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Determination of the Enantiomorphic Composition of Cocaine Using the Chiral Lanthanide Shift Reagent Europium Tris-*d*-Trifluoroacetyl-Camphorate

The discovery of lanthanide shift reagents [*1*] and the examination of their influence on the nuclear magnetic resonance (NMR) spectra of various Lewis bases [*2*] have established their importance in structural determination for organic chemistry. More recently, chiral lanthanide tris-*d*-3-acyl-camphorates have been applied to the direct determination of enantiomorphic compositions [*3-6*].

Cocaine isolated from coca leaves is the levo isomer, while syntheses of cocaine usually result in a racemic mixture. Federal and state laws regarding cocaine have been construed as in effect excluding dextro cocaine. It has therefore become necessary to distinguish the enantiomorphs of cocaine. Previously reported methods for the determination of the enantiomorphic composition of cocaine rely primarily on mixed melting point, microcrystalline, and polarimetric data.[2] Criticisms of present methods focus on the following characteristics: nonspecificity, sample size, and excessive analysis time. Use of a single method is often inadequate.

This paper describes a rapid, simple, and reliable analytical procedure to identify and determine the enantiomorphic composition of cocaine samples. The method involves the complexation of a cocaine sample with the chiral lanthanide shift reagent europium tris-*d*-trifluoroacetyl-camphorate (Eu[TFAC]$_3$). The induced separation of the *d*- and *l*-acetate resonances is used for the identification and quantification of the respective enantiomorphs.

Experimental Procedure

Reagents

The Eu(TFAC)$_3$ reagent was obtained from Norell Chemical Co. and was used without further purification. Substrates were obtained as follows; *d,l*-cocaine was obtained from the Drug Enforcement Administration Special Testing and Research Laboratory, Washington, D.C., as the hydrochloride salt. A basic extraction was performed and the *d,l*-cocaine free base was isolated as a white crystalline powder melting at 77°C. Analytical grade *l*-cocaine obtained from Mallinckrodt Chemical Co. was used without further purification. There were no detectable resonances resulting from impurities; the *l*-cocaine melted at 98°C. Deuterochloroform was supplied by Norell Chemical Co. and was thor-

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oughly dried over 4A molecular sieves for 48 h before use to remove traces of acid that might decompose the complex.

Nuclear Magnetic Resonance Measurements

The NMR spectra were obtained on a Perkin-Elmer R12B spectrometer at a probe temperature of 35 ± 1 °C. Spectra were recorded at sweep rates of 1 Hz/s for chemical shift measurements. Chemical shifts are in δ units (ppm) from internal tetramethylsilane (0.2 ml/100 ml).

Procedure

A 100 mg/ml stock solution of $Eu(TFAC)_3$ and a 40 mg/ml stock solution of *l*-cocaine were prepared and stored over 4A molecular sieves for 48 h prior to use. Three solutions, labeled A, B, and C, were prepared and an NMR spectrum of each was recorded. Solution A contained 0.4 ml of a 13.3 mg/ml solution of *d,l*-cocaine. Solution B was obtained by addition of 0.01 ml of the $Eu(TFAC)_3$ stock solution to Solution A. Solution C was prepared by addition of 0.05 ml of the *l*-cocaine stock solution and 0.005 ml of the $Eu(TFAC)_3$ stock solution to Solution B. The *d*- and *l*-components were qualitatively determined from the *d*- versus *l*-acetate peak heights of the Solution C spectrum, that is, the acetate peak showing a relative increase is due to *l*-cocaine. Quantitatively, the percentage of the *d*-enantiomorph is given by

$$\% \; d\text{-enantiomorph} = \frac{\text{acetate peak height } (d\text{-enantiomorph}) \times 100\%}{\text{total acetate peak height } (d\text{- plus } l\text{-enantiomorph})} \tag{1}$$

and the percentage of *l*-enantiomorph can be found as follows:

$$\% \; l\text{-enantiomorph} = 100\% - \% \; d\text{-enantiomorph} \tag{2}$$

The baseline used for determining the peak height data is shown in Fig. 1 as a dashed segment.

Results and Discussion

The enantiomorphic composition of the chiral cocaine was determined by resolution of the signal for the acetate protons (3.68 ppm) of cocaine, as seen in Fig. 1*A*. Figure 1*B* shows the spectrum of Solution B containing *d,l*-cocaine to which the $Eu(TFAC)_3$ solution was added, and the acetate protons show a nonequivalence of 0.08 ppm. Figure 1*C* shows the effect of the addition of the *l*-cocaine stock solution. From this spectrum it can be deduced that the resonance in Fig. 1*C* at 3.40 ppm is due to *d*-cocaine and the resonance at 3.48 ppm is due to *l*-cocaine. A spectrum of a control solution containing pure *l*-cocaine and $Eu(TFAC)_3$ yielded a single peak for the acetate resonance. If we assume the nearly equal peak heights of the *d,l*-mixture are due to a 50-50 mixture, the unresolved baseline shift can be taken as equal in the two isomers, so that we expect a 5% isomer detection limit within the signal to noise ratio of the instrument of 30:1. Comparative quantitative results are shown in Table 1 for Solution C.

Difficulties in obtaining a sample of pure *d*-cocaine have thus far precluded doping experiments on the racemic mixture with *d*-cocaine in the same manner that was conducted with *l*-cocaine.

