that the "better" measures won't improve power to find genetic effects. However, cigarette consumption can be measured very reliably (i.e., precisely and accurately), but it still is not necessarily a reliable measure of actual tobacco exposure. Years of education can certainly be measured precisely, but it is still a noisy phenotype given the wide range of attainment and experiences that may result from the same number of years of education. Ultimately, in the case of the study by Rietveld *et al.*, the question remains: What, exactly, is being measured? It seems that a genetic association has been observed for "something," but exactly what will require considerably more work. The

nebulous nature of the phenotype makes this task considerably more difficult than in the case of heaviness of smoking.

A reasonable assumption is that educational attainment, and the years spent in schooling, partly reflects intellectual ability; those with a higher intelligence quotient (IQ) generally do better at school. So is this, by the backdoor, the first successful study of the genetics of IQ? That will certainly reignite some old disputes.

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CHEMISTRY

Seeing the Reaction

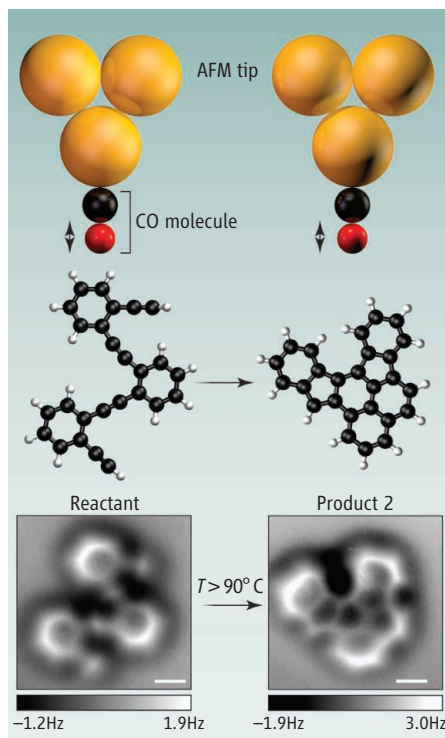**Franz J. Giessibl**

A molecule is imaged at atomic resolution as it undergoes a chemical reaction.

What happens as a molecule goes through a chemical reaction? Model studies have provided important insights into these processes, but it remains extremely difficult to follow all the atomic rearrangements of a chemical reaction experimentally. In many cases, a reaction cannot be observed directly in real space, for example, because the reactants are in the gas state, zooming around at the speed of sound. On page 1434 of this issue, de Oteyza *et al.* (*1*) report atomically resolved imaging of a complex molecule as it undergoes a chemical reaction on a metal surface.

The authors investigated the molecule phenylene-1,2-ethynylene ($C_{26}H_{14}$) adsorbed on a silver surface. Upon heating above 90°C, the molecule split into several different chemical products (see the figure). The authors imaged several different products with scanning tunneling microscopy and identified them with the help of noncontact atomic force microscopy (*2*). They calculated the reaction pathway by density functional theory.

Three challenges had to be met to successfully perform this experiment. First, the authors had to find and synthesize a molecule that undergoes a reaction within the experimentally accessible temperature range, with both reactants and products remaining attached to the metal substrate

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Before and after. Schematic view of the reactant phenylene-1,2-ethynylene molecule (left) and product 2, one of three different products imaged by de Oteyza *et al.* with atomic force microscopy (AFM). Previous AFM studies focused on imaging individual molecules. Several challenges had to be overcome to extend the method to imaging both the reactant and the reaction products.

surface within a viewing field accessible by the microscope.

Second, they had to overcome the "fat and sticky finger problem" (*3*), which arises because the metal atoms of the probe are large relative to the hydrogen and carbon atoms in organic molecules and exert relatively large attractive forces (*4*). Meyer and co-workers have found a fine solution to this problem by attaching a carbon monoxide

molecule to the end of the metal tip, which enabled unprecedented spatial resolution of pentacene, an organic molecule (*5*). This is the imaging method used by de Oteyza *et al.*

Third, the force sensor that holds the metal tip had to be sufficiently sensitive to probe the tiny forces between the carbon monoxide molecule and the organic molecule to be probed. To obtain their results, de Oteyza *et al.* had to operate their atomic force microscope in the small-amplitude mode and perform highly precise frequency measurements (*6*). Further challenges were associated with the complex sample and tip preparation and with heating the sample to initiate the reaction and then cooling it to image acquisition temperature. Overall, the work is a masterful experimental achievement.

