proteases themselves, but also those that bind to their substrates.

Substrate-targeted drugs are an attractive prospect, because they are expected to be much more selective for their proteins than protease-targeted inhibitors could be. Proteases invariably have many different substrates, so that even the most specific protease inhibitors will affect dozens, if not hundreds, of different reactions. The potential for unwanted side effects *in vivo* is therefore significant. But a substrate-targeted inhibitor could, in theory, specifically block the cleavage of the targeted substrate by binding not only to the substrate's cleavage site, but also to surfaces flanking the site[7]. Such surfaces provide unique 'signatures' to distinguish the protein from the many other competing substrates (Fig. 1). The cleavage site would thus effectively be cloaked from the protease by the inhibitor. This scenario might well apply in Kukar and colleagues' study[1], as some of the molecules under investigation inhibited the cleavage of APP by γ-secretase, but not that of other substrates for the enzyme.

The elucidation of the structural basis of the drug–APP interactions will be eagerly awaited. One would assume that the cleavage-site region in APP assumes some three-dimensional structure that is recognized by the drug. But more surprises may be in store, because the cleavage sites in protease substrates are generally found in loops that extend away from the body of the protein, rather than forming a pocket. In the longer term, any information that aids the rational design of substrate-targeted inhibitors of γ-secretase will be invaluable for investigating these compounds as possible drugs in the fight against Alzheimer's disease. ■

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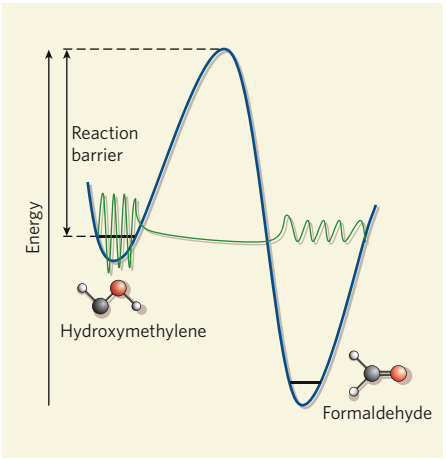

Figure 1 | Quantum tunnelling of hydroxymethylene. Schreiner *et al.*[1] have made and characterized hydroxymethylene (HCOH), an unstable organic molecule, for the first time. They observe that HCOH decomposes to form formaldehyde. The graph (blue line) shows the calculated total energy of the atoms in HCOH as the reaction proceeds. The energy reaches a peak mid-way through the process; the difference in energy between the ground state of HCOH and the peak is known as the reaction barrier. At the low temperatures used in Schreiner and colleagues' study, HCOH molecules have insufficient thermal energy to overcome the reaction barrier. Instead, the molecules 'tunnel' through. This behaviour results from the wave–particle duality of the molecule: the waveform of HCOH (green) extends into the energy well of formaldehyde, allowing molecules to bypass the barrier.

PHYSICAL CHEMISTRY

Cool it, baby

Markku Räsänen

A long-sought but short-lived molecule has been made and characterized for the first time. This compound decays at low temperatures using an unusual trick — a mechanism known as quantum tunnelling.

Chemists are now so skilled at making organic compounds that you might think that all the smallest molecules (containing fewer than 10 atoms) have been made and characterized. This might be true for stable molecules, but some compounds that have weak bonding or high reactivity are short-lived, and have remained elusive. On page 906 of this issue, Schreiner *et al.*[1] report the formation and detection of one of these bashful beasts — hydroxymethylene (HCOH). This molecule is one of the simplest members of a family of compounds known as singlet carbenes, which have recently gained prominence as molecular components of catalysts for organic synthesis. Schreiner and colleagues' findings might cast fresh light on the chemistry of these fascinating compounds, and could even lead to the discovery of new reactions.

