Evidence for a Symmetrical Fluoronium Ion in Solution
Mark D. Struble *et al.*
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Evidence for a Symmetrical Fluoronium Ion in Solution

Mark D. Struble, Michael T. Scerba, Maxime Siegler, Thomas Lectka*

Halonium ions, in which formally positively charged halogens (chlorine, bromine, and iodine) are equivalently attached to two carbon atoms through three-center bonds, are well established in the synthetic chemistry of organochlorides, bromides, and iodides. Mechanistic studies of these ions have generated numerous insights into the origins of stereoselectivity in addition and displacement reactions. However, it has not been clear whether fluorine can form a halonium ion in the same manner. We present chemical and theoretical evidence for the transient generation of a true symmetrical fluoronium ion in solution from an appropriately configured precursor.

Halonium ions are organic compounds in which formally positively charged halogens (Cl, Br, and I) are equivalently attached to two carbon atoms through three-center bonds (Fig. 1). Since the 1930s, halonium ions have been known to be a great source for unique synthetic pathways and insight into reaction mechanisms (1, 2). Iodonium ions are relatively stable, often isolable, and synthetically useful as reagents (3). Bromonium ions are generally transient, occasionally isolable, but nonetheless well-documented intermediates in dibromination and various bromo-functionalization reactions, often taking the form of bromacyclopropane rings (4). Chloronium ions are somewhat less well documented, although Stoyanov, Reed, and co-workers have recently synthesized some remarkably stable examples (5).

In contrast, the best evidence to date for a fluoronium ion has been obtained in the gas phase as a result of a neutral products analysis of a mass spectrometry experiment that showed conclusive fluorine shifts (Fig. 1A) (6). Several reasons may explain the absence of such compounds in solution, not the least of which is fluorine's high electronegativity, which lowers the propensity for sharing its lone pairs of electrons through bridging. Perhaps the closest a lab has come to the synthesis of a fluoronium ion in solution stems from the work of Gabbai, who generated a cation in which a C-F bond of normal length engages in an electrostatic interaction (C-F distance 2.44 Å) with a positively charged center (7).

In any case, symmetrical fluoronium ions in solution represent a major missing link in halonium ion chemistry. In light of fluorine's ability to impart many unusual and beneficial properties to organic compounds (such as its ability to fundamentally alter a drug's therapeutic properties), information on the mechanisms through which it reacts is of great interest (8). A fluoronium ion would also represent a long-sought goal in synthetic and mechanistic organic chemistry, as it would demonstrate that fluorine can react through halonium ion pathways. Here, we provide strong evidence, based on isotopic labeling studies, control experiments, stereochemistry, and calculations, for the transient generation of fluoronium ion 1 (Fig. 1B) in solution from an ideally configured precursor.

Given fluorine's electronegativity and limited capacity for hypervalent bonding, fluoronium ion detection rests critically on the nature of the system, which must favor symmetrical ion formation to the exclusion of all other reasonable possibilities. We deemed a hydrolytically labile precursor molecule such as 2 (Fig. 1B) to be suitable for the following reasons: (i) It has a rigid, cagelike framework in which F resides in close proximity to an electrophilic carbon bearing a reactive triflate (OTf) leaving group that should lead through a low-energy, least-motion pathway to ion 1. In a recent publication, we synthesized

