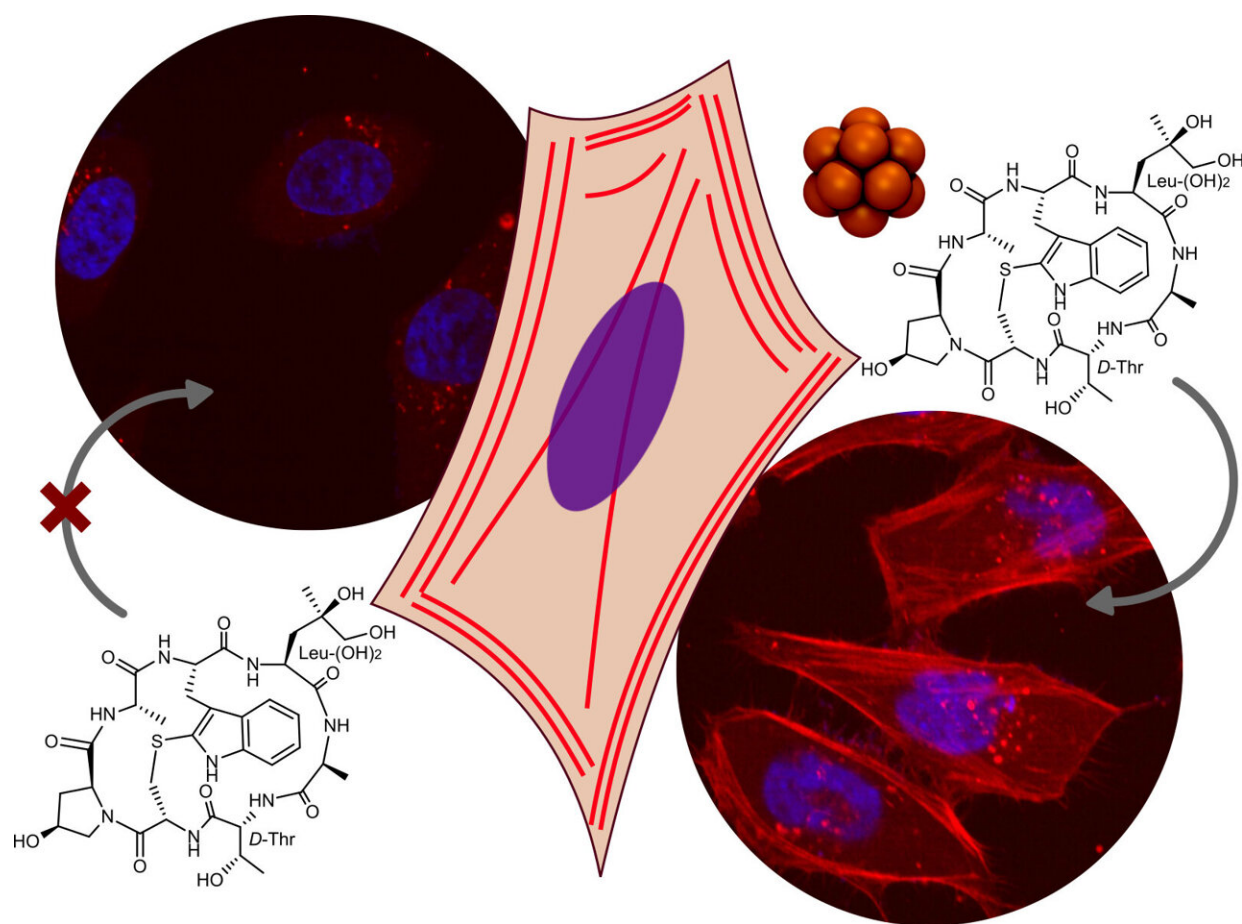


# A new way to enter the cell using superchaotropic properties of boron clusters

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Superchaotropic boron clusters showed carrier activity not only in model vesicles, but also in living cells. Credit: CiQUS

