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Application of High-field NMR Spectroscopy for Differentiating Cathinones for Forensic Identification

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Application of High-field NMR Spectroscopy for Differentiating Cathinones for Forensic Identification

Cover Page Note

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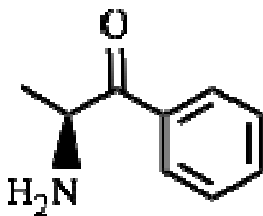
Authors

Jessica N. Krummel, Lauren N. Russell, Danniebelle N. Haase, Susan M. Schelble, Ethan Tsai, and Kelly M. Elkins

Introduction

Synthetic cathinone family compounds are the major naturally-occurring psychostimulant and hallucinogenic designer drugs that are used illegally in the U.S. and several other countries for their cocaine, methylenedioxymethamphetamine (MDMA), and amphetamine-like effects (http://www.deadiversion.usdoj.gov/fed_regs/rules/2014/fr0307_2.htm) [1-2]. Cathinone (Figure 1) is a natural product found in the leaves of the *Catha edulis* plant, also known as khat, chewed by Middle Eastern and African populations in Yemen and Somalia [3-5]. Cathinone has no accepted medical use and has been determined to be highly addictive by the Drug Enforcement Agency (DEA) in the U.S.; it is a member of the United States (U.S.) Controlled Substances Act (CSA) Schedule I. The cathinone in khat converts to cathine (d-norpseudoephedrine) upon aging and drying [6]. Both cathinone and cathine exhibit structural similarities to amphetamine but the cathine is less potent [6]. Members of the cathinone family may be used for therapeutic purposes (e.g., Bupropion (Wellbutrin®), not controlled; Diethylpropion (Tenuate®), CSA Category IV; Pyrovalerone (Centroton®), CSA Category V) but within the last decade synthetic cathinones have been used for recreational purposes as a “legal high” with varying biochemical effects [1-3, 7-8].

Figure 1 Cathinone (also known as benzoylethanamine or β -ketoamphetamine)



A growing number of novel recreational drug substances abused by young people in the U.S., Europe and Australia are designer cathinones [3]. Synthetic pathways for producing drugs have been available in the literature since 1912 (e.g., MDMA) but synthetic drugs only started appearing in seized drugs in the U.S. in 1979 with China White in California [2]. Synthetic cathinones have been presented in the literature for almost a hundred years. Methcathinone, the first synthetic cathinone, was synthesized in 1928 [2]. Designer cathinones are crystalline white or yellow solids, depending upon the purity. Due to their simple structures, designer cathinones are simple to synthesize; this partly explains their

growing popularity as per unit costs are relatively low. At the present time, most of the designer cathinones are reported to originate in China or India [1].

Most forensic laboratories began to encounter designer cathinones in casework in 2009 with a significant increase by 2011-2012 (National Drug Intelligence Center, Product Number 2011-S0787-004) [2, 9-11]. In 2009, poison control centers received no calls reporting bath salt overdose but 303 calls were fielded in 2010, and 5625 calls were received in 2011 [3]. As long as the particular compounds are not controlled, designer cathinones may be sold in “head shops,” “smart shops,” gas stations, convenience stores, or the Internet [1-2, 11]. To avoid federal and state legislative restrictions, designer cathinones are sold as “bath salts,” “fertilizer,” “plant food,” and “research chemicals” and labeled “not for human consumption” or “not tested for hazards or toxicity” [1-2, 11]. As the ingredient list on purchased products gives the user no indication of the presence of psychoactive compounds, there is the potential for serious harm and toxicity - and no or little safety information is provided [1].

Users take the drugs—bought and sold in the form of powders, capsules and tablets—most commonly by insufflation (snorting), intravenous or intramuscular injection, ingestion as pills or with other liquids, but also rectally, in the eye (“eye-balling”), and subcutaneously [1-2].

Around 2010 the most prevalent were mephedrone (4-methylmethcathinone) and MDPV (3,4-methylenedioxypropylvalerone) [1]. Due to their increased prevalence and no accepted medical use in the U.S., in March 2014, one of the synthetic cathinones in this study, pentylone, among others, was one of the 10 synthetic cathinones temporarily placed in Schedule I of the U.S. CSA - but more than 30 designer cathinones have been observed in Europe [1] and more are observed each year worldwide.

