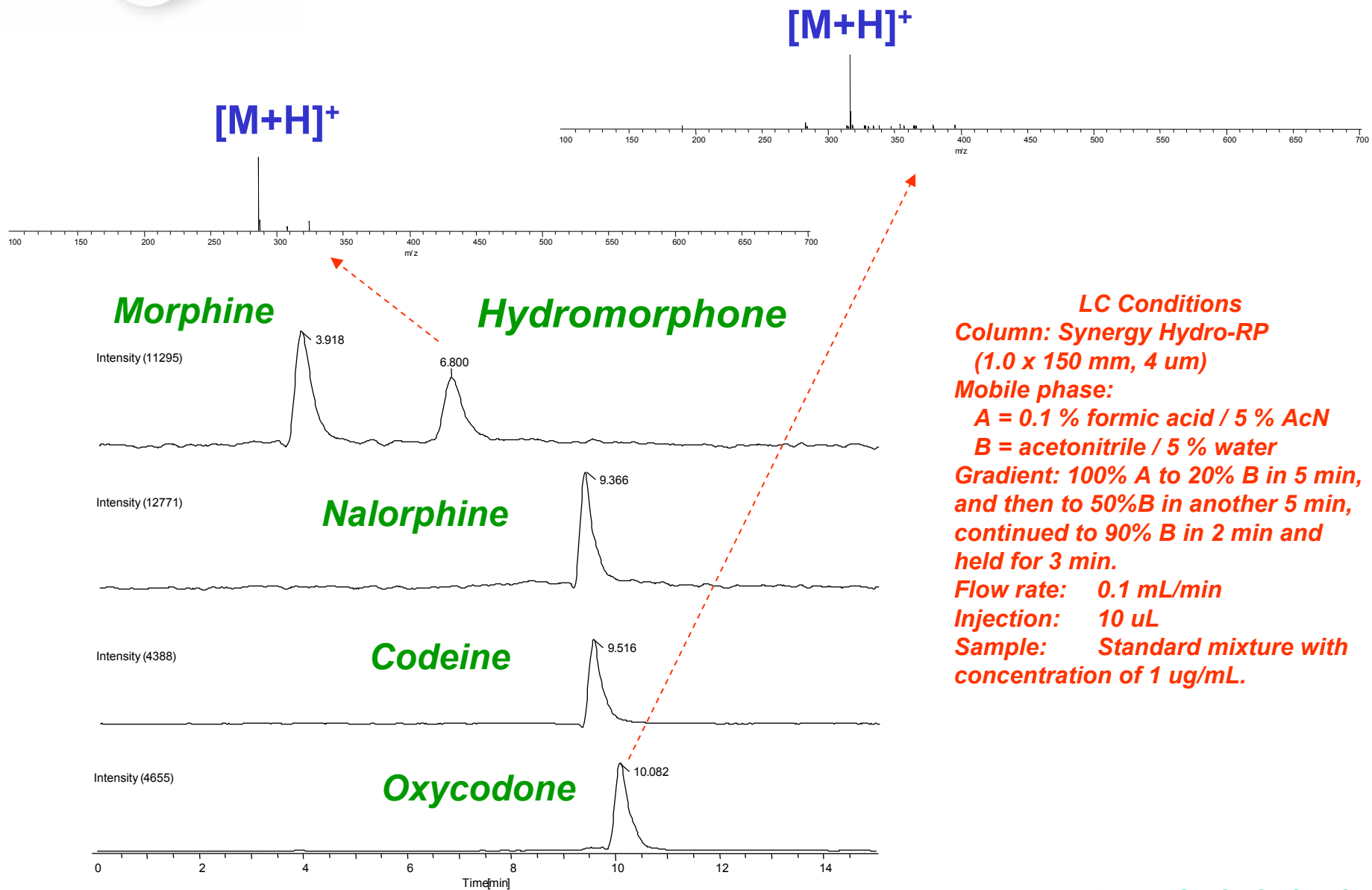
APCI

Scale: 1X

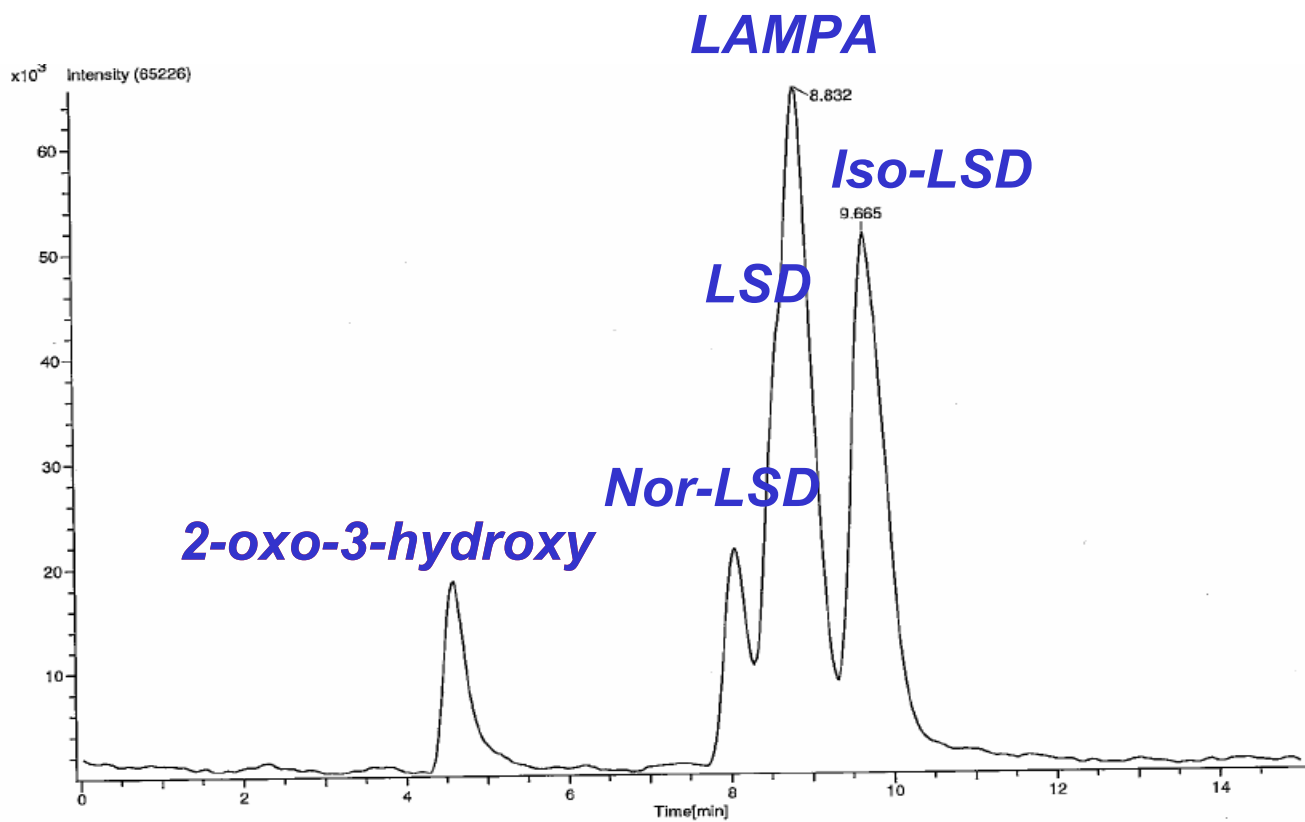


DART

LC/DART of Opiates



LC/DART Separation of LSD Metabolites and Isomers

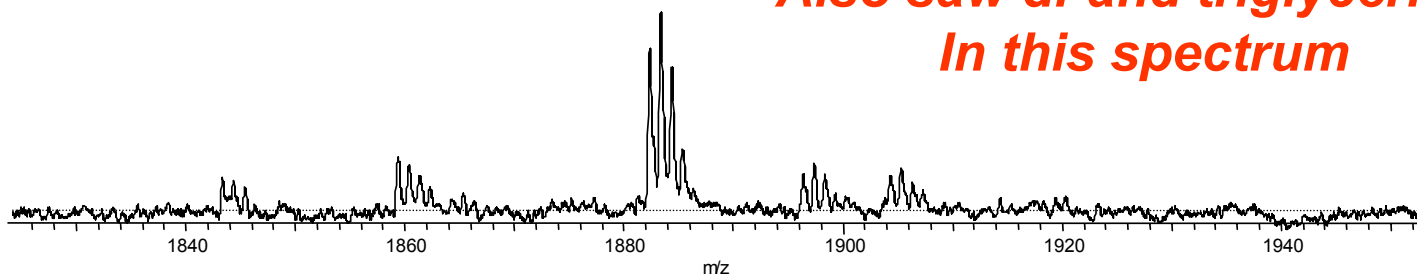


Polar and Nonpolar

Val-Gramicidin A

MH⁺

*Also saw di- and triglycerides
In this spectrum*