All previous attempts to conclusively identify HCOH have failed. This is puzzling, as theoretical studies[2] suggest that it should be a relatively stable molecule. Until Schreiner and colleagues' report[1], the best evidence for the molecule's existence came from studies[3] of a light-induced reaction of isotopically labelled formaldehyde (a stable isomer of HCOH). The incorporation of isotopes from formaldehyde into the products suggested that HCOH is an intermediate in these reactions, but this evidence is indirect.

Despite the lack of convincing evidence, chemists have always been confident that HCOH exists. Perhaps most intriguingly, some have speculated that it might form in interstellar clouds, where it could participate in the formation of larger organic molecules[4]. What is known for sure is that certain larger carbenes, in which the hydrogen atoms of HCOH are replaced with chemical groups, are perfectly stable. Indeed, such carbenes are the basis of a rich branch of chemistry and have many applications in organic and organometallic syntheses[5]. They also have a central role in combustion and atmospheric chemistry.

So how does one go about identifying an ephemeral molecule? Several methods have been developed. Spectroscopic measurements can now be taken with femtosecond resolution (1 femtosecond = 10^{-15} seconds), allowing the detection of extremely short-lived molecules. Alternatively, the lifetime of such molecules can be increased by lowering the temperature of the experimental sample, so providing time for a more leisurely investigation using slower spectroscopic techniques. For gas-phase experiments, cooling is achieved by rapidly expanding the volume of the gas being studied. Molecules can also be trapped in an inert medium at low temperatures, allowing them to be studied in the solid phase. The second method is called matrix isolation[6], and was pioneered by the chemist George Pimentel, whose slogan was "cool it, baby".

Schreiner *et al.*[1] used matrix isolation in their identification of HCOH. They prepared the target compound by heating glyoxylic acid ($HCOCO_2H$) in a high vacuum; under these conditions, carbon dioxide is eliminated from the starting material, yielding HCOH directly. The authors isolated the product in solid argon at a temperature of about 10 kelvin, and characterized it using a combination of spectroscopic techniques, supporting their interpretation of the results with predictions from quantum-chemical calculations. In this way, they provided the first unambiguous proof for the formation of HCOH.

The reason most short-lived molecules have such a fleeting existence is because they easily react to form something else. To put it another way, the amount of energy required by the molecules for an onward reaction — the reaction barrier — is low. The lifetime of a short-lived molecule is lengthened by cooling because it

reduces the amount of thermal energy available to the molecule to overcome its reaction barrier. But some remarkable reactions occur without the need for thermal excitation, through a process known as quantum tunnelling. Schreiner *et al.*[1] report that just such a process occurs for HCOH — when the molecule adopts a certain conformation, it decays to produce formaldehyde in a matter of minutes, even though the calculated barrier for the reaction is too high to be overcome at the temperatures used in the experiments. Instead, the hydrogen atom in the hydroxyl group (OH) of HCOH 'tunnels' through the barrier, in a process that relies on the wave–particle duality of the atom (Fig. 1). This unexpected reaction might explain why previous attempts to detect HCOH failed — the product decayed before it was found and analysed.

The authors[1] investigated the quantum tunnelling process by replacing the hydrogen atom of the hydroxyl group with deuterium (a heavy isotope of hydrogen). They found that the deuterated form of HCOH is essentially stable under their experimental conditions. This stabilizing effect occurs because the wave associated with the deuterium atom decays before reaching the exit of the barrier (unlike the wave for the hydrogen atom), and provides direct evidence of quantum-tunnelling. Turning again to theoretical predictions to validate their results, the authors modelled the tunnelling process computationally. The half-life for HCOH at close to zero kelvin was predicted to be 122 minutes, whereas that of deuterated HCOH was predicted to be more than 1,200 years, in good agreement with their experimental observations.