Dealers increase their product and profits by extending the quantity of “drug” by adding other cheap, white, nearly indistinguishable powders called cutting agents or adulterants. The cutting agents may impart little (e.g., caffeine, lidocaine) to no (e.g., sugar) drug-like effects. The designer cathinones often contain various concentrations (<2–96%) of adulterants including benzocaine, lidocaine, caffeine, benzocaine, piperazines and paracetamol, among others [1-2]. In many cases, drug paraphernalia shows evidence of more than one drug and more than one cathinone. For example, 4-methylethcathinone (4-MEC) is a designer drug that is structurally similar to mephedrone [10]. The purity was observed at 51-78% in casework; it was found in mixtures with other substituted cathinones including MDPBP, MDPV, MPPP, pentylone, benzedrone, and other substances [10]. Ten synthetic cathinones, including MDPV, MDPBP, 4-fluoromethcathinone (4-FMC), butylone, mephedrone, naphyrone, 4-MEC, ethcathinone, α -pyrrolidinopentiophenone (α -PVP), and 3-methyl- α -pyrrolidinopropiophenone (3-MPPP) were found in 14 street samples; MDPV was

among the most common of the designer cathinones [12]. In a review of casework in Arkansas, the designer stimulants MDPV, methylone, and α -methylaminovalerophenone (pentedrone) were commonly detected; α -PBP and pentylone cases were also documented [11].

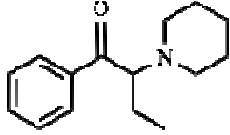
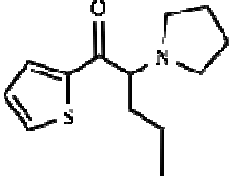
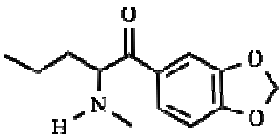
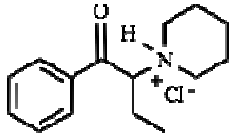
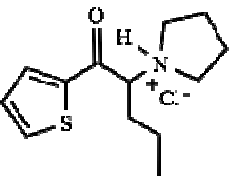
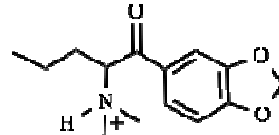
Common field test kits, drug-detecting canines, routine urine drug screens, and many toxicology protocols fail to detect synthetic cathinones. Forensic drug identification and quantitation analysis utilizes FT-IR and GC-MS as the core methods although various types of liquid chromatography and mass spectrometry are also employed [7-10, 12-15]. However, these methods rely upon comparing the spectra of the unknown evidence material to a library of known compounds for identification and often require time-consuming extraction, purification, and derivatization steps prior to analysis. As these methods do not perform total structure determination, if the compound is not present in the library, the forensic lab cannot assign an identity to the submitted evidence.

NMR has been used in previous studies for determining the structures of new synthetic and casework cathinones to facilitate their inclusion in library spectra [6-9, 13, 16-22] and quantitative ^1H -NMR (qHNMR) has been used in the pharmaceutical, food and natural products industries to probe compounds of interest [6]. Specifically, the enantiomers of methamphetamine, ephedrine, pseudoephedrine, and methcathinone were analyzed by NMR; ephedrine and pseudoephedrine are starting materials for synthesis. Dagne et al. [6] reported ^1H NMR spectra for cathinone oxalate and pure cathinone. Brandt et al. [7] analyzed mixtures of synthetic cathinones in NRG-1 (also referred to as naphthylpyrovalerone or Naphyrone) and NRG-3 samples. One NRG-1 consisted of a mixture of 4 cathinones: 4-fluoromethcathinone, 1-(3,4-methylenedioxyphenyl)-2-(methylamino)pentan-1-one (pentylone), 3,4-methylenedioxy- α -pyrrolidinobutyrophenone (MDPBP) and 3,4-methylenedioxypropylpyrovalerone (MDPV) [7]. Another NRG-1 sample consisted of pentylone and MDPBP [7]. The NRG-3 consisted of 4-methyl- α -pyrrolidinopropiophenone (MPPP) and pentylone [7]. 4-methylmethcathinone, methylone, and bk-MBDB were characterized by ^1H - and ^{13}C -NMR spectroscopy [14] and also to investigate (\pm)-4'-methylmethcathinone (mephedrone) [8]. Kavanagh et al. [9] synthesized 2,3-isomers of MDPV, butylone and methylone and characterized the isomers using ^1H and ^{13}C NMR. qHNMR was shown to be a quick and efficient tool for determination of drugs, including cathinone and cathine, in urine [6].

In these previous studies on cathinones, NMR was performed on pure compounds [18-22] but forensic labs often encounter mixtures of drugs and cutting agents. Recently Balayssac et al. [15] reported the use of ^1H -NMR and 2D DOSY ^1H -NMR experiments to characterize heroin, its main related impurities (6-acetylmorphine, acetylcodeine, morphine, noscapine and papaverine) and

cutting agents (caffeine and acetaminophen in nearly all samples as well as lactose, lidocaine, mannitol, piracetam) and establish spectral signatures of the cathinones in a solvent that resulted in most of the cutting agent not dissolving. The purpose of this work is determine if high-field NMR can be used as a screening tool to detect three adulterated cathinones (Table 1) in the presence of commercial powdered sugar (sucrose) as a representative cutting agent in two solvents of differing polarity.

