ABSOLUTE STEREOCHEMISTRY AND STEREOSELECTIVE BIOACTIVITY OF THE CHIRAL TRIAZOLE FUNGICIDE DIFENOCONAZOLE

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Difenoconazole (DFZ) is a chiral antimycotic agent belonging to the class of triazoles, which is extensively used as a pesticide in agriculture and is also employed as a drug in the treatment of fungal skin infections. The interest in the stereochemical characterization of pesticides is growing steadily in the field of environmental chemistry, similarly to what happened in medicinal chemistry. The stereoisomers of chiral pesticides may show stereoselective activities and toxicities, which can play a fundamental role in the development of enhanced formulations with increased potency and decreased environmental impact. The fungicidal bioactivity of DFZ shows this behaviour: the stereoisomer with the highest activity towards pathogens is also the least toxic towards non-target organisms and the least persisting in the environment, while the least active stereoisomer is also the most toxic and polluting. [1] The replacement of the commercial mix of stereoisomers with a stereoisomerically enriched formulation of the most active DFZ stereoisomer is therefore a promising strategy to reduce the environmental pollution arising from the use of this pesticide.
The stereochemical characterization of the 4 DFZ stereoisomers (2 chiral centres) was carried out by a multidisciplinary approach which combines experimental spectroscopic techniques, such as 1D- and 2D-NMR and electronic circular dichroism (ECD), and *ab initio* calculations of the theoretical ECD spectra by time-dependent density functional theory (TD-DFT). [2] The relative configuration of the 2 enantiomeric pairs was determined by NMR, and the ECD spectra of all stereoisomers were recorded. Calculations were then carried out on one enantiomer for each of the 2 enantiomeric pairs: (2*S*,4*S*)- and (2*S*,4*R*)-DFZ. A total number of 37 input structures were considered in the calculations; a B97D/TZ2P level was used for DFT geometry optimizations, while a PBE0/TZ2P was used for TD-DFT calculations. The combination of this computational protocol with experimental spectroscopies allowed to assign the absolute configuration to each of the 4 DFZ stereoisomers, therefore assessing the stereochemistry of the most active stereoisomer as (2*R*,4*S*) and of the most toxic stereoisomer as (2*S*,4*S*). [1]

References

[1] F. Dong, J. Li, B. Chankvetadze, Y. Cheng, J. Xu, X. Liu, Y. Li, X. Chen, C. Bertucci, D. Tedesco, R. Zanasi, Y. Zheng, *Environ. Sci. Technol.*, **2013**, 47, 3386-3394.
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