NEWS & VIEWS

QUANTUM CHEMISTRY

The little molecule that could

Chris H. Greene

The creation of diatomic molecules bound by roaming electrons that allow a huge internuclear distance is some achievement. It opens the door to further experimental exploitation of the principles involved.

Decades ago, chemists and physicists identified the various types of molecular bonding that are possible, including the standard ionic and covalent schema presented today in every introductory chemistry text. In the meantime, most practitioners of quantum chemistry have meandered on to larger species with the goal of predicting and elucidating the properties of huge molecules containing dozens, hundreds or even thousands of atoms. Yet the simplest molecules of all, the diatomics, which have a mere two atoms, still present puzzles and surprises. A case in point is the beautiful experiment by Bendkowsky *et al.*[1], described on page 1005 of this issue. The authors used the delicate techniques of ultracold atomic physics to create and detect molecules made up of two rubidium atoms that are bound together by a ghostly quantum-mechanical force field at distances as large as 100 nanometres — greater than the size of a small virus.

The interaction depends on one of the partners being a 'Rydberg atom' — an atom in an excited state with at least one electron having a high principal quantum number, meaning that it roams far from its parent nucleus. When a roaming Rydberg electron manages to bind together two atoms separated by distances of 100 nm or more, it resembles a sheepdog that keeps its flock together by roaming speedily to the outermost periphery of the flock and nudging back towards the centre any member that might begin to drift away. In Bendkowsky and colleagues' experiment, it is a distant rubidium atom in its ground (lowest-energy) state that this spirited Rydberg pup keeps from drifting away; and the spectroscopic signature measured precisely in laser-light absorption is strong evidence that the atom is in fact trapped and vibrating back and forth in a delicate potential well as one member of a diatomic molecule. The measured vibrational binding energy, in temperature units, is only around 1 millikelvin, or 4 billionths of an electronvolt, which explains why, in practice, such a molecule can be formed only in an ultracold experimental environment.

The diatomic molecules one normally encounters, for any pair of atoms in the periodic table, have a single characteristic shape for their 'potential curve', which represents the effective potential energy between the atoms, averaged over the much faster electrons, as a function of interatomic distance R. This potential energy $U(R)$ is repulsive at small distances, but attractive at large distances. Choose any two ground-state atoms in the periodic table, and you will be guaranteed to find this basic topology for the potential curve, with a single potential minimum where the molecule normally resides in a happy compromise between repulsion and attraction. These bond lengths range from 0.05 to 0.2 nm for most atom pairs, with only a few exceptions such as the helium–helium dimer, for which the mean atomic separation is around 10 nm.

In the 1970s and 1980s, several groups[2–4] came up with observations of what initially seemed to be an academic peculiarity. They demonstrated, for certain diatomic molecules in highly excited electronic Rydberg states, a totally different topology for the force field or potential-energy curve that oscillates as a function of the interatomic distance. Owing to the explosive growth in the science of the ultracold, these observations led in 2000 to a prediction[5]: that these oscillatory force fields can actually bind molecules in delicate stable (or metastable) states with a huge atom–atom separation. Subsequent theoretical studies[6–8] provided independent evidence for the validity of that prediction. But until the experiment of Bendkowsky *et al.*[1], no direct creation nor detection of such molecules in quantized states of vibration had been achieved. And the evidence of that successful creation is highly convincing. The authors observed not just one such quantum state, but several — following