Table 1 Chemical data for each cathinone provided by Cayman Chemical

Cathinone	α -PBP	α -PVT	Pentylone
Formal Name	1-phenyl-2-(1-piperidinyl)-1-butanone, monohydrochloride	2-(pyrrolidin-1-yl)-1-(thiophen-2-yl)pentan-1-one, monohydrochloride	1-(1,3-benzodioxol-5-yl)-2-(methylamino)-1-pentanone, monohydrochloride
Structure, high pH (e.g., solution in acetone)			
Structure, pH < 10, (e.g., solution in water or D ₂ O)			
CAS Number	92728-82-0		17763-01-8
Molecular Formula	C ₁₅ H ₂₁ NO•HCl	C ₁₃ H ₁₉ NOS•HCl	C ₁₃ H ₁₇ NO ₃ •HCl
Formula Weight (Da)	267.8	273.8	271.7
Formulation	White, crystalline solid	White, crystalline solid	White, crystalline solid
λ_{\max} (nm)	252	268, 296	235, 281, 318

Materials and Methods

Reagents

Alpha-piperidinobutiophenone hydrochloride (α -PBP) (Cayman Chemical product #9001513), alpha-pyrrolidinopentiothiophenone hydrochloride (α -PVT) (Cayman Chemical product #14182) and pentylone hydrochloride (Cayman Chemical product #9000746) standards were purchased from Cayman Chemical Company (Ann Arbor, MI) in 50 mg quantities. The structures and chemical properties of the compounds are shown in Table 1.

NMR-spectroscopy (NMR)

About 10 mg of the respective hydrochloride salts were each dissolved in 5 mL of acetone- d_6 or D_2O , with and without approximately 10 mg commercial powdered sugar (sucrose, $C_{12}H_{22}O_{11}$), and were immediately analyzed by 1H - and ^{13}C -NMR spectroscopy. α -PBP was collected in acetone- d_6 or D_2O ; all other experiments were conducted in D_2O . D_2O was used because the cathinones are polar, ionic compounds that are water soluble due to hydrogen bonding and less soluble in other solvents including acetone. The sugar is also more soluble in D_2O .

1H NMR data for α -PBP-HCl in acetone- d_6 (9.5 mg (~ 7 mg dissolved) in 1.2 mL of acetone- d_6)

1H NMR ($(CD_3)_2CO$) δ (ppm): 8.25 (d, $J = 7.8$ Hz, 2H), 7.80 (t, $J = 7.8$ Hz, 1H), 7.66 (t, $J = 7.8$ Hz, 2H), 5.13 (t, $J = 6.4$ Hz 1H), 3.64-2.88 (m, 6H), 2.6-2.2 (m, 2H), 2.10-2.0 (m, 4H), 0.905 (t, $J = 7.56$, 3H).

1H NMR data for α -PVT-HCl in D_2O (9.9 mg in D_2O)

1H NMR (D_2O) δ (ppm): 7.685 (d 1H_a), 7.472 (d, 1H_b), 7.036 (t, 1H_c), 5.141 (t, $J = 5.5$ Hz 1H_d), 4.23-3.47 (m, 8H on pyrrole ring), 2.752 (br s, H on amine), 1.98 (m, 2H_e), 1.23 (m. 2H_f), 0.860 (t, $J = 7.32$, 3H).

1H NMR data for pentylone-HCl in D_2O (10.2 mg dissolved in 4.79 mL of D_2O)

1H NMR (D_2O) δ (ppm): 7.6572 (d, $J = 8.24$ Hz 1H_a), 7.449 (s, 1H_b), 7.011 (d, $J = 8.24$ Hz, 1H_c), 6.1085 (s, 2H_d) 5.0248 (t, $J = 5.5$ Hz 1H_e), 0.8392 (s, methyl on nitrogen 3H), 1.98 (m, 2H_f), 1.24 (m, 2H_g), 0.8392 (t, $J = 7.32$, 3H). The two H on the amine were not detected. They may have exchanged with deuterium on the solvent or were broad and not integrated.

Equipment

The one-dimensional 1H -NMR and ^{13}C -NMR measurements were performed on a JEOL 400SS NMR spectrometer (Peabody, MA) with a z-gradient unit at 300 K and 8 scans with 400 MHz for 1H and 100 MHz for ^{13}C , respectively, employing the manufacturer's pulse programs and the Delta NMR Control and Processing

Software v.4.3.6 (2006). Spectra were replotted using MNova NMR (Mestralab Research, Escondido, CA). Chemical structures of the cathinones were drawn with ChemDraw.

