David R. Morello,[1] *B.S. and Richard P. Meyers,*[1] *M.S.*

Qualitative and Quantitative Determination of Residual Solvents in Illicit Cocaine HCl and Heroin HCl

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ABSTRACT: Methodology has been developed which utilizes static headspace-gas chromatography-mass spectrometry (SHS-GC-MS) to identify and quantitate residual solvents occluded in illicit cocaine HCl and heroin HCl. The liberation of the occluded solvents was ensured by complete solubilization of the crystal matrices in aqueous 22% sodium sulfate. Ion trap mass spectrometry is used for both identification and quantitation; five deuterated, structurally related internal standards are utilized for more accurate quantitation. Overall method precision for 25 commonly encountered solvents averaged 6.7% RSD. Minimum detection limits ranged from 3 to 87 ppm for a 15 mg equivalent cocaine sample weight, and from 2 to 43 ppm for a 30 mg equivalent heroin sample weight. Qualitative and quantitative data for the 25 most commonly encountered occluded solvents in cocaine HCl and heroin HCl exhibits are presented.

KEYWORDS: forensic science, criminalistics, drug chemistry, cocaine, heroin, gas-chromatography-mass spectrometry, residual solvents, illicit drug identification

With a few exceptions (notably "crack" cocaine), virtually all illicit amine-based drugs are prepared and marketed as salts, most commonly as hydrochloride salts. Such salts are typically prepared either by adding concentrated hydrochloric acid or by bubbling hydrogen chloride gas into an organic solution of the respective free base. Both procedures generally result in rapid precipitation, commonly giving crystal matrices containing significant quantities of occluded (that is, trapped) solvents. These residual solvents may be subjected to rigorous qualitative and quantitative analysis for both strategic and tactical intelligence [*1*].

At present, development of intelligence via solvent analysis is most critical for illicit cocaine HCl and heroin HCl (hereafter cocaine and heroin). Qualitative analysis provides a means for monitoring current use trends in the chemical underground; this information is important for determining which solvents should be targeted for diversion control. Quantitative analysis allows differentiation of primary solvent(s) from trace level solvent impurities present in the original reaction mixtures. Finally, comprehensive solvent analysis offers another complementary technique for direct sample-to-sample comparative analysis [*1*].

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[1]Senior Forensic Chemists, U.S. Drug Enforcement Administration Special Testing and Research Laboratory, McLean, VA.

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The identification of residual solvents in cocaine [*2–7*] and heroin [*8*] has been previously performed using a variety of analytical procedures, including nuclear magnetic resonance (NMR) spectroscopy, gas chromatography-mass spectroscopy (GC-MS) and static headspace-gas chromatography-mass spectrometry (SHS-GC-MS). However, with one exception, these procedures have focused primarily only on qualitative analysis; Avdovich et al. [*2*] provided a quantitative estimation for five residual solvents encountered in cocaine.

In order to perform simultaneous qualitative and quantitative analyses, a new methodology utilizing SHS-GC-MS was developed. Separation and concentration of the residual solvents from the drug matrices was accomplished by static headspace; this preconcentration technique was found to be especially amenable to automation. In this approach, the respective HCl salt is completely solubilized in aqueous 22% sodium sulfate within a closed headspace vial, thereby liberating all occluded solvents. Unlike dynamic headspace analysis (i.e., purge and trap), where analytes are purged in an open system, static headspace relies upon the equilibrium of the solvents between the liquid and gas phases in a closed system [*9*]. Similar preconcentration approaches have been implemented for the analysis of residual solvents in environmental [*10–13*] and pharmaceutical [*14–17*] samples.

GC-MS was chosen to provide the necessary resolution, sensitivity and specificity required to identify and quantitate a wide range of volatile organic solvents. Injection of the equilibrated headspace is automatically performed by the headspace analyzer. Subsequent resolution of the solvents is performed by temperature programmed capillary GC. Resolved solvents elute directly into the mass spectrometer, where detection, identification and quantitation are performed. Instrumental parameters were specifically designed for the resolution and analysis of the 25 most commonly encountered residual solvents in illicit cocaine and heroin; however, the system also allows for qualitative and quantitative determination of new residual solvents.

Herein, we present the results of SHS-GC-MS analysis of 75 uncut cocaine and 826 uncut heroin exhibits. In addition, the applicability of the methodology for adulterated exhibits was investigated; 19 adulterants commonly encountered in cocaine and heroin exhibits were also analyzed. From these results, guidelines are presented for the determination of residual solvents in both uncut and adulterated exhibits.

