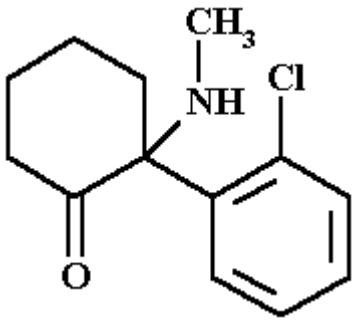
KETAMINE

Latest Revision: May 13, 2005



1. SYNONYMS

CFR: Ketamine

CAS #: Base: 6740-88-1
Hydrochloride: 1867-66-9

Other Names: 2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone

2. CHEMICAL AND PHYSICAL DATA

***2.1.* CHEMICAL DATA**

Form	Chemical Formula	Molecular Weight	Melting Point (°C)
Base	$C_{13}H_{16}CINO$	237.7	92-93
Hydrochloride	$C_{13}H_{16}CINO \cdot HCl$	274.2	258-261

***2.2.* SOLUBILITY**

Form	A	C	E	H	M	W
Base	I*	PS	I*	***	FS	FS

A = acetone, C = chloroform, E = ether, H = hexane, M = methanol and W = water, VS = very soluble, FS = freely soluble, S = soluble, PS = sparingly soluble, SS = slightly soluble, VSS = very slightly soluble and I = insoluble.

3. SCREENING TECHNIQUES

***3.1.* COLOR TESTS**

REAGENT	COLOR PRODUCED
Janovsky reagent	Hydrochloride: Purple precipitate Base: Weak purple color over time

3.2. CRYSTAL TESTS

REAGENT	CRYSTALS FORMED
Platinic iodide in 30% HOAc	Rhomboidal plates, rosettes of plates over time

3.3. THIN LAYER CHROMATOGRAPHY

Visualization

Acidified iodoplatinate spray

COMPOUND	Relative R_f	
	System TLC 15	System TLC 6
cocaine	0.8	0.4
diazepam	1.0	1.3
heroin	0.6	0.4
lysergic acid	0.8	0.1
methamphetamine	0.3	0.2
methaqualone	0.9	1.4
methocarbamol	0.9	0.9
ketamine	1.0	1.0

3.4. GAS CHROMATOGRAPHY

Method KETA-GCS1

Instrument: Gas Chromatograph operated in split mode with FID

Column:	5% phenyl/95% methyl silicone 30 mm x 0.25 mm x 0.25 µm film thickness
Carrier gas:	Helium at 27.9 cm/sec
Temperatures:	Injector: 270°C Detector: 285°C Oven program: 1) 175°C initial temperature for 0.5 min 2) Ramp to 210°C at 8°C/min and hold for 0.5 min 3) Ramp to 260°C at 40°C /min and hold for 3.4 min
Injection Parameters:	Split Ratio = 105:1, 1 µL injected

Samples are to be dissolved in chloroform and filtered.

COMPOUND	RRT	COMPOUND	RRT
dimethylsulfone	0.31	carisoprodol	0.99
amphetamine	0.35	**ketamine**	**1.00 (5.83 min)**
methamphetamine	0.37	diphenhydramine	1.01
ephedrine	0.46	lidocaine	1.03
pseudoephedrine	0.46	phencyclidine	1.08
MDA	0.53	theophylline	1.09
MDMA	0.57	psilocin	1.16
benzocaine	0.59	procaine	1.20
MDEA	0.62	dextromethorphan	1.36
guaifenesin	0.68	cocaine	1.42
acetaminophen	0.69	acetylcodeine	1.88
methylphenidate	0.81	flunitrazepam	2.05
meprobamate	0.86	heroin	2.11
caffeine	0.92	clonazepam	2.62

3.5. HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Method KETA-LCS1

Instrument:	High performance liquid chromatograph equipped with diode array
Column:	3 µm Partisil ODS, 3.2 mm x 150 mm
Detector:	UV, 220 nm
Flow:	0.75 mL/min
Injection Volume:	5 µL
Buffer:	870 mL water, 10 mL *o*-phosphoric acid (85% by weight), 30 mL 2 N sodium hydroxide, 4 mL hexylamine, pH 2.5 with 2 N sodium hydroxide
Mobile Phase:	Buffer/acetonitrile 92:8

Samples are to be dissolved in buffer: acetonitrile 92:8, sonicated, then filtered with a 0.45-micron filter.

COMPOUND	RRT	COMPOUND	RRT
ephedrine	0.38	caffeine	1.19
psilocin	0.38	methylphenidate	1.45
pseudoephedrine	0.39	cocaine	2.16
procaine	0.43	guaifenesin	2.25
amphetamine	0.46	dextromethorphan	2.28
MDA	0.53	acetylcodeine	2.32
methamphetamine	0.53	clonazepam	2.35
acetaminophen	0.55	heroin	2.72
MDMA	0.62	phencyclidine	4.42
theophylline	0.68	benzocaine	**
lidocaine	0.73	diphenhydramine	**
MDEA	0.77	benzethonium chloride	**
ketamine	**1.00 (6.5 min)**		

4. SEPARATION TECHNIQUES

Ketamine is often found as a powder or in an aqueous form. The powder can be extracted with an organic solvent, such as chloroform and the aqueous form may be evaporated to obtain Ketamine. Ketamine has a dissociation constant (pKa) of 7.5 and may be extracted from aqueous alkaline solutions using organic solvents.

5. QUANTITATIVE PROCEDURES

5.1. GAS CHROMATOGRAPHY

Method KETA-GCQ1

Internal Standard Stock Solution:
4.6 mg/mL *n*-docosane in chloroform.

Standard Solution Preparation:
Accurately weigh and prepare a standard solution of ketamine hydrochloride at approximately 0.8 mg/mL in chloroform using the internal standard stock solution diluted 1 to 10.

Sample Preparation:
Accurately weigh an amount of sample into an appropriate volumetric flask so the final concentration approximates the standard concentration or falls within the linear range. Dissolve the sample with a small amount of methanol. Add an appropriate amount of internal standard stock solution diluting it to a ratio of 1 to 10 with chloroform.

Instrument:	Gas Chromatograph operated in split mode with FID
Column:	5% phenyl/95% methyl silicone 30 m x 0.25 mm x 0.25 µm film thickness
Carrier gas:	Helium at 27.9 cm/sec
Temperatures:	Injector: 270°C Detector: 285°C Oven Program: 1) 175°C initial temperature for 0.5 min 2) Ramp to 210°C at 8°C/min and hold for 0.5 min 3) Ramp to 260°C at 40°C/min and hold for 3.4 min
Injection Parameters:	Split Ratio = 105:1, 1µL injected
Typical Retention Time:	Ketamine: 5.8 min Docosane: 8.2 min
Linear Range:	0.13 to 1.75 mg/mL
Repeatability:	RSD less than 3.0%
Correlation Coefficient:	0.9999

Accuracy: Error less than 5%

COMPOUND	RRT	COMPOUND	RRT
dimethylsulfone	0.31	carisoprodol	0.99
amphetamine	0.35	**ketamine**	**1.00 (5.83 min)**
methamphetamine	0.37	diphenhydramine	1.01
ephedrine	0.46	lidocaine	1.03
pseudoephedrine	0.46	phencyclidine	1.08
MDA	0.53	theophylline	1.09
MDMA	0.57	psilocin	1.16
benzocaine	0.59	procaine	1.20
MDEA	0.62	dextromethorphan	1.36
guaifenesin	0.68	cocaine	1.42
acetaminophen	0.69	acetylcodeine	1.88
methylphenidate	0.81	flunitrazepam	2.05
meprobamate	0.86	heroin	2.11
caffeine	0.92	clonazepam	2.62

5.2. HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Method KETA-LCQ1

Standard Solution Preparation:
Accurately weigh and prepare a standard solution of ketamine hydrochloride at approximately 0.3 mg/mL using the buffer solution.

Sample Preparation:
Accurately weigh an amount of sample into a volumetric flask and dilute with buffer solution. If necessary dilute the sample so the final concentration approximates the standard concentration or falls within the linear range. Filter sample with a 0.45-micron filter.

