whose by-product after reaction is water.

The products of the catalytic reaction described by Uyanik et al. create the framework for a number of natural products with varied biological effects. The benzofuran products can form the starting point for the synthesis of more complex pharmaceutical candidates. For example, tremetone has both antifungal and insecticidal properties and is derived from a plant extract. A similar plant isolate, rotenone, is a potent anti-leukemic drug candidate as well (14). In 2005, the Merck Company reported the synthesis of a drug candidate with this same backbone that modulates the levels of serum triglycerides and high-density lipoprotein in the blood (15). A synthesis of this target with this new method could be accomplished in fewer steps than the 2005 method, produce less waste, and reduce cost.

The future of hypervalent iodine is likely to be as varied as the chemists working in this area. Elucidating the mechanism, including the steps that lead to a chiral product, will allow for further improvements in selectivity. Ideally, this catalyst system, like any catalyst developed, will be tested on other substrates and reactions involving iodine-containing catalysts. Iodine chemistry, with its versatile reactivity, is an excellent area to discover new, more environmentally friendly, greener organocatalysts. The chemistry described by Uyanik et al. is but a taste of what is to come.

Guiding iodine catalysts to their targets. (**A**) In the reaction described by Uyanik et al., hydrogen peroxide reacts with the salt formed by a chiral ammonium cation (R_4N^+) and iodide, making water and oxidized iodine. This hypervalent (hypo)iodite then reacts with the ketophenol to generate the chiral benzofuran skeleton, where X can be one of many different functional groups. The reaction shows excellent selectivity for one of the two products that differ in handedness (in this case, the favored product has the COX group behind the plane formed by the rest of the molecule; the other enantiomer has this group in front). The compound is a starting point for a host of pharmaceutical candidates. (**B**) The structural formula of the chiral ammonium cation is shown on the left. The three-dimensional rendering of the chiral ammonium salt on the right has the nitrogen atom in blue and carbon atoms in gray; hydrogen and fluorine atoms are omitted for clarity.
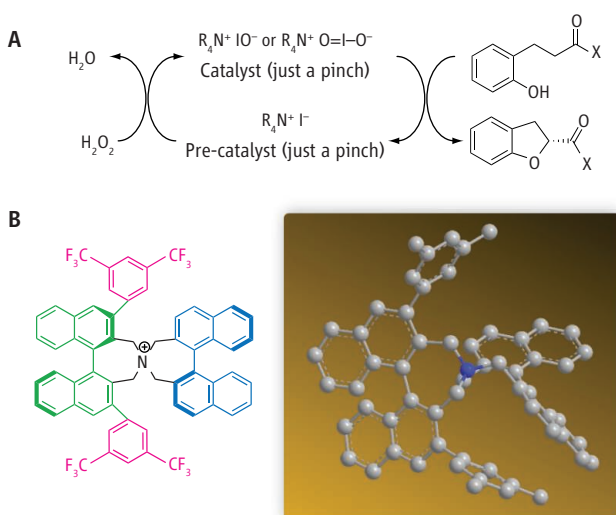
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ATMOSPHERIC SCIENCE

Getting to the Critical Nucleus of Aerosol Formation

A better understanding of how aerosols form in the atmosphere could greatly improve climate models.

Renyi Zhang[1,2,3]

Atmospheric aerosols—microscopic particles suspended in Earth's atmosphere—are a major environmental problem. They degrade visibility, negatively affect human health, and directly and indirectly influence climate by absorbing and reflecting solar radiation and modifying cloud formation. Researchers do not, however, fully understand at the molecular level how aerosols form, creating one of the largest sources of uncertainty in atmospheric models and climate predictions (1). Recent findings suggest a path to a better understanding of aerosol formation (2–4).

Aerosols can be directly emitted into the atmosphere—for example by plants, combustion, or sea spray—or form through a chemical process known as nucleation, in which gaseous molecules bond. Nucleation produces a large fraction of atmospheric aerosols, and investigators have frequently observed nucleation in various environments, including urban, forested, and marine areas (5). New particle formation is commonly considered to be a two-step process: First, nucleation forms a "critical nucleus," which then grows to a detectable size (6). Classical nucleation theory reveals that when the critical nucleus forms, the free energy of the nucleating system reaches a maximum—"the nucleation barrier"—beyond which aerosol growth becomes spontaneous. The rate at which nucleation occurs is related to the chemical makeup of the critical nucleus and the gaseous concentrations of the nucleating species (7). That rate is an important variable in simulations of aerosol formation in atmospheric models (8).

Previous studies, however, have not been able to directly measure nucleation rates

[1]State Key Joint Laboratory of Environmental Simulation and Pollution Control, College of Environmental Sciences and Engineering, Peking University, Beijing, 100871, China. [2]College of Environmental Science and Engineering, Fudan University, Shanghai, 200433, China. [3]Departments of Atmospheric Sciences and Chemistry, Center for Atmospheric Chemistry and the Environment, Texas A&M University, College Station, TX 77843, USA. E-mail: renyi-zhang@tamu.edu

or the chemical composition of the critical nucleus in binary or multicomponent systems like those found in the atmosphere. Theoretical methods have also failed to reliably identify the nucleation barrier (9, 10). As a result, investigators have indirectly inferred the composition of the critical nucleus by measuring the dependence of the nucleation rate on the gaseous concentrations of the nucleating species (2–5, 11–13).