The internalization of impermeable molecules into cells is a current

challenge in drug development, as many water-soluble bioactive molecules cannot cross the cell membrane. To facilitate the cell entry of these molecules, artificial transporters, such as polymers, lipids, or cationic penetrating peptides, have been devised. To date, most of these carriers have been conceived relying on one particular property that allow them to cross the lipid bilayer: the amphiphilicity. Amphiphilic molecules possess differentiated regions that allow them to interact with the water-soluble cargo and the lipid membrane. All membrane carriers known until today share a similar molecular amphiphilicity that allows them to interact with the amphiphilic membrane. However, these transporters usually face limitations due to intrinsic features of amphiphilic molecules, like for example, the toxicity associated to their detergent-like behavior that can damage cell membranes, or their aggregation tendency, which can limit the concentrations at which they can be useful.

The recent study published in *Nature* by researchers from the Centre for Research in Biological Chemistry and Molecular Materials (CiQUS, USC), in collaboration with Jacobs University (Bremen, Germany), presents a novel class of membrane carriers that leaves behind the amphiphilic paradigm. These new carriers are based on halogenated dodecaborate [cluster](#) anions, with a globular shape of barely 24 atoms, that have a [negative charge](#) and an excellent water solubility. Despite their anionic charge and the absence of differentiated domains, these clusters also present affinity for lipid membranes due to their superchaotropic nature. This chaotropic property can be considered as an ability of these clusters to disorder water molecules, which is now shown to allow a dehydration of the hydrophilic cargos and thus allow them to travel across the hydrophobic membranes.

These clusters can interact with hydrophilic cargos without encapsulating or forming aggregates with them. Using model vesicles, in the group of Prof. Werner Nau (Jacobs University, Bremen), it was found that the

smallest, and least chaotropic, cluster ( $B_{12}H_{12}^{2-}$ ) was inactive, while the largest and most chaotropic one ( $B_{12}I_{12}^{2-}$ ) interacted too strongly with the lipid membrane. However, dodecaborate clusters with balanced chaotropicity, such as the halogenated  $B_{12}Cl_{12}^{2-}$  and  $B_{12}Br_{12}^{2-}$ , activated the translocation of different cargos across the lipid bilayer without destroying the integrity of the membrane. Particularly, the brominated  $B_{12}Br_{12}^{2-}$  emerged as the optimal candidate of a new class superchaotropic boron carriers. "These new carriers show very distinctive transport properties" says Dr. Andrea Barba-Bon, a researcher from JU and co-first author of the study. "In contrast to classical amphiphilic transporters, their activity was not affected by the sequence of cluster and cargo addition to the vesicles, or the vesicle's [membrane](#) charge."

With the exception of negatively charged molecules, this carrier was able to deliver a wide variety of cargos, ranging from [small molecules](#) to larger peptides. Moreover, superchaotropic boron clusters showed carrier activity not only in model vesicles, but also in living cells. The clusters could efficiently transport inside living cells different molecules into cells as shown by the group of Prof. Javier Montenegro (CIQUS, USC). The boron clusters were able to deliver a fully functional phalloidin cargo—an impermeable cyclic peptide traditionally employed for labeling the cytoskeleton of fixed cells—into the cytosol of living cells and staining the actin cytoskeleton of several cellular types. The broad spectrum of bioactive cargos that could be transported also included the low permeable PROTAC dBET1 or the antineoplastic monomethyl auristatin F, which were internalized 2-3 times more efficiently in the presence of the boron cluster. "We have identified a new class of transporters that can be used to deliver many different molecules into cells. Superchaotropic anions are a new tool for the transport of hydrophilic molecules into cells, whose potential is only starting to be explored," says Giulia Salluce (CiQUS), Ph.D. student in Montenegro's group and co-first author of the study.

**More information:** Werner Nau, Boron clusters as broadband membrane carriers, *Nature* (2022). [DOI: 10.1038/s41586-022-04413-w](https://doi.org/10.1038/s41586-022-04413-w).  
[www.nature.com/articles/s41586-022-04413-w](https://www.nature.com/articles/s41586-022-04413-w)

Provided by Center for Research in Biological Chemistry and Molecular Materials (CiQUS)

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