Instrument: High performance liquid chromatograph equipped with diode array

Column: 3 µm Partisil ODS, 3.2 mm x 150 mm

Detector: UV, 220 nm

Flow: 0.75 mL/min

Injection Volume: 5 µL

Buffer: 870 mL water, 10 mL o-phosphoric acid (85% by weight), 30 mL 2 N sodium hydroxide, 4 mL hexylamine, pH 2.5 with 2 N sodium hydroxide

Mobile Phase: Buffer: acetonitrile 92:8

Typical Retention Time: Ketamine: 6.5 min

Linear Range: 0.04 - 1.26 mg/Ml

Repeatability: RSD less than 2.0%

Correlation Coefficient: 0.9997

Accuracy: Error less than 5%

COMPOUND	RRT	COMPOUND	RRT
ephedrine	0.38	caffeine	1.19
psilocin	0.38	methylphenidate	1.45
pseudoephedrine	0.39	cocaine	2.16
procaine	0.43	guaifenesin	2.25
amphetamine	0.46	dextromethorphan	2.28
MDA	0.53	acetylcodeine	2.32
methamphetamine	0.53	clonazepam	2.35
acetaminophen	0.55	heroin	2.72
MDMA	0.62	phencyclidine	4.42
theophylline	0.68	benzocaine	**
lidocaine	0.73	diphenhydramine	**
MDEA	0.77	benzethonium chloride	**

ketamine	**1.00 (6.5 min)**		

5.3. CAPILLARY ZONE ELECTROPHORESIS

Method KET-CEQ-1

Internal Standard Stock Solution:
Prepare a 1.0 mg/mL solution containing thiamine hydrochloride in 0.01 N HCl.

Standard Solution Preparation:
Accurately weigh and prepare a standard solution of ketamine hydrochloride at approximately 0.2 mg/mL, adding an appropriate amount of the internal standard stock solution.

Sample Preparation:
Accurately weigh an amount of sample into a volumetric flask and add the appropriate amount of internal standard stock solution. Dilute with 0.01 N HCl so that the concentration approximates that of the standard. Filter sample with a 0.45-micron filter.

Instrument:	Capillary electrophoresis equipped with diode array detection
Mode:	Free Zone
Column:	34 cm x 50 µm (I.D.) fused silica capillary
Detector:	UV, 207 nm
Injection Volume:	2.5 s hydrodynamic at 50 mbar/sec
Buffer:	100 mM lithium phosphate, pH 2.3 (prepared by titrating 100mM phosphoric acid with LiOH to pH 2.3)
Voltage:	14.5 kV
Temperature:	15°C
Rinse Time:	2.5 min
Typical Migration Time:	Ketamine: 4.0 min
Linear Range:	0.05 - 1.2 mg/mL
Repeatability:	RSD less than 1.0%
Correlation Coefficient:	0.99998

Accuracy: Error less than 2%

COMPOUND	RMT	COMPOUND	RMT
ephedrine	0.92	caffeine	**
pseudoephedrine	0.92	methylphenidate	1.05
triprolidine	072	cocaine	1.27
phenylpropanolamine	0.87	niacinamide	0.75
amphetamine	0.82	dextromethorphan	1.05
methamphetamine	0.82	oxycodone	1.07
phentermine	1.27	codeine	1.1
acetaminophen	**	chlorpheniramine	0.70
MDMA	0.97	thiamine	0.67
ketamine	**1.00 (4.0 min)**	hydrocodone	1.10
MDEA	1.07	MDA	1.11

6. QUALITATIVE DATA

6.1. ULTRAVIOLET SPECTROPHOTOMETRY

SOLVENT	MAXIMUM ABSORBANCE (NM)
0.1 M Hydrochloric acid	269

See spectra on the following pages for FT-IR, Raman, Mass Spectrometry, Nuclear Magnetic Resonance, and Vapor Phase IR.

7. REFERENCES

Clarke, E.G.C., *Analysis of Drugs and Poisons, 3rd Edition*, The Pharmaceutical Press, 2004.

Budavari, S., *The Merck Index, 13th Edition*, Merck and Co., Inc., 2001.

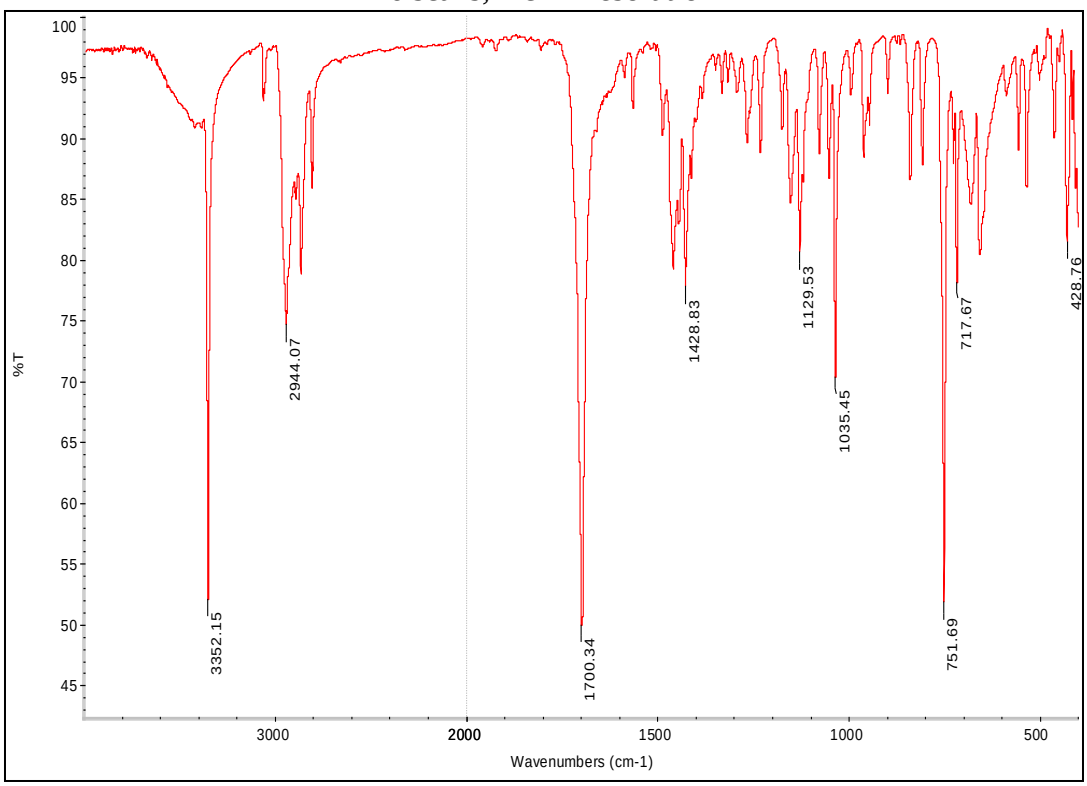
Butler, W. P., *Methods of Analysis for Alkaloids, Opiates, Marihuana, Barbiturates and Miscellaneous Drugs*, The Internal Revenue Service.

