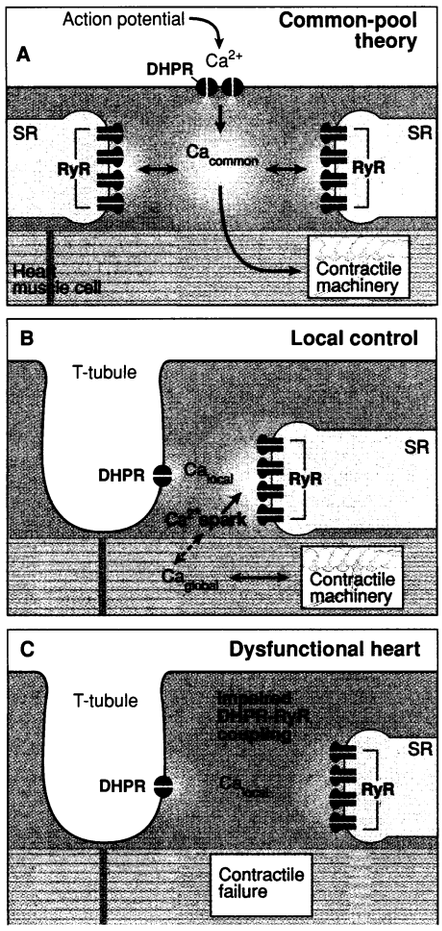

Excitation-contraction coupling in heart, then and now. (**A**) Classic, common-pool theory of EC coupling. (**B**) Current, local-control mechanism of EC coupling. (**C**) Defect in EC coupling during heart dysfunction (*1*).

has proven problematic for the common-pool theory. The most striking evidence for a new "local-control" mechanism of EC coupling comes from confocal microscopic visualization of punctate, transient increases of intracellular Ca^{2+} ("Ca^{2+}sparks") (*7*), thought to arise from the opening of one or a tight cluster of RyRs in close proximity to one (or a few) DHPRs in the t-tubules (part B). In the local-control mechanism, the intimate juxtaposition of a DHPR and a cluster of RyRs (forming a local response element) may enable Ca^{2+} influx through one opening of a single DHPR to increase a local pool of Ca^{2+} (Ca_{local}) sufficiently to open adjacent RyRs, thereby producing a Ca^{2+} spark. All of this can occur locally, without appreciable perturbation of a global pool of Ca^{2+} (Ca_{global}). If enough DHPRs open, multiple Ca^{2+} sparks are recruited and coalesce to increase Ca_{global}, resulting in macroscopic activation of the contractile machinery.

The new results in this issue (*1*) reveal which steps in the local-control mechanism are impaired in two forms of cardiac dysfunction. In hypertension, heart cells compensate for the increased pressure afterload by growing larger (hypertrophy). Despite their enhanced stature, hypertrophied cardiac cells can demonstrate impaired contraction. By relating the magnitude of Ca^{2+} currents flowing through DHPRs to the rate of Ca^{2+}-spark production, the authors cleverly deduce that the ability of DHPR openings to activate adjacent RyRs is markedly suppressed in hypertrophied cells. Surprisingly, additional experiments exclude the involvement of other steps in the local-control mechanism, such as altered DHPR or RyR function, revealing impaired coupling between adjacent DHPR and RyR molecules as the primary defect in the overall contractile failure. If hypertension persists, hypertrophied hearts may progress to a form of congestive heart failure. The investigators find a remarkably similar defect in DHPR-RyR coupling of cells derived from such failing hearts, hinting that a common defect may underlie various forms of cardiac dysfunction. One possible explanation for the impaired coupling is that changes in the microarchitecture of local response elements result in suboptimal spacing between adjacent DHPR and RyR molecules (part C).

Whether this defect in EC coupling generalizes to other forms of heart dysfunction remains to be explored. In addition, in skeletal and smooth-muscle myocytes, as well as neurons, Ca^{2+}-signaling molecules are also juxtaposed to permit rapid, tête-à-tête communication through Ca^{2+} sparks or their analogs (*8*). Coupling defects between adjacent signaling molecules may be the basis for disease in other tissues, as well.

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ORGANIC CHEMISTRY

Catching an Elusive Cation

G. K. Surya Prakash

One of the major achievements of modern chemistry was the development of methods for the direct spectroscopic characterization of short-lived reaction intermediates. The observation of positively charged carbocation intermediates in the condensed phase under long-lived stable ion conditions in superacidic media was pioneered by Olah in the early sixties (*1*). With superacids as the reaction media, a wide variety of trivalent carbenium ions, hypercoordinated carbonium ions, acylium, carboxonium, halonium, oxonium, sulfonium, azonium, and related systems have been subsequently prepared and characterized by a host of spectroscopic techniques, including single-crystal x-ray diffraction studies (*1*, *2*). The formyl cation (HCO^+) is one of the most significant intermediates invoked in electrophilic formylation reactions of aromatic compounds [the Gatterman-Koch reaction (*3*)], but it has eluded direct observation under long-lived conditions in the condensed phase. As de Rege *et al.* report on page 776 of this issue, the formyl cation has been now characterized (*4*).