Results and Discussion

The cathinone standards were chosen for their structural diversity and purchased in analytical quantities from a respected supplier. The solubility of the powdered sugar and the α -piperidinobutiophenone (hydrochloride) in an organic solvent, such as acetone was examined to determine if it was possible to use the solubility as a basis in which to distinguish between cathinones and cutting agents at a pH > 10 where they are not ionic (Table 1). Popular cutting agents tend to be water soluble but insoluble in organic solvents. Adulterants, cutting agents, and other added materials can reduce solubility of the designer cathinone samples [12].

Representative ^1H -NMR stacked spectral plots for pure α -PBP and α -PBP with sugar in acetone- d_6 are represented in Figure 2. The ^1H -NMR assignments for each proton are indicated. The ^{13}C -NMR results and assignments for pure α -PBP are shown in Figure 3. Despite some signal broadening due to sample variation, it is clear that a simple proton assay by ^1H -NMR was capable of detecting the α -PBP. Additionally, there is minimal signal in the carbohydrate region of the spectrum, indicating little sucrose was actually dissolved in the deuterated acetone, making isolation of the cathinone reasonably straightforward. As observed by Balayssac et al. [15] in their study of heroin, its main related impurities and cutting agents, the designer cathinone and sucrose peaks line up giving a precise identification of the constituents. Similarly to Balayssac et al. [15] it was observed with more non-polar solvents that, little of the polar sugar cutting agent was soluble in the less polar acetone solvent, making interpretation easier.

Figure 2 Spectral overlay of two NMR spectra (protons assigned) acquired in acetone- d_6 containing α -PBP: pure α -PBP-HCl shown in blue, and an “adulterated” sample of α -PBP and sucrose shown in red. It is immediately clear that the NMR instrument is capable of detecting signature peaks from the α -PBP that are inconsistent to carbohydrates (e.g., 7.5 ppm-8.5 ppm). There is very good matching in the overlay, showing only minor variation and line broadening due to variation in temperature and sample loading. Inset A shows some of the minor signal shifting observed, though the degree of variation is expected in inconsistent sample contents endemic to sampling across varying mixtures of adulterated cathinone. Inset B shows line some line broadening, again due to variations in sample concentrations and contents after extraction into acetone- d_6 versus a “clean” spectrum observed with the pure α -PBP-HCl; though as seen in inset C, the solvent peak expected for acetone- d_6 was observed to be sharp and easily referenced in both samples. The structural insert of α -PBP shows proton

