

Detection of ^{14}N and ^{35}Cl in Cocaine Base and Hydrochloride Using NQR, NMR, and SQUID Techniques

James P. Yesinowski,* Michael L. Buess,† and Allen N. Garroway

Chemistry Division, Code 6122, Naval Research Laboratory, Washington, DC 20375-5342

Marcia Ziegeweid and Alexander Pines

Department of Chemistry, University of California, and Materials Sciences Division, Lawrence Berkeley Laboratory, Berkeley, California 94720

Results from ^{14}N pure NQR of cocaine in the free base form (cocaine base) yield a nuclear quadrupole coupling constant (NQCC) e^2Qq/h of 5.0229 (± 0.0001) MHz and an asymmetry parameter η of 0.0395 (± 0.0001) at 295 K, with corresponding values of 5.0460 (± 0.0013) MHz and 0.0353 (± 0.0008) at 77 K. The NQR peaks of a sample of cocaine base containing $\sim 1\%$ impurities are a factor of 3 broader than those of a recrystallized sample, but spin–lattice and spin–spin relaxation times are essentially unchanged. Both pure NQR (at 295–77 K) and a superconducting quantum interference device (SQUID) detector (at 4.2 K) were used to measure the very low (< 1 MHz) ^{14}N transition frequencies in cocaine hydrochloride; at 295 K the NQCC is 1.1780 (± 0.0014) MHz and the asymmetry parameter is 0.2632 (± 0.0034). Cocaine hydrochloride exhibits a broad ^{35}Cl pure NQR resonance at 2.53 MHz. The ^{35}Cl NMR spectrum at 7.0 T is that of a central $1/2 \rightarrow -1/2$ transition greatly broadened by second-order quadrupolar effects. Stepping the carrier frequency enables one to obtain a powder pattern without the severe intensity distortions that otherwise arise from finite pulse power. A powder pattern simulation using an NQCC value of 5.027 MHz and an asymmetry parameter η of 0.2 agrees reasonably well with the experimental stepped-frequency spectrum. The use of pure NQR for providing nondestructive, quantitative, and highly specific detection of crystalline compounds is discussed, as are experimental strategies.

Nuclear quadrupole resonance (NQR) is a radio frequency spectroscopy offering rather special possibilities for the analytical detection of chemical substances in solid form. When carried out in the absence of an external magnetic field, the technique is referred to as “pure NQR”. Both continuous-wave (CW) and pulsed versions of pure NQR are feasible. Pure NQR has a number of advantageous characteristics as an analytical technique, since it is (1) highly specific with regard to the chemical and crystalline form of a substance; (2) nondestructive; (3) quantitative; (4) capable of detecting compounds heterogeneously distributed over large volumes; (5) able to yield results quickly (in favorable

cases), with no sample preparation; (6) sensitive to the presence of cocrystallized impurities in the sample; (7) not limited by the requirement of an external magnetic field, as is the case with other magnetic resonance techniques; and (8) relatively inexpensive. Some of these same advantages may, in a different context, instead be weaknesses (points 1 and 6 in particular). Also, one serious limitation to the more widespread use of pure NQR as an analytical technique is the general requirement for samples containing many grams or tens of grams of the compound being detected, although schemes mentioned in this paper can offer significant improvements in sensitivity in appropriate cases. Furthermore, it is usually time-consuming, and often impracticable, to use pure NQR to search for unknown NQR transition frequencies. As will be shown in this paper, the use of superconducting quantum interference device (SQUID) techniques to determine unknown NQR frequencies for pulsed NQR detection represents a potentially useful strategy that may enable wider use of NQR as an analytical technique for a greater variety of substances.

Nitrogen is present as a heteroatom in many compounds of pharmacologic and biological interest. The ^{14}N stable isotope of nitrogen has a natural abundance of 99.635%, a nuclear spin $I = 1$ with a corresponding nuclear electric quadrupole moment, and pure NQR transitions at frequencies ranging from 0 to 6 MHz.¹ The frequency of the NQR peaks depends primarily upon the distribution of the electrons in the bonds surrounding the nitrogen atom of interest and, more specifically, upon the electric field gradient (EFG) tensor resulting from this distribution. Knowledge of the latter quantity, obtained from pure NQR measurements, is of some interest from the standpoint of theoretical chemistry. From an analytical chemistry point of view, knowledge of the ^{14}N NQR frequencies and other parameters is important because of the possibility of using ^{14}N NQR as a *compound-selective* technique for the identification of specific crystalline substances in the solid state. The number of reported ^{14}N NQR resonance frequencies taken from a database of $\sim 10\,000$ compounds² (not necessarily containing nitrogen) reaches a maximum of ~ 600 in the range 2.5–3.0 MHz. For *representative* ^{14}N NQR line widths of < 1 kHz, it is apparent that few “NQR interferences” should arise within this set of compounds. Where such interferences do arise, observation of both ν_+ and ν_- transitions in the same sample, as

* Yesinows@nrlfsl.nrl.navy.mil

† SFA, Inc., Landover MD 20875.