cage compounds in which fluorine interacts closely with a C=C or C-H bond (9). In the case of the present system, we aimed to bring F into even closer proximity to the opposing bridge in order to promote fluoronium ion formation. For example, the optimized structure of 2 at density functional theory (DFT) level B3LYP/6-311++G** and Møller-Plesset level MP2/6-311++G** reveals a close interaction of the inner fluorine and C of the opposite bridge of 2.78 Å. (ii) Carbocationic rearrangements of 1 should be suppressed by the fact that virtually all reasonable isomeric competitors are higher in energy. (iii) Hydrolysis of precursor 2 is likely to occur through a cationic S_N1 mechanism rather than an extended S_N2 mechanism [$S_N2(e)$], as a result of both fluorine's poor leaving-group ability and steric hindrance to nucleophilic attack (Fig. 1B) (10). For example, 7-norbornyl substrates are known to undergo S_N1 solvolysis, in contrast to most other secondary systems, by virtue of nonclassical ion formation with attendant steric blockage of backside attack (11, 12). The $S_N2(e)$ pathway is expected to be very strained by virtue of nonbonded interactions of the nucleophile and leaving group with the proximate two one-carbon bridges (in the manner of the 7-norbornyl system). As can be seen in models, the trajectory for approach of a nucleophile to the backside of the C-F bond is nonoptimal. On the other hand, the S_N1 reaction to form the fluoronium 1 is expected to release a substantial amount of strain energy.
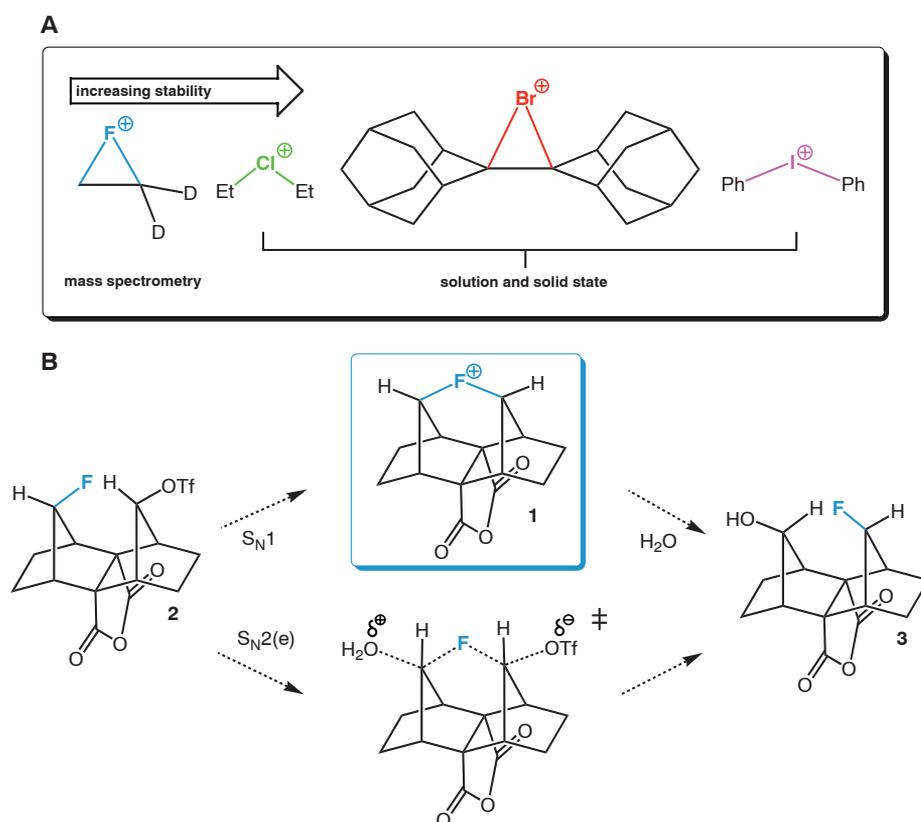

Fig. 1. Milestones in halonium ion chemistry. (**A**) Observed halonium ions from references (6), (5), (4), and (3), respectively. (**B**) The approach to fluoronium ion 1.

Department of Chemistry, Johns Hopkins University, Baltimore, MD 21218, USA.

*Corresponding author. E-mail: lectka@jhu.edu

Ion **1** is predicted to be a stable, C_{2v}-symmetric minimum at suitable levels of theory [HF, MP2, DFT (B3LYP, EDF1, EDF2, PBEPBE)], all employing the 6-311++G** and cc-pVTZ basis sets), even in the presence of various dielectric constants and solvent models (*13*). Competing asymmetric "nonfluoronium" forms (especially those that would result from simple ionization of the precursor) are not found to be stable according to acceptable HF-, MP2-, and DFT-based levels of theory. Theoretical predictions of carbocation geometries are very often definitive, as they are closed-shell species with a reduced electron correlation problem (*14*). The fluoronium structure results from any number of asymmetric starting geometries in which C-F bonds or interactions are inequivalent. An intramolecular hydride shift to form an undesired but stable α-fluoro cation (a process that plagues nonrigid precursors) is stereo-electronically precluded.