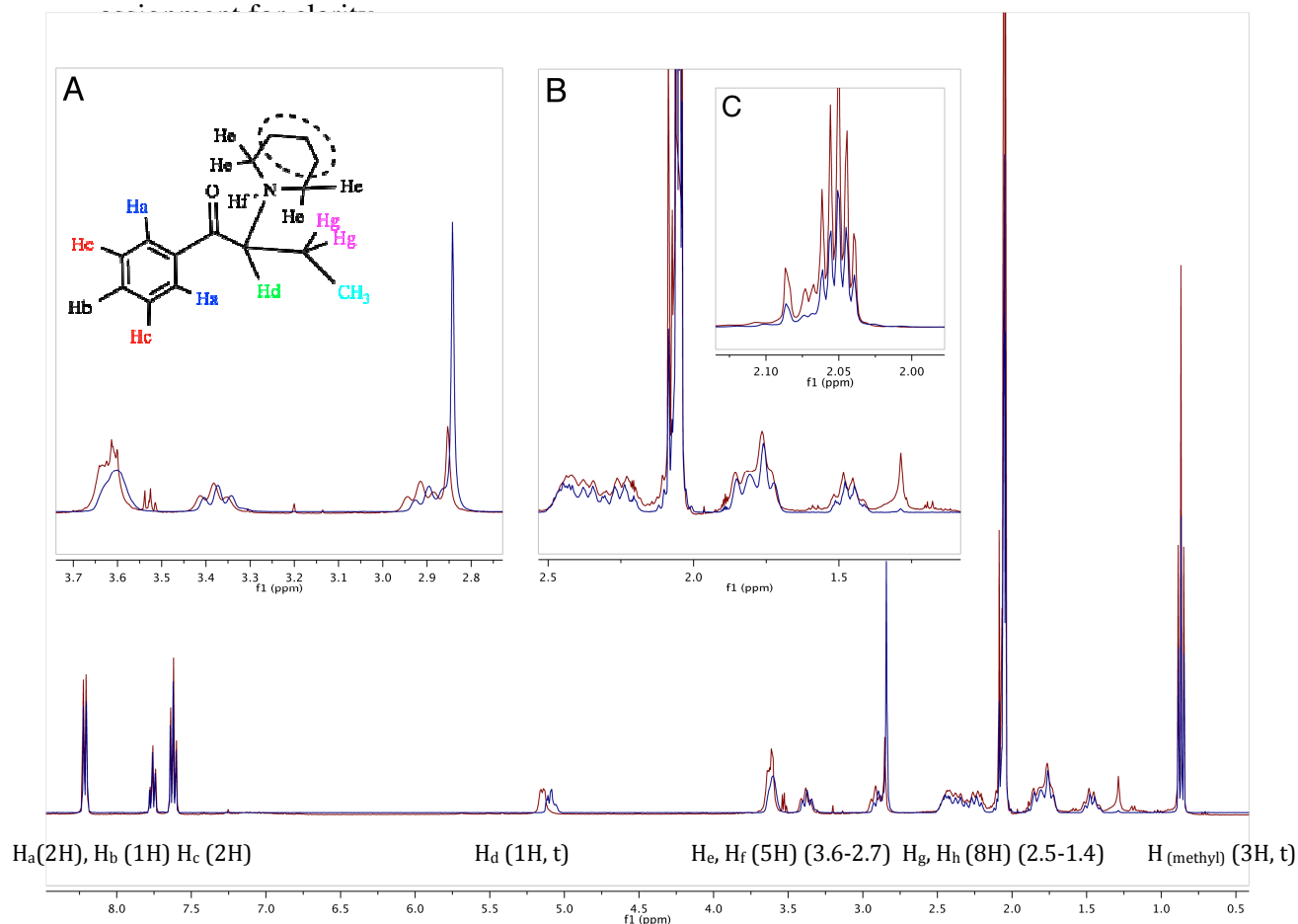
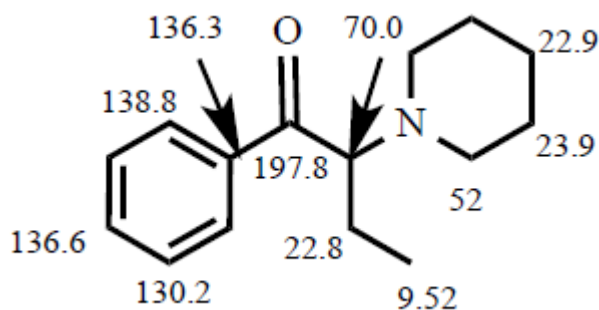


Figure 3 ^{13}C NMR assignments for α -PBP in acetone- d_6

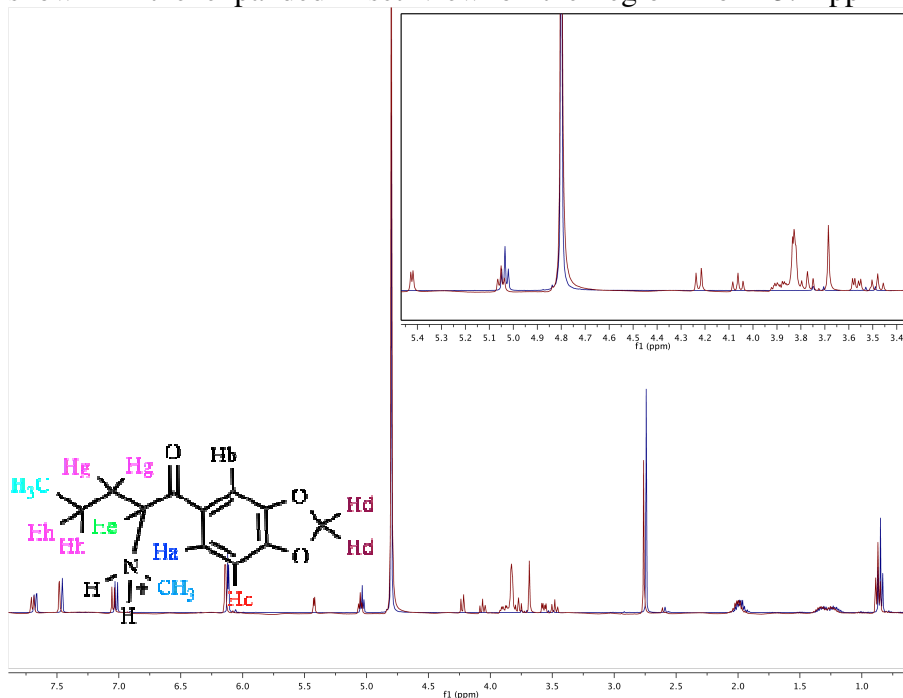
^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) δ (ppm): 197.8 (1C, ketone), 138.8 (2C, *ortho*-aromatic), 136.6 (1C, *para*-aromatic), 136.3 (1C, *ipso*-aromatic), 130.2 (2C *meta*-aromatic), 70.0 (1C), 52 (2C, piperidine), 23.9 (2C, piperidine), 22.8 (1C, piperidine), 22.8 (1C), 9.52 (1C).