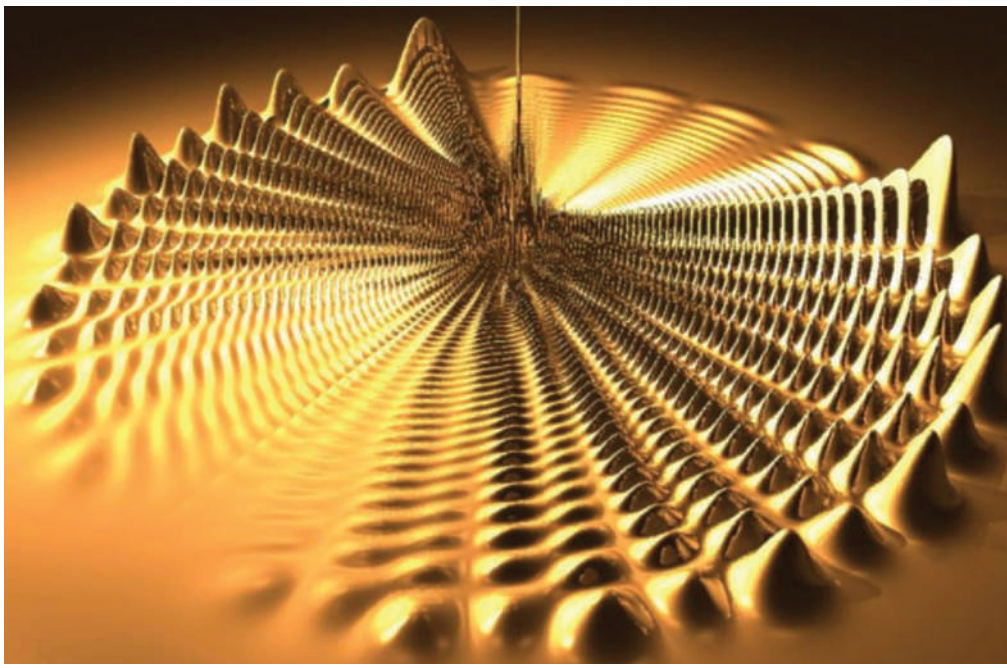

Figure 1 | A different class of Rydberg molecule. This is a depiction, shown in polar coordinates, of the theoretical quantum-mechanical electron density in the ultra-long-range 'butterfly' Rydberg molecule[7] composed of two rubidium atoms. This particular state has a level of excitation (expressed as a principal quantum number, $n = 70$) that is about twice that seen by Bendkowsky *et al.*[1]. Creation of this highly polar molecule might now be possible given the experimental advances made by this group[1]. (Figure produced by E. L. Hamilton.)

the anticipated basic pattern[5] — in more than one state of vibration, and also several different electronic excitations.

Intriguingly, the key to understanding the existence of such molecules goes back to Enrico Fermi's idea[9] of a 'zero-range pseudopotential', which gives the effective interaction at very low energies between two quantum particles that have no electrostatic force between them. That fruitful idea has subsequently found application in many different contexts in which the interacting particles have a long quantum (de Broglie) wavelength, most notably in modern times in the description of degenerate quantum gases at nanokelvin temperatures.

One reason why this new experiment[1] is important is that it provides a confirmation of the theoretical approximations, based on Fermi's pseudopotential, that were invoked for the original prediction of such odd molecules. This is an energy range well beyond current capabilities in theoretical quantum chemistry, which are almost exclusively limited to expansions into Gaussian basis sets[10]. Altogether different techniques are needed to treat long-range Rydberg molecules such as the ones formed in Bendkowsky and co-workers' experiment[1], and the agreement between theory and experiment showcased in their Figure 3 (page 1006) suggests that Fermi's elegant idea might provide a theoretical description of some such species that remain beyond today's brute-force numerical computations.

Bendkowsky and colleagues' work opens up exciting possibilities. One is that a second class of much more strongly bound Rydberg molecules could be formed by carrying out additional excitations of the molecules that have just been created. The most striking of these is polar[5], with an electronic wavefunction that resembles the ancient trilobite, whereas another variety[7] brings a butterfly to mind (Fig. 1). These two types could be particularly important because they have huge electric dipole moments that would facilitate their slowing or manipulation by applied fields. Another avenue for exploration arises from a theoretical proposal[8] to dock more than one ground-state atom in these oscillatory potential wells, and thereby create huge Rydberg molecules with three or more atoms.