Experimental

Headspace-Gas Chromatography-Mass Spectroscopy

Two SHS-GC-MS instrument configurations were used for this work. In both cases, a headspace analyzer was used to isolate and

quantitatively transfer residual solvents from their original drug matrix to the GC. Following GC resolution, identification and quantitation were performed by ion trap mass spectroscopy.

Solvent concentration was performed by two Tekmar 7000/7050 Headspace Autosampler Carrousel Combinations (ver. #1.04 and #1.10), each fitted with a 2.0 mL stainless steel sample loop and a heated nickel transfer line. The headspace settings were as follows; platen temperature, 80°C; transfer line temperature, 180°C; valve/line temperature, 180°C; vial size, 22 mL; mixer time, 15 or 30 min; mixer power, 1; vial pressurize time, 0.3 min; pressure/loop equilibration time, 0.05 min; loop fill, 0.2 min; inject time, 1.5 min. Only the setting for mixer time was unique for the two analyzers; the newer Tekmar 7000/7050, used in GC-MS configuration 2, incorporated a modified mixer assembly that allowed the lower (15 min) setting.

GC-MS Configuration 1

A Hewlett-Packard model 5890 Series II Gas Chromatograph was utilized and fitted with a 75 m × 0.53 mm I.D. fused silica capillary column coated with 3 μm DB-624. Helium (UHP) was used as carrier gas, at an average linear velocity of 23 cm/s. The GC oven was temperature programmed as follows: (level 1) initial temperature, 35°C; initial hold, 14 min; (level 2) temperature program rate, 7°C/min; final temperature, 210°C; final hold, 3 min; the injector temperature was 180°C and all injections were split at a ratio of 8:1.

Detection and quantitation was performed by a Finnigan-MAT Model 800 Ion Trap Detector (ITD) equipped with a Compaq 386/20 Data Station and accompanying ITD quantitation software. Instrument settings were as follows: scan range, 29–220 amμ; seconds/scan, 1.0 (7 μs); acquire time, 35 min.; transfer line temperature, 200°C; manifold temperature, 200°C; scan mode, full; peak threshold, 1; filament/multiplier delay, 275 s; mass defect, 100 mmμ/100 amμ; open split interface flow, off.

GC-MS Configuration 2

A Varian Model 3400 Gas Chromatograph was utilized and fitted with a 60 m × 0.25 mm I.D. fused silica capillary column coated with 1.4 μm DB-624. Helium (UHP) was used as carrier gas, at an average linear velocity of 33 cm/s. The GC oven was temperature programmed as follows: (level 1) initial temperature, 35°C; initial hold, 12 min; (level 2) temperature program rate, 6°C/min; final temperature, 170°C; final hold, 0 min; the injector temperature was 180°C and all injections were split at a ratio of 16:1.

Detection and quantification was performed by a Finnigan-MAT Magnum™ (MAG-ITD) equipped with a Gateway 486/33 Data

TABLE 1—*Commonly Encountered Occluded Solvents in Illicit Cocaine HCl and Heroin HCl[a] (Listed in Order of Decreasing Prevalence)*

Cocaine HCl (% of Samples)[b]	Heroin HCl (% of Samples)[c]
Methyl Ethyl Ketone (65%)	Ethyl Acetate (81%)
Hexanes (61%)	Acetone (57%)
Toluene (59%)	Ethyl Ether (34%)
Benzene (55%)	Methyl Ethyl Ketone (25%)
Acetone (52%)	Toluene (25%)
Methylene Chloride (41%)	Xylenes (19%)
Xylenes (31%)	Ethanol (10%)
Ethyl Ether (31%)	Isopropanol (5%)
Cyclohexane (27%)	Hexanes (3%)
Ethyl Acetate (23%)	Methyl Acetate (3%)

[a]Results represent cocaine samples analyzed during 1994 and heroin samples analyzed during 1993–1994.
[b]Number of samples = 75.
[c]Number of samples = 826.

TABLE 2—*Linearity and precision data for target solvents.*

Target Solvent	Linearity Range (μg)[a]	Precision (% RSD)[b]
1,1,1-Trichloroethane	0.1–18.8	5.6
1,1,2-Trichloroethane	0.1–10.5	8.2
Isopropanol	0.2–35.2	6.5
Isobutanol	0.1–20.1	4.8
Isobutyl Acetate	0.1–8.3	7
Acetone	0.2–19.9	4.8
Benzene	0.05–7.7	6
Chloroform	0.2–22.7	4.5
Cyclohexane	1.3–8.0	4.8
Cyclopentane	2.4–23.5	10.4
Ethanol	0.6–18.2	4.6
Ethyl Acetate	0.1–8.8	8.4
Ethyl Ether	3.5–35.3	8.5
n-Hexane	0.5–4.6	8.1
m-Xylene	0.05–7.8	9.5
Mesityl Oxide	0.05–3.8	7
Mesitylene	0.06–4.4	9
Methanol	4.9–49.2	9.5
Methyl Acetate	0.2–26.0	7.9
Methyl Ethyl Ketone	0.2–11.5	5.6
Methylene Chloride	0.1–16.4	5
n-Butanol	1.0–37.6	9.6
n-Butyl Acetate	0.1–5.3	6.6
o-Xylene	0.05–7.8	6.3
Toluene	0.05–8.1	5.6

[a]μg in headspace vial.
[b]$n = 9$.