The synthetic route to the precursor molecule **2** is shown in Fig. 2. The first step was the reaction of the known dienophile **4** with silylated diene **5** under high pressure (a similar reaction, conducted under heating at 1 bar, produced no desired products) (*9*, *15*). This results in a complex mixture of diastereomers from which **6** could be separated by careful column chromatography in 23% yield. Alkene **6** was susceptible to desilylation and was rapidly carried forward through Fleming-Tamao oxidation and reduced with a palladium/carbon catalyst under hydrogen at 2 bar to afford alcohol **7** in 92% yield for the two steps (*16*). The mostly through-space coupling (^{13}C-^{19}F) of the opposing atoms [R_2CH^{19}F and R_2(OH)H^{13}C] in the nuclear magnetic resonance (NMR) spectrum of **7** is 48 Hz (calculated at B3LYP/6-311++G** to be 48 Hz as well; the one-bond C-F coupling is 212 Hz), indicating substantial interaction between the bridges (*17–19*); coupling constant calculations were performed on the Gaussian 09 and Spartan '06 programs (*13*, *20*, *21*).

We also obtained a crystal structure of the precursor alcohol **7** in which the fluorine atom seems poised to attack the opposite bridge given an opportunity (C-F distance 2.83 Å; note agreement with calculation: 2.83 Å at B3LYP/6-311++G**). Consequently, the strain with which the bridges repel each other should be relieved during cation formation (Fig. 2B). The alcohol **7** was converted to **2** under standard conditions (Tf$_2$O, pyridine, room temperature). Crude triflate **2** was partitioned between methylene chloride and water, which yielded a fairly pure sample (>96% by NMR) that was quickly characterized by ^{19}F and ^{1}H NMR spectroscopy because of its tendency to decay over time. The triflate was then dissolved in 2,2,2-trifluoroethanol (TFE) in the presence of variable quantities of water (v/v). Smooth reaction, over 6 to 10 hours at 60°C, converted triflate **2** back to the starting alcohol (and small amounts of the corresponding 2,2,2-trifluoroethyl ether) cleanly and in high yield (96% after work-up and isolation; Fig. 2A). To our gratification, no measurable quantities of skeletally rearranged or defluorinated products were detected by ^{19}F or ^{1}H NMR, in accord with our prediction of a fairly simple potential energy surface for the reaction of this caged system.

However, the fundamental problem with triflate **2** is that its reaction with water through either mechanism gives rise to only one identifiable product, namely, the starting alcohol. No means to differentiate between the extended $S_N2(e)$ substitution leading to inversion and an S_N1 reaction involving fluorine assistance (associated with the fluoronium ion) would be evident. Nucleophilic trapping of a fluoronium intermediate from either one-carbon bridge yields the very same product that is expected for the hypothetical $S_N2(e)$ process. For completeness, one other less plausible alternative should be mentioned: an S_N1-type reaction with retention. In this case, fluorine may act as an anchimeric assistor, without full fluoronium ion formation, or else simply

blocks backside attack. There exist examples in the literature in which hydrogen may play such an anchimeric role (*22*).

At this point we sought to synthesize a system in which a minor isotopic perturbation would render the precursor spectroscopically and stereo-chemically asymmetric, thus allowing us to differentiate between the major mechanistic possibilities. In fact, it was precisely stereochemical evidence that helped establish the existence of bromonium ions (*23*). One way to do this without fundamentally altering the electronic nature of the fluoronium ion itself is through a remote isotopic substitution on a two-carbon bridge. Such a substitution presumably gives rise to potential γ-deuterium kinetic isotope effects; in a sterically and electronically similar case, the solvolysis of 7-norbornyl triflates, small positive γ-deuterium isotope effects were observed ($k_H/k_D = 1.024$ to 1.038). These were interpreted as being steric effects that originate during departure of the leaving group (*12*). As we do not compare labeled and unlabeled isomeric substrates, this question does not apply to our system. On the other hand, a small steric isotope effect on product distribution may occur, although it would be within the error limits in which we quantified our results, and would favor slight retention over inversion.