8. ADDITIONAL RESOURCES

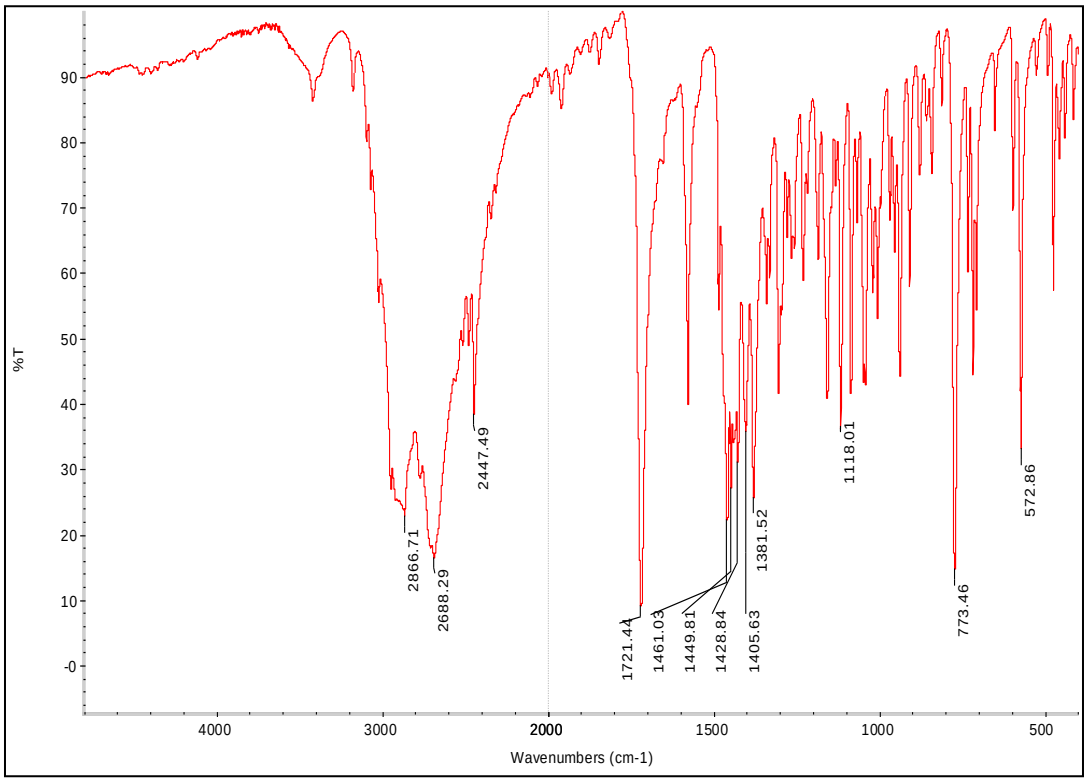
Forendex

Wikipedia

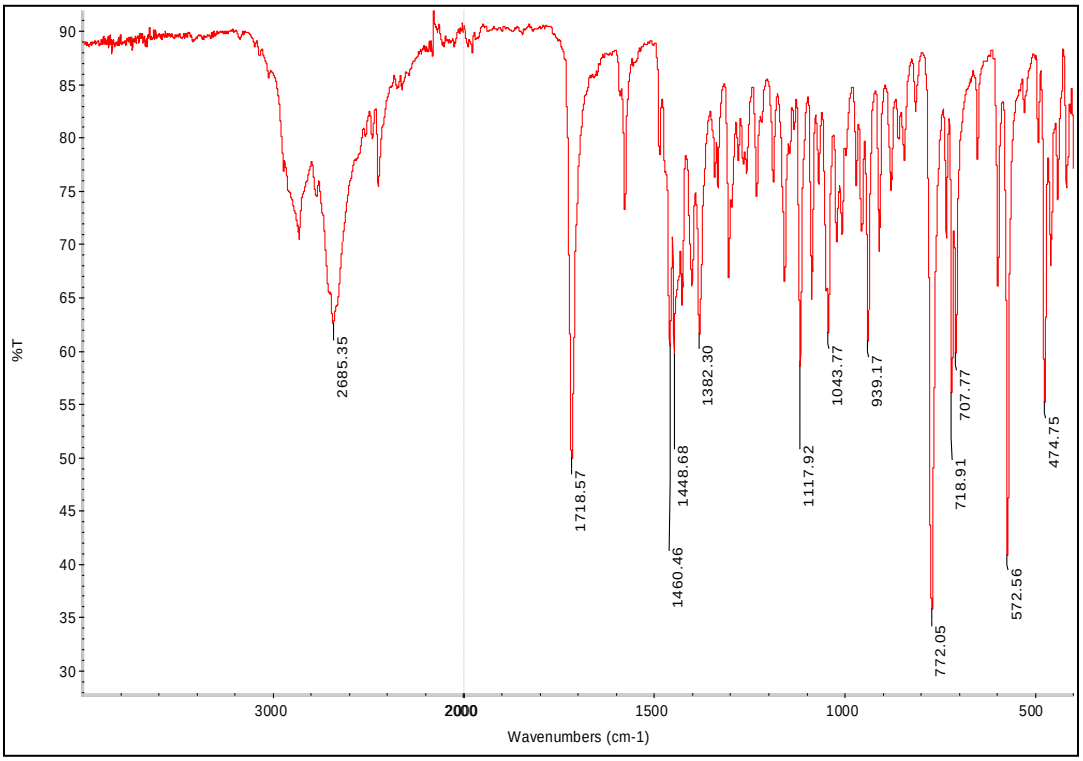
FTIR: Ketamine base in KBr
16 scans; 4 cm^{-1} resolution



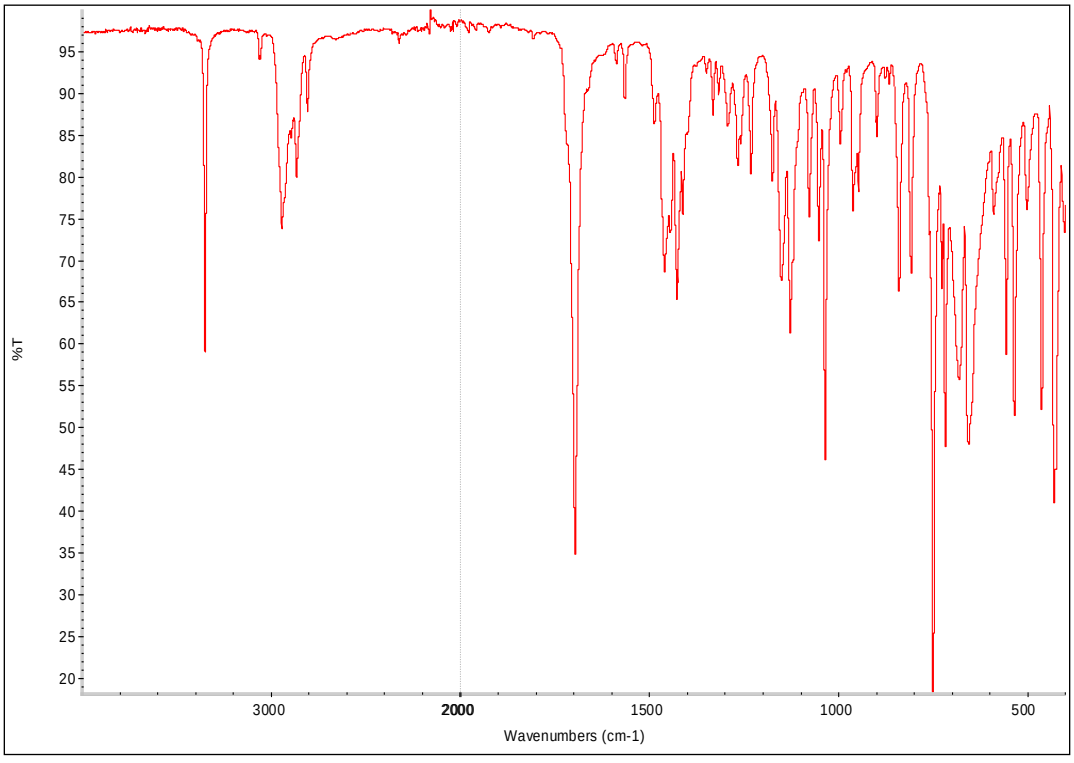
FTIR: Ketamine HCl in KBr
16 scans; 4 cm^{-1} resolution



FTIR (ATR): Ketamine HCl
DTGS KBr Detector, Avatar System 370
16 scans; 4 nm resolution

