*Journal of Inclusion Phenomena and Molecular Recognition in Chemistry* **11**: 281–282, 1991.



*News Item*

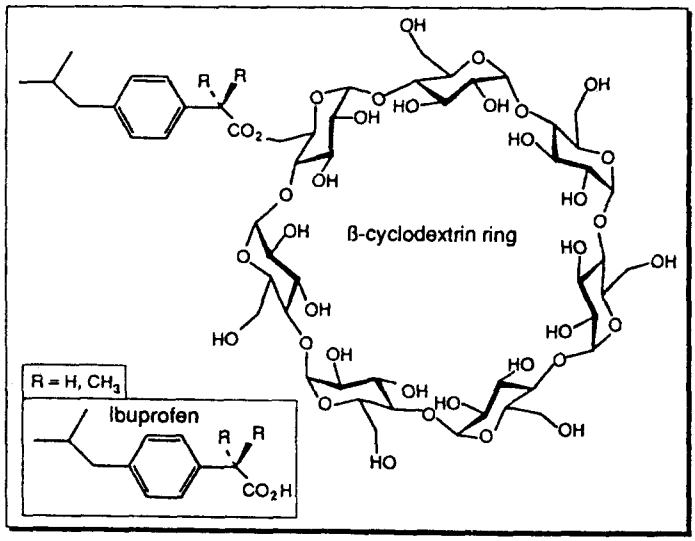
# Handy Way to a More Effective Painkiller

Chemists in Australia have developed a technique that could halve the necessary dose of some drugs. They have come up with a way of separating the biologically active form of the painkiller ibuprofen from its less active form.

Ibuprofen is widely used to treat such conditions as migraine and postoperative pain. In principle, the technique could be extended to other common drugs such as the anti-inflammatory drug flurbiprofen and to some food additives. As well as reducing the amount of chemical needed, the separation has the added benefit of removing any side effects caused by the presence of the second, unwanted form.

Ibuprofen is one of hundreds of "chiral" molecules – it exists in a left-handed (*S*) and a right-handed (*R*) form. The *R* and *S* forms, or enantiomers, often have very different biological properties. The left-handed form of thalidomide, for example, is an effective tranquilliser, while the right-handed form severely disrupts fetal development. Such compounds must be separated into their left and right-handed forms before they can be given as drugs.

Ibuprofen is sold as a 1:1 mixture of the *R* and the *S* form. Although neither form is dangerous at normal dosage, (*S*)-ibuprofen is far more effective at stopping pain and reducing inflammation than is (*R*)-ibuprofen. So it would be better to use only the (*S*) form.




*The cyclodextrin ring provides a chiral cavity for ibuprofen.*

Chemists can tackle this problem in two ways. Either they can overhaul the manufacturing process by designing a whole new synthetic procedure. Or they can devise a chemical separation technique that enables them to produce more of the active form. Chris Easton and colleagues at the University of Adelaide chose the latter (*J. Chem. Soc. Commun.* 1991, p 759).

Separating enantiomers is notoriously difficult as most of their chemical properties are virtually identical. Chemists have devised various techniques but these are often laborious and expensive. The researchers' method is relatively simple: it uses a readily available compound known as cyclodextrin.

Cyclodextrin, a doughnut-shaped molecule, reacts with ibuprofen in such a way that the (*R*) and (*S*) forms are released from the mixture at different rates, allowing one to be tapped off before the other.

The success of the method depends on the chemical structure of cyclodextrin, which consists of six or more glucose molecules linked in a ring. Small organic molecules or parts of larger ones – such as drug molecules – can become trapped inside the cavity if they are the right shape and size. On top of this, cyclodextrin is chiral itself, which allows it to discriminate between the chiral forms of molecules that become trapped.

First, the chemists took (*R*, *S*)-ibuprofen and mixed it with a modified cyclodextrin in which they had replaced a hydroxy group with a sulphur-containing group. The ibuprofen molecules displaced the sulphur group, producing two different 'prodrug' molecules in equal proportions: (*R*)-ibuprofen–cyclodextrin and (*S*)-ibuprofen–cyclodextrin.

To split the prodrugs, they incubated the mixture in an alkali. In doing so, they discovered that the (*R*) form is released about 10 times more quickly than the (*S*). According to Easton, the rate of release depends on how tightly the cyclodextrin binds the different forms of Ibuprofen, and this depends on its chirality. He thinks part of the (*S*) form might be held by the 'greasy' cavity in the ring, so that it is released more slowly. The chemical make-up of the drug is not altered by the separation.

The research marks the first use of cyclodextrins to form prodrugs for separation. Previously, chemists have used cyclodextrins merely as passive carriers for enantiomers rather than molecules that can react with enantiomers to separate them. The researchers hope that scaling up the reaction will lead to an effective industrial process.

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