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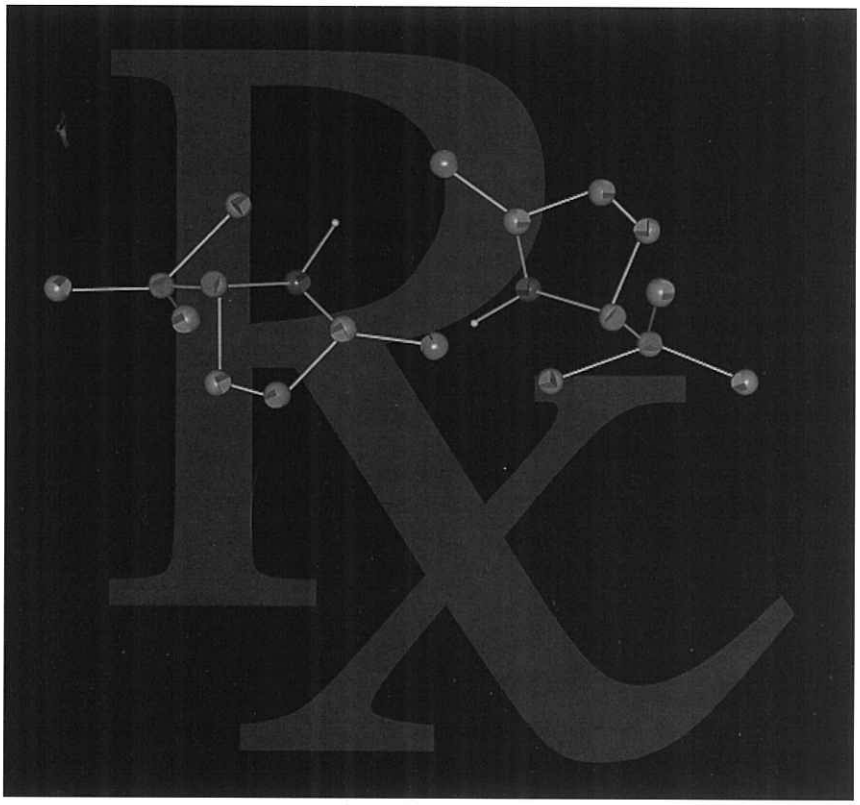


CN93-554

Selenium-Based Reagents for the Evaluation of Chiral Molecular Structures

The arrangement of the atoms in this selone molecule is based on x-ray diffraction studies performed at Los Alamos by Dr. Mary E. Barr. The x-ray structure clearly shows all the atoms heavier than hydrogen. The ring systems are nearly planar with the tertiary butyl groups protruding above and below the plane. The carbon-selenium bond lengths are on the order of 1.8 angstroms, which is indicative that the carbon atom has two bonds to the selenium atom. In the solid state, the unit cell consists of a selone dimer that has the two molecules held together by pairs of selenium hydrogen bonds.

Louis A. Silks III, Isotope and Nuclear Chemistry Division, Los Alamos National Laboratory; Jerome D. Odom and R. Bruce Dunlap, Department of Chemistry and Biochemistry, University of South Carolina

The race is on in the pharmaceutical industry to develop chirally pure drugs because of their increased safety and effectiveness. Chirally pure drugs are the purified form of either the right- or left-handed drug molecule. We developed chemical reagents that, when reacted with a chiral molecule, enhance the detection of that molecule's chirality using nuclear magnetic resonance (NMR). Co-developed with the University of South Carolina's chemistry and biochemistry department, these reagents can detect the presence and quantify the proportion of right- and left-handed molecules in a sample.

Chiral molecules exist in two different forms. These forms are identical in their chemical composition and in the way their atoms are connected, but are different in the way the atoms are arranged so that the two forms are mirror images of each other. The three-dimensional structures have the characteristic of "handedness," which is analogous to the difference between our left and right hands. Thus, the structures of chiral molecules are characterized as right- or left-handed.

Chirality may seem to be a subtle distinction, but structural handedness has important effects on the action of drugs. The biological molecules that form our cells and act as chemical messengers in our bodies have a specific chirality. This biological chirality acts as a glove that will only accept the hand (the drug molecule) with a particular three-dimensional shape. Chirality will, in part, determine whether or not the drug has the desired biological effect, has no effect, or has an unknown, perhaps dangerous, effect.

A tragic example of how chirality can have unknown, dangerous effects is the chiral drug thalidomide. This drug was given to thousands of European women in the late 1950s for morning sickness and more than 7,000 children were born with severe birth defects. Scientists later learned that although one chiral form of thalidomide was effective in alleviating morning sickness, the other chiral form caused birth defects. Unfortunately, thalidomide was prepared and administered as a mixture of the two chiral forms. However, not all researchers attribute thalidomide's birth-defect inducing properties to its chirality (*Chemical and Engineering News*, July 12, 1993).

