Researchers develop NMR method for drug structure elucidation

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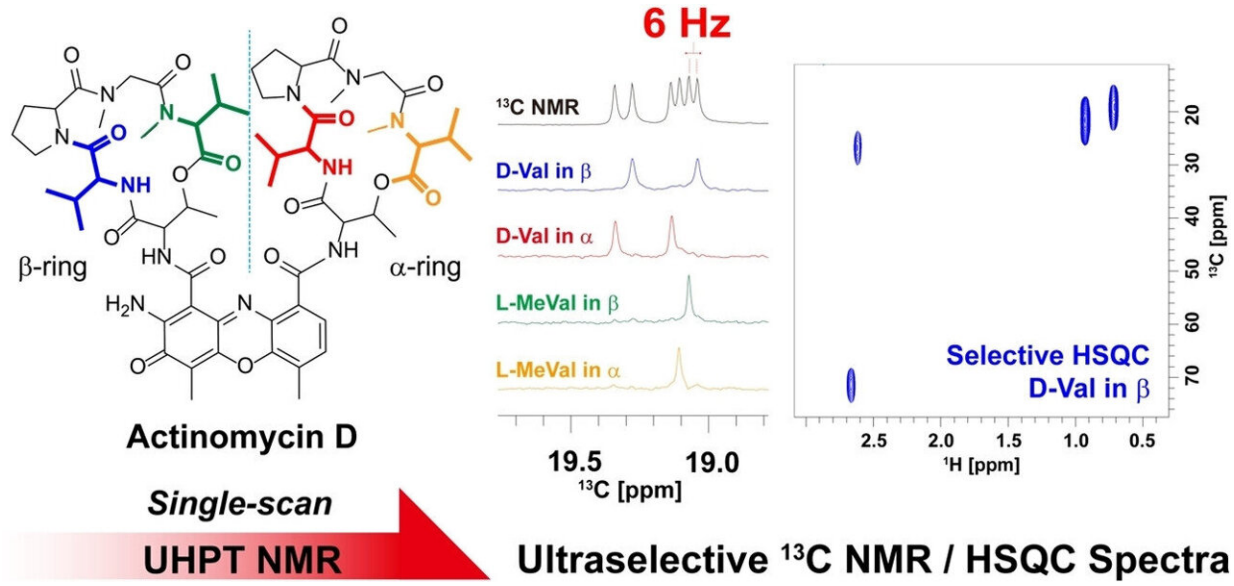


A single-scan ultraselective heteronuclear polarization transfer (UHPT) NMR method is presented. When applied to chromopeptide pharmaceuticals and a diastereomeric mixture of a fungicide with highly complex NMR signals in both the ^{1}H and ^{13}C dimension, this method provided accurate ^{1}H-^{13}C correlation and ^{13}C NMR spectra of individual subunits, which enabled unambiguous structure assignment. Credit: *Angewandte Chemie International Edition* (2023). DOI: 10.1002/anie.202304196

