autoimmune diseases, including diabetes and multiple sclerosis (*13*). Do these polymorphisms directly affect regulatory T cell function? A fusion protein composed of CTLA-4 and immunoglobulin protein (called Abatacept, developed by Bristol-Meyers-Squibb) has been approved to treat rheumatoid arthritis and is thought to inhibit stimulation of T cells by blocking the interaction of CD80/CD86 with CD28 (*14*). Could this therapeutic regimen also inhibit regulatory T cell function and promote an autoimmune response after prolonged administration? Anti–CTLA-4 is now in clinical trials to boost tumor immunity and is thought to stimulate antitumor effector T cells by blocking inhibitory signaling by CTLA-4 (*15*). As the development of autoimmune disease is a side effect of this therapy, it remains to be determined whether some of the effects of the CTLA-4–specific antibody are secondary to an inhibition of regulatory T cell function that may be required for an optimal antitumor response.

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10.1126/science.1164872

PHYSICS

Cold Molecules Beat the Shakes

Due to their relative complexity, molecules have been harder to cool than atoms, but that is beginning to change.

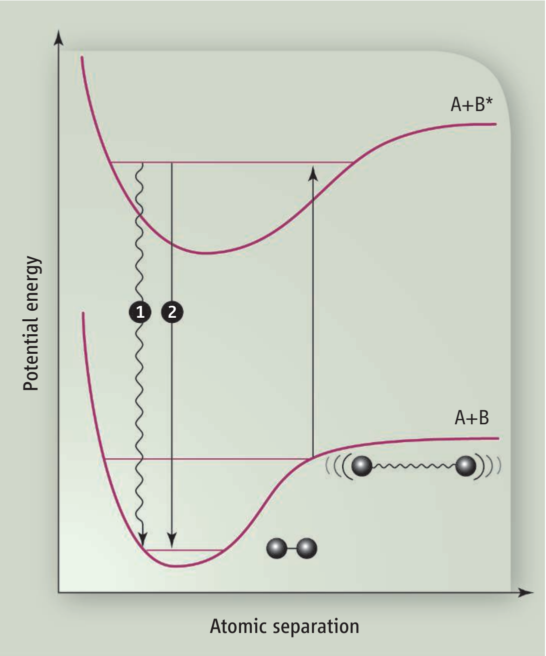
P. L. Gould

Laser cooling of atoms began more than 25 years ago and has led to spectacular advances in areas such as atomic clocks, Bose-Einstein condensation, degenerate Fermi gases, and ultracold collisions. Molecules, due to their complexity relative to atoms (*1*), have been slower to jump on the ultracold bandwagon but are now firmly on board. Three recent papers (*2*–*4*) describe techniques for efficiently and substantially reducing the vibrational motion of molecular ensembles, thus approaching the goal of large numbers of molecules that are cold in all their degrees of freedom, both external and internal.

In molecules, not only can electrons be excited but also the atoms themselves can vibrate and rotate, leading to a multitude of energy levels. Traditional laser cooling relies on momentum kicks from repeated cycles of photon absorption and emission and therefore only works if the excited state decays back to the original ground state. Certain atoms, such as alkali metals, have these "cycling" transitions; molecules do not. Alternative methods for producing cold molecules are therefore required. Along the way, an important question arises: What is meant by molecular temperature? With atoms, there is little ambiguity: Temperature describes their translational motion. However, molecules also have internal energy due to vibration and rotation. Molecules can be very cold translationally but still have high vibrational energy.

Cold molecule production has generally followed one of two strategies: Either start with hot molecules and cool them, or start with cold atoms and assemble them into molecules. Examples of the first category include cooling by collisions with cold He buffer gas (*5*) and slowing a molecular beam with pulsed electric fields (*6*). These direct cooling techniques can provide molecules in their lowest internal state, but the sub-kelvin translational temperatures achieved so far are not considered ultracold. The second category includes photoassociation (*7*), in which laser light excites a pair of cold atoms into a bound molecular state, and the process of magneto-association (*8*), whereby a ramped magnetic field is applied to bind the atoms. Both techniques yield extremely low translational temperatures (sub-mK or sub-µK) but generally leave the molecules in barely bound levels of high vibrational excitation. Although there has been some progress in populating the lowest vibrational states (*9*–*11*), the recent breakthrough (*2*–*4*) is true vibrational cooling: the efficient removal of a large fraction of this vibrational energy.

Viteau *et al.* (*2*) photo-associate ultracold Cs atoms to form Cs_2 molecules in the lowest electronic state but in a distribution of vibrational levels. By repeatedly optically pumping these molecules with broadband light to an electronically excited state (see the figure), which then radiatively decays back to the ground electronic state, the excited vibrational levels are eventually transferred into the lowest possible vibrational level, $v = 0$. The optical pumping



Cool it. Potential energy curves of a diatomic molecule AB. The lower curve is the ground electronic state; the upper curve is an excited electronic state. Ultracold molecules are produced initially in the ground electronic state but in a level of high vibration. They are transferred to a lower level of vibration by absorbing laser light (upward arrow), then returning to the ground state by either radiative decay [path 1, used in (*2*)] or stimulated emission with another laser [path 2, used in (*3, 4*)].