The synthesis of the labeled isomer was easily accomplished by Fleming-Tamao oxidation of anhydride **6** followed by diastereoselective reduction with dideuterodiimide (67% yield) and triflation to afford **2**-*2d* (deuterium incorporation is >97% by mass spectrometry; Fig. 3) (*24*). In this case, trapping of a fluoronium ion (generated by the classical S_N1 process) by water should give rise to two labeled isomeric alcohols in comparable amounts. With the labeled triflate isomer in hand, we monitored its conversion back to alcohol **7**-*2d* in a solution of 20% water in TFE v/v at 60°C [to minimize autocatalysis, we added 1.5 equivalents (eq.) of the weak base 2,6-lutidine to absorb the generated triflic acid] at
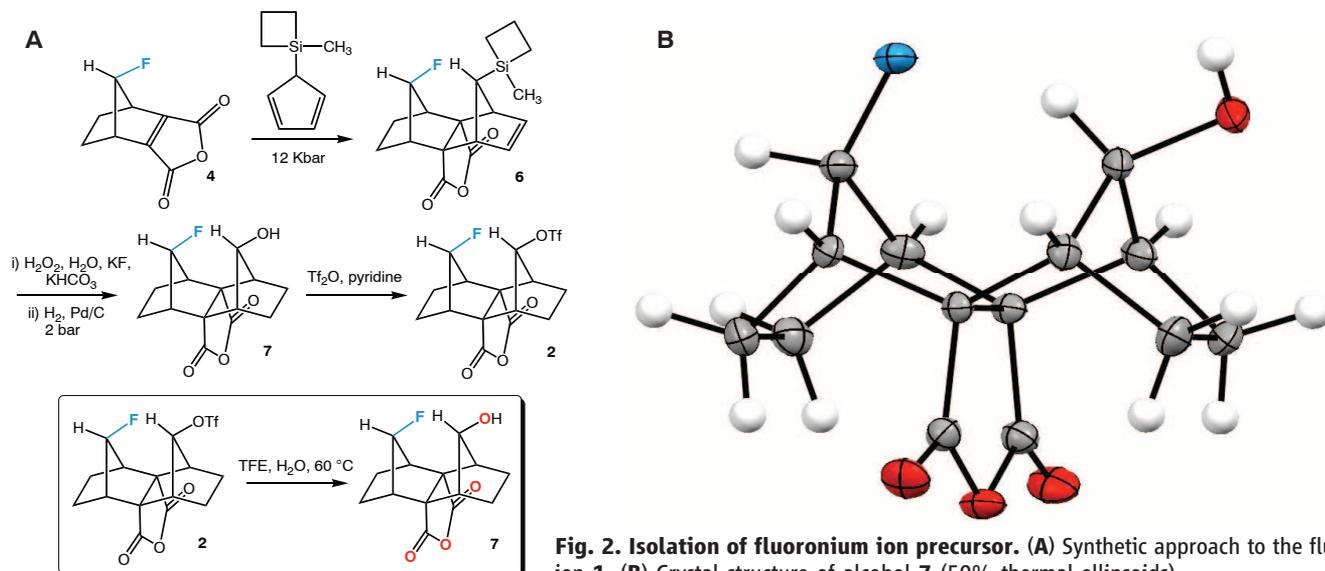

Fig. 2. Isolation of fluoronium ion precursor. (A) Synthetic approach to the fluoronium ion **1**. **(B)** Crystal structure of alcohol **7** (50% thermal ellipsoids).

60°C (25). The reaction provided a 1:1 mixture of labeled isomers **7**-*2d(a)* and **7**-*2d(b)* in 96% yield, along with a small amount of a 1:1 mixture of the corresponding TFE ethers, **8**-*2d(a)* and **8**-*2d(b)* (26). Labeled isomers were quantified by integration of ^{1}H spectra and of isotope-shifted,

split ^{13}C NMR peaks. Experimental and calculated chemical shifts were found to be in good agreement for both ^{19}F and ^{13}C (13, 27). When an analogous experiment was performed in pure TFE (60°C, 1.5 eq. 2,6-lutidine), 99% of the TFE ether isomers, **8**-*2d(a)* and **8**-*2d(b)*, also in a 1:1 ratio, were obtained.