To obfuscate the signals and replicate mixtures that could be observed by the forensic lab, we changed to the more polar D_2O as a solvent. The cathinones and the sugar were all very soluble in D_2O . Representative ^1H -NMR stacked spectral plots for pure pentylone and pentylone with sucrose sugar in D_2O are shown in Figure 4. The ^1H -NMR assignments for each proton are indicated. Note that the contribution from the sugar is increased due to its improved solubility in D_2O . With the sugar, characteristic carbohydrate peaks at 3.4 ppm to 5.4 ppm are attributed to the cutting agent. Data for pentylone has already been published in 2012 by Westphal et al [18]. For comparison, the ^1H -NMR assignments for pure α -PVT are shown in Figure 5 with a stacked plot of α -PVT and sucrose and insets showing the aromatic and carbohydrate regions. Figure 6 shows α -PVT, sucrose and the α -PVT / sucrose mixture. From these spectra, it is obvious that each of the cathinones have characteristic proton NMR patterns, which can be used to distinguish them in a screening assay, even with a solvent that dissolves both the drug and adulterant components of the mixture.

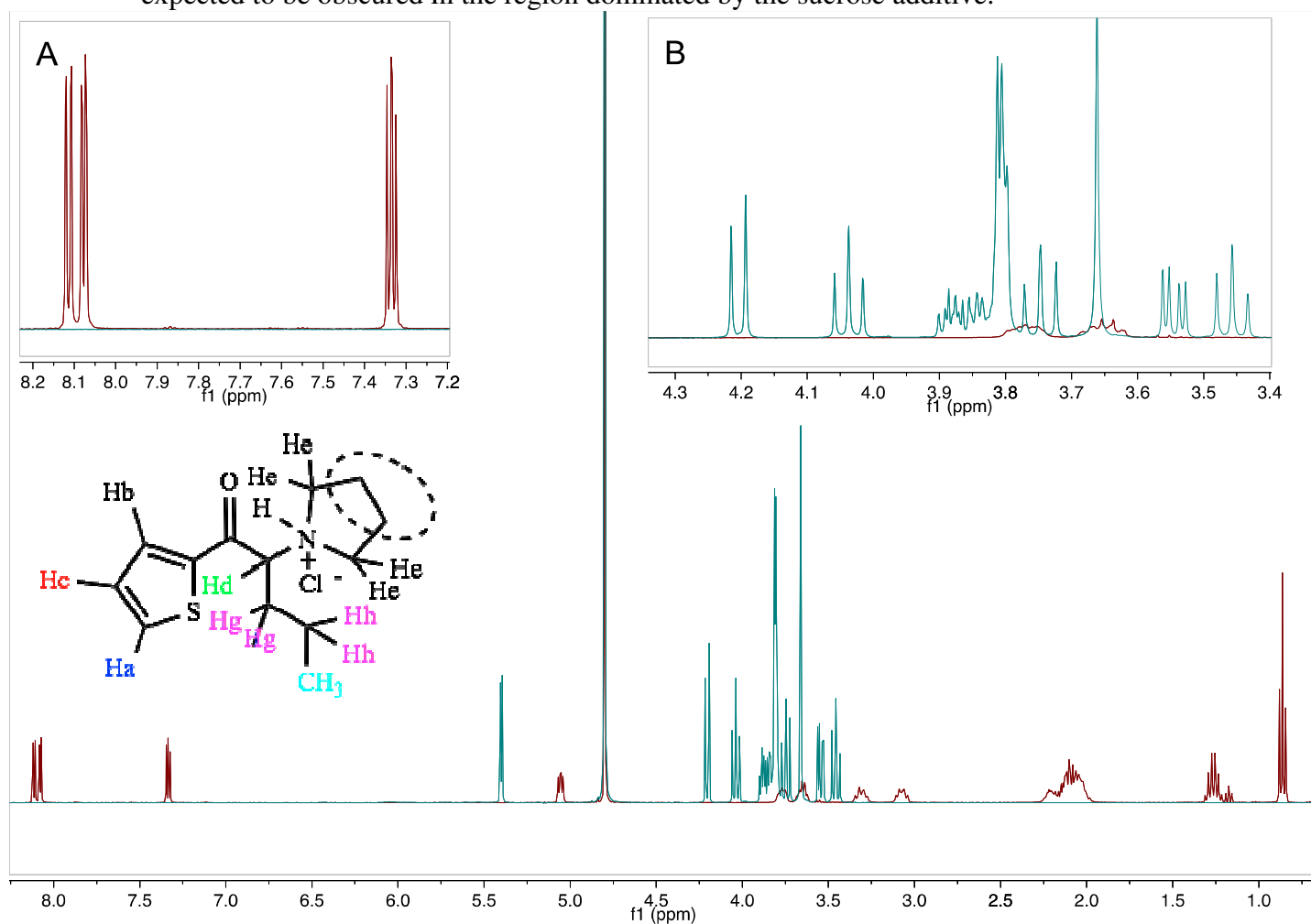
Concentration and quantity of the drug is also of concern to forensic chemists. Using an internal standard, concentration can be determined if the experiments are performed so that the baseline is absolutely flat and factors including pH, viscosity, etc. are controlled. These experiments are expected to be more expensive than using high-field NMR as a screening tool for a cathinone drug mixed with a cutting agent.