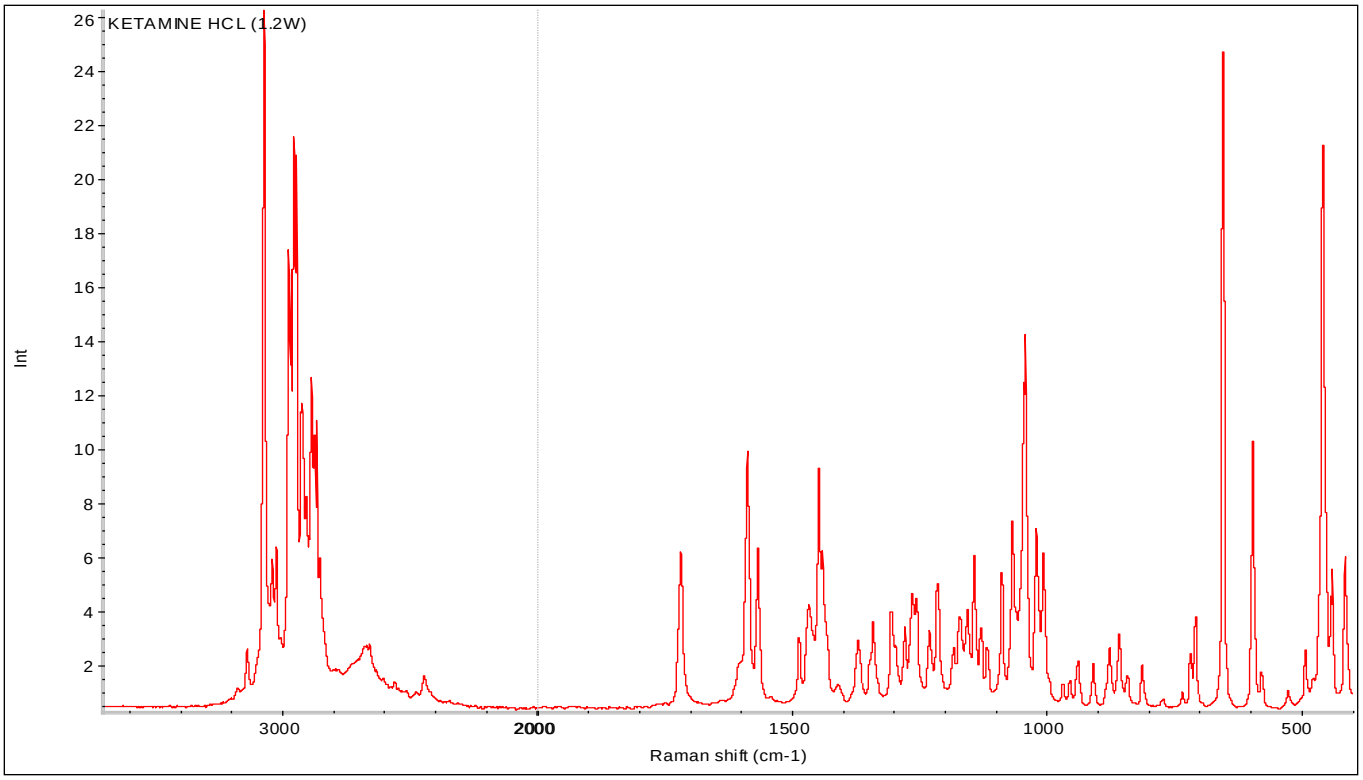


FTIR (ATR): Ketamine Base
DTGS KBr Detector Avatar System 370
16 scans; 4 nm resolution



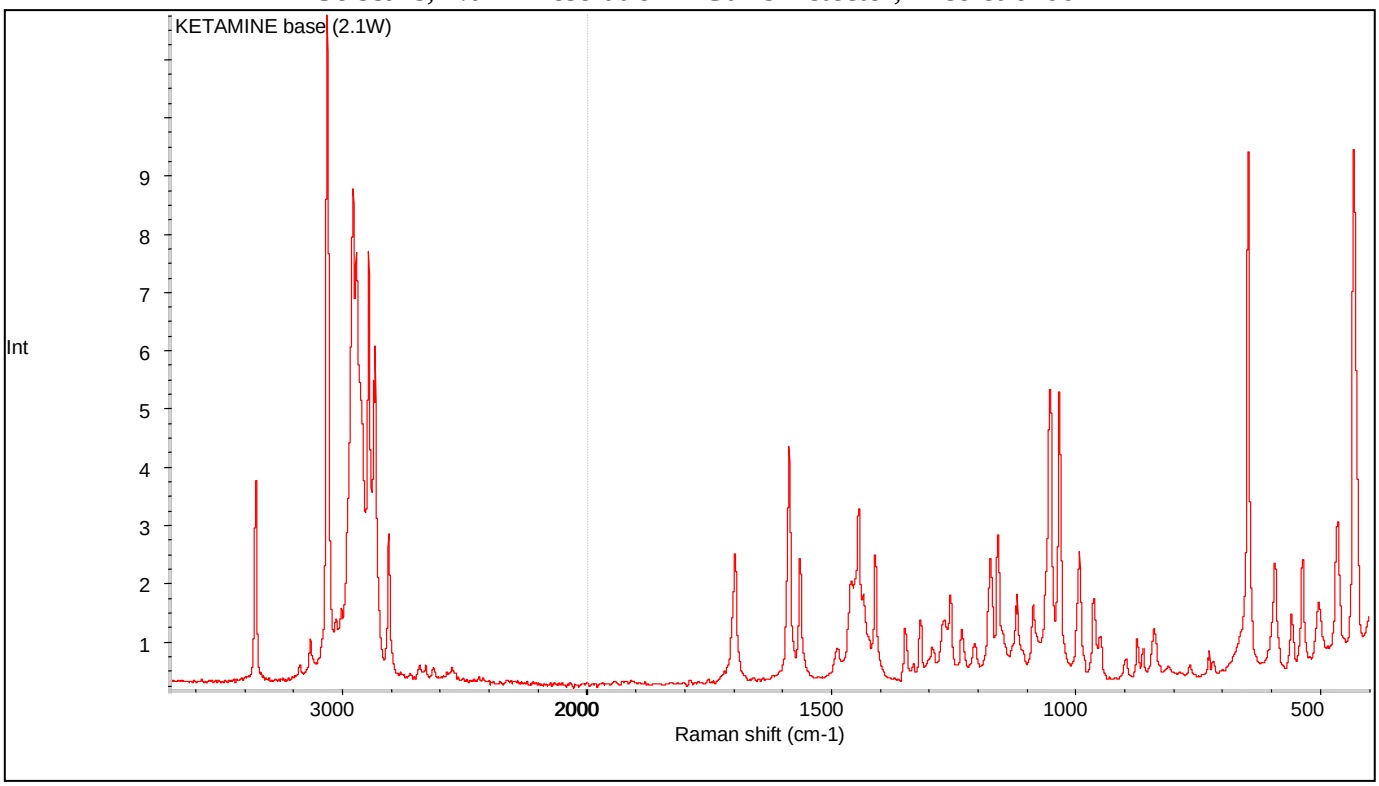
RAMAN: Ketamine HCl

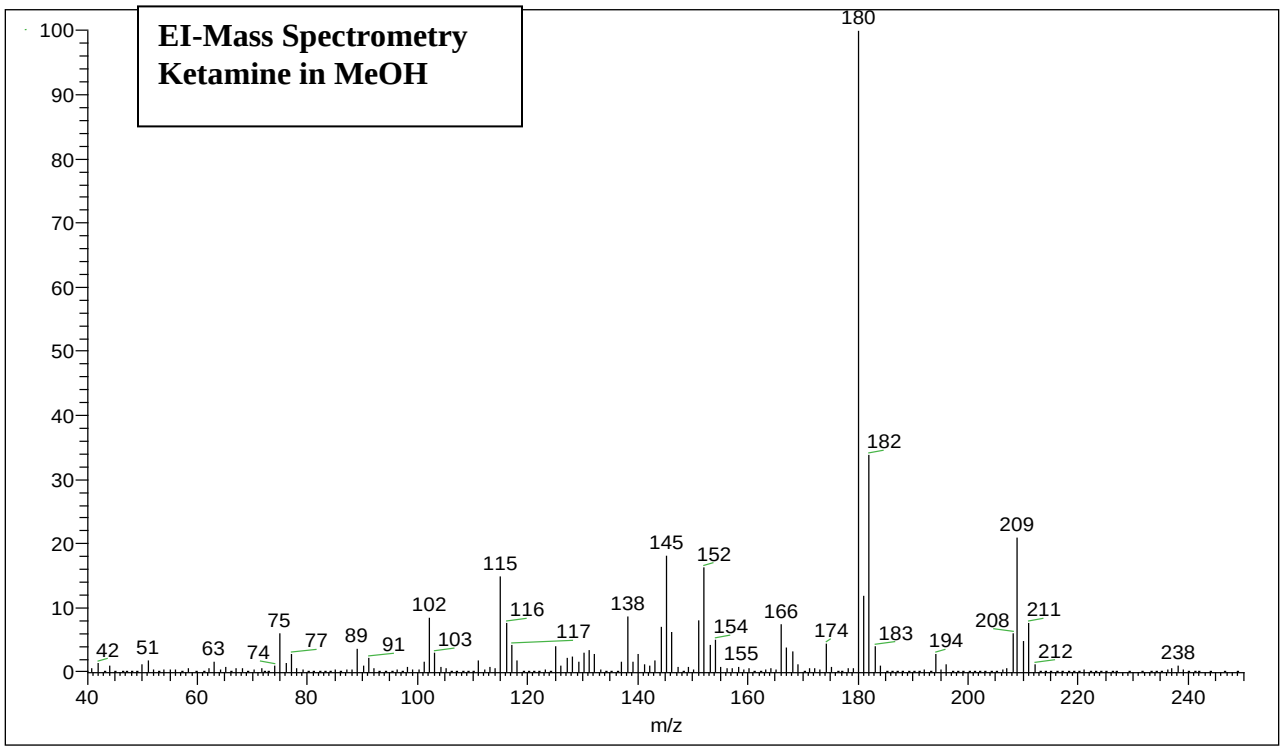
256 scans; 4.0 nm resolution InGaAs Detector, Nicolet 6700