Evidence for the generation of a fluoronium ion in solution is as follows: (i) The equivalent ratio of labeled isomers **7**-*2d* (and **8**-*2d* in pure TFE) is consistent with a scenario in which the predominant solvolytic pathway results from nucleophilic attack on either bridge of a symmetrical ionic intermediate in which counterions do not interfere (Fig. 3A). (ii) The conditions of the reaction are consistent with what we would expect for the S_N1 process (relatively non-nucleophilic medium and high dielectric constant) (28). Schneider and Schmidt have used 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) to observe pure S_N1 reactions on cyclohexyl tosylates (29); we performed a hydrolysis in similar conditions, but results were less accurate because of difficulties experienced in the integration of small quantities of the product alcohols. (iii) A Grunwald-Winstein kinetic analysis using Y_{OTf} parameters yielded an *m* value of 1.54, indicating a S_N1 reaction, as expected (*m* values that trend >1 indicate a solvent response indicative of an S_N1 reaction, whereas *m* values of 0.25 to 0.35 indicate S_N2 reactions) (30). (iv) Alternative pathways—including the $S_N2(e)$ reaction, the S_N1 reaction with retention, or an unsymmetrical ion-pairing effect in the S_N1 reaction—operate only to a very small extent, if at all. The fact that strictly 1:1 ratios of labeled isomeric products were obtained in various mixtures of water and cosolvents argues for a pure S_N1 reaction as well. (v) As stated, ion **1** is computationally stable at all suitable levels of theory, whereas the conceptual nonfluoronium (asymmetric or nonbridging) isomer, with all its attendant strain and steric hindrance to nucleophile trapping, is not stable at any suitable level of theory.

Another eventuality to rule out in order to support the case concerns the possibility that sequential $S_N2(e)$ reactions occur after hydrolysis that scramble the labeled isomeric positions through oxonium intermediates. The inclusion of 2,6-lutidine was in part meant to suppress this potential process; however a control experiment, under vigorous conditions, was performed as confirmation. Heating labeled isomer **7**-*2d(a)* in 0.5 N perchloric acid at 80°C for 6 hours resulted in virtually quantitative re-isolation of unrearranged substrate (Fig. 3B); note that the sterically encumbered anhydride group of **7** and related molecules is virtually inert to hydrolysis. On the other hand, imagine that a hypothetical, nonfluoronium alternative could exist. A one-carbon bridge could be pushed back from an interaction with F, toward the two-carbon bridge (structure **9**), in a manner analogous to that observed in the 7-norbornyl cation or the skeletally similar *exo-exo*-5,8-dimethanonapthalene system (12, 31).
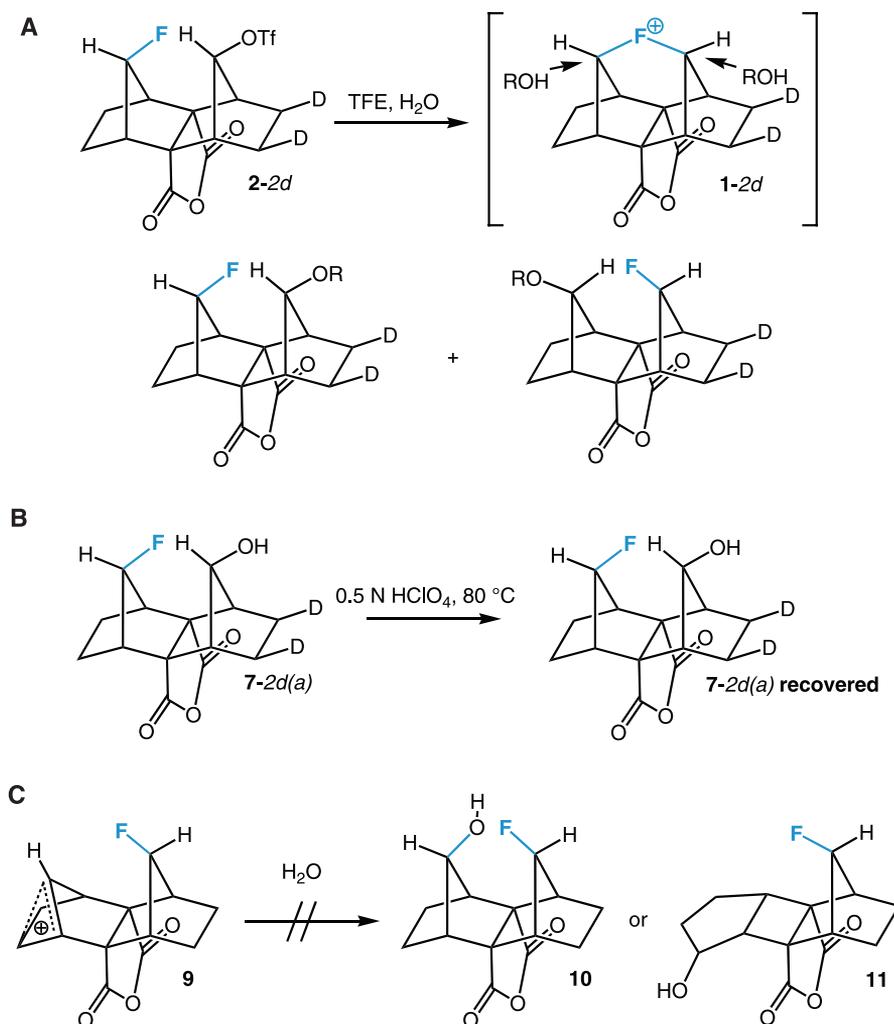