Work is continuing on the application of chiral shift reagents to resolving enantiomorphs of the other three pairs of geometrical stereoisomers of methyl benzoylecgonine.

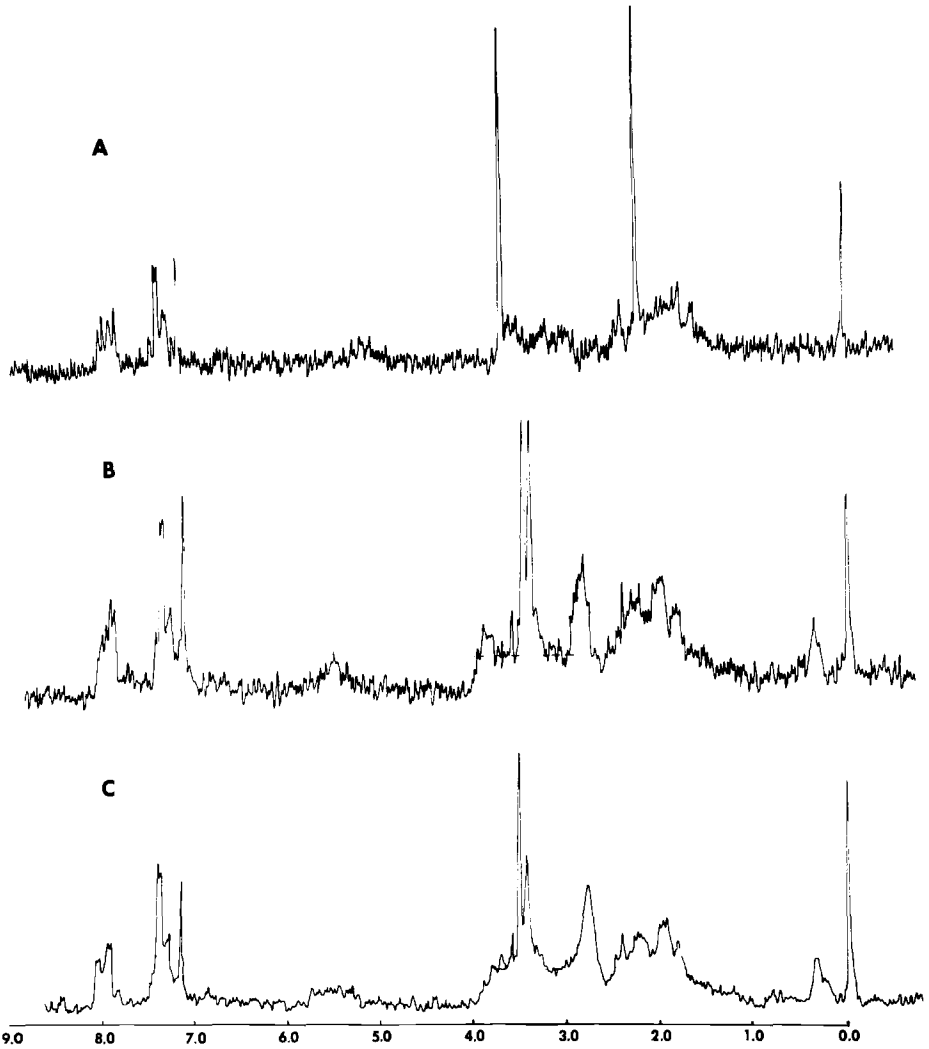

FIG. 1—*Effect of the addition of Eu(TFAC)$_3$ to cocaine solutions;* (A) *13.3 mg/ml solution of* d,l-*cocaine;* (B) *Solution A plus 0.01 ml of Eu(TFAC)$_3$ stock solution; and* (C) *Solution B plus 0.05 ml of* l-*cocaine stock solution plus 0.005 ml of Eu(TFAC)$_3$ stock solution.*

Chiral lanthanide complexes provide practical reagents for direct spectroscopic determination of the enantiomorphic purity of cocaine. The principal virtues of the procedure are the convenience and the relative ease of interpretation offered by the use of spectral data. Little chemical manipulation of the sample is required and the chiral shift reagents are easily obtained from commercial suppliers. It is possible to carry out quantitative

TABLE 1—*Comparative quantitative results.*

Isomer	Calculated, %	Experimental Result, %
l-cocaine	63.7	64.9
d-cocaine	36.3	35.1

determination of the enantiomorphic composition on a relatively small amount of sample. Separation of signals has been observed on samples as low as 2.0 mg of cocaine in this laboratory. With a Fourier-transform-equipped NMR this limit could be much smaller. One can thus conclude that chiral shift reagents offer a potent method for determining optical isomer composition of cocaine samples. This method is currently employed by this laboratory in the routine analysis of cocaine samples.

Summary

An NMR method for the determination of the enantiomorphic composition of cocaine is described. The method involves the complexation of a cocaine sample with the chiral lanthanide shift reagent europium tris-*d*-trifluoroacetyl-camphorate. The induced separation of the *d*- and *l*-acetate resonances is used for the identification and quantification of the respective enantiomorphs. The advantages of this procedure are convenience, small sample size requirement, and ease of interpretation. Separation of signals has been observed on samples as small as 2 mg. The optimum range is 5 to 10 mg. The isomer detection limit is about 5% within the signal to noise ratio of instrument of 30:1.

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