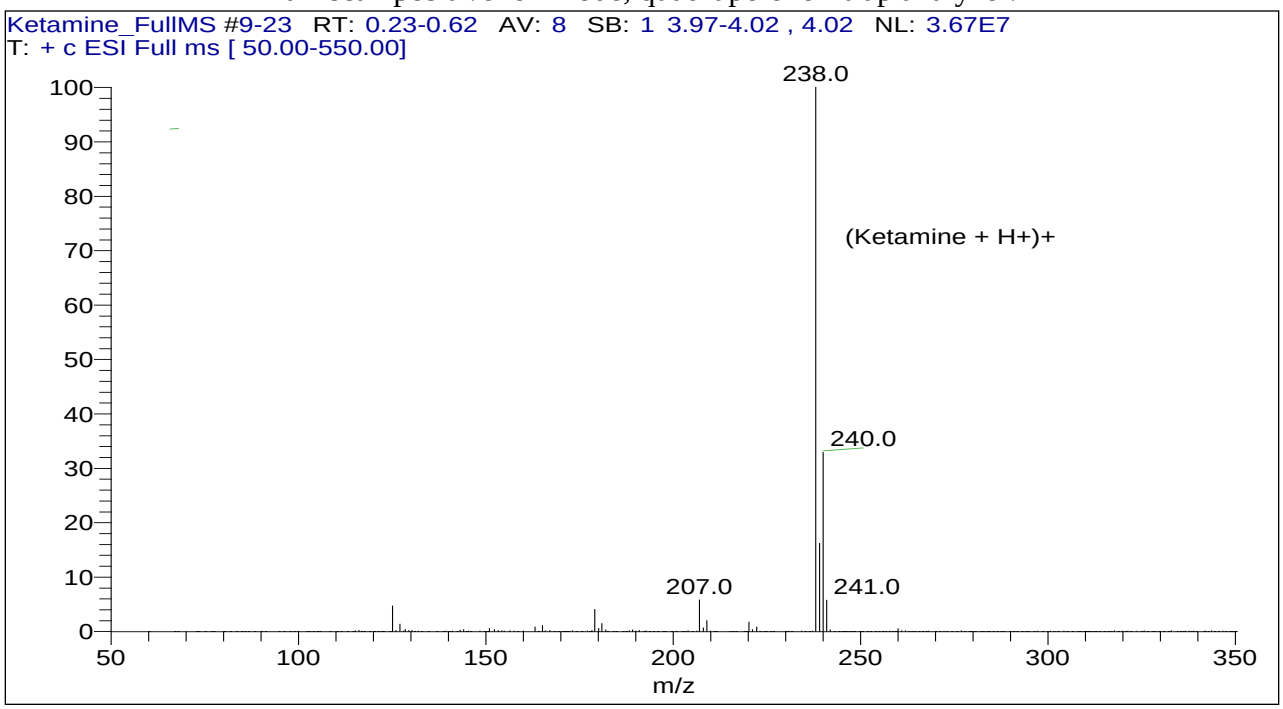
RAMAN: Ketamine base

256 scans; 4.0 nm resolution InGaAs Detector, Nicolet 6700

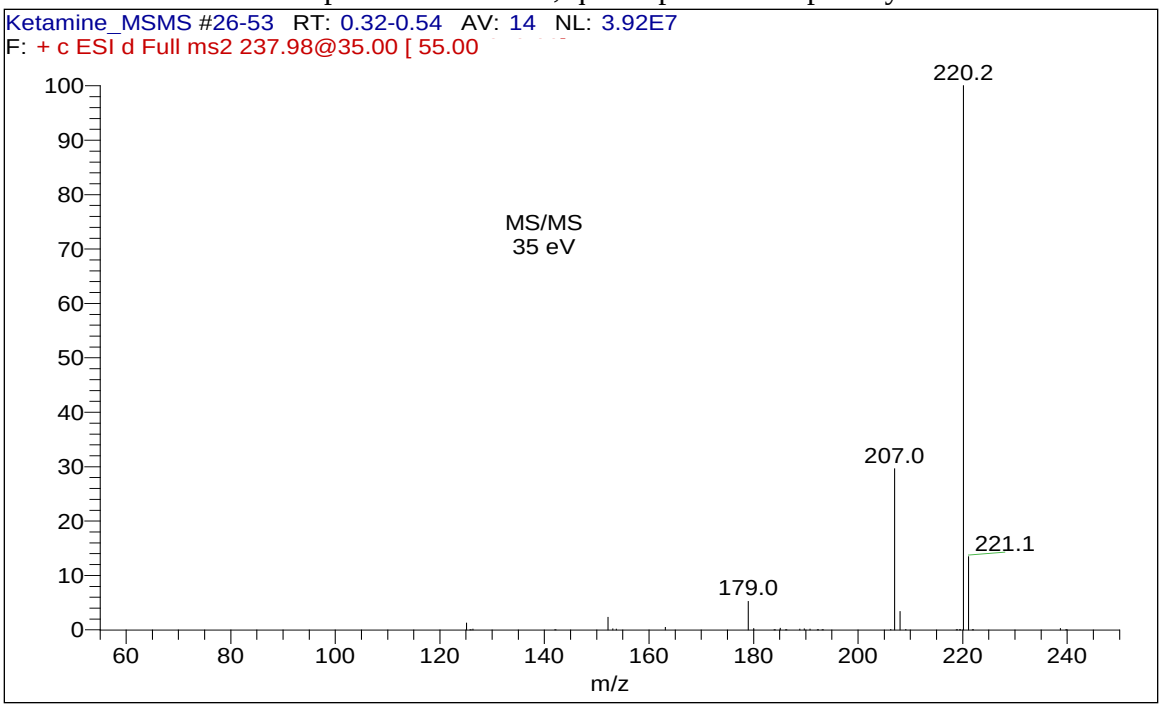


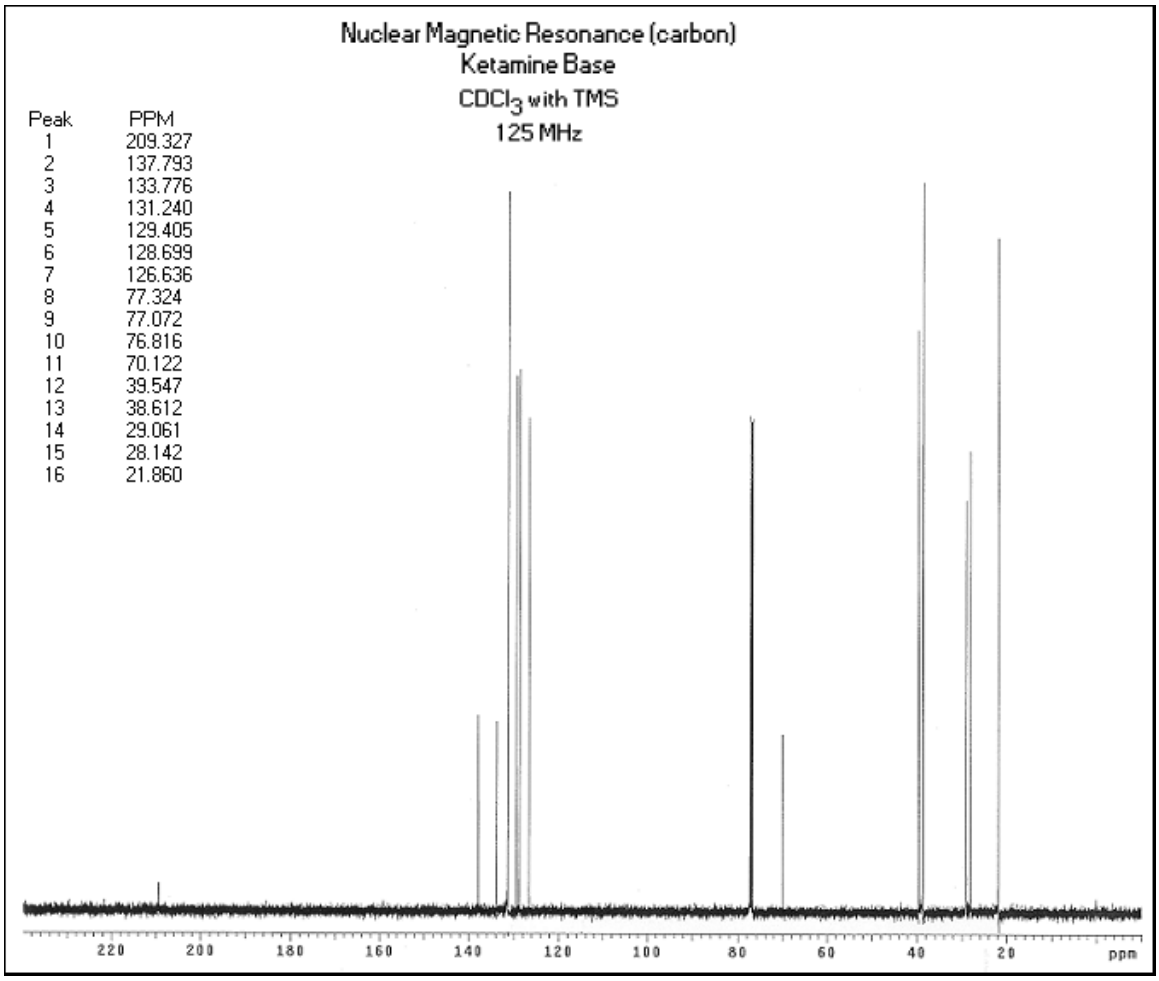


ESI-MS: Ketamine in MeOH; electrospray ionization
Full-scan positive ion mode; quadrupole ion-trap analyzer.