TABLE 3—*Internal standard and quantitation ion assignments for 25 target solvents.*

Internal Standard	Target Solvent	Quantitation Ion(s)-(m/z)
2-Chloro-2-methylpropane-d_9	1,1,1-Trichloroethane	97 + 99
2-Chloro-2-methylpropane-d_9	1,1,2-Trichloroethane	83 + 97 + 99
Isopropanol-d_8	Isopropanol	43 + 45
Isopropanol-d_8	Isobutanol	45 + 59
Acetone-d_6	Isobutyl Acetate	43 + 57
Acetone-d_6	Acetone	43
Toluene-d_8	Benzene	50 + 78
2-Chloro-2-methylpropane-d_9	Chloroform	83 + 85
n-Hexane-d_{14}	Cyclohexane	41 + 56
n-Hexane-d_{14}	Cyclopentane	55 + 69
Isopropanol-d_8	Ethanol	45
Acetone-d_6	Ethyl Acetate	43 + 61
Acetone-d_6	Ethyl Ether	59 + 74
n-Hexane-d_{14}	*n*-Hexane	41 + 56
Toluene-d_8	*m*-Xylene	91 + 106
Toluene-d_8	Mesityl Oxide	83
Toluene-d_8	Mesitylene	105 + 120
Isopropanol-d_8	Methanol	31 + 32
Acetone-d_6	Methyl Acetate	43 + 74
Acetone-d_6	Methyl Ethyl Ketone	43 + 72
2-Chloro-2-methylpropane-d_9	Methylene Chloride	49 + 84
Isopropanol-d_8	*n*-Butanol	41 + 56
Acetone-d_6	*n*-Butyl Acetate	43 + 56
Toluene-d_8	*o*-Xylene	91 + 106
Toluene-d_8	Toluene	91

TABLE 4—*Minimum Detection Limits for Residual Solvents in Cocaine and Heroin HCl.*

Target Solvent	Cocaine HCl[a] (ppm)	Heroin HCl[b] (ppm)
1,1,1-Trichloroethane	8	4
1,1,2-Trichloroethane	9	5
Isopropanol	15	8
Isobutanol	9	5
Isobutyl Acetate	7	4
Acetone	17	8
Benzene	3	2
Chloroform	10	5
Cyclohexane	27	14
Cyclopentane	50	25
Ethanol	39	19
Ethyl Acetate	9	5
Ethyl Ether	30	15
n-Hexane	31	15
m-Xylene	3	2
Mesityl Oxide	3	2
Mesitylene	4	2
Methanol	87	43
Methyl Acetate	11	6
Methyl Ethyl Ketone	10	5
Methylene Chloride	7	4
n-Butanol	64	32
n-Butyl Acetate	9	5
o-Xylene	3	2
Toluene	3	2

[a]Concentrations based upon a 15 mg equivalent sample weight of cocaine HCl.

[b]Concentrations based upon a 30 mg equivalent sample weight of heroin HCl.

TABLE 5—*Residual solvents found in common commercially available adulterants.*

Adulterant[a]	Residual Solvent(s)
Acetaminophen	None Detected
Acetylprocaine HCl	Acetone
Aspirin	None Detected
Caffeine	None Detected
Calcium Carbonate	None Detected
Corn Starch	None Detected
Dextrose	None Detected
Diphenhydramine HCl	Toluene
Inositol	None Detected
Lactose	None Detected
Mannitol	None Detected
Potato Starch	None Detected
Procaine HCl	Toluene, Xylenes
Quinine HCl	None Detected
Salicylic Acid	None Detected
Sodium Bicarbonate	None Detected
Sodium Carbonate	None Detected
Sodium Chloride	None Detected
Sucrose	None Detected
Wheat Starch	None Detected

[a]Approximately 100 mg of each adulterant was analyzed.

Station and accompanying ITD quantitation software. Instrument settings were as follows: scan range, 29–220 amμ; seconds/scan, 1.0 (7 μs); acquire time, 35 min; transfer line temperature, 200°C; manifold temperature, 200°C; scan mode, full; GC connection, direct; peak threshold, 1; filament/multiplier delay, 275 s; mass defect, 100 mmμ/100 amμ; auto ion control, on; ionization mode, EI.