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is special in two regards. First, it uses ultrafast laser pulses that are spectrally broad enough to excite all the relevant vibrational levels. Second, the spectrum is shaped to eliminate all frequencies that would excite from $v = 0$. As a result, molecules are trapped in $v = 0$, so after many incoherent cycles of excitation and decay, they accumulate in this "dark" state. Ironically, it is exactly this dark-state population trapping that has prevented traditional laser cooling of molecular motion. Here, it is put to good use: vibrationally cooling molecules that are already translationally cold.

Danzl *et al.* (*3*) also work with Cs_2 but use magneto-association of a Bose-Einstein condensate of Cs atoms to initially form the molecules. Rather than relying on broadband light to induce multiple absorption/emission cycles, they use a pair of laser beams with precisely defined frequencies to coherently drive the population from the initial state of high vibration, through an electronically excited intermediate state, then back down to a state of low vibration (see the figure). One difficulty with this process is the poor overlap of the wave functions of the highly excited and low-lying vibrational states. However, the lasers used for this two-photon process are locked to a frequency comb, and therefore highly coherent, allowing a long interaction time (10 µs) and efficient transfer (80%) to the lower energy state. Danzl *et al.* can remove 0.13 eV of vibrational energy, which puts them one-fourth of the way to $v = 0$. They are optimistic that by applying one more judiciously chosen two-photon process, they can reach the absolute ground state.

The technique used by Ni *et al.* on page 231 of this issue (*4*) is very similar to that of Danzl *et al.* but is applied to a rather different molecule, KRb. They report 56% transfer from the barely bound initial state to $v = 0$ of the lowest triplet electronic state, which is bound by 0.03 eV. Even more impressive is their demonstration of 83% transfer, using an intermediate state of mixed triplet-singlet character, to $v = 0$ of the lowest singlet electronic state. This is the absolute ground state of the system, bound by a whopping 0.52 eV. The fact that the KRb molecule is composed of two different atoms means that, as observed in this experiment, it possesses an electric dipole moment.

There is currently a great deal of interest in dipolar systems at low temperatures and high densities. Interactions between dipoles are both long range and anisotropic: Two dipoles oriented head-to-tail attract; side-by-side they repel. So, for example, a confined pancake-shaped sample will tend to be stable, whereas a cigar-shaped sample will tend to collapse. Such dipolar effects have begun to be observed in systems of magnetic dipoles (*12*), but the interactions will be much stronger between electric dipoles, enabling applications such as the modeling of complex many-body systems. Dipole-dipole interactions may also enable communication between cold molecule qubits in a quantum computer (*13*) and affect ultracold chemical reactions. For all these potential applications, a large dipole moment is desired. In states of high vibrational excitation, the atoms live far apart and the dipole moment is small; hence, the motivation for eliminating vibration.

Another compelling reason for going to the absolute ground state is a purely practical one: stability. All other states are unstable against inelastic collisions, which is a problem at high density. This recent progress toward populating the lowest-energy state therefore bodes well for producing a stable Bose-Einstein condensate or degenerate Fermi gas of molecules. Such systems will prove useful in exploring exotic quantum phases of matter and performing quantum simulations of highly correlated condensed matter systems.

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10.1126/science.1164990

EVOLUTION

Armor Development and Fitness

The fitness of stickleback fish that develop different numbers of external bony plates varies between oceanic and freshwater environments.

William A. Cresko

Nearly 150 years after the publication of the *Origin of Species*, it is humbling to contemplate how well Darwin outlined the processes of evolution. The heritable basis of traits confounded him, however, and evolutionary biologists have since attempted to connect the processes of natural selection and genetic drift with the origin and distribution of genetic variation in the wild (*1*, *2*). A flurry of recent work mapping phenotype to genotype has identified the molecular genetic basis of some traits in natural populations (*3*, *4*), but documenting the fitness consequences of these genes has been more elusive. An important study by Barrett *et al.* on page 255 in this issue (*5*) attempts to fill this gap by studying changes in allele frequencies in replicate populations of the threespine stickleback (*Gasterosteus aculeatus*), thereby adding an intriguing new wrinkle to a rapidly developing story.

Stickleback that originate in the ocean and subsequently become isolated in freshwater environments rapidly evolve the loss of external bony lateral plates (*6*). A major genetic factor on linkage group IV (the part of the genome corresponding to the largest stickleback chromosome) was implicated in this loss of armor in multiple populations (*7*, *8*). "Low" alleles of the gene *ectodysplasin-A* (*Eda*)—which encodes a signaling molecule involved in ectodermal outgrowths such as hair, scales, and teeth—were subsequently associated with the loss (*9*). Barrett *et al.* screened thousands of oceanic stickleback to find those heterozygous at the *Eda* locus—carrying one low and one "complete" allele, the latter of which encodes for the development of a full set of lateral plates. These fish were then introduced into freshwater ponds and quickly produced offspring that were sampled and genotyped at *Eda* throughout a full year (one stickleback generation). As expected, there was very strong selection (a selection coefficient of $s \sim 0.5$) for the low *Eda* allele in offspring fish that became large enough to have developed the complete set of plates (see the figure). This fitness differential could be due to the burden of forming and maintaining lateral plates, with the low *Eda* allele conferring higher

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