

N-Methyl Inversion and Accurate Equilibrium Structures in Alkaloids: Pseudopelletierine

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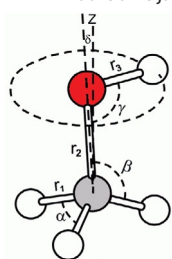
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Invited for the cover of this issue are the groups of Natalja Vogt at the University of Ulm, Alberto Lesarri at the University of Valladolid and Emilio J. Cocinero at the University of Pais Vasco. The image depicts the family tree of tropane alkaloids, to which pseudopelletierine belongs, and their occurrence in nature. Read the full text of the article at [10.1002/chem.201702232](https://doi.org/10.1002/chem.201702232).

What is the most significant result of this study?

Previous studies in tropane alkaloids suggested possible connections between their axial/equatorial isomerism (*N*-methyl inversion) and biological role, indicating that the nature, position, arrangement and stereochemistry of substituents may have a crucial role in the bioactivity of these molecules. For these reasons, several systematic studies in our group (tropinone, scopoline, scopolamine and tropinone...H₂O) have previously addressed the conformational flexibility, substituent effects, *N*-methyl inversion and the role of hydration in tropane alkaloids. The present study compares the structural effects associated to the larger ring of pseudopelletierine and the presence of the carbonyl group. Two conformers corresponding to the *N*-methyl group being axial or equatorial were identified, in which the axial conformer was more stable. An accurate equilibrium structure has been determined from microwave data and theoretical models computed at the coupled-cluster level of theory.

What was the inspiration for this cover design?

The cover design revolves around two main ideas: the role of pseudopelletierine as part of the tropane family and its presence in nature. On one hand, pseudopelletierine, as well as some other tropane alkaloid derivatives shown in the tree, are natural compounds that can be found in different plants such as progremates, mandrakes, nightshades and others. On the other hand, all the molecules set in the tree (one in each branch) have a common sub-structure and they all belong to the same family. They differ, from a chemical point of view, in the substitutions at different positions on the bicycle. Those substitutions that characterize each tropane are represented using drops containing the different chemical compounds. Thus, the family tree perfectly connects both ideas: the chemical nature of pseudopelletierine and its presence in natural compounds.

How did the collaboration on this project start?

This project required the technical and intellectual powers of three scientific groups to combine experiment and theory. The rotational spectrum (parent species and ¹³C, ¹⁵N and ¹⁸O isotopic species in natural abundance) was measured in Bilbao to provide the experimental moments of inertia used in the structural calculations. The theoretical calculations performed in Ulm modelled the molecule up to the CCSD(T) level of theory, which is considered the golden standard in computational chemistry. The combination of experimental and theoretical data resulted in a very accurate equilibrium structure, offering comparison with other systems.