Fig. 3. Solvolysis experiments. (A) Labeling study as test for ion **1** formation. Reaction with 20% (v/v) H$_2$O in TFE affords a 1:1 mixture of isomers **7**-*2d(a)* and **7**-*2d(b)* (R = H). Reaction with pure TFE affords a 1:1 mixture of **8**-*2d(a)* and **8**-*2d(b)* (R = CH$_2$CF$_3$). **(B)** Control experiment to rule out sequential S_N2 reactions. **(C)** Hypothesized outcome of unsymmetrical ion trapping.
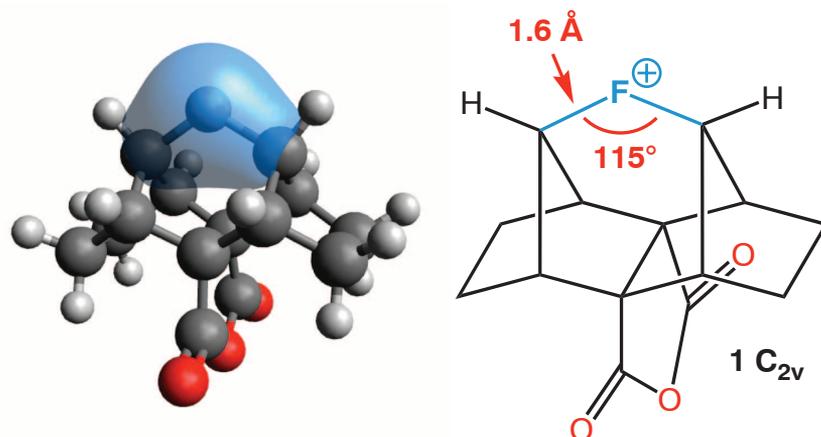

Fig. 4. σ-Molecular orbital of the three-center C-F-C bond (0.02 isosurface value, −1.31 eV) and structure of **1** at B3LYP/6-311++G**.

Such an entity may trap water from the inner position, resulting in alcohol **10**, or in a rearranged product, namely cyclobutane **11**. Neither **10** nor **11** (nor derived labeled isomers) are observed in the reaction (Fig. 3C).

