High Resolution FT-MRR Spectroscopy: Trace Residual Impurities Analysis
*Without Chromatography*

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Analytical Chemistry Tools

Pervasive challenge - dealing with gaps between instrumentation capabilities

Spectroscopy
+ Simple, non-destructive
+ High degree of automation
+ Molecular specificity
- Poor selectivity in complex mixtures
- High detection limits

Chromatography
+ High selectivity and applicability
+ Low detection limits
- High degree of customization
- Complex methods
- Identification ambiguity

We want the best of both
Reinvention of Rotational Spectroscopy*

A Technique that Bridges the Gap?

Molecular Rotational Resonance (MRR)

- Absolute specificity: direct structure “calculation” vs. structure “elucidation”
- Excellent selectivity: baseline resolved, highly specific spectral fingerprint

... So, where has this been all of our lives?
MRR – microwave to millimeter wave

Direct absorption of transient, gas-phase molecules (*Klystrons, BWOs, Gunn oscillators, Schottky multipliers*)

- Glow discharge, astrochemical studies
- Hewlett-Packard MW spectrometer (1960s)
- Millimeter, submillimeter spectrometers (1960s, 70s)

[gas mixtures ≥ 300 K - high temp complicates spectral profile]

Pulsed jet, FT-spectroscopy for weakly bound complexes (*digital electronics – synthesizers and AWGs*)

- Fourier Transform cavity enhanced spectrometers (1970s)
- Chirped-pulse broadband spectrometers (2004)

[gas mixtures < 10 K – low temp simplifies spectral profile]

The Fourier transform evolution event !!!
Re-invention of FT-MRR

100X sensitivity improvement

Essential advances:
① Chirped-pulse innovation (physical chemistry)
② High power, solid state, light sources (telecommunication industry)
③ High speed digital electronics (digital warfare)

Now, FT-MRR is ready for analytical chemistry
Enhanced Capabilities with FT-MRR
FT-MRR Applications

CPAC 2015

Chiral Analysis

Molecular Rotational Resonance Spectroscopy - Chiral Analysis without Chromatography
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CPAC 2016

Trace Residual Impurities
10 minute, static headspace FT-MRR spectrum

**Chemically specific spectral fingerprint**

**High dynamic range**

**Baseline resolved, no chemometrics**

Solvents dissolved in N,N Dimethylacetamide at ~0.1 mg/mL. Chemical ID by spectral reference library match.
Target Analytes for FT-MRR

Millimeter-wave FT-MRR:
- small (< 100 amu), conformationally rigid, branched molecules
- polar (> 0.1 D), non-zero dipole moment
- volatile (Pvap > 500 mTorr 25 C)

Spectral Library currently contains 150 molecules (and growing…)

- Residual Solvents
  - Methanol, Acetone, Methylene Chloride, Toluene, THF, Pyridine, Acetonitrile…
- Toxic Industrial Chemicals (TICs)
  - Formaldehyde, Ethylene Oxide/Propylene Oxide, Cyanides…
- Other:
  - Haloalkanes, Haloalcohols, Mercaptans, Amines …
For discovery, when you don’t know what’s there

Broadband FT-MRR
central process R&D – survey mode

For control, when you know what to look for

Targeted FT-MRR
process analysis and quality control – selective excitation mode
Headspace Analysis – at-line?

**Residual solvent**
- 5 minute cycle time
- 10 – 100 ppm detection limit

**Genotoxic impurity**
- 10 minute cycle time
- 10 – 100 ppb detection limit
Volatile, **strong** FT-MRR emitter:
Detection limit – **8 ppm**
Linearity – $R^2 = 0.9997$
RSD avg – < 10 %

Volatile, **weaker** FT-MRR emitter:
Detection limit – **200 ppm**
Linearity – $R^2 = 0.996$
RSD avg – 6.3% (2 % real sample)
Evolved gas analysis by FT-MRR

Thermal evolution from dry powders – development goals:
• < 1 ppm detection limits
• Oxygen starved heating
• Truly direct, investigative analysis

Residual solvent - measured detection limits:
• Isopropanol (< 10 ppm)
• Dichloromethane (< 10 ppm)
• Diethyl Ether (< 10 ppm) → library match by simulation
• Isobutylene (< 10 ppm) → ID initially by structure intuition, the add to library
• Acetaldehyde (< 0.100 ppm)
• Formaldehyde (< 0.100 ppm)
• Sulfur Dioxide (< 10 ppm)
• Hydrogen cyanide (< 0.010 ppm)
Advanced analysis modes with FT-MRR
Selective excitation mode

Zero false-positives

Absolute specificity of broadband FT-MRR without broadband data

Presented Spring (2015)
Chiral Analysis

First instrument installation to an academic group (Valladolid, Spain) – November 2015

Capabilities:
- Absolute structure determination (diastereomer resolution) for molecules with multiple chiral centers, as well as molecular complexes
- Direct enantiomeric excess measurement with no chromatography using a patented three-wave mixing technique

BrightSpec Chiral FT-MRR Analyzer

S. Lobsinger, C. Perez, L. Evangelisti, K.K. Lehmann, and B.H. Pate, J. Phys. Chem. Lett. 6, 196-200 (105)

Chiral Analysis

**Upcoming work:** Collaboration with University of Virginia (Brooks Pate) and Virginia Commonwealth University (Frank Gupton) – Sponsored by Virginia Biosciences Health Research Corporation

The goal for BrightSpec is direct, rapid (<1 minute) diastereomer and enantiomer ratio analyses coupled to a continuous flow reactor.

Initial results presented at the International Symposium on Chiral Discrimination (July 2015):

- Validation of the application of rotational spectroscopy to dihydroartemisinic acid (5 chiral centers)
- Structural confirmation against *ab initio* theory (~1% error on rotational constants)
- For single-frequency analyses, 1000:1 signal-to-noise ratio (99.9% purity) expected within a minute

*Dihydroartemisinic Acid* (precursor to artemisinin)
Thank You

FT-MRR for Analytical Chemistry …

… and Scientific Discovery

Chemists, solving chemistry problems

BrightSpec Inc. Charlottesville, VA
- Instrument Sales, Trials, Demos
- Method Development
- Analytical Services

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