The Food and Drug Administration recently issued new guidelines on the marketing of drugs as chiral mixtures. These new guidelines attempt to address the issues that have arisen from the thalidomide tragedy, recent progress in the technology of chiral chemistry, and other drug efficacy issues. Most drug companies have now decided to market new drugs as pure chiral forms.

Use of our reagents with NMR provides a flexible and sensitive analytic technique for characterizing and quantifying chiral molecular systems. For this reason, our selenium-based reagents won a 1993 R&D 100 Award, an honor given annually by *R&D Magazine* to the 100 most significant technical innovations of the year.

The Invention—Characteristics and Advantages

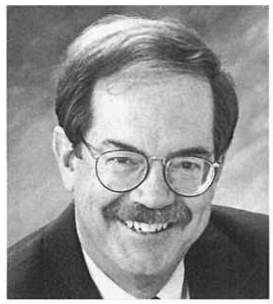
In NMR, a material—in our case a chemical compound—is placed in a strong magnetic field and irradiated using radio waves of varying frequency. The atomic nuclei of particular atoms absorb radio-frequency energy at particular frequencies. This absorption behavior, or NMR spectrum, gives information about the type and arrangement of atoms

in the material. When our selenium reagents are reacted with a chiral drug mixture, the chemically bonded selenium atoms cause the NMR spectrum to shift depending on which chiral form they are bonded to. Thus, the right- and left-handed forms can be distinguished from one another.

Our selenium-based reagents offer three major advantages over other NMR reagents used to detect chirality. First, our reagents are 1000 times more sensitive than nonselenium reagents. Second, our reagents can be attached to a wide variety of chemical groups or compounds; other nonselenium reagents can be attached only to alcohols and amines or to carboxylic acids. Third, our reagents allow NMR measurements to be made in seconds rather than minutes.

Application

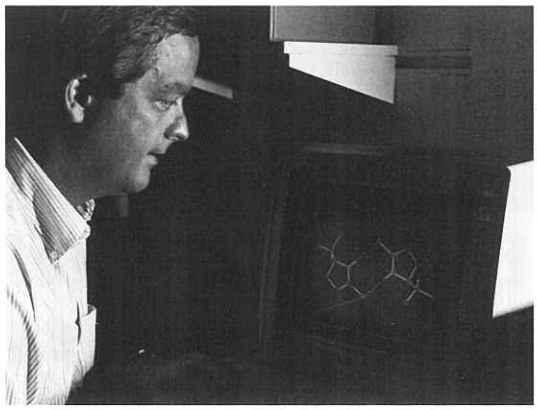
The principal application of our selenium-based reagents is to detect the presence and quantify the proportion of right- and left-handed molecules in a sample. We expect the pharmaceutical industry will use these reagents to prepare chirally pure forms of drugs. According to *Chemical and Engineering News*, of the 1327 synthetic drugs on the market today, 528 exist as chiral drugs. Yet, only 61 of these 528 chiral drugs are marketed as pure chiral forms; the remainder are marketed as chiral mixtures. Our reagents also can be used by organic and inorganic chemists and by biochemists in basic research. ■



The inventors of the selenium-based reagents. Left: Pete Silks examines a computer-generated model of a selone molecule. Above: Jerome Odom (top) and Bruce Dunlap.

Louis A. "Pete" Silks is a staff member at the Division of Isotope and Nuclear Chemistry. He joined the Laboratory in 1990 from the University of South Carolina where he was an Associate Professor. Pete earned his Ph.D. at Boston University in 1985 in the areas of organic synthesis and photochemistry. Pete began developing selenium-based reagents for the evaluation of chiral molecular systems with Bruce Dunlap and Jerome Odom beginning in 1988 at the University of South Carolina. Pete's current interests include the synthesis of stable isotope derivatives of biological molecules for NMR studies, organoselenium chemistry, and the use of chelators in toxic metal separation. Pete has been awarded 11 grants and is the author of one patent and 30 publications.

Jerome Odom is a Professor in the Department of Chemistry at the University of South Carolina. Jerome earned his Ph.D. in chemistry in 1968 at Indiana University and worked as a Postdoctoral Associate in Bristol University, England, with F.G.A. Stone. Jerome has authored 149 publications, including eight review articles and three general chemistry textbooks. He has been awarded one patent and has several outstanding teacher awards. Jerome's research interests include the biochemistry of the trace element selenium, the use of selenium and tellurium as NMR and X-ray crystallography probes, and inorganic synthesis.



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Bruce Dunlap is currently the Weissman Professor of chemistry and biochemistry at the University of South Carolina, an Adjunct Professor at the School of Medicine Department of Pediatrics, and the Director of Research at the South Carolina Cancer Center and the Richland Memorial Hospital. Bruce earned his Ph.D. in biochemistry at Indiana University in 1968. He is the author of 131 published papers and has been awarded 29 grants. Bruce's research interests include molecular biochemistry with emphasis on protein structure and enzyme reaction mechanisms.

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