What is the nature of the three-center bond in putative fluoronium ion **1**? According to calculations, much of the positive charge is sustained by adjacent carbons and hydrogen atoms (although fluorine itself is considerably more positively charged than in a typical C-F bond). For example, the two C-F bond distances in **1** are equivalent (B3LYP/6-311++G**, 1.60 Å; MP2/6-311++G**, 1.57 Å; PBEPBE/6-311++G**, 1.61 Å) and allow hypervalent fluorine to position itself snugly within a C_{2v} symmetric polycyclic cage composed of interlocking five- and six-membered carbocyclic rings. The C-F-C bond angle is 115° in the former calculations (114° at PBEPBE), permitting F to fit optimally within the lattice of the cage, and associated electron pairs to maximize repulsion. Figure 4 depicts the filled, very low-lying (−1.31 eV), delocalized σ orbital that is primarily responsible for three-center C-F-C bonding. Why would ion **1** trap solvent in such a clean fashion rather than decompose? A calculated barrier to unimolecular decomposition may provide a clue. Electron impact mass spectrometry of **1** shows a fragment corresponding to the cyclopent-2-en-1-yl cation, a resonance-stabilized allylic system. The loss of this species through a calculated barrier of 24.5 kcal/mol (B3LYP/6-311++G**) defines a potential low-energy pathway to unimolecular decomposition. It is thus justifiable to conclude that nucleophilic trapping of **1** would be much faster.

Our study points to fluorine's potential role as an anchimeric assistor to open up possibilities for new reactions that can capitalize on a fluoronium intermediate to control regioselectivity, diastereoselectivity, and overall reactivity in organofluorinated molecules. Fundamental insights into the mechanisms by which fluorine reacts in organic molecules are of great importance to several fields, especially synthetic and medicinal chemistry.

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Photochemical Route for Accessing Amorphous Metal Oxide Materials for Water Oxidation Catalysis

Rodney D. L. Smith, Mathieu S. Prévot, Randal D. Fagan, Zhipan Zhang, Pavel A. Sedach, Man Kit Jack Siu, Simon Trudel,* Curtis P. Berlinguette*

Large-scale electrolysis of water for hydrogen generation requires better catalysts to lower the kinetic barriers associated with the oxygen evolution reaction (OER). Although most OER catalysts are based on crystalline mixed-metal oxides, high activities can also be achieved with amorphous phases. Methods for producing amorphous materials, however, are not typically amenable to mixed-metal compositions. We demonstrate that a low-temperature process, photochemical metal-organic deposition, can produce amorphous (mixed) metal oxide films for OER catalysis. The films contain a homogeneous distribution of metals with compositions that can be accurately controlled. The catalytic properties of amorphous iron oxide prepared with this technique are superior to those of hematite, whereas the catalytic properties of a-$Fe_{100-y-z}Co_yNi_zO_x$ are comparable to those of noble metal oxide catalysts currently used in commercial electrolyzers.

The scalable storage of renewable energy by means of converting water to hydrogen fuels (H₂) electrochemically hinges on fundamental improvements in catalytic materials. A large overpotential (η) is usually required to produce H₂ at a practical rate, which is primarily the result of slow oxygen (O₂) evolution kinetics. Despite recent advances in the development of heterogeneous catalysts to negotiate the OER (Eq. 1; $E°$ is the standard potential and NHE is the normal hydrogen electrode) (*1–4*), substantial market penetration by commercial electrolyzers has been hindered by the absence of inexpensive catalytic materials that exhibit high current densities (j) (>0.5 A cm⁻²) at low η (<0.3 V) over prolonged time periods.

$$2H_2O(l) \rightarrow O_2(g) + 4H^+(aq) + 4e^-$$
$$E° (O_2/H_2O) = 1.23 \text{ V versus NHE} \qquad (1)$$
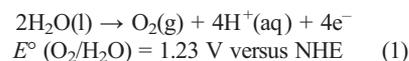
Metal oxides are the most durable and active water oxidation catalysts (*1, 2*). Although IrO₂ and RuO₂ are among the best OER catalysts (*5, 6*), a myriad of perovskite (*3, 7*) and spinel (*8*) solids have proven to be competent catalysts. In recent years, amorphous metal oxides have also been demonstrated to be excellent OER catalysts (*4, 9*), including when integrated with photoactive electrodes (*10–12*). Although an increasing number of amorphous metal oxide catalysts have been reported (*4, 9, 13–17*), most have been

Department of Chemistry and Centre for Advanced Solar Materials, University of Calgary, 2500 University Drive NW, Calgary, Canada T2N1N4.

*Corresponding author. E-mail: trudels@ucalgary.ca (S.T.); cberling@ucalgary.ca (C.P.B.)