Materials

Deionized water, filtered to remove trace organics by a Milli-Q™ System (Millipore, Bedford, MA), was used for all sample and standard solutions. All chemicals and solvents used were reagent grade or better. Dimethylsulfoxide (DMSO) was obtained from Aldrich Chemical Co. (Milwaukee, WI). Acetone-d_6, isopropanol-d_8, toluene-d_8, 2-chloro-2-methyl propane-d_9 and *n*-hexane-d_{14} were all obtained from MSD Isotopes at a purity of 99.5% or better. The following solvents were used in the calibration standard mixture: acetone, benzene, *n*-butanol, isobutanol, *n*-butyl acetate, isobutyl acetate, chloroform, cyclohexane, cyclopentane, ethanol, ethyl acetate, ethyl ether, *n*-hexane, methanol, mesitylene, mesityl oxide, methyl acetate, methyl ethyl ketone, methylene chloride, isopropanol, toluene, 1,1,2-trichloroethane, 1,1,1-trichloroethane, *m*-xylene and *o*-xylene.

Reaction vials and corresponding Mininert™ valve caps used to store standard solutions were supplied by Pierce (Rockford, IL) and Supelco (Bellefonte, PA), respectively. Headspace vials were clear, 20 mL, 20 mm × 75 mm glass with corresponding silicone/teflon septa crimp caps (Phase Separations, Inc., Norwalk, CT).

Internal Standard Solution

A stock solution (IS-Stock) of the five deuterated internal standards in 5:1 DMSO/water was prepared at the following concentrations: acetone-d_6, 6.0 mg/mL; 2-chloro-2-methyl propane-d_9, 3.5 mg/mL; *n*-hexane-d_{14}, 1.5 mg/mL; isopropanol-d_8, 7.5 mg/mL; toluene-d_8, 1.5 mg/mL; DMSO was used since the most common diluting solvents (that is, methanol or methylene chloride) are potential target solvents. In addition, the SHS-GC-MS system was determined to be quite insensitive for DMSO, thereby minimizing potential interference. The internal standard stock solution was determined to be stable for up to two months when stored at −10°C; deuterium exchange was not observed.

Calibration Standard Solutions

A stock calibration standard solution (Cali-STDS-1) containing the 25 target solvents in 5:1 DMSO/water was prepared at the following concentrations: methanol, ethanol, acetone, isopropanol, *n*-butanol and isobutanol at 0.4 mg/mL; methyl ethyl ketone, ethyl acetate, chloroform, methylene chloride, 1,1,2-trichloroethane, ethyl ether, methyl acetate, cyclopentane, isobutyl acetate, *n*-butyl acetate and 1,1,1-trichloroethane at 0.2 mg/mL; cyclohexane, benzene, toluene, *n*-hexane, *o*-xylene, *p*-xylene, mesitylene and mesityl oxide at 0.08 mg/mL. Different concentrations of target solvents were used in the calibration solution to compensate for the HS-GC-MS system's inherent variation in sensitivity to different solvents. Serial dilutions of Cali-STDS-1 were made to create two additional calibration solutions; Cali-STDS-2 was made by diluting 10.0 mL of Cali-STDS-1 to 50.0 mL with 5:1 DMSO/water, while Cali-STDS-3 was made by diluting 10.0 mL of Cali-STDS-2 to 50.0 mL with 5:1 DMSO/water. All stock solutions were stored at −10°C and were determined to be stable for four weeks. The detector was calibrated daily using these stock calibration solutions.

Standard and Sample Preparation

An aqueous 22% sodium sulfate solution (220 g/1000 mL), spiked with 100 μL of the IS-Stock solution per 100 mL, was

A = Methanol
B = Ethanol
C = Ethyl Ether
D = Acetone-d_6
E = Acetone
F = Isopropanol-d_8
G = Isopropanol
H = Methyl Acetate
I = Methylene Chloride
J = Cyclopentane
K = 2-Chloro-2-methylpropane-d_9
L = n-Hexane-d_{14}
M = n-Hexane
N = Methyl Ethyl Ketone
O = Ethyl Acetate
P = Isobutanol
Q = Chloroform
R = 1,1,1-Trichloroethane
S = Cyclohexane
T = Benzene
U = n-Butanol
V = Toluene-d_8
W = Toluene
X = Isobutyl Acetate
Y = 1,1,2-Trichloroethane
Z = Mesityl Oxide
AA = n-Butyl Acetate
AB = o-Xylene
AC = m-Xylene
AD = Mesitylene