The interpretation of image data is comparatively simple for flat hydrocarbons [such as pentacene (*5*) and phenylene-1,2-ethynylene studied by de Oteyza *et al.*], where the submolecular contrast is due to Pauli repulsion between the oxygen atom that terminates the tip and the carbon and hydrogen atoms that constitute the molecule (*7*). The flat orientation of the molecule results in a

constant van der Waals background force between the tip and the metal substrate, also simplifying data interpretation. Recently, Gross et al. were even able to determine the bond orders within cyclic hydrocarbons and fullerenes with force microscopy (8).

When elements such as nitrogen and oxygen are present, as in the case of cephalandole A (9), image interpretation becomes more complicated, because whereas the carbon monoxide tip is repelled by carbon and hydrogen, it is attracted to nitrogen and oxygen. Atomic identification of single chemical species by force spectroscopy, pioneered by Sugimoto et al. (10) for semiconductor surfaces, might become feasible for the chemical analysis of individual atoms in single molecules. This would allow the study of reactions of more complex individual molecules.

The study of molecules that are not flat is also very challenging, because force microscopy senses short- and long-range forces (6), and long-range forces change dramatically with distance. Recently, Repp and co-

workers successfully imaged dibenzo[a,h]thianthrene, a butterfly-shaped molecule with the body flat on the surface and the two wings reaching up from the surface (11). The authors brought the oscillating tip very carefully to the molecule and used a combined method of tunneling current feedback while recording the frequency shift for determining the adsorption site. To extend the method to even more challenging three-dimensional molecules such as DNA, not only the tip-terminating carbon monoxide molecule at the front end would be important but the overall sharpness and crystallographic orientation of the tip would need to be known (12).

The observation of chemical reactions by force microscopy at submolecular resolution reported by de Oteyza et al. is of great value in cases where a reaction results in an ensemble of products, as in the decay of phenylene-1,2-ethynylene. It also appears possible to induce the formation of chemical bonds by forces exerted by the tip of the atomic force microscope, similar to reactions induced by tunneling currents (13) or

the flipping of atom dimers on a semiconductor surface (14). Twenty-seven years after Binnig, Quate, and Gerber introduced the atomic force microscope (15), it remains exciting to watch what this technological marvel holds in store for the future.

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SOCIOLOGY

A Theory of City Size

Michael Batty

A theory explaining how the attributes of cities scale with city size may help to inform urban planning.

As cities get bigger, they generate economies and diseconomies of scale, referred to by Marshall more than a century ago as the effects of agglomeration (1). Simple theories assume that cities exist due to a trade-off between these positive and negative forces of agglomeration and that the benefits continue to outweigh the costs of cities as they grow ever larger (2). But precisely what happens as cities grow? On page 1438 of this issue, Bettencourt (3) shows that the ways in which people interact with one another in cities lead to power laws—or allometric laws—that relate population, area, and attributes of the population to scale.

Bettencourt et al. have previously demonstrated the qualitative changes associated with the scale of cities (4). The larger a city, the greater the benefits with respect to attributes such as income earned, but also the greater the costs with respect to social interactions such as crime (4). There are also gains in efficiency of infrastructure provision, because as

cities get larger, they use less space per capita for utilities, transport routes, and residential living. These allometric laws are demonstrable for socioeconomic attributes such as income, the production of patents, financial services, and crime, all of which scale superlinearly with respect to population.

There is substantial evidence for these scaling relationships in countries such as in the United States, where cities are widely spaced and do not generally merge into one another. It is even consistent for countries that have dominant, or so-called single primate cities unrivaled by others, such as London, which tend to be outliers in city systems that do not manifest clear scaling. Bettencourt develops a theory based on a social dynamic that accounts for these observations. His argument turns on associating the trade-off between the positive feedback associated with social interactions generating more than proportionate increases in resources and the negative feedbacks resulting from mixing of populations over ever larger areas as cities get bigger. These negative feedbacks include those associated with travel and congestion.

This simple but appealing and plausible idea resonates with what we know about cities. The power of Bettencourt's analysis is to show how the trade-off between benefits and costs leads to increases in quantities that vary superlinearly with population size, such as income and resources, and infrastructures that vary sublinearly, such as the areas and lengths of physical links such as streets. He disentangles this theory by associating the ways in which we build infrastructures incrementally as treelike networks, showing that his derivations of scaling relations can be related to the underlying fractal geometry of the cities under scrutiny (5).

Bettencourt develops a recursive formulation for this geometry, using analogies with electric circuits to show how energy dissipates and scales like human interactions, with the ratio of income to total power used being a constant with respect to city size. He then reworks this framework using a maximization of the differences between income and energy with respect to average social outputs subject to known constraints. This implies the same kinds of scaling that are introduced in his initial discussion of

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Editor's Summary

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