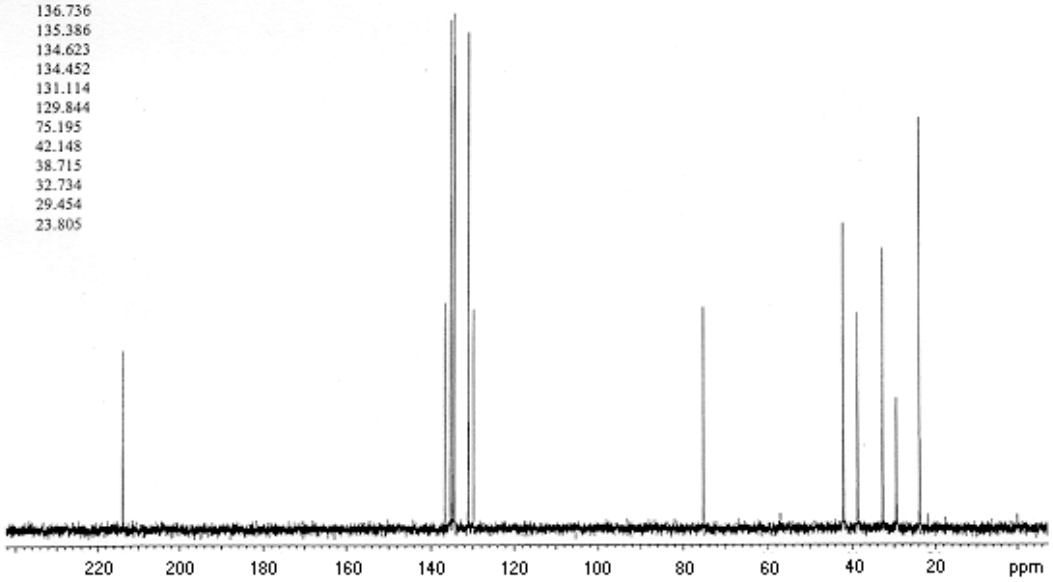
MS/MS: Ketamine in MeOH, electrospray ionization
MS/MS positive ion mode; quadrupole ion-trap analyzer.



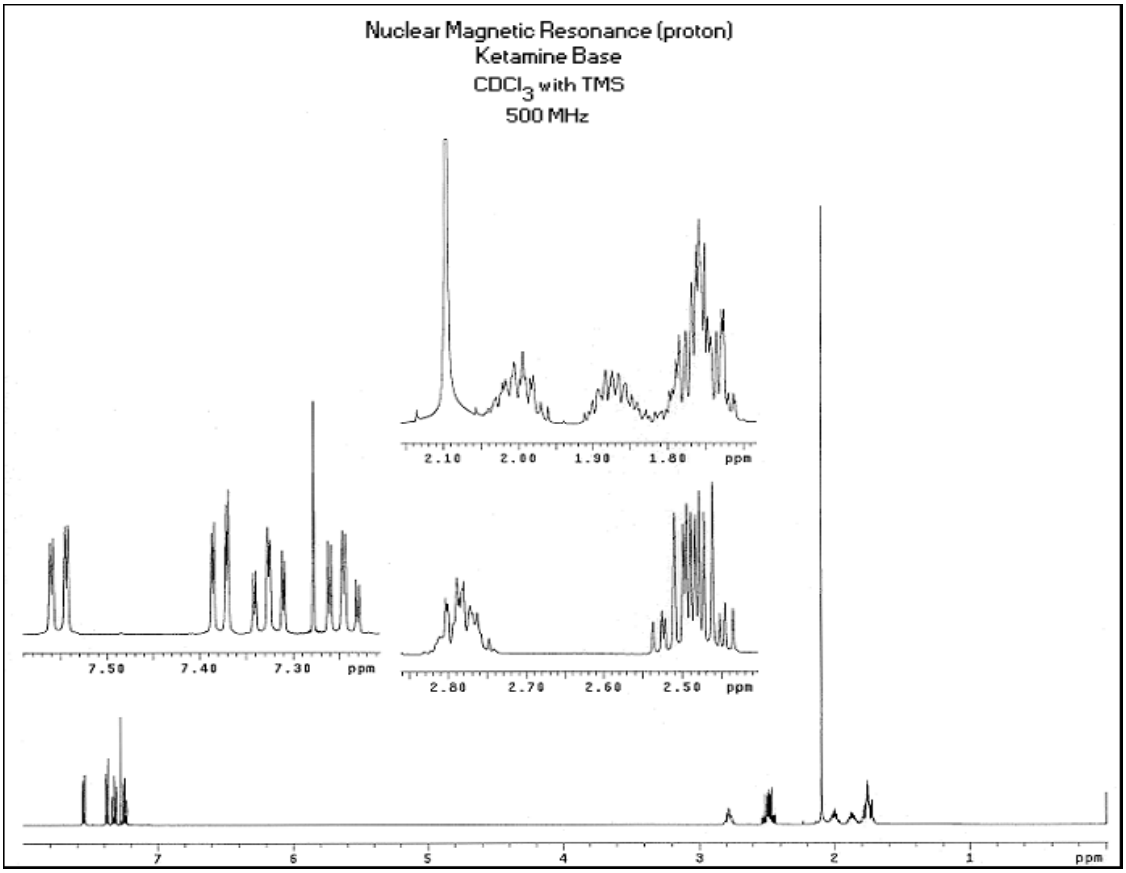


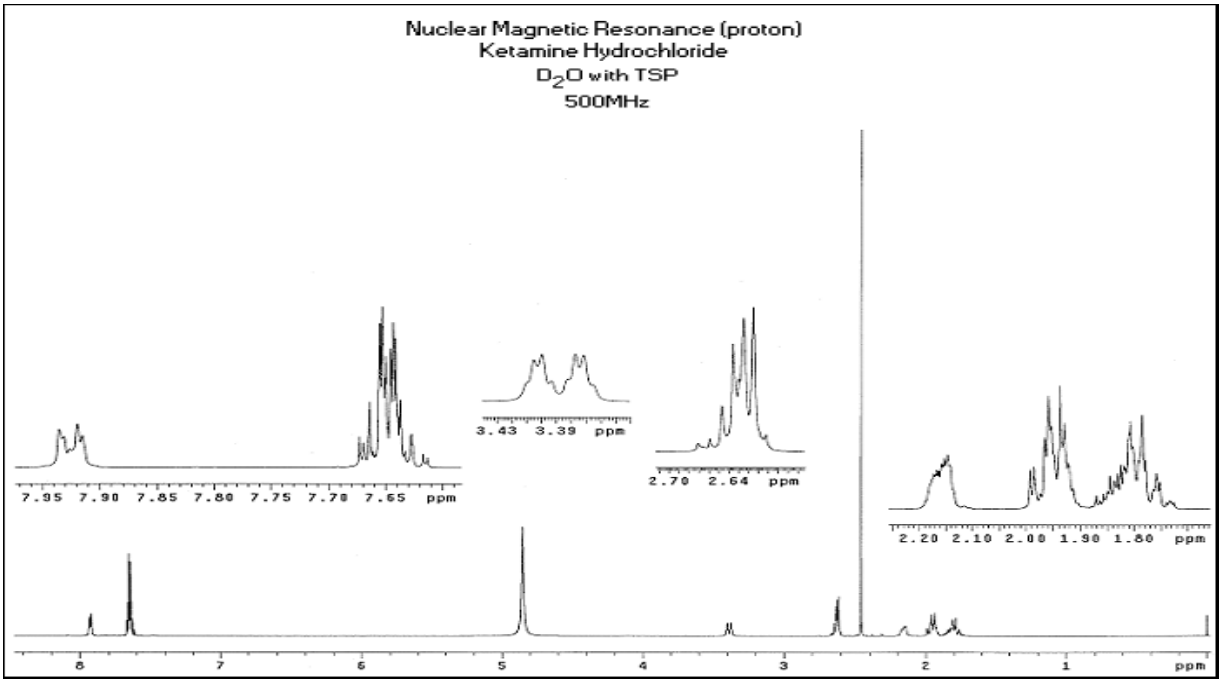
Nuclear Magnetic Resonance (carbon)
Ketamine Hydrochloride
D_2O with TSP
125 MHz