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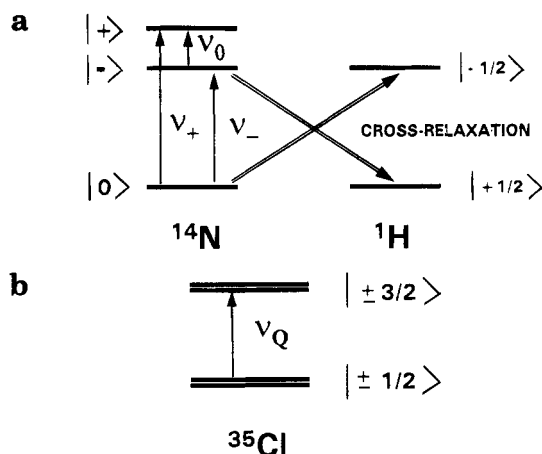


Figure 1. Energy level diagrams of quadrupolar nuclear spins. (a) ^{14}N ($I = 1$) in a weak magnetic field, illustrating the matching of the energy level separations of the nitrogen (ν_- transition) and those of a nearby proton ($I = 1/2$), which results in cross-relaxation. Sweeping the frequency region near the ν_+ transition generates a SQUID signal, as seen in Figure 5. Additional saturation of the third transition ν_0 enhances the signal. For pure ^{14}N NQR, transitions ν_+ and ν_- can be observed directly in zero magnetic field; the ν_0 transition at lower frequency is often much weaker and not observed. (b) ^{35}Cl ($I = 3/2$) in zero magnetic field. The resultant pure NQR spectrum consists of only a single transition between the doubly degenerate states at frequency ν_Q .

discussed below and shown on the left portion of Figure 1a, should provide a unique signature.

Two rather different techniques have been used to obtain ^{14}N NQR data in this paper, pure NQR (using pulsed techniques) and detection using a SQUID. Pulsed pure NQR techniques have proven applicable to the detection of ^{14}N nuclei in large sample volumes of the order of 300 L.³ Such techniques can also yield reliable information about line widths and the spin–lattice (T_1) and spin–spin (T_2) relaxation times of the ^{14}N nucleus. Pulsed pure NQR techniques are also useful for investigating the effect of impurities in the sample upon these parameters. Only cocrystallized impurities are expected to have an effect, since a simple physical admixture will have parameters characteristic of the individual components. On the other hand, techniques using the SQUID take advantage of its high sensitivity to measure transitions at low frequencies that are more difficult to detect with pulsed pure NQR using Faraday law detectors. The continuous-wave spectrometer used for these SQUID experiments detects the change in magnetic flux proportional to ΔI_z , where I_z is the component of the spin along an externally applied magnetic field. Because of the quenching of the nitrogen magnetic moment in zero and low magnetic fields,⁴ the SQUID does not detect the nitrogen transition directly, but rather is employed to probe the effect of the nitrogen transitions on the protons via the nitrogen–proton dipolar interaction. The CW SQUID spectrometer also has the advantage of being able to sweep wide frequency ranges and, therefore, is useful in searching for and identifying transitions.

Nuclei with spin $I = 1$ such as ^{14}N are subject to the electric quadrupole interaction described by the quadrupole Hamiltonian $H_Q = (e^2Qq/4)[3I_z^2 - I^2 + \eta(I_x^2 - I_y^2)]$.¹ The nuclear electric quadrupole moment, eQ , interacts with the electric field gradient,

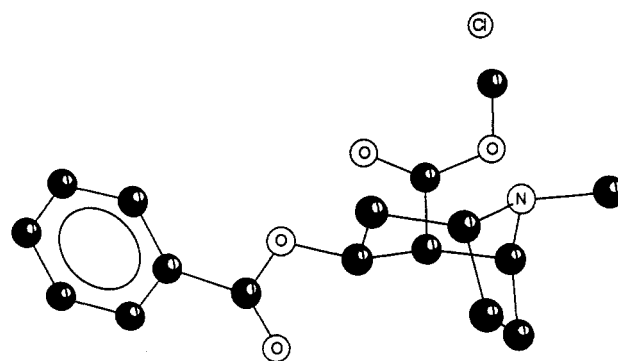


Figure 2. Structure of cocaine hydrochloride, from coordinates of X-ray crystallographic structure given in ref 26. Hydrogen atoms are not shown, including the unlocated acidic hydrogen atom presumed to form a hydrogen bond between the N and Cl atoms.

eq , and its associated asymmetry parameter, η , which arise from the local electronic environment surrounding the nucleus. The nuclear quadrupole coupling constant (NQCC) e^2Qq/h and the asymmetry parameter η contain structural information about this environment. In zero magnetic field the quadrupolar eigenstates $|+\rangle = (|1\rangle + |-1\rangle)/(2)^{1/2}$, $|-\rangle = (|1\rangle - |-1\rangle)/(2)^{1/2}$, and $|0\rangle$ (where $|1\rangle$, $|0\rangle$, and $|-1\rangle$ denote states having projections of nuclear spin along the z direction of 1, 0, and -1 , respectively) give rise to three transitions at frequencies:

$$\nu_+ = (e^2Qq/h)(3 + \eta)/4$$

$$\nu_- = (e^2Qq/h)(3 - \eta)/4$$

$$\nu_0 = \nu_+ - \nu_- = (e^2Qq/h)(\eta/2)$$

as shown schematically in Figure 1a. Knowledge of two transition frequencies is sufficient to determine the quadrupolar parameters, if the transitions can be assigned to ν_+ , ν_- , or ν_0 . The transition energies change slightly in the presence of a weak magnetic field;⁵ the data in this paper have been corrected for this effect.