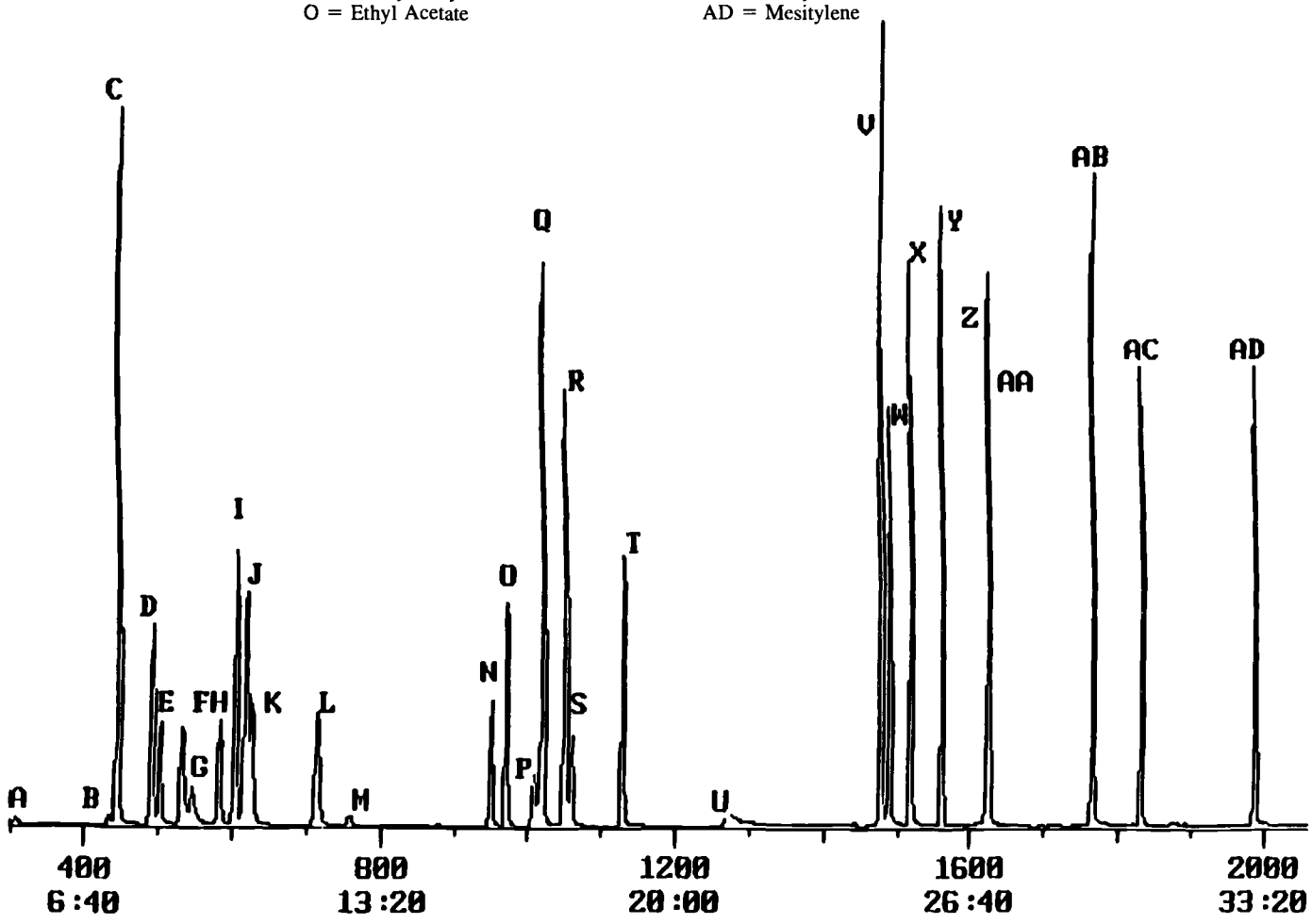

FIG. 1—*Reconstructed total ion chromatogram of 25 calibration standards and five deuterated internal standards. Peak identification.*

prepared daily (Dil-SOLN). This diluting solution is nearly saturated with sodium sulfate and is used for all samples and standards.

Standard calibration headspace vials were prepared by accurately pipeting 5.0 mL of fresh Dil-SOLN into three headspace vials, which were immediately crimp capped. All calibration solutions were allowed to reach room temperature prior to use. Exactly 50 μL of the three calibration stock solutions (Cali-STDS-1, Cali-STDS-2 and Cali-STDS-3) were added to the three headspace vials by uncrimping the vials, adding the aliquot of standard solution and immediately recrimping the vials with new caps. A fourth vial containing only 5.0 mL of Dil-SOLN served as the method blank.