Sulfuric acid, for instance, is a major nucleating component in the atmosphere. Its presence in gaseous concentrations of 10^6 to 10^7 molecules cm^{-3} or more is a necessary condition for new particle formation (5). Atmospheric measurements have suggested that nucleation rates depend weakly on sulfuric acid concentrations, implying that just one or two sulfuric acid molecules are present in the critical nucleus (5). In contrast, laboratory studies suggest that nucleation rates depend more strongly on sulfuric acid concentrations, corresponding to a critical nucleus of four to nine sulfuric acid molecules (11–13). This larger number agrees with predictions under classical nucleation theory (7).

In recent laboratory experiments, Sipilä et al. reported rapid binary nucleation of sulfuric acid at concentrations comparable to those found in the atmosphere; their finding implicated a critical nucleus consisting of one or two sulfuric acid molecules (2). The difference between these results and previous laboratory measurements is explained by the authors' use of an improved instrument that can count particles as small as 1.5 nm. Previous measurements were limited by a low counting efficiency for particles smaller than 3 nm, resulting in appreciable underestimates of the nucleation rate. Sipilä et al.'s conclusion that nucleation weakly depends on the concentration of sulfuric acid raises an important question: Are one or two sulfuric acid molecules (a monomer or dimer) enough to form a critical nucleus?

Several lines of evidence suggest that the answer should be "no." Molecular dynamics simulation, for instance, suggests that a hydrated sulfuric acid dimer has a diameter of 0.7 nm, which is commonly believed to be too small to overcome the nucleation barrier (7). Quantum chemical calculations show the existence of two medium-strength hydrogen bonds in the sulfuric acid dimer, and the available thermodynamic data predict that the dimers would rapidly decompose under typical atmospheric concentra-

1.4 nm
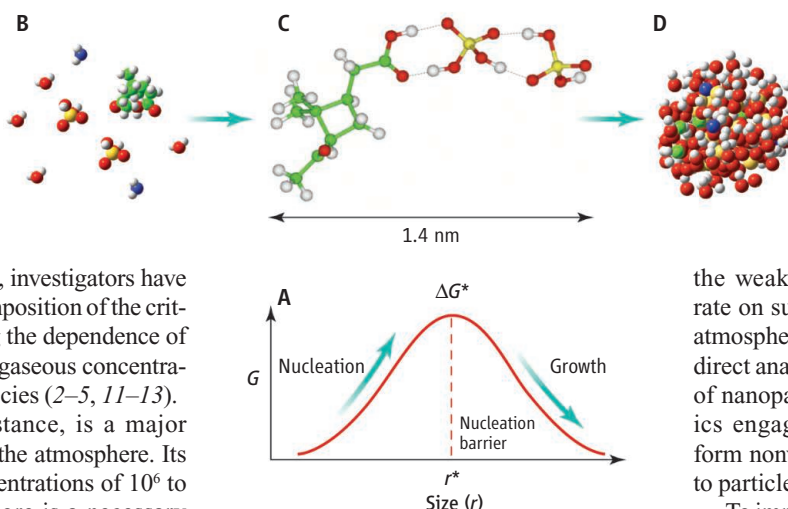
Organics-assisted aerosols. In aerosol formation, bonding particles must cross an energy threshold—the nucleation barrier—beyond which aerosol growth becomes spontaneous (**A**). Organic acids (**B**) (carbon in green) that mingle with gaseous sulfuric acid (sulfur in yellow) could facilitate the crossing of the barrier by creating a critical nucleus with one or two sulfuric acid molecules (**C**), leading to aerosol growth (**D**). Knowing the composition of the critical nucleus would enable researchers to predict the nucleation rate, an important variable in atmospheric models (16).

tions of sulfuric acid (10^6 to 10^8 molecules cm^{-3}) (9, 10).

Metzgera et al. and others, however, suggest that it is highly plausible that the answer is "yes" if other sulfuric acid–stabilizing species are involved in nucleation and are present in the critical nucleus (3, 8). One candidate is organic acids, because they form larger and more stable heterodimers with sulfuric acid (4, 9, 10, 12). The interaction between an organic acid and sulfuric acid involves one strong and one medium-strength hydrogen bond, with a binding energy that is 2 to 3 kcal mol^{-1} larger than that of the sulfuric acid dimer (9, 10), and the heterodimer has a vacant OH group in the sulfuric acid moiety to allow further growth through hydrogen-bond formation. A dimer of two organic acids also has a large binding energy (9), but no hydrogen acceptor or donor group is available for subsequent growth, so organic acid dimers contribute negligibly to new particle formation (4).

Several studies indicate that the critical nucleus consists of only one molecule of the organic species (3, 4). The presence of organic acids in laboratory-produced nanoparticles has been confirmed in particles as small as 4 nm (4). In addition, atmospheric concentrations of organic acids are expected to be much higher than that of sulfuric acid,

because of photochemical oxidation of volatile organic compounds abundantly emitted by biogenic and anthropogenic sources (8, 14). The presence of organic acids could enable fewer sulfuric acid molecules to form a critical nucleus (see the figure), and would explain the weaker dependence of the nucleation rate on sulfuric acid concentration found in atmospheric measurements (3, 8). Moreover, direct analyses of the chemical compositions of nanoparticles have suggested that organics engage in heterogeneous reactions to form nonvolatile compounds that contribute to particle growth (15).

To improve models used to assess the environmental and climate impacts of aerosols, it is imperative for future studies to precisely quantify the chemical makeup of the critical nucleus. This may be accomplished by augmenting advanced theoretical approaches (i.e., quantum chemical or molecular dynamics simulations) with simultaneous measurements of the size and chemical composition of freshly nucleated nanoparticles in the laboratory and in the field.

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