The formyl cation has previously been spectroscopically detected as an abundant species in interstellar dust clouds (*5*), and its identification has been confirmed in the gas phase by a variety of methods including microwave, infrared, and mass spectrometry (*6*). It is easily generated in the gas phase by electron-impact ionization of CH_3OH or by direct protonation of CO (which has a high proton affinity of 145.6 kcal/mol). In spite of the stability of the formyl cation in the gas phase, all previous attempts (*7*) to observe it under long-lived superacidic conditions were unsuccessful. Direct protonation of CO in highly acidic media such as FSO_3H-SbF_5 [known as Magic Acid (*1*)] or HF-SbF_5 at atmospheric pressures was inconclusive. Ionization of formyl fluoride in SbF_5 or by cleavage of protonated formic acid in superacid was also futile (*7*). In these experiments, only dissolved CO was observed by ^{13}C nuclear magnetic resonance (NMR) spectroscopy, indicating the difficulty in generating the

The author is at the Loker Hydrocarbon Research Institute and the Department of Chemistry, University of Southern California, Los Angeles, CA 90089–1661, USA. E-mail: prakash@methyl.usc.edu

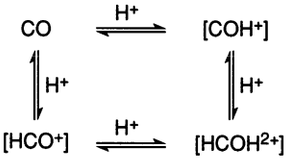
long-lived HCO^+ under such conditions in sufficiently high concentration. On the other hand, CO readily reacts with carbocations (*1*) and halogen cations (*8*) to give the corresponding stable acylium cations (RCO^+, R = alkyl, aryl, vinyl, halogen, and so on). In fact, the acetyl cation (CH_3CO^+) was isolated as the BF_4^- salt as early as 1940 by Seel (*1*).

In an elegant study, chemists from Exxon and the University of Utah (*4*) report the spectroscopic observation of the formyl cation in HF-SbF_5 medium [one of the most powerful Brönsted acids in the condensed phase, about 10^{18} times stronger than 100% sulfuric acid (*1*)] under CO pressure. This intriguing work became possible through a technique developed by the Exxon coauthor, Horváth, which permits the in situ examination of reaction mixtures by NMR and infrared spectroscopy at high pressures, up to 200 atm, with sample tubes constructed of single-crystal sapphire fitted with a titanium head and valve (*9*).

The reaction of ^{13}C-enriched CO with fluoroantimonic acid under varying carbon monoxide pressures up to 85 atm was investigated (*4*). At lower pressures, the O-complexed formyl fluoride–SbF_5 adduct was observed as a doublet of doublets centered at a ^{13}C NMR chemical shift of 179 parts per million (ppm) along with a single peak at 145 ppm in the proton-coupled spectrum at room temperature. Upon additional increase in CO pressure, the signal at 145 ppm moved to 139.5 ppm, with an increase in relative intensity compared with the formyl fluoride complex. At higher temperatures, the two sets of signals merged, indicating an exchange. The single peak at 139.5 ppm has been assigned to the formyl cation, which is consistent with the calculated value in idealized gas phase (136 ppm) by means of the GIAO-MP2 method (*10*). The authors (*4*) have tentatively assigned the 2110-cm^{-1} infrared absorption band to the formyl cation somewhat modified by the influence of the complex anions present in the superacid solution.

Another interesting observation reported is that no ^{13}C-^1H scalar coupling was observed in the ^{13}C NMR spectrum, indicating a fast proton exchange with the acid. This hypothesis was corroborated in the proton NMR spectrum, wherein no separate signal for the formyl cation was observed. Selective decoupling of the acid proton signals results in nuclear Overhauser enhancement of the formyl cation signal in the ^{13}C NMR spectrum. This enhancement is consistent with a rapid proton exchange on the NMR time scale. The authors were unable to freeze-out the exchange by lowering the temperature because of problems related to the viscosity. Furthermore, use of co-solvents of low nucleophilicity to alleviate the viscosity problems did not allow observation of the formyl cation. Interestingly, the acidity of Magic Acid (*1*) was not sufficient for the observation of HCO^+.

The authors' (*4*) interpretation of the fast proton exchange in the formyl cation involving the protoformyl dication and isoformyl cation is still speculative (see reaction scheme). Although protolytic activation of electrophiles to superelectrophiles (*11*) is a well-recognized concept, activation of the formyl cation to protosolvated formyl cation by the acid ($HCO^+\cdots H{\cdot}A$) can also explain the exchange results.



The invoked isoformyl cation (COH^+) has been characterized in the outer space as well as in the gas phase (*6*). However, the energy difference between formyl and isoformyl ions is too large (around 34 kcal/mol) for the latter (*6*) to be involved in the free state during the exchange process.

The report (*4*) does provide convincing evidence for the formation of long-lived formyl cation. The direct spectroscopic characterization of the formyl cation with the novel high-pressure technique may give further impetus for the quest to identify other elusive species such as CH_5^+ (an important intermediate in the superacid-catalyzed polymerization of methane to higher hydrocarbons) (*1*) in the condensed phase.

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Molecules on display

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Arabidopsis central

genome-www.stanford.edu/Arabidopsis/

To call it a small weed would be accurate but unjust. Over the last 20 years, *Arabidopsis thaliana* has become one of the most important model organisms for molecular biology and flowering plant genetics. The *Arabidopsis thaliana* Database is a compilation of links to resources, including genetics data, conferences, and the lab manual for the Cold Spring Harbor course on *Arabidopsis* molecular genetics. Other items include a collection of *Arabidopsis* experimental protocols, and information on the *Arabidopsis* Genome Initiative, a multinational effort to sequence the entire genome.

Monkey brain maps

rprcsgi.rprc.washington.edu/~atlas/

The Template Atlas of the Primate Brain contains 63 drawings created from cryosections of the brain of the long-tailed macaque monkey, an animal widely used in neuroscience research. Ideal for use with noninvasive imaging, the drawings were made from digitized photographs of the cryosections and are presented with stereotaxic coordinates. The images can be viewed with a Web browser or downloaded in Adobe portable document format (PDF) for viewing with the free Acrobat Reader software.

Edited by David Voss

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