Each cocaine or heroin sample is prepared by accurately weighing a 15 mg or a 30 mg equivalent, based on percent purity, into a headspace vial. A 5.0 mL portion of the Dil-SOLN is added followed by crimp capping; both cocaine and heroin are easily solubilized in this solution.

Results and Discussion

Qualitative Results

Baseline resolution was observed for most target solvents and deuterated internal standards, with the exception of the following solvent combinations: methylene chloride-cyclopentane, 1,1,1-trichloroethane-cyclohexane and mesityl oxide-n-butyl acetate; however, these were all easily distinguished by differing fragmentation patterns. The reconstructed total ion chromatogram (TIC) for Cali-

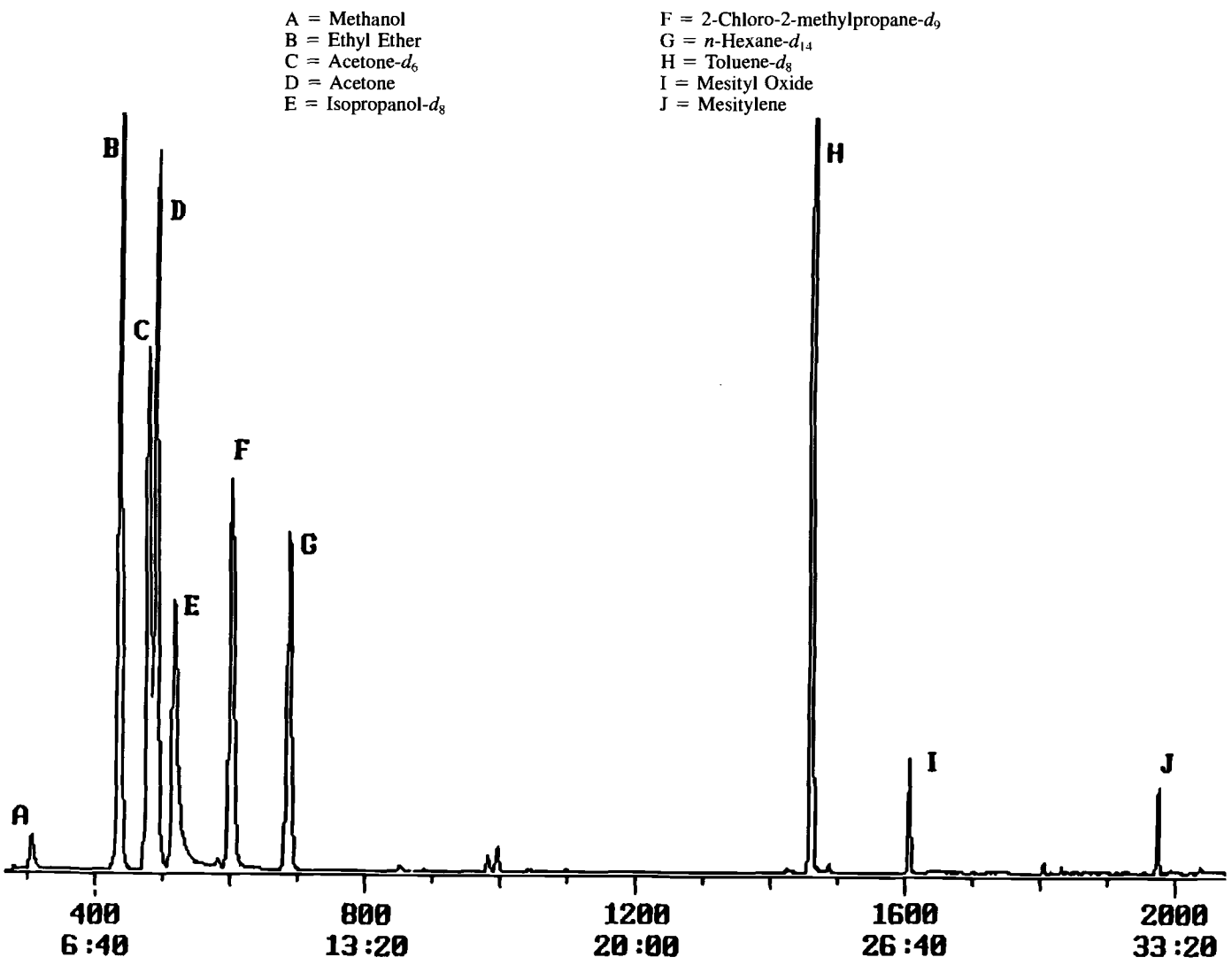

FIG. 2—*Reconstructed total ion chromatogram of residual solvents present in an uncut cocaine HCl sample. Peak identification.*

STDS-1 is illustrated in Fig. 1. Sufficient sensitivity and resolution existed for detection of new residual solvents. Figures 2 and 3 illustrate TIC's for typical illicit cocaine and heroin samples, respectively. For this study, 75 cocaine and 826 heroin exhibits were analyzed. Table 1 summarizes the most commonly encountered residual solvents detected in these exhibits. From 2 to 14 residual solvents were detected in individual cocaine samples, and from 0 to 8 in individual heroin samples. Generally, cocaine samples contained a larger number of residual solvents per sample.

