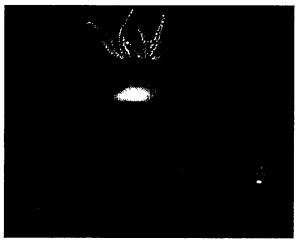
proach called "association analysis" that, while offering compelling evidence, falls short of giving absolute proof that a particular gene influences a given trait. This is where Tanksley and co-workers break new ground. Having cloned *fw2.2*, they transformed the wild version of the gene into a cultivated tomato, and the transformed plants showed the expected decrease in fruit weight. Remarkably, the observed decrease in the fruit weight of transformed plants was of the expected magnitude, demonstrating that there are no additional fruit weight QTLs nearby on the chromosome. The use of transformation to confirm the cloning of a gene has been the "gold standard" in most areas of genetics, but prior to this, quantitative geneticists relied almost exclusively on statistical or correlative evidence.



You like tomato, and I like tomah-to. Fruits from the wild tomato species *Lycopersicon pimpinellifolium* **(right)** and the cultivar Giant Red (*L. esculentum* cv), bred to produce very large tomatoes **(left)**. [Source: (*2*)]

The difficulties associated with the analysis of quantitative traits have left many questions unanswered. For example, how many QTLs typically control quantitative traits, and how large are their effects? One viewpoint has been that the number of QTLs for each trait is so large (100 or more) and their individual effects so small that there is no hope of studying QTLs individually (*8*). Given the nature of the experimental evidence, this is a reasonable position. However, in the case of *fw2.2*, this view does not apply. The effects of *fw2.2* are sufficiently large (adding 17 grams to a tomato) that one can easily see the difference [see Fig. 1B in (*2*)]. Again, because Tanksley and colleagues have used transformation, skeptics will not be able to dismiss their results as correlative. As additional QTLs are cloned and transformation experiments performed, the genetic control of quantitative traits will come more sharply into focus.

The cloning of *fw2.2* is a remarkable achievement, but from beginning to end it has taken a decade to accomplish. One might expect that cloning of the next 27 QTLs for fruit weight will require a couple of centuries. Happily, advances in genomics will greatly expedite QTL cloning in the future. Publicly available high-density marker maps will enable researchers to zero in on QTLs rapidly, eliminating the need for each lab to pioneer the development of markers around their QTLs. Once the mapping is done, the complete sequence of the genome will enable researchers to order their genes from clone banks, eliminating the tedious process of constructing and screening genomic libraries.

Unlocking the secrets of quantitative variation is probably the greatest challenge facing geneticists in the 21st century. For even after genomes have been sequenced and the functions of most genes revealed, we will have no better understanding of the naturally occurring variation that determines why one person is more disease prone than another, or why one variety of tomato yields more fruit than the next. Identifying genes like *fw2.2* is a critical first step toward attaining this understanding.

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PERSPECTIVES: CHEMISTRY

Superacids—It's a Lot About Anions

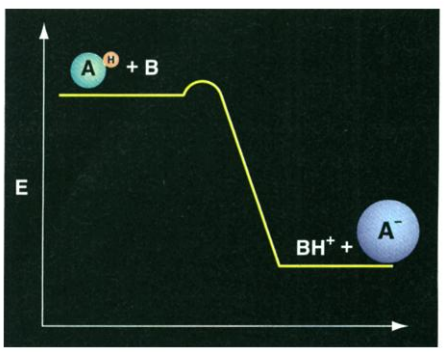
Darryl D. DesMarteau

The term superacid was first proposed in 1923 by Conant to describe acid systems stronger than conventional mineral acids (*1*). Much later, Olah popularized the term in the study of stable carbocations in highly acidic media (*2*). According to Gillespie's arbitrary but now widely accepted definition, a superacid is an acid system stronger than 100% sulfuric acid (*3*). On page 101 of this issue, Reed *et al.* (*4*) report the synthesis of a new superacid that is not only strong, but also gentle. This remarkable acid can protonate and stabilize HC_{60}^+, and its conjugate base can stabilize C_{60}^+.