The longest-lived of the molecules produced by Bendkowsky *et al.*[1] survives for only 18 microseconds. This is less than a third of the corresponding Rydberg atom's lifetime, and the reason for this shortened lifetime remains unclear. A mere 20 millionths of a second might seem much too fleeting to be of interest, but such survival times are truly metastable when compared with the Rydberg electron's orbital period, a million times shorter. Nevertheless, a future challenge will be to understand the reasons for this fast decay, and to find macromolecular species that live long enough to be manipulated. ■

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SCHIZOPHRENIA

A point of disruption

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Much is still to be learned about the molecular basis of mental disorders. The identification of a signalling pathway that is affected in schizophrenia, and which thus provides potential therapeutic targets, is a welcome advance.

The biology of many mental illnesses, including schizophrenia, bipolar disorder and depression, is incompletely understood. But it probably involves subtle abnormalities in neuronal development and associated signalling pathways[1]. The illnesses might be caused by dysfunction in the migration and maturation of neurons in the cerebral cortex, and by alterations in neuron formation (neurogenesis)[1–3]. Studies in cell and mouse models have implicated the *DISC1* (disrupted in schizophrenia 1) gene. But although a plethora of proteins are known to interact with DISC1 (ref. 4), the pathways by which this protein changes the cellular properties affected in mental disorders remain elusive. In a paper published in *Cell*, Mao *et al.*[5] identify a signalling pathway that is regulated by DISC1. Their finding not only provides insight into the role of this protein in the proliferation of neural progenitor cells, but, even more strikingly, also highlights potential targets for the development of therapeutic drugs.

The *DISC1* gene was discovered during an analysis of a chromosomal translocation, in which chromosomes 1 — where *DISC1* is located — and 11 are broken and rejoined to each other. This translocation, which results in a truncated *DISC1*, was found to be associated with both schizophrenia and affective disorder in a large Scottish family[6,7]. The disrupted gene either fails to express normal DISC1 protein or produces a truncated protein that interferes with the function of normal DISC1. Either way, loss of DISC1 function is believed to be the outcome.

The known functions of DISC1, based on cell and animal studies, include mediation or modulation of nucleokinesis (the movement of cell nuclei, critical for neuronal migration); intracellular transport; the migration and maturation of cortical neurons; and the regulation of synaptic communication between neurons and of gene transcription[8,9]. Moreover, *in vivo* studies[10,11] have shown that DISC1 is active in the adult human brain, regulating neurogenesis, migration of neurons and integration of their synapses into functional circuitry in the hippocampus. The molecular pathways through which DISC1 exerts these effects, however, have remained poorly understood.

Mao *et al.*[5] combine elegant biochemical, cellular and mouse-behavioural analyses to show that DISC1 modulates the Wnt signalling pathway, which is known[12] to regulate neurogenesis in the adult hippocampus. The authors show that DISC1 interacts physically with GSK3β, an enzyme involved in many cellular signalling pathways, including Wnt[13]. They define the interacting regions of DISC1 and GSK3β, and identify a small peptide that can inhibit the interaction. When GSK3β binds to DISC1, there is a decrease in the number of phosphate groups that it carries and thus in its ability to phosphorylate the downstream signalling molecule β-catenin[5]. Consequently, β-catenin becomes stabilized and can move into the nucleus, where it acts as a transcription factor to induce the expression of a set of genes necessary for neurogenesis. These results clearly identify DISC1 as a key regulatory factor in the GSK3β–β-catenin signalling pathway (Fig. 1).

Mao *et al.* further show that reducing DISC1 levels leads not only to loss of neurogenesis, but also to changes in the behaviour of the mice similar to those observed in mouse models of schizophrenia or depression induced by mutations in *DISC1*. These behavioural changes are detected using tests such as novelty-induced hyperactivity in open-field testing and the forced swim test. What's more, the authors find that these abnormalities can be overcome by inhibiting GSK3β using a chemical compound called SB 216763. Thus, in addition to linking DISC1 to GSK3β-mediated signalling, Mao and colleagues' data provide clues, albeit speculative ones, to the development of DISC1-related psychiatric disorders.

Intriguingly, as the authors point out, the