Peak	PPM
1	213.927
2	136.736
3	135.386
4	134.623
5	134.452
6	131.114
7	129.844
8	75.195
9	42.148
10	38.715
11	32.734
12	29.454
13	23.805



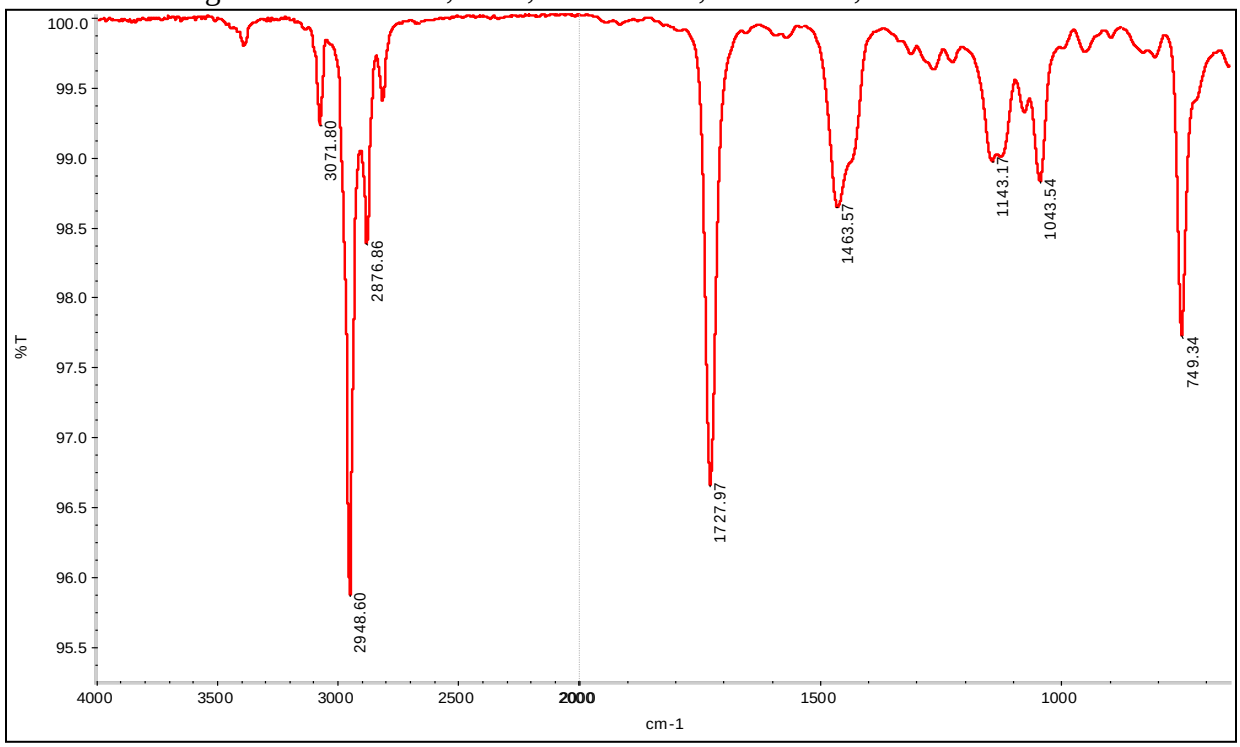
Nuclear Magnetic Resonance (proton)
Ketamine Base
$CDCl_3$ with TMS
500 MHz