The ideal superacid, HA, should be capable of protonating a weak base, B, in a variety of solvents, and the resulting A^- should not interact with the BH^+ formed. One can envisage HA as a large ball with a small proton attached (see the figure), soluble in an unreactive solvent and able to donate a proton to a weak receptor (see the figure). Upon loss of the proton, the negative charge is delocalized over the entire sphere, thus stabilizing it and providing little if any interaction with BH^+. Reed *et al.* (*4*) report the discovery of such an ideal superacid in the carborane species $H(CB_{11}H_6X_6)$, with X = Cl, Br. The large stable sphere is the $(CB_{11}H_6X_6)^-$ icosahedral cluster. The use of this novel superacid has already led to exciting new insights into the chemistry of the C_{60} fullerene.

Well-known examples of superacids include the oxyacids FSO_3H, CF_3SO_3H, and ClO_4H. The conjugate bases of these acids are the resonance-stabilized anions FSO_3^-, $CF_3SO_3^-$, and ClO_4^-. But in the presence of strong electrophiles, these small anions exhibit important interactions through their oxygen atoms and, in case of FSO_3^-, also the fluorine atom. These interactions can lead to a number of undesirable effects, such as oxidation and fluoride ion transfer.

The acidity of many Bronsted acids (proton donors) can be greatly enhanced by the addition of a strong Lewis acid (an electrophilic substance) (*5*), because the Lewis acid increases the concentration of solvated protons in the acid medium by forming a complex with the conjugate base of the acid. Antimony pentafluoride is the most powerful Lewis acid; when added, for example, to FSO_3H, the acidity is increased by many orders of magnitude over the pure FSO_3H. Also, the larger $FSO_3SbF_5^-$ anion (and other more complex anions formed) is a weaker nucleophile than FSO_3^- alone. These factors combine to allow the study of much stronger



The role of the anion in superacids. Efficient delocalization over the anion is important to avoid strong interactions with the protonated base.

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electrophiles than is possible with pure FSO_3H.

The highest known acidities have been achieved with HF/SbF_5 (*6*). Anhydrous HF is a relatively weak acid, but at near $HF/SbF_5 = 3/1$, the acidity is enormous. However, this mixture is rather unsuitable for many applications requiring a superacid: SbF_5 is strongly oxidizing, the mixture is somewhat of a vegetable soup of complex ions, it is poorly soluble in and reacts with many cosolvents, and HF is a very hazardous chemical. This system shows clearly that for many applications of superacids, more is needed than just very high acidity. A user-friendly conjugate base is equally important, allowing strong electrophiles to be studied in solution and the solid state without strong interactions with the solvent or the conjugate base of the superacid. The study of acid-base reactions in the gas phase also requires a superacid capable of existing as a molecular species in the gas phase.

Research toward these general goals has evolved in two related but different directions: new molecular acids in which the conjugate base would be more stabilized and less reactive and very weakly coordinating anions as the conjugate bases of hypothetical superacids.

One route to potential new molecular superacids involved moving away from oxyacids. Using the powerful electron-withdrawing group CF_3SO_2, very strong acids based on nitrogen and carbon can be prepared. Examples are $(CF_3SO_2)_2NH$ and $(CF_3SO_2)_3CH$, the parent members of the more general families $(R_fSO_2)_2NH$ and $(R_fSO_2)_3CH$, where R_f are a wide variety of fluorinated groups. In the conjugate bases of these acids, the negative charge is delocalized over more atoms than in the related oxyacid CF_3SO_3H. The high acidity of these species has been demonstrated in the gas phase, where they are stronger acids than CF_3SO_3H. The strongest acid yet measured in the gas phase is the sulfonimide $(C_4F_9SO_2)_2NH$ (*7*). The sulfonimides are a particularly versatile class of acids. They can be prepared in a large variety and are easily incorporated into polymeric systems. They are currently of interest in many applications including lithium batteries, polymer membrane fuel cells, photoacid generators, ionic liquids, and catalysis (*8*).