Nuclei with $I = 3/2$ such as ^{35}Cl give rise to only a single transition at a frequency of $\nu_Q = (e^2Qq/2h)(1 + \eta^2/3)^{1/2}$, as shown in Figure 1b.¹ Thus, standard pure NQR experiments cannot separate the NQCC from the asymmetry parameter. Observation of the “central” transition between the $1/2$ and $-1/2$ states in high-field NMR experiments can provide such information if a second-order quadrupolar-broadened pattern is observed.⁶ We note that there are two stable isotopes of chlorine with $I = 3/2$, ^{35}Cl and ^{37}Cl . The ^{35}Cl isotope is more favorable for NQR detection, since it has a higher natural abundance (75.4% vs 24.6% for ^{37}Cl) and a larger nuclear quadrupole moment.¹

In this paper we report experimental results for ^{14}N NQR signals in samples of cocaine free base ($\text{C}_{17}\text{H}_{21}\text{NO}_4$, CAS 50-36-2) and cocaine hydrochloride ($\text{C}_{17}\text{H}_{22}\text{NO}_4\text{Cl}$, CAS 53-21-4), whose crystal structure is depicted in Figure 2. Measuring ^{14}N NQR transition frequencies using the SQUID for detection is shown to represent a useful search strategy in pure NQR studies. We also report both pure ^{35}Cl NQR and high-field stepped-frequency ^{35}Cl NMR results for cocaine hydrochloride; the combined results enable accurate determination of both the NQCC and the asym-

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metry parameter. We also discuss a number of different issues related to searching for unknown resonances, identifying NQR transitions, determining impurity effects, measuring parameters that influence the sensitivity of detection, and using different pulse schemes to improve this sensitivity.

EXPERIMENTAL SECTION

Cocaine Base. The sample of cocaine base (nominal purity 99%) was obtained from the U.S. Customs Service, a nontraditional supplier of specialty chemicals. Its identity was confirmed by high-resolution ^{13}C NMR,⁷ which revealed some unidentified impurities, and by a measured mp of 92–93 °C (cf. 98 °C for l-cocaine⁸). In order to remove the impurities, a portion of the sample was dissolved in absolute ethanol (USP), heated to the boiling point, filtered, and allowed to crystallize over several days at room temperature. The white powder collected by filtration initially appeared to melt well below the expected melting point of cocaine; however, after drying in open air for over 1 week, the measured melting range was 95.5–97 °C, very close to the reported value. This recrystallized sample (12.9 g) is referred to throughout as “recrystallized”. The remainder (150 g) of the original sample is referred to throughout as “as-received.”

Cocaine Hydrochloride. A cocaine hydrochloride sample (117.5 g) of 88% purity (mp 186–187 °C) obtained from the U.S. Customs Service was dissolved in 300 mL of hot ethanol (near boiling), filtered, and allowed to cool to room temperature slowly. Filtration yielded a white powder, which after drying on a watch glass in a vacuum dessicator lost 4.5% by weight and yielded 60.0 g of sample with mp 190–192 °C, comparing reasonably with the reported melting point of the hydrochloride of 197 °C.⁸

Pure NQR (Pulsed). All ^{14}N and ^{35}Cl NQR data were obtained with a home-built pulse Fourier transform spectrometer of standard design at the Naval Research Laboratory. We used various combinations of transmitter powers and coil geometries (up to 60 mm diameter) throughout this investigation such that the pulse widths maximizing the free induction decay (FID) signal in powdered samples were typically 10–30 μs . A Faraday shield was used to reduce the electric field component of the radio frequency, since the non-centrosymmetric cocaine hydrochloride structure results in piezoelectric ringing that otherwise would obscure the NQR signal. The shield used for these experiments consisted of strips of copper taped to the bottle in the form of a “hula skirt”. However, a thin sheet of copper slightly longer than the sample, wrapped around the sample slightly exceeding its circumference, separated by insulating tape in the region of overlap, and grounded to the chassis appears to work at least as well (a “jelly roll” design). A $90^\circ\text{-}\tau\text{-}180^\circ$ spin-echo pulse sequence with a pulse interval τ of 335 μs and a repetition period of 200 ms was used to search for the ^{14}N pure NQR lines in both cocaine base samples at room temperature. Two NQR lines were observed in each sample and later confirmed to be ν_+ and ν_- .^{9,10}

We detected the ^{14}N NQR lines of the as-received cocaine base sample at 77 K by immersing the sample in liquid nitrogen; because of the apparently long ^{14}N T_1 , we used a version of the steady-state free-precession (SSFP)^{11,12} pulse sequence with a pulse width of 20 μs and a pulse interval of 5 ms.

We measured the ^{14}N and ^{35}Cl spin–lattice relaxation times T_1 with either the inversion–recovery technique¹³ or a two-pulse method.¹⁴ We measured spin–spin relaxation times T_2 by the $90^\circ\text{-}\tau\text{-}180^\circ$ spin-echo method.¹³ Relaxation time measurements are estimated to be accurate to within $\pm 10\%$.

We searched for the companion ^{37}Cl NQR transition in cocaine hydrochloride at a frequency lower by a factor of 0.787 (the ratio of the nuclear quadrupole moments); however, interference from an acoustic ringing signal prevented unambiguous identification of the ^{37}Cl transition.

We assigned the two ^{14}N NQR peaks in each sample to ν_+ and ν_- transitions of a *single* nitrogen nucleus by measuring the NQR signal intensity as a function of an applied Zeeman magnetic field provided by Helmholtz coils. The magnetic field was parallel to the rf coil and ranged from 0 to 5.5 mT. The field strength was measured directly by a Group 3 DTM-141DS digital teslameter equipped with a Hall probe. The maximum reduction in the signal intensity occurs when the Larmor frequency of the protons in the magnetic field is matched to the ^{14}N ν_0 transition frequency.¹⁵

^{35}Cl NMR. A Bruker MSL-300 NMR spectrometer at the Naval Research Laboratory with a high-power probe containing a 10 mm i.d. solenoidal rf coil was used to obtain ^{35}Cl NMR data at a Larmor frequency of 29.4 MHz. The 90° pulse length determined using NaCl was 8 μs ; in the cocaine hydrochloride spectra the corresponding 90° pulse length was half of this, since only the central $1/2 \rightarrow -1/2$ transition was observed.¹⁶ A $90_x\text{-}\tau\text{-}180_{xy}\text{-}\tau$ phase-cycled spin-echo sequence described in ref 16a, and analyzed in ref 16b, was used to reduce probe ring-down effects.¹⁶ The rf field strength used was not sufficient to provide accurate spectral intensities over the wide range of frequencies in the powder pattern. To overcome this problem, we stepped the (central) carrier frequency in typically 2 or 4 kHz increments over the entire spectral width, retuning the probe as needed so that the carrier frequency was never more than 30 kHz from the frequency to which the probe was tuned. We processed the spin echo using a line broadening of 5 kHz and measured the absolute intensity of a single point near the center of the Fourier transform spectrum (selected to be 3.9 kHz to high frequency of the carrier, in order to eliminate the influence of zero-frequency artifacts).