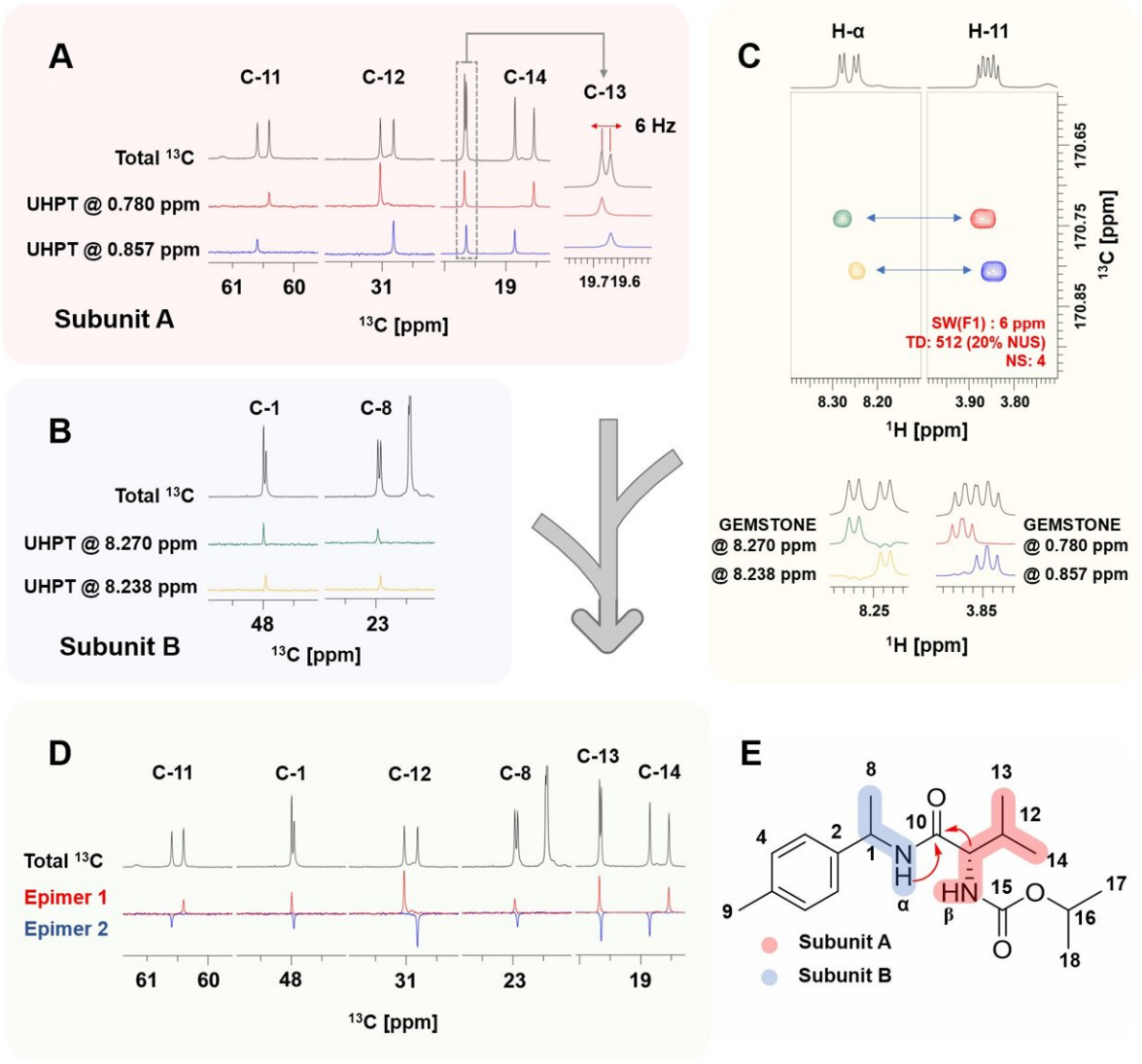
In the late 1950s and 1960s, more than 12,000 malformed babies with short arms and legs were born as a side effect of thalidomide, a drug sold

to pregnant women to prevent morning sickness. The tragedy was caused by the drug's side effect, which exists in a racemic mixture of two mirror-image forms.

Research to determine the molecular structure of various compounds is essential for understanding biological phenomena and developing drugs to treat diseases and is mainly based on the interpretation of frequency signals measured by nuclear magnetic resonance spectroscopy (NMR).

Drs. Jinwook Cha and Jinsoo Park of the Natural Product Informatics Research Center at the Korea Advanced Institute of Science and Technology (KIST) announced that they have developed the first NMR method (ultraselective heteronuclear polarization transfer method, or UHPT) that can selectively measure the information of carbon atom nuclei linked to specific hydrogen in a single measurement. The work is published in the journal *Angewandte Chemie International Edition*.

Even with existing ultra-high field NMR equipment, only selective NMR signal measurement of specific hydrogen nuclei was possible. Still, rapid measurement of carbon nuclei signals was not possible, making it difficult to secure a satisfactory level of specific hydrogen-carbon NMR signal resolution. In addition, there were limitations in identifying the chemical structure of pharmaceutical raw materials and drugs of toxicity concern.



Chemical structure analysis process of diasteromeric mixture using UHPT method. Credit: Korea Institute of Science and Technology

With the UHPT method, the researchers were able to distinguish the carbon associated with a specific hydrogen atom nucleus in a single measurement among complex carbon-carbon NMR signals, with a signal resolution of several hertz (Hz). The method enabled them to clearly analyze the structure of natural products with complex molecular

structures, such as the anticancer drug dactinomycin, which is composed of optical isomers of amino acids. It also enabled the accurate assignment of the fungicide iprovicarb, a mixture of diastereoisomers.

The UHPT method is fast, accurate, and economical compared to conventional methods. When applied to NMR equipment owned by universities and companies, it has been confirmed that equivalent NMR signal resolution can be achieved in about one-fifth the measurement time of ultra-high field NMR equipment.

"The new NMR method can be used as a standard analysis technique for identifying and standardizing the active ingredients of new materials in the natural product bio industry," said Dr. Jin-Wook Cha of KIST.

"It is expected to contribute to the development of the natural product bio industry by solving the challenges of the drug development process by using it to identify the structure of partial particulate matter, which plays a crucial role in determining the efficacy and safety of drugs."

More information: Jin Wook Cha et al, A Single-Scan Ultraselective Heteronuclear Polarization Transfer Method for Unambiguous Complex Structure Assignment, *Angewandte Chemie International Edition* (2023). DOI: 10.1002/anie.202304196

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