Scent Prediction

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The scent of lily of the valley hangs in the air for readers of the journal *Angewandte Chemie*: just rub the journal's cover and enjoy a lily-of-the-valley scent.

Lily-of-the-valley scent components can also be found within the pages of the journal: an interdisciplinary team headed by Reinhold Tacke (Inorganic Chemistry, University of Würzburg), Philip Kraft (Scent Research, Givaudan Schweiz Inc.), and Hanns Hatt (Cell Biology, University of Bochum) have attempted a "scent prediction" to test their computer model of lily-of-the-valley fragrance receptor hOR17-4. This molecule was characterized in detail as the first human scent receptor by Hatt and his co-workers, who also discovered it in sperm.

A fragrance is usually composed of a mixture of many different scented substances. Each of these individual substances can react with several of the approximately 347 scent receptors in our nose and show a complex scent. "When developing new fragrances, we have to rely on correlations between structure and effect derived from model substances as well as intuition," says Kraft. With the help of sperm, however, it is possible to study the lily-of-the-valley receptor in virtual isolation and simulate the primary process of scent sensing by computer.

An olfactory receptor responds to a scent molecule when it fits into the receptor's binding cavity. If the structure of the cavity is known, it should be possible to use computer models to predict whether a scent activates the receptor in question and to what degree. To prove this theory, the scientists investigated how the replacement of one carbon

atom with a silicon atom affects the scent of lily-of-the-valley fragrance components lilial and bourgeonal, and whether this subtle alteration, which has minimal influence on the molecular shape, can also be predicted quantitatively. The human nose was indeed fooled. Tacke says, “All four of the synthesized compounds had the typical floral aldehydic lily-of-the-valley fragrance, but didn’t smell completely identical.” However, near their threshold levels, it was no longer possible to tell these scents apart. “Only the most sensitive lily-of-the-valley receptor is activated at these concentrations,” explains Hatt.

On the basis of calculated binding energies, the team had made a prediction of the scent intensities as well as the sensitivity of sperm to the test molecules. These predictions corresponded very closely to the experimentally observed results. As expected, the odor thresholds were significantly higher for the silicon analogues than for lilial and bourgeonal.

“Our computer calculations are exclusively based on the surface shape of the scent molecules, which is defined by their electrons,” explain the researchers. “These results thus unambiguously prove that it is this electronic surface structure of a molecule that determines the interaction between a scent molecule and its olfactory receptors—and thus defines its fragrance.”

Citation: Reinhold Tacke, Prediction of Perception: Probing the hOR17-4 Olfactory Receptor Model with Silicon Analogues of Bourgeonal and Lilial, *Angewandte Chemie International Edition* 2007, 46, No. 18, 3367–3371, doi: 10.1002/anie.200605002

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