SQUID Detection. A SQUID spectrometer at Lawrence Berkeley Laboratory was used to detect the ^{14}N ν_+ and ν_- transitions of cocaine hydrochloride. The direct detection of the nitrogen transitions is difficult since the SQUID detects the changes upon excitation in the expectation values of the magnetic

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Table 1. Variable-Temperature NQR Data for Cocaine Base and Cocaine Hydrochloride

sample	temp (K)	nucleus	transition	frequency (MHz)	line width (Hz)	T_1 (ms)	T_2 (ms)	e^2qQ/h (MHz)	η
cocaine base (as received)	77	^{14}N	ν_-	3.740 ± 0.001	~ 2300	nd ^a	nd ^a	5.0460 ± 0.0013	0.0353 ± 0.0008
			ν_+	3.829 ± 0.001	~ 2300	nd ^a	nd ^a		
cocaine base (as received)	295	^{14}N	ν_-	3.7176 ± 0.0001	870	nd ^a	nd ^a	5.0229 ± 0.0001	0.0395 ± 0.0001
			ν_+	3.8168 ± 0.0001	860	210	85		
			ν_-	3.7175 ± 0.0001	270	75	75		
cocaine base (recrystallized)	295	^{14}N	ν_+	3.8168 ± 0.0001	260	160	81	$5.0228_7 \pm 0.0001$	$0.0395_4 \pm 0.0001$
			ν_-	3.7175 ± 0.0001	270	75	75		
cocaine hydrochloride	4.2 (SQUID)	^{14}N	ν_-	0.815 ± 0.003		nd ^a	nd ^a	$1.186_7 \pm 0.004$	0.258 ± 0.005
			ν_+	0.965 ± 0.003		nd ^a	nd ^a		
	77	^{14}N	ν_-	0.813 ± 0.001	~ 5000	360	22	$1.182_7 \pm 0.0015$	$0.250_3 \pm 0.0035$
			ν_+	0.961 ± 0.001	~ 5000	370	25		
	141	^{14}N	ν_-	0.811 ± 0.001	~ 5000	nd ^a	nd ^a	$1.180_7 \pm 0.0015$	$0.252_4 \pm 0.0035$
			ν_+	0.960 ± 0.001	~ 5000	820	6		
	295	^{14}N	ν_-	0.806 ± 0.001	$\sim 4000^b$	2000	$> 0.3^c$	1.178 ± 0.0015	$0.263_2 \pm 0.0035$
			ν_+	0.961 ± 0.001	$\sim 5000^b$	700	1.5		
	295	^{35}Cl	ν_Q	2.53 ± 0.01	$\sim 20000^d$	57	0.15	$5.027^e \pm 0.02$	0.2^e

^a Not determined. ^b These transitions were 15%–30% broader in less pure samples (93% and 88% purity). ^c Based on spin–lock spin-echo experiments. ^d The line width increased to $\sim 25\,000$ Hz for a less pure sample (93% purity). ^e From parameters of a simulation providing a good fit to the experimental ^{35}Cl NMR powder pattern and the ^{35}Cl NQR frequency (see Results section).

moments for nondegenerate quadrupolar eigenstates, and these are zero in the absence of a magnetic field. The application of the low magnetic fields used here does not induce a sufficiently large moment to allow direct detection of the signal. The spectrometer design¹⁷ and experimental technique¹⁸ have been described previously. Briefly, the experiment begins with thermal equilibrium between the proton spin system at the appropriate Zeeman field strength and one of the nitrogen spin subsystems. When rf is swept through a different nitrogen transition frequency, the population of one of the nitrogen eigenstates coupled to the protons changes and causes cross-relaxation to occur until the proton system and nitrogen subsystem equilibrate to a new common spin temperature (Figure 1a). It is the change in proton population, as monitored by the SQUID detector, that provides the indirect measurement of the nitrogen NQR spectrum (in weak magnetic field). Further enhancement can be realized by the additional saturation of the third nitrogen transition. In the limit of complete saturation and fast cross-relaxation times, the full proton signal becomes available to detect the nitrogen transitions. Simultaneous or consecutive excitation of two transitions, used mainly to enhance the signal, can also be used to correlate resonances arising from the same nitrogen site. Additionally, the magnitude, sign, and width of the signals, selective saturation results, and estimates of the quadrupole coupling constant and asymmetry parameter can all support the assignment of the transition frequencies to different nitrogen sites. The SQUID is operated at 4.2 K. Sweeps are usually broken up into 250 kHz scans lasting 100–250 s. Combinations of forward and reverse frequency sweeps are used to remove distortions arising from saturation, relaxation, and instrumental artifacts.