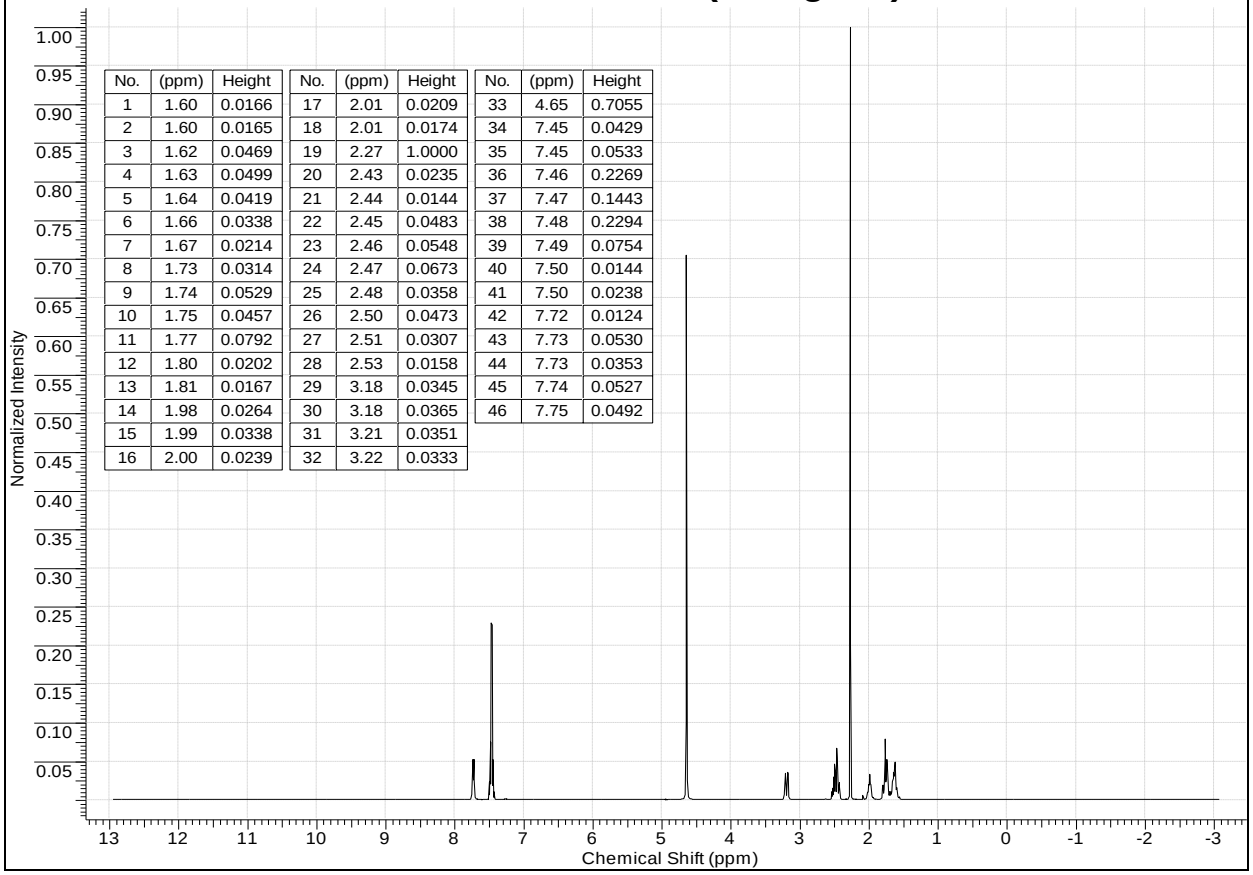


IR (VAPOR PHASE) Ketamine

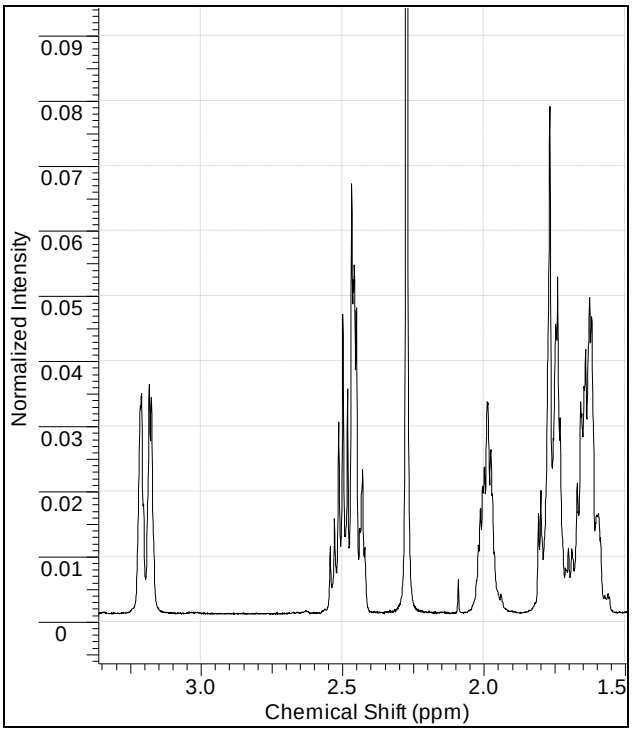
1 mg/mL MeOH HP-5, 25 m, 0.32 mm ID, 1.5 scans/s, 4 cm^{-1} resolution

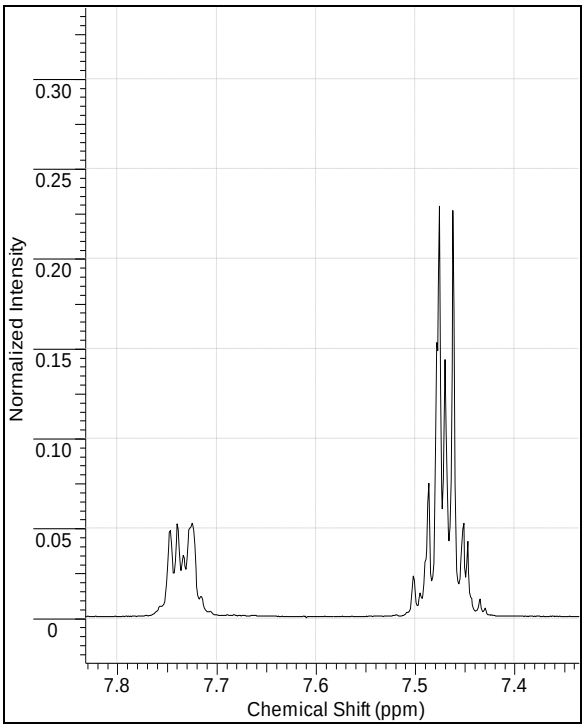


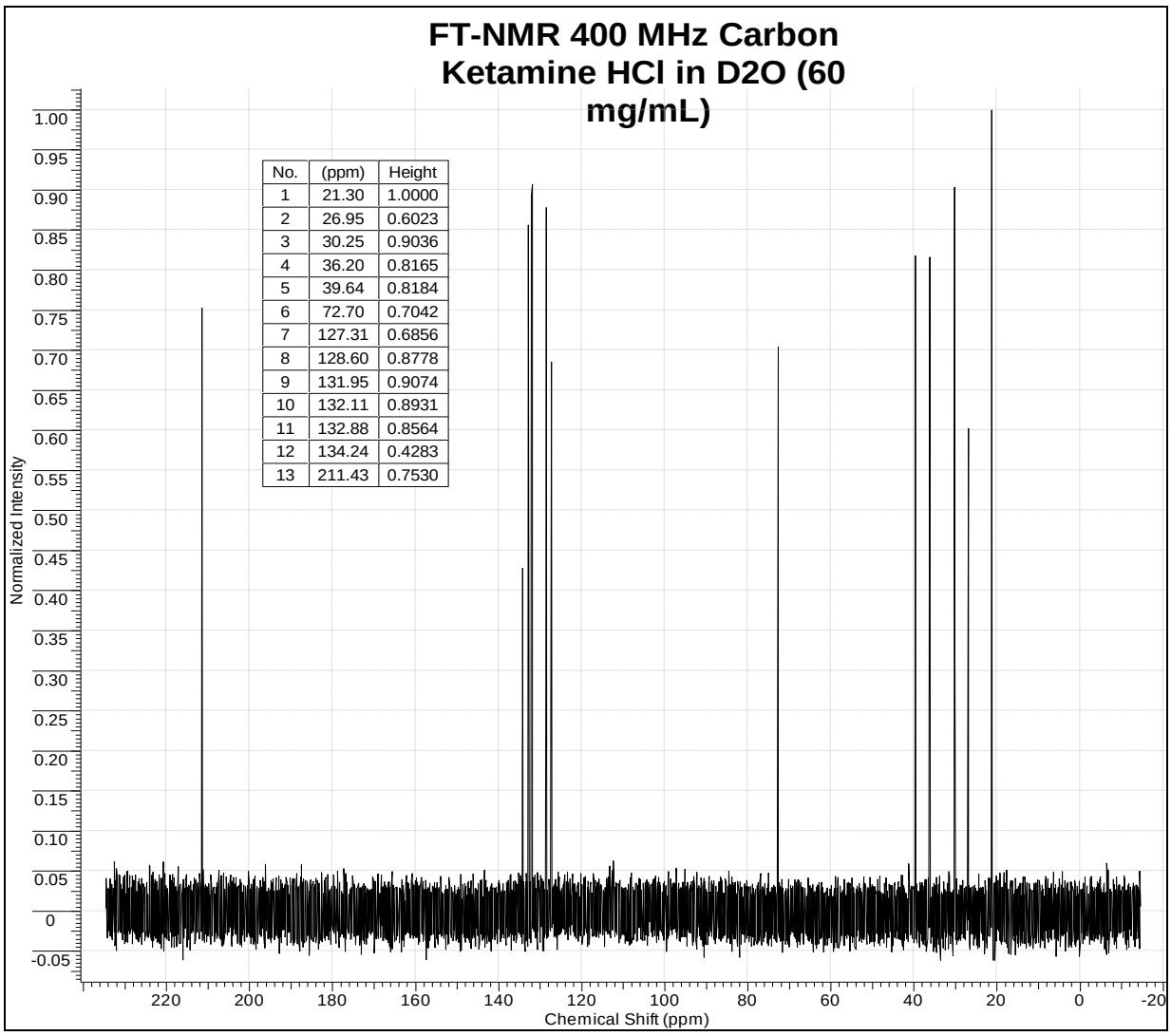
FT-NMR 400 MHz Proton
Ketamine HCl in D2O (60 mg/mL)



No.	(ppm)	Height	No.	(ppm)	Height	No.	(ppm)	Height
1	1.60	0.0166	17	2.01	0.0209	33	4.65	0.7055
2	1.60	0.0165	18	2.01	0.0174	34	7.45	0.0429
3	1.62	0.0469	19	2.27	1.0000	35	7.45	0.0533
4	1.63	0.0499	20	2.43	0.0235	36	7.46	0.2269
5	1.64	0.0419	21	2.44	0.0144	37	7.47	0.1443
6	1.66	0.0338	22	2.45	0.0483	38	7.48	0.2294
7	1.67	0.0214	23	2.46	0.0548	39	7.49	0.0754
8	1.73	0.0314	24	2.47	0.0673	40	7.50	0.0144
9	1.74	0.0529	25	2.48	0.0358	41	7.50	0.0238
10	1.75	0.0457	26	2.50	0.0473	42	7.72	0.0124
11	1.77	0.0792	27	2.51	0.0307	43	7.73	0.0530
12	1.80	0.0202	28	2.53	0.0158	44	7.73	0.0353
13	1.81	0.0167	29	3.18	0.0345	45	7.74	0.0527
14	1.98	0.0264	30	3.18	0.0365	46	7.75	0.0492
15	1.99	0.0338	31	3.21	0.0351			
16	2.00	0.0239	32	3.22	0.0333			






FT-NMR 400 MHz Carbon
Ketamine HCl in D2O (60 mg/mL)
No. (ppm) Height
1 21.30 1.0000
2 26.95 0.6023
3 30.25 0.9036
4 36.20 0.8165
5 39.64 0.8184
6 72.70 0.7042
7 127.31 0.6856
8 128.60 0.8778
9 131.95 0.9074
10 132.11 0.8931
11 132.88 0.8564
12 134.24 0.4283
13 211.43 0.7530
Normalized Intensity
Chemical Shift (ppm)