The data provided by this study[1] will be invaluable for those searching for HCOH under different conditions, for example in the gas phase, where it is expected to participate in many reactions. For such studies, it will be necessary to find out if the tunnelling process is similar in gases and solids — that is, does the matrix surrounding the HCOH molecules in Schreiner and colleagues' experiments have some role in the mechanism? The findings also provide a well-defined system of small molecules that will be a perfect model for studying the mechanisms of tunnelling reactions in solids. Far from being yesterday's news, small molecules still have much to teach us. ■

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ANIMAL BEHAVIOUR

Guardian caterpillars

Parasites are in the business of hijacking their hosts for their own purposes. A dramatic example is described by Amir Grosman and colleagues who studied behavioural changes induced in the Brazilian geometrid moth *Thyrinteina leucocerae* by a braconid parasitic wasp of the genus *Glyptapanteles* (A. H. Grosman *et al. PLoS ONE* **3,** e2276; 2008).

The wasp lays up to 80 eggs in a moth caterpillar, where they hatch, grow and then exit to form pupae on nearby leaves three weeks later. At this point the caterpillar ceases its previous activity, and instead stands guard over the wasp pupae (pictured). While 'guarding' the pupae, caterpillars make violent swings of their heads towards any passing insect or other potential threat.

Grosman *et al.* show that this behaviour is a direct result of parasite infestation and profits the wasp. Unlike the parasitized caterpillars, their unparasitized siblings failed to take up sentry duty when placed by wasp pupae, continuing to feed as normal. Also, the head butts of parasitized caterpillars proved effective protection for the pupae, repelling nearly half of the attacks by predatory stinkbugs (*Supputius cincticeps*) in the laboratory.

Such behaviour has no fitness advantage for the caterpillars, who die soon after the adult wasps emerge from the pupae. But the wasps profit hugely, the presence of a guarding caterpillar almost halving the mortality of pupae in field experiments.

J. LINO-NETO

Although the mechanism by which these parasites influence their hosts is not clear, live wasp larvae were found in the bodies of caterpillars even after their broodmates had departed. Such 'brain worms' have also been seen with trematode and liver fluke parasites that modify the behaviour of their ant hosts.

Christopher Surridge

HUNTINGTON'S DISEASE

Genetics lends a hand

Stéphane Palfi and Bechir Jarraya

A monkey model of Huntington's disease created by gene transfer is only a work in progress. But as a technological feat it offers great promise for fathoming this devastating condition.

Huntington's disease is a heritable disorder that affects more than 1 in 10,000 people. Its associated neurological symptoms are severe, and there is no therapy to halt or slow its progress. To understand its pathology, and with the ultimate hope of finding a treatment, researchers have generated several experimental models of this disease[1], in organisms such as flies and rodents. Although these models have led to tremendous progress in understanding the pathogenic mechanisms of Huntington's disease, none of them can replicate all the behavioural changes seen in the human disease or the changes that occur at the tissue level. The need for a primate model of the disease is thus clear.

On page 921 of this issue, Yang *et al.*[2] describe their attempt to generate a transgenic monkey model of Huntington's*. Although only a 'proof-of-principle', their achievement is a step forward, and will undoubtedly be welcomed by those involved in developing a cure for this distressing condition.

Initial symptoms of Huntington's disease, which generally appear between the ages of 30 and 40, include changes in personality, a progressive cognitive decline and a spectrum of motor disturbances ranging from abrupt to slow and sustained involuntary movements. At a cellular level, features of the human disease include severe neuronal loss in the striatum, a deep brain structure that regulates movement and the cognitive and emotional aspects of behaviour. At the molecular level, the disease is caused by mutation in the *HTT* gene, which encodes the huntingtin protein. This protein normally contains a chain of 6–35 glutamine amino-acid residues. But when *HTT* is mutated, the number of repeats of the CAG trinucleotide, which encodes glutamine, is greatly expanded, leading to extension of the glutamine chain in huntingtin by anything from 36 to 180 repeats[3].

The technique of transgenesis is used to generate organisms carrying a specific mutation, and involves the introduction of a foreign gene into an organism. The first transgenic primate,

*This News & Views article and the paper concerned[2] were published online on 18 May 2008.