RESULTS

Cocaine Base. The ^{14}N NQR frequencies and line widths for cocaine base at 295 and 77 K are given in Table 1. Only two resonances were observed in each sample (see Figure 3). We assigned these to the ^{14}N ν_- and ν_+ transitions on the basis of room-temperature Zeeman-field experiments discussed in the

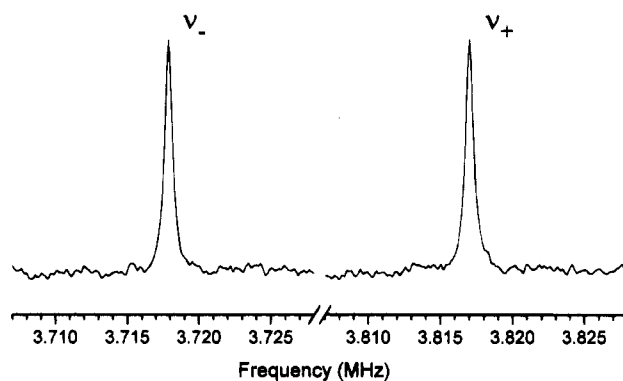


Figure 3. ^{14}N pure NQR composite spectrum of recrystallized cocaine base (12.9 g), obtained in two separate one-pulse experiments. The peak at right, ν_+ , was obtained with a spectrometer carrier frequency of 3.816 95 MHz, while the peak at left, ν_- , was obtained with a carrier frequency of 3.717 88 MHz. In both cases the pulse width was 14 μs , the pulse repetition period was 0.5 s, and 200 scans were accumulated. An exponential apodization corresponding to a line broadening of 250 Hz was used prior to Fourier transformation.

Experimental Section; results are shown in Figure 4. The nuclear quadrupole coupling constants e^2qQ/h (NQCC) and asymmetry parameters η obtained from these assignments are also given in Table 1.

The small asymmetry parameter ($\sim 4\%$) of cocaine is typical of nitrogen bonded to three nearly equivalent atoms (of carbon).¹⁹ Although for both samples of differing purity the respective ν_- and ν_+ frequencies are identical, the lines in the as-received sample are over 3 times as broad as those in the recrystallized sample. Such NQR line broadening by impurities has been observed elsewhere and is attributed to a random distribution of electric field gradients in the vicinity of the impurity.²⁰ The additional line broadening in the as-received cocaine base at 77 K is most likely due to lattice distortions created by rapid cooling when the sample was immersed in liquid nitrogen.²¹

The measured room-temperature ^{14}N relaxation times of cocaine base are also given in Table 1. The T_1 data for the

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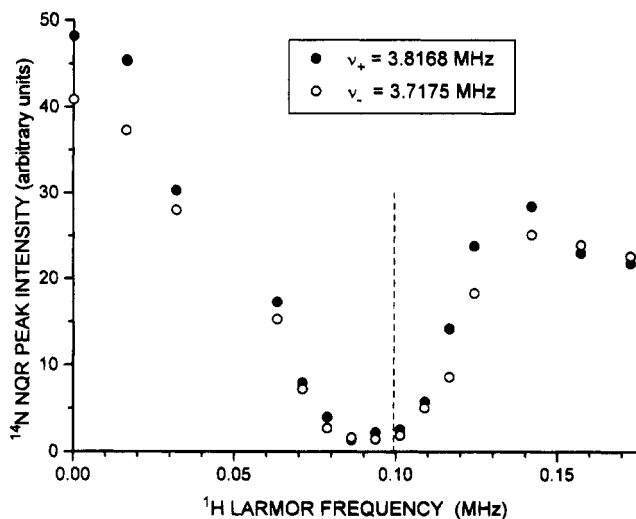


Figure 4. Intensity of ^{14}N ν_+ and ν_- peaks in the as-received cocaine base sample as a function of applied magnetic field, expressed as corresponding proton Larmor frequency. A vertical dashed line indicates the position of the $\nu_+ - \nu_- = \nu_0$ difference frequency; the decrease in peak intensities at this dashed line verifies the assignments of the two peaks (see text).

recrystallized sample for recovery times less than 300 ms (data not shown) were fit to a single exponential; we did not attempt to analyze recovery times longer than 300 ms, which might reveal biexponential behavior characteristic of a three-level system. The measured relaxation times for the ν transition in the recrystallized sample are $T_2 = 76$ ms and $T_1 = 74$ ms; since T_2 generally does not exceed T_1 , an average value of 75 ms is reported for both. A previous study of the effects of impurities on the ^{35}Cl pure NQR relaxation times in *p*-dichlorobenzene showed T_1 and T_2 to be independent of sample composition.²⁰ This is also the case within experimental error for T_2 of the ^{14}N ν_+ line of cocaine base. The difference between the T_1 values for the two cocaine base samples lies somewhat outside of experimental error; however, additional data using the same T_1 measurement technique for both samples are required to determine whether or not the difference is real. In any case, T_1 as measured in the as-received sample is only one-third longer than that in the recrystallized sample, whereas there is a factor of 3 difference in line widths. We conclude that the unspecified impurities present in the as-received cocaine base sample have an effect on ^{14}N spin-lattice relaxation that is small or negligible compared with their line broadening effect.

Cocaine Hydrochloride. Figure 5 shows the SQUID ^{14}N NQR results at 4.2 K for the recrystallized cocaine hydrochloride sample. The assignment of the ν_+ and ν_- transitions, whose frequencies are listed in Table 1, was established via field dependence studies. The ν_0 transition, which was expected to be weak, could not be seen.