Optimization of the various headspace parameters, particularly mixing time, resulted in enhanced sensitivity for all target solvents. Mixing during sample heating has been shown to dramatically reduce the time necessary to reach equilibrium [*18*]. Aqueous salt solutions have been previously demonstrated to encourage greater partitioning into the headspace due to the "salting out" effect [*19*]. Maximum benefits are typically obtained with saturated or near saturated solutions. In this methodology, the greatest sensitivity was achieved through the use of aqueous 22% sodium sulfate; in comparison, other salts (for example, potassium carbonate, sodium chloride, or sodium citrate) proved to be inferior. In addition, sodium sulfate did not inhibit the full solubilization of either cocaine HCl or heroin HCl.

Close observation of the method blank indicated minuscule to no hydrogen exchange (that is, acetone-d_6 to acetone) of the deuterated internal standards. When minor hydrogen exchange occurred, the target solvents with corresponding deuterated analogs (for example, acetone, isopropanol, n-hexane and toluene) were not considered to be present in a heroin or cocaine exhibit until the area counts were two times the counts of the method blank.

Quantitative Results

Precision and linearity data are presented in Table 2. Quantitative ions for the 25 target solvents are presented in Table 3. Calculations were based on the ratios of the area of target solvent ion(s) to their corresponding deuterated internal standards. Correlation coefficients ranged from 0.998–1.000. Method precision was found to be comparable with similar static and dynamic headspace procedures [*20–22*]. Linearity ranges were sufficiently wide for the quantitation of most residual solvents encountered in illicit samples