Figure 4 Spectral overlay of two ^1H -NMR spectra acquired in D_2O containing pentylone-HCl: pure pentylone-HCl shown in blue, and a “cut” sample of pentylone-HCl in commercial powdered sugar shown in red. Both spectra were pseudo-referenced to the D_2O peak (set to 4.8 ppm) in the spectra, though some error in chemical shift overlay is expected due to the less strict temperature and pH control of the samples. It is immediately clear that the NMR instrument is capable of detecting signature peaks from the pure cathinone (notably the existence of the aromatic moiety the carbohydrates lack, as well as the terminal methyl group of the cathinone and the single α -proton vis-à-vis the carbonyl). Additionally, it is clear that the mismatch in the overlaid ^1H -NMR spectra exists in the region of the proton spectrum classically associated with carbohydrates, as shown in the expanded inset view of the region from 3.4 ppm to 5.4 ppm.



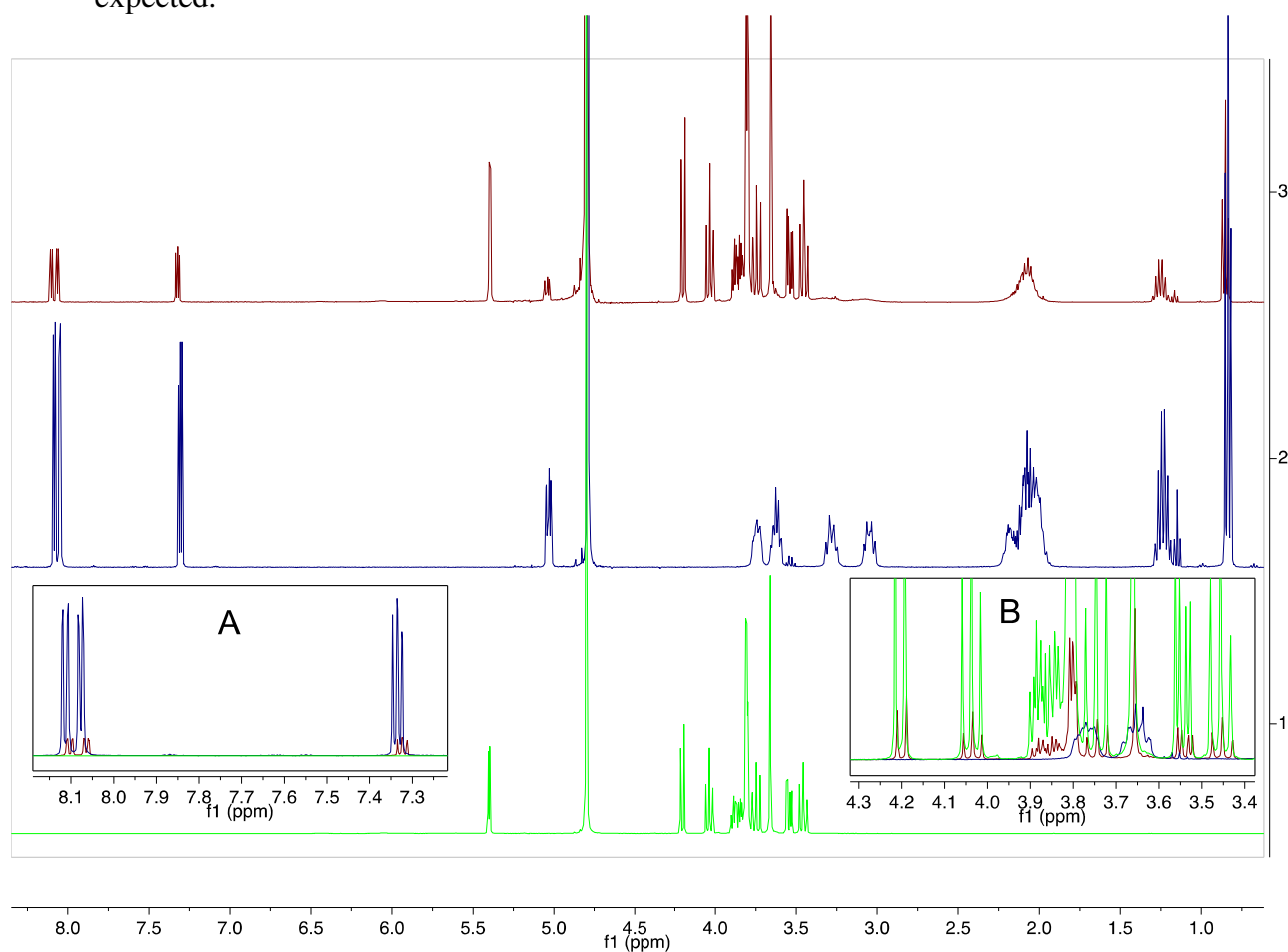
^1H NMR (D_2O) δ (ppm): 7.6572 (d, $J = 8.24$ Hz 1 H_a), 7.449 (s, 1 H_b), 7.011 (d, $J = 8.24$ Hz, 1 H_c), 6.1085 (s, 2 H_d), 5.0248 (t, $J = 5.5$ Hz 1 H_e), 0.8392 (s, methyl on nitrogen 3H), 1.98 (m, 2 H_g), 1.24 (m, 2 H_h), 0.8392 (t, $J = 7.32$, 3H). The two H on the amine were not detected. They may have exchanged with deuterium on the solvent or were broad and not integrated.