Using the ^{14}N frequencies that were determined from the SQUID experiments, we were able to finally detect the pure NQR signal, with some difficulty. A composite ^{14}N pure NQR spectrum of cocaine hydrochloride at room temperature showing the ν_+ and ν_- transitions is shown in Figure 6. The assignments to ν_+ and ν_- were made at 77 K by the Zeeman field technique described in the Experimental Section. The 961 kHz signal is observed to vanish at a magnetic field of ~ 3.5 mT, corresponding to a proton Larmor frequency of 148 kHz, thus confirming the pairing of the 961 and 813 kHz lines ($961 - 813 = 148$). The spin-lattice relaxation time T_1 of the ν_+ peak was estimated to

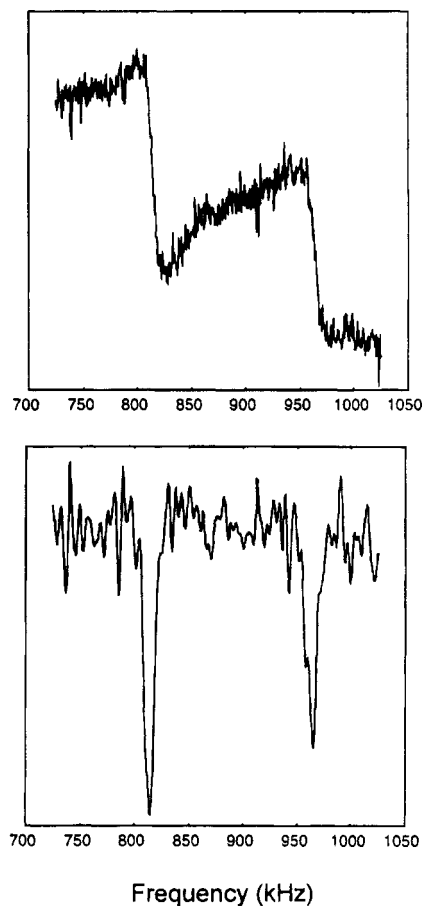


Figure 5. SQUID results at 4.2 K for 144 mg of cocaine hydrochloride. The raw data are shown at top, a derivative mode of presentation emphasizing peak positions at bottom.

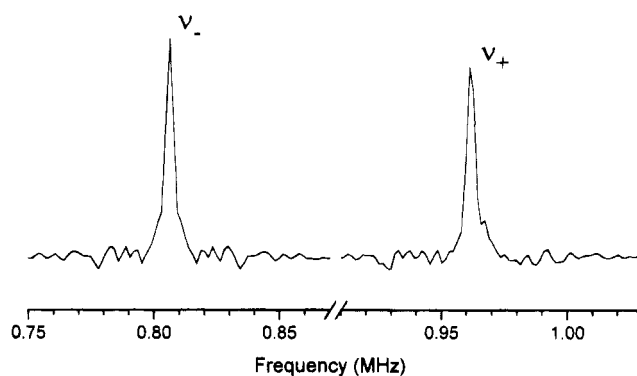


Figure 6. Composite ^{14}N pure NQR spectrum of cocaine hydrochloride (60 g) at 295 K obtained in two separate SLSE experiments (see text). The peaks at right and left (ν_+ and ν_-) were obtained at spectrometer carrier frequencies of 0.961 and 0.806 MHz, respectively. In both experiments the pulse widths were 28 μs , the pulse spacing within the SLSE train was 600 μs , and the first 16 echoes in the train were accumulated and coherently summed. The ν_+ time domain data were obtained with a sequence repetition period of 1 s and a total of 151K scans, while the ν_- data were obtained from 50K scans with a repetition period of 2 s. (The spectral data in the above figure have been normalized to the number of accumulated scans for comparison purposes). An exponential apodization corresponding to a line broadening of 1000 Hz was applied starting at the echo maximum.

be 2 s by comparing the relative peak heights obtained using relaxation delays of 0.2, 1, and 10 s (16%, 42%, and 100%, respectively) with theoretical curves given in ref 22. To improve the sensitivity of detection in order to measure relaxation times, a

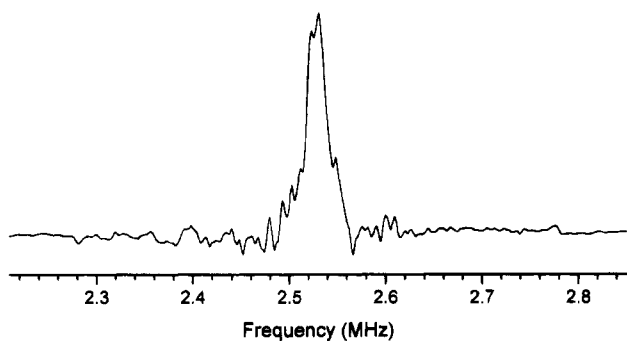


Figure 7. ^{35}Cl pure NQR spectrum of recrystallized cocaine hydrochloride (60 g) obtained using a two-pulse spin-echo sequence with $13\ \mu\text{s}$ pulses separated by $150\ \mu\text{s}$, a carrier frequency of 2.530 MHz, and 32K acquisitions at 60 ms intervals. Exponential apodization corresponding to a line broadening of 5000 Hz was applied.

pulsed-spin-locking sequence²³ of the form $90_x-\tau-90_y-2\tau-90_y-2\tau-90_y \dots$ was used, with a τ delay of $300\ \mu\text{s}$, and the first eight echoes in the middle of the 2τ periods were added together and processed. Data exhibiting the dependence of the ^{14}N frequencies and relaxation times upon temperature to 77 K are given in Table 1.

A broad ^{35}Cl pure NQR resonance was observed for cocaine hydrochloride at 2.53 MHz (see Figure 7 and Table 1). This frequency is in reasonable agreement with the value of 2.547 MHz reported in ref 10, which also reported the associated ^{37}Cl NQR signal at 1.998 MHz. As discussed above, observation of the single pure NQR peak for an $I = 3/2$ nucleus such as ^{35}Cl does not enable one to disentangle the NQCC from the asymmetry parameter η , but the NMR results described below do so.