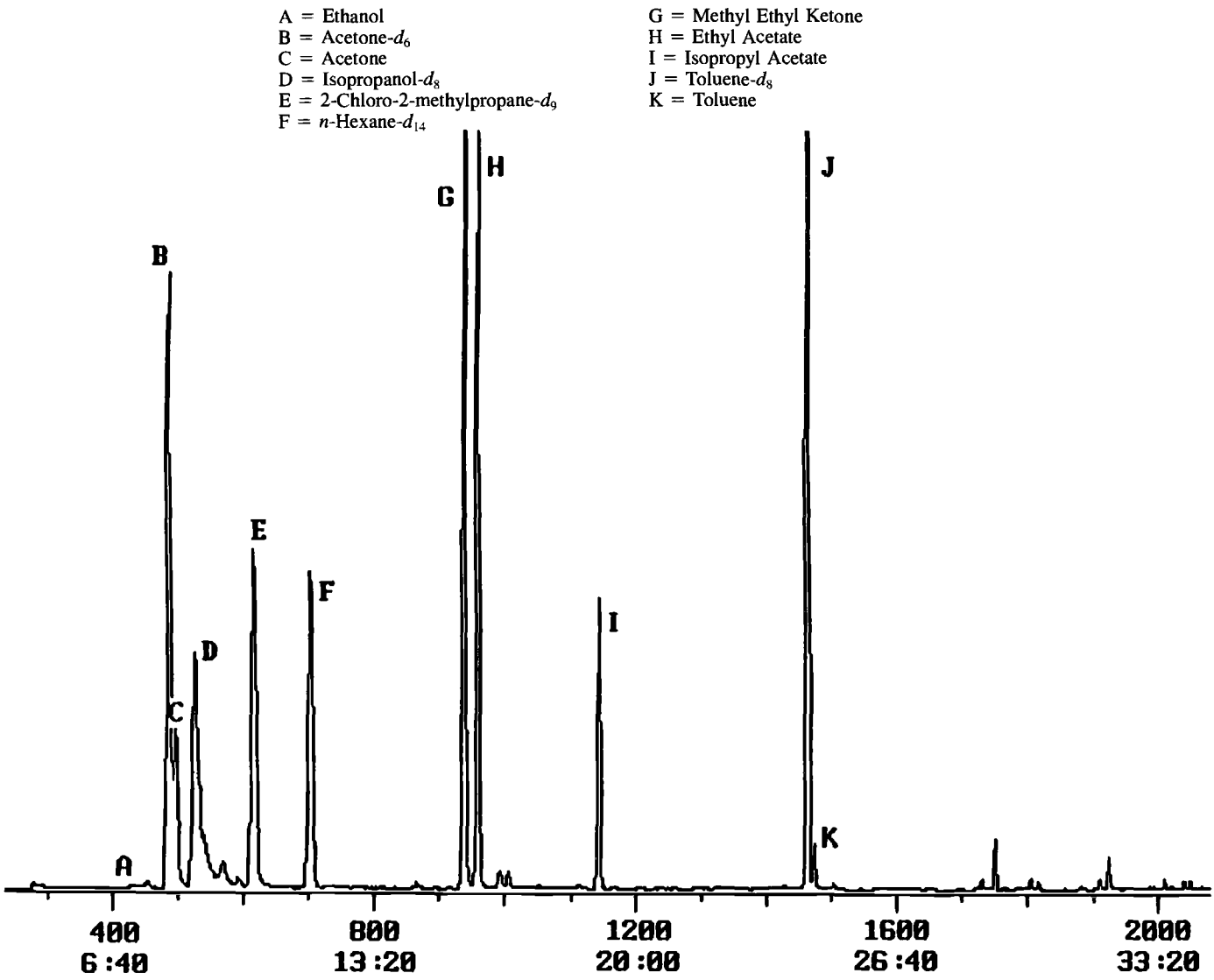

FIG. 3—*Reconstructed total ion chromatogram of residual solvents present in an uncut heroin HCl sample. Peak identification.*

(however, reanalysis is warranted if individual solvents fall outside the linear range).

Minimum limits of detection for each target solvent are presented in Table 4. The methodology provided outstanding overall sensitivity; total residual solvents ranged from 0.07 to 1.2% for cocaine, and from 0.0083 to 0.6% for heroin. Minimum detection limits ranged from 3 to 87 ppm for a 15 mg equivalent cocaine sample weight, and from 2 to 43 ppm for a 30 mg equivalent heroin sample weight. For cocaine, both the number of unique solvents and their corresponding quantitative levels exceeded those for heroin samples. Generally, cocaine has a much larger crystal size than heroin [*23*], which may account for its ability to retain greater amounts of occluded solvents.

In headspace quantitation, a potential source of error is the introduction of the matrix itself into the headspace vial [*24*]. This is more critical when the matrix is insoluble in the liquid phase (as is the case with soil, sand or polymeric samples). A standard addition study was therefore performed to determine if such matrix effects existed for cocaine and heroin exhibits. Cocaine, heroin and a known concentration calibration standard were all quantitatively analyzed; portions of the same cocaine and heroin exhibits were then spiked with the calibration standard to determine if the quantitation values would vary with the introduction of drug. Neither the introduction of cocaine or heroin affected the calculated amount of any solvent by more than the method RSD. Clearly, the relatively small amounts of cocaine or heroin added to the headspace vial, as well as their complete solubilization in the sodium sulfate solution, minimize any matrix effects.

Adulterated Samples

While the described methodology was designed for uncut samples, it is also applicable to the determination of residual solvents in *some* adulterated cocaine and heroin samples. Common adulterants and diluents can themselves contain detectable amounts of residual solvents. Nineteen frequently encountered cutting agents, obtained from commercial sources, were therefore analyzed individually by the SHS-GC-MS methodology. The results of these analyses are

presented in Table 5. Only those compounds existing as the hydrochloride salt or ion-pair (for example, diphenhydramine HCl) contained detectable amounts of residual solvents. A systematic study of these commercial products is beyond the scope of this study, however, it is expected that the presence and amounts of residual solvents in commercial compounds will vary by manufacturer.

An final study was performed to determine if the presence of these adulterants in the headspace vial would affect the determination of residual solvents in cocaine and heroin. Cocaine and heroin exhibits were first analyzed individually and again after being spiked with 75 mg of 5 common adulterants. These spiked adulterants were previously determined to be free of residual solvents. In all instances, the addition of adulterant had no significant effect on the quantitative determination of residual solvents present.

Based on these findings, adulterated exhibits containing sugars, starches and inorganics can be analyzed by this methodology with little probability of qualitative or quantitative interference. For neutral and basic ion-pair salts, however, a more conservative approach is necessary. In these instances, only exhibits adulterated with less than 20% total ion-pair salt are amenable to analysis.

Other Applications

Although beyond the scope of this study, it is expected that the presented methodology would be fully applicable to other illicit amine-based drugs prepared as hydrochloride salts; these include, for example the amphetamines, methamphetamines, methcathinone, the methylenedioxyamphetamines and phencyclidine.

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Address requests for reprints or additional information to
David R. Morello
US DEA
Special Testing and Research Laboratory
7704 Old Springhouse Rd.
McLean, VA 22102-3494