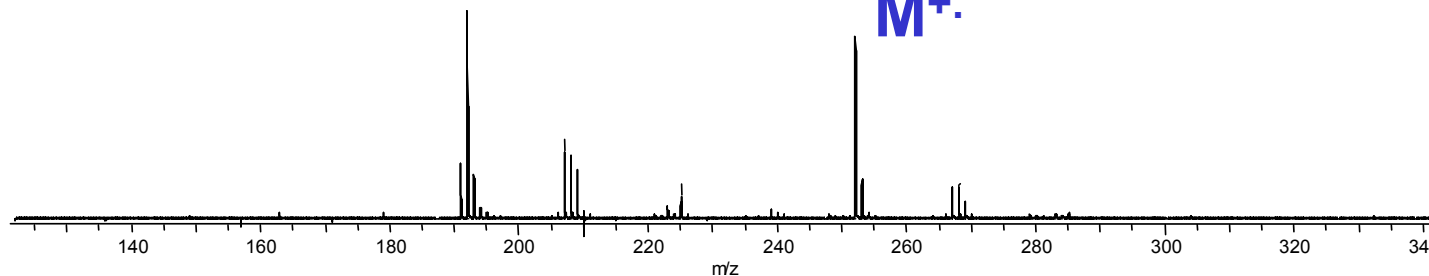


9-Methyl anthracene

M⁺

Benzo[a]pyrene

M⁺



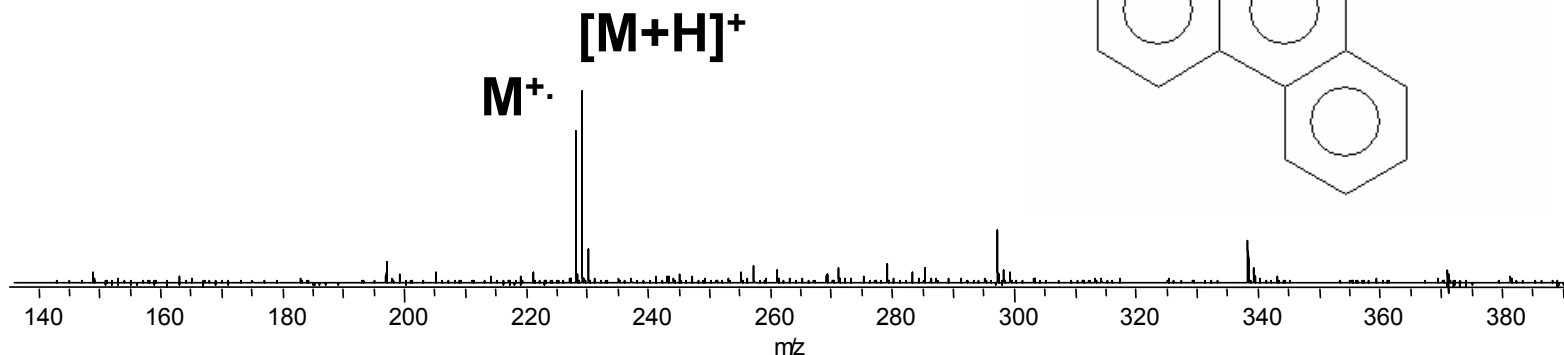
Solvent for non-polar compounds

He DART

Flow injection of 75 ppm
triphenylene in Hexane/MeCl₂

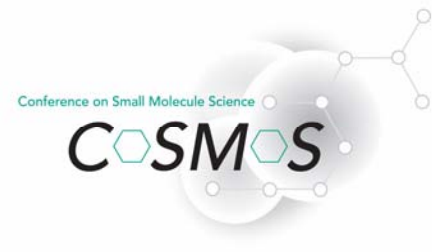
No triphenylene signal is observed
if mobile phase is acetonitrile

Normal-phase chromatography
should work



We acknowledge contributions from:

- In alphabetical order,
- Mr. Daniel Banquer, Mr. Drew McCrady, Dr. William Creasy, Dr. Michael Nilles, Mr. Edward Owen, Dr. Gary Samuelson Dr. Philip Smith, Dr. John Stuff, Mr. Dean Tipple



Thank you!