The ^{35}Cl NMR spectra obtained using a spin-echo sequence of both the starting 88% purity material (not shown) and the purified cocaine hydrochloride (shown in Figure 8a) are virtually identical, and the spectrum does not change from room temperature to 173 K, the lowest temperature investigated. The spin-lattice relaxation time T_1 was estimated to be several hundred milliseconds at room temperature, and the transverse relaxation time T_2 was measured to be $540 \pm 50\ \mu\text{s}$ from peak integration as a function of τ in the echo sequence. The ^{35}Cl NMR spectrum in Figure 8a, which extends over 135 kHz, shows an artifactual decrease in the intensity of the spectrum away from the central carrier frequency arising from the finite excitation power; such an effect is observable under similar conditions in spectra in ref 16a. The resultant distorted powder pattern does not resemble a classical second-order broadened central transition powder pattern for any value of the asymmetry parameter.⁶ However, obtaining the ^{35}Cl NMR spectrum by stepping the carrier frequency and measuring the absolute intensity of a particular frequency in the spectrum near the carrier frequency greatly reduces these distortions (solid circles in Figure 8b). This improvement is particularly noticeable in the increased intensity of the two outermost "horns".

Figure 8b shows a comparison of the stepped-frequency ^{35}Cl NMR spectrum with theoretical simulations for three different values of the asymmetry parameter η . A program was written using the mathematical analysis program MATLAB and the expressions for the second-order central-transition frequency given

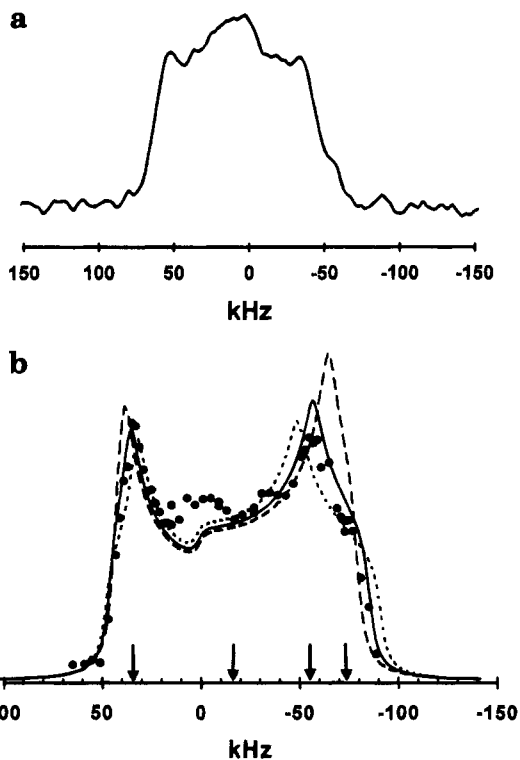


Figure 8. ^{35}Cl NMR spectra at 29.4 MHz of recrystallized cocaine hydrochloride (1.1 g): (a) obtained using a spin-echo sequence (see text) with a τ delay of $200\ \mu\text{s}$, a relaxation delay of 200 ms, 50K scans, and an exponential apodization corresponding to a line broadening of 5 kHz; zero-frequency corresponds to the carrier frequency, not to the isotropic chemical shift of the powder pattern as in (b); (b) stepped-frequency spectrum (solid circles) obtained from spin-echo sequence with $\tau = 50\ \mu\text{s}$ as described in the Experimental Section. Each point represents a 1 h accumulation (18K scans). The vertical arrows represent the various frequencies to which the probe was tuned. Theoretical simulations of second-order quadrupolar powder patterns are plotted on an arbitrary intensity scale for three different values of the asymmetry parameter η : 0.1 (dashed), 0.2 (solid), 0.3 (dotted). The NQCC value was constrained as described in the Results section, and an exponential apodization corresponding to a 6 kHz line broadening was used for the simulations. The best agreement is obtained with $\eta = 0.2$.

in ref 6b. The polar coordinates were incremented uniformly by 0.3° , and the calculated (weighted sum) time-domain response was apodized using an exponential function corresponding to a line broadening of 6 kHz. This latter action helps compensate for the exponential apodization corresponding to 5 kHz line broadening that was applied to each stepped-frequency acquisition. A variety of different values of the NQCC, asymmetry parameter, offset frequency, and line broadening were tried, subject to the constraint that the resultant predicted pure NQR frequency (see above) be that actually observed (2.53 MHz). This requirement served to restrict the available parameter space to a region around $\eta = 0.2$, which was deemed to be the best value. The simulation using $\eta = 0.2$ and an NQCC of 5.0266 MHz is shown as a solid line. The agreement is quite reasonable, except for some apparently larger intensity in the experimental spectrum near zero frequency that could possibly arise from an anisotropy in T_2 , impurities, or other artifacts. The fact that the right "horn" of the experimental spectrum is slightly less than the simulation predicts can be plausibly attributed to a slight distribution of NQCC values that broadens this horn more than the other one, which is only half as far from the center frequency.²⁴ In order to

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demonstrate that the asymmetry parameter can be determined with reasonable accuracy from our results, simulations for η values of 0.1 and 0.3 are shown as dashed and dotted lines, respectively, in Figure 8b, using the constrained NQCC values of 5.0516 and 4.9858 MHz, respectively. Clearly the fit is not as good, especially in the position of the horns. Therefore, our simulations indicate that the true asymmetry parameter is close to 0.2, with an estimated error of $\sim\pm 0.05$.

The ^{35}Cl NMR chemical shift of the powder pattern can best be determined from the frequency offset needed to produce agreement between the frequency-stepped spectrum and the theoretical simulation in Figure 8b. The chemical shift thus determined was equal to that of NaCl (=0 ppm) within experimental error.

