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Methamphetamine and Mirror Images

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Methamphetamine can exist in two forms; one a legal over-the-counter medication and the other a Drug Enforcement Agency Schedule II substance (medicinal value but highly addictive with a high potential for abuse). It is critical to differentiate between these two forms for clinical diagnosis and law enforcement because of their profoundly different biological effects and legal considerations.

These two different forms of methamphetamine are mirror images of each other but otherwise they are completely identical with respect to composition and chemical properties. They are mirror images in the same sense that your right and left hands are mirror images of each other and are not superimposable. These different configurations are known as enantiomers and such molecules are said to be chiral (from the Greek χειρ (kheir).[1] As a hand fits into a glove, only the right or left handed enantiomer may fit a molecular receptor at a drug's desired site of action. A compound containing an equal proportion of each enantiomer is called a racemic mixture. Natural compounds are often single enantiomers (levothyroxine, levodopa, l-noradrenaline). In contrast, many commercially synthesize drugs are a racemic mix (adrenaline, warfarin, fluoxetine, omeprazole).

These properties were discovered by chemists in the mid-1800s who observed that products from some natural sources had a particular crystalline shape and rotated plane-polarized light in a certain direction, but the same molecules synthesized in the laboratory did not exhibit these properties.[2]

The early researchers classified molecules as dextrorotatory (d) and levorotatory (l) depending on how they rotated light from a plane-polarized source and used this to distinguish between them. Much of this early nomenclature still permeates the chemical and food industries. Sucrose is a common white table sugar and is comprised of two smaller chemically combined sugar molecules; dextrose (glucose) and laevulose (fructose). Dextrose is named for its ability to rotate the light source to the right (from the Latin *dexter*). Fructose is also known as levulose because it rotates the light source to the left (from the Latin *laevus*). Karo syrup used in baking is an inverted sugar syrup because after the hydrolysis of sucrose into dextrose and fructose, the mixture "inverts" the rotation of the light source from right to left.

Many drugs have chiral forms that are much more biologically active than their corresponding enantiomer. Methamphetamine is a good example of this. l-methamphetamine has very little biological activity and is used in over-the-counter decongestant medications such as nasal inhalers[3], however, d-methamphetamine is controlled under Drug Enforcement Administration Schedule II because it has pronounced stimulant effects such as euphoria, sleeplessness, anorexia, hyperthermia and tachycardia and has a high potential for abuse.[4]

Because enantiomers have the same mass spectra, very specific procedures must be used to separate the enantiomers from each other before detection. Enantiomers can't be separated unless they are in the presence of another enantiomeric substance, therefore chromatographic separation of enantiomers requires the use of a chiral stationary phase (e.g. GC or LC column), or chiral derivatization of the enantiomers prior to separation on a non-chiral stationary phase.[5,6]

SAMHSA requires laboratories to determine total methamphetamine and then reflex-test for enantiomers. Workplace drug testing cutoff concentrations are 500 ng/mL total methamphetamine, of which at least 20% must be d-methamphetamine.[7] Other methodology uses a chiral derivative and quantitates total d-methamphetamine directly.[8] By either methodology, a chiral separation of methamphetamine is paramount to the determination of the actual controlled enantiomer for treatment or legal purposes.

Prescriptions may be the cause of methamphetamine in the urine. Prescriptions for d-methamphetamine itself (Desoxyn®, Abbott Laboratories) are available to treat obesity, narcolepsy, and attention deficit disorder. Benzphetamine (Didrex®, Pfizer) may be used as an anorectic, which will metabolize to d-methamphetamine. Although these are distinct possibilities, prescriptions of this kind are rare and will show up on the prescription record. Selegiline (Eldepryl®, Somerset Pharmaceuticals) will produce only l-methamphetamine, not the Schedule II d-enantiomer. Other substances that metabolize to d-methamphetamine are dimethylamphetamine, famprofazone, fencamine and furfenorex but these substances are available only outside of the United States or are no longer being manufactured.

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