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News Item

Ringing the Changes to Make Medicine Easy to Swallow

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Doughnut-shaped cyclodextrin molecules used as catalysts, enzyme mimics, drug carriers and food stabilisers, have been studied for more than a decade. But they have a serious shortcoming which restricts their use: the only chemical group attached to the ring is the hydroxy group (OH). Now researchers in the US have discovered how to modify cyclodextrins to take other chemical groups, opening the way to making related compounds with useful new properties.

Cyclodextrin molecules are made from a ring of six, seven or eight hexagonal sugar units linked end to end. Certain microorganisms produce them naturally when fed starch, whose molecules are made up of long strands of sugar units. The compounds can be made in the laboratory by treating a starch solution with cyclodextrin transglycosylase, an enzyme extracted from the same microorganisms.

In the past, chemists have added chemical groups to the ring's 'primary' side. However, it is the so-called 'secondary' side of cyclodextrins that is the real business end of the molecule.

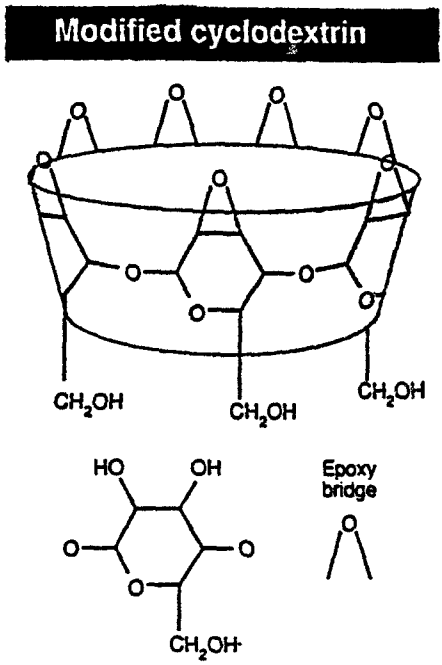
Valerian D'Souza, Abdul Khan and Lawrence Barton of the University of Missouri in St Louis have now found a way of producing a key intermediate compound. They believe that this molecule will allow them to make cyclodextrins with a variety of chemically distinct 'functional groups' on the secondary side.

D'Souza's team used an efficient reaction to make the intermediate, heptakis-2,3-epoxy-β-cyclodextrin, from a known silicon-containing derivative of β-cyclodextrin (*Journal of the Chemical Society, Chemical Communications*, 1992, p. 1112).

"It will be possible to append almost any desired functional group to the epoxy derivative," says D'Souza. The epoxy intermediate is very stable, and can be stored without the need to be specially protected from light, moisture and so on.

To add the desired functional groups, the researchers will treat the epoxy intermediate with appropriate chemical reagents. First, they plan to try compounds which seek out positive charge, or are 'nucleophilic', such as ammonia, hydroxyamines and thiols. The reactions of some of these compounds have had encouraging results, they say.

Last year, two groups led by Jacques Defaye at the French National Research Centre CNRS, and Fraser Stoddart, then at the University of Sheffield, independently reported making another cyclodextrin derivative, per (3,6-anhydro)cyclodextrin. Stoddart described this as being a key chemical modification with the potential to release cyclodextrin from its 'structural straightjacket' (*Angewandte Chemie, International Edition*, **30**, pp. 78 and 80, 1991).



Drugs ring: by adding any desired functional group to the modified cyclodextrin, it may be possible to make a range of useful components, including drug carriers

"The ability to functionalise cyclodextrins will widen their use as complexing agents and catalysts," says D'Souza, who believes his epoxy derivative holds even greater promise than these earlier attempts. For example, it should be easy to replace hydroxy (OH) groups with carboxy groups (COO^-) and so allow the cyclodextrin to form complexes with positively charged species. New cyclodextrins will have "interesting binding and other physical properties", he says.

Cyclodextrins have been used to deliver drugs because they can trap complex hydrophobic (greasy) molecules in their hydrophobic cavity. The outside of the doughnut, being hydrophilic, makes the molecule as a whole partially soluble in water. So a hydrophobic or otherwise 'insoluble' drug can be made orally active and be absorbed from the gut rather than having to be injected.