DISCUSSION

Cocaine Base. As can be seen from Figure 3, cocaine base represents a favorable sample from the standpoint of ^{14}N NQR detection. The detection sensitivity (see caption for conditions) can be improved further as described below. Since the signal to noise ratio improves as the square root of the number of scans, an improvement in detection sensitivity means that smaller amounts of sample can be detected in a given time, less time can be used for data acquisition, or more accurate quantitation results can be obtained. Both the SSFP pulse sequence¹¹ (in NQR spectroscopy also called SORC, for strong off-resonant comb¹²) and spin-lock spin-echo (SLSE) sequence²³ are useful sensitivity-enhancement techniques that are most effective for pulse intervals $\tau \ll T_2$, a condition that is easily satisfied for cocaine base. Indeed, both sequences yielded significant improvements in detection sensitivity for cocaine base. We have used numerical simulations to show that the improvement using the SSFP sequence can be accounted for by the Bloch equations, whereas in other compounds in which $T_1 \gg T_2$ additional factors appear responsible.²⁵ (For ^{14}N , as well as ^{35}Cl , in cocaine hydrochloride, where the direct detection sensitivity is much poorer, the SSFP sequence did not yield a signal even for pulse intervals as short as 340 μs for ^{14}N ; the SLSE sequence yielded a rather modest improvement in sensitivity in both cases.)

Cocaine Hydrochloride. The crystal structure of cocaine hydrochloride is orthorhombic with space group $P2_12_12_1$ and $Z = 4$.²⁶ Low-frequency Raman spectra of this compound have been reported at room temperature and 9 K and assigned; no evidence of any change in the crystalline phase between these temperatures was mentioned.²⁷ The piperidine ring of the tropane nucleus has the chair form, with the CH_3 group on the N equatorial; the C–N bonds and C–N–C angles are close to normal²⁶ (see Figure 2). Although the location of the acidic hydrogen atom could not be determined, the short N–Cl bond distance (306.9 pm) suggests the presence of a hydrogen bond between the nitrogen and chlorine, not necessarily a linear one.²⁶

It is interesting to note that the ^{14}N spin–lattice relaxation time T_1 of cocaine hydrochloride decreases as the temperature is lowered from room temperature to 77 K. This might be indicative

of motions involving the hydrogen-bonded proton that are not yet frozen out at 77 K. In ammonium perchlorate, a very short ^{14}N T_1 value of 63 ms was measured at 1.5 K using a dc SQUID and attributed to fluctuating electric field gradients.²⁸

The ^{35}Cl quadrupole coupling constant (NQCC = 5.0266 MHz, $\eta = 0.2$, $\nu_Q = 2.53$ MHz) can be analyzed in terms of a Townes–Dailey approach neglecting the asymmetry parameter to yield an estimated “ionicity” of the chloride ion of 95%. (A free chloride ion with 100% “ionicity” would have an NQR frequency of zero, whereas in the covalent chlorine molecule with 0% ionicity the NQR frequency is 54.5 MHz.)¹ The ν_Q value of 2.53 MHz may be compared to the lower NQR frequencies that have been observed for ^{35}Cl in *n*-decylammonium chloride²⁹ (1.215 MHz) and trissarcosine calcium chloride³⁰ (2.16 MHz) and predicted from NMR results for calcium chloroapatite³¹ (0.8 MHz). The latter represents a chloride ion having no opportunities for hydrogen bonding, whereas the former two compounds have possibilities for N–H–Cl hydrogen bonding. For cocaine hydrochloride we have shown that the ^{35}Cl asymmetry parameter η is rather small (0.2), consistent with the picture that an axially symmetric, nonzero ^{35}Cl NQCC is created by the hydrogen bond to a proton. It would be worthwhile to further study the relationship between ^{35}Cl NQR coupling constants and asymmetry parameters and the associated hydrogen-bonding geometries in compounds where both are known.

In order to estimate the broadening of the ^{35}Cl NQR spectrum due to dipolar coupling to protons, distances from hydrogen atoms on the same and on neighboring molecules to the chlorine atom were calculated from the X-ray structure coordinates, excluding the non-observed acidic hydrogen.²⁶ The closest distance was 270 pm, to H(17) on C(16) on the same molecule as the Cl (numbering according to ref 26), corresponding to a dipolar coupling on the order of only 1 kHz; even a H–Cl distance of 150 pm for the acidic hydrogen would yield a dipolar coupling only \sim six times as large. The observed 20 kHz line width therefore cannot be attributed predominantly to static dipolar interactions or to the $1/\pi T_2$ contribution of 2 kHz. Instead, a distribution of field gradients is likely to be responsible, as is also suggested by the ^{35}Cl NMR simulations (see above).

CONCLUSIONS

We have demonstrated that ^{14}N pure NQR offers a means for the quantitative identification of both cocaine base and cocaine hydrochloride and that ^{35}Cl pure NQR can be used to identify cocaine hydrochloride. The specificity of the technique is inherently extremely high. Several general points can be made regarding the extension of this approach to other compounds of interest. First, use of SQUID detection to determine ^{14}N transition frequencies represents a valuable approach, given the difficulty of locating unknown resonances using pulsed pure NQR. Second, high-field stepped-frequency ^{35}Cl NMR of fairly ionic chloride ions can provide values for the ^{35}Cl NQCC and asymmetry parameter that enable one to predict the pure NQR frequency. Third, significant variations in the sensitivity of detection (signal strength

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per sample mass) are related to relaxation parameters such as T_1 and T_2 , as well as to the NQR frequency and line widths. Finally, multipulse techniques such as SSFP and SLSE can provide substantial sensitivity advantages for pure NQR detection, but may require some optimization of both the pulse sequence parameters and the NQR probe characteristics.

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