Another route to very weakly coordinating anions uses bulky electron-withdrawing groups around a typical Lewis acid central atom. Here, the parent superacid HA might not exist as an isolable compound or might not be a superacid in the usual sense. The forerunner to this approach is the tetraphenylborate anion $B(Ph)_4^-$. Incorporating fluorine atoms and fluorinated groups onto the phenyl rings, as in $B(C_6F_5)_4^-$ and $B[3,5\text{-}C_6H_3(CF_3)_2]_4^-$, lowers the coordinating ability. Very weakly coordinating anions were realized with the large electron-withdrawing substituent TeF_5O (*9*). For example, the anions $Nb(OTeF_6)_6^-$ and $Sb(OTeF_6)_6^-$ were prepared based on the strong Lewis acids NbF_5 and SbF_5. The negative charge of these large spherical anions is distributed over the 36 fluorine atoms, which form a protective shield around the central atoms and lead to high kinetic stability of the anions. Salts of electrophiles, such as $AgSb(OTeF_5)_6$, are remarkably soluble in low-polarity solvents like dichloromethane. The resultant naked Ag^+ is then forced to become less "naked" by coordinating to the dichloromethane, a phenomenon not previously observed.

However, even these large anions show weak interactions with electrophiles in the solid state through the fluorine atoms of the TeF_5O groups. To obtain even more weakly coordinating anions, chemists turned to carboranes as a potential building block for the ultimate superacid.

The carborane anion $CB_{11}H_{12}^-$ was recognized as having high potential for this purpose. The challenge was how to modify it into the conjugate base of a superacid. Several approaches have been pursued by substituting the hydrogen by halogens (F, Cl, and Br) and fluorinated groups like trifluoromethyl. These new directions in superacids are exciting and hold promise for both fundamental science and novel applications. The late Robert W. Taft dreamed of a superacid so strong that it would undergo spontaneous ionization into a plasma of protons in the gas phase. This dream may be coming closer to reality.

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PERSPECTIVES: MOLECULAR BIOLOGY

Transposase Team Puts a Headlock on DNA

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Transposable DNA elements (transposons) populate the genomes of numerous organisms, from bacteria to humans. These genetic elements "jump" from old to new DNA locations, a process that mutates genes, rearranges chromosomes, and transmits genetic information between cells. Transposons, along with their retroviral cousins (for example, HIV), relocate through a common set of DNA cleavage and joining reactions (*1*). The proteins catalyzing these reactions (transposases and integrases, respectively) are encoded in the DNA of the mobile element and share structurally related catalytic regions (*2*). How do these proteins cleave both ends of the linear element (which may be far apart) and then join them to a new, distant DNA site? The first structure of a transposase-DNA complex, described by Davies *et al.* (*3*) on page 77 of this issue, begins to reveal the molecular details of this process.

Transposition and retroviral integration start with assembly of a protein-DNA complex. By binding to sequences near each end of the mobile element, transposases and integrases pair both DNA ends within the complex. Only after formation of this complex can these enzymes catalyze their reactions. In the bacterial Tn5 transposase-DNA complex reported by Davies *et al.* (*3*), two transposase molecules (subunits) pair the two DNA ends in a manner poised for catalysis. How does assembly of this DNA-protein complex control catalytic activity? One possibility is that the enzyme's active sites are constructed only upon formation of the complex. The Tn5 structure shows, however, that each active site is composed entirely of amino acids from one subunit. The geometry of the catalytic amino acids closely resembles that found in the active site of a non–DNA-bound version of the protein (*4*). This similarity suggests that, at least for Tn5 transposase, most features of the active site are not dependent on complex assembly.

Given that each transposase molecule comes armed with an intact active site, why does enzyme activity require complex assembly? Within the Tn5 complex, each DNA end is positioned within an active site by extensive protein-DNA contacts made by both transposase subunits. Amino acids near the

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