Figure 5 Overlaid ^1H -NMR spectral data for α -PVT (maroon) and sucrose (teal). Both spectra were obtained in D_2O and the solvent peak referenced to 4.8 ppm. It is clear that there is minimal spectral overlap, and characteristic peaks for both the cathinone and the sucrose cutting agent should be abstracted from a spectrum of the composite. Inset A displays the aromatic portion of the spectrum, with clear representation of the thiophene protons from the cathinone. Inset B displays the busiest portion of the sucrose portion of the spectrum. Of note is the reasonably small overlap in peaks in this region. Only two of the cathinone peaks are expected to be obscured in the region dominated by the sucrose additive.



^1H NMR (D_2O) δ (ppm): 7.685 (d, 1H_a), 7.472 (d, 1H_b), 7.036 (t, 1H_c), 5.141 (t, $J = 5.5$ Hz 1H_d), 4.23-3.47 (m, 8H on pyrrole ring), 2.752 (br s, H on amine), 1.98 (m 2 H_g), 1.23 (m, 2H_h), 0.860 (t, $J = 7.32$, 3H).

Figure 6 Stacked ^1H -NMR data for samples of: α -PVT-HCl and sugar (maroon), α -PVT-HCl (blue), and sucrose (green) as referenced to the D_2O peak (4.8 ppm). It is abundantly clear that the mixture corresponds very well with the individual spectra for α -PVT-HCl and sucrose. The expected spectrum of the mixture (as shown in Figure 2) matches neatly with the actual spectrum. Inset A and B correspond to the spectral windows for the aromatic region and the sucrose window respectively. The mixture (maroon) exhibits the expected signals in each spectral window, though intensities are not equivalent as spectral data was acquired without normalizing sample quantities or buffering pH in the D_2O solvent. There is some signal shifting of the sample, as shown in Inset A, but well within the expected amount for unbuffered samples. Moreover, given the solvent and hydrochloride salt form of the α -PVT, the lack of ammonium salt proton is expected.



Conclusion

NMR does not require common pre-processing steps including extraction, purification, or derivatization, and it does not require pure samples. And, as NMR is non-selective—unlike other methods—it can simultaneously detect all compounds in a mixture in a single experiment provided they are soluble in the solvent and have the nucleus being probed in sufficient quantity for detection and assignment. One of the problems crime labs face when analyzing submitted drug evidence is that the samples are often mixtures and can contain one or more of several cutting agents. Without knowing the mixture components, it is impossible to select a solvent that will (ideally) only dissolve the drug of interest for interpretation. In this work, high field NMR was used to capture ^1H spectra for three structurally distinct cathinone compounds encountered by forensic laboratories both in pure form and when extended in quantity with the cutting agent commercial powdered sugar, or sucrose. High field NMR can be used to provide a spectral assignment and structure determination of a sample of an unknown cathinone and spectral signatures for screening, even when the cutting agent is also very soluble. In the future, 2D experiments will be performed to further characterize cathinones and “cut” cathinone mixtures by NMR. The NMR spectra provide evidence that rapidly acquired ^1H spectra can be used to strongly indicate the identity of cathinones in a sample if they are present in a library. Additionally, NMR can be used alone with pure samples for total structure determination or in combination with other laboratory techniques for further analysis.

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