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Tetra- and Pentacationic Electrophiles and Their Chemistry

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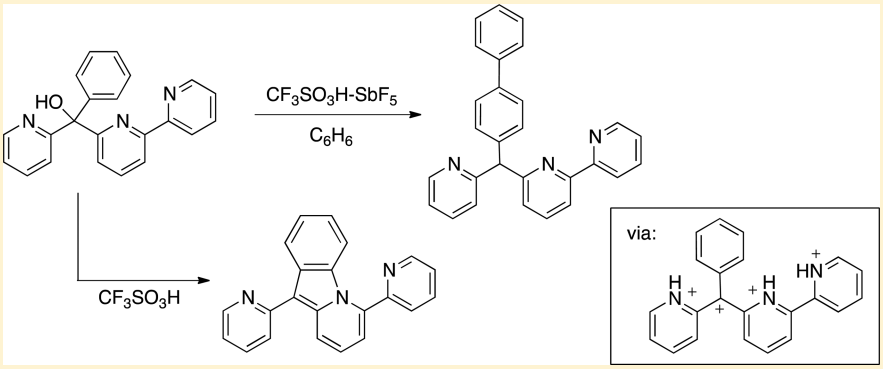
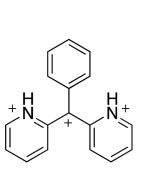
Supporting Information



ABSTRACT: A tetracationic electrophile has been generated in superacid and shown to undergo an arylation reaction with benzene. A cyclization product is also obtained in the absence of benzene, presumably from a tricationic intermediate. Using low-temperature NMR, the tetracationic species is directly observed from a FSO_3H-SbF_5-SO_2ClF solution. Similar chemistry is described with a system involving penta- and tetracationic intermediates. These highly ionized structures and their chemistry were also examined by DFT calculation.

INTRODUCTION

Highly charged organic ions are known to exhibit unusual chemistry, including undergoing reactions with exceptionally weak nucleophiles and participating in deep-seated rearrangements.[1] The chemistry of these ions has been studied both in the gas and solution phases. In the latter case, the highly charged ions are usually generated and studied in superacidic media.[2] Olah first recognized the novel reactivities of such species and described them as superelectrophiles.[3] The earliest examples of superelectrophiles included the protionitronium ion (NO_2H^{2+}), the protioacetylium ion (CH_3COH^{2+}), and the protio-*tert*-butyl dication.[3] Numerous dicationic superelectrophiles have been described in the literature, and several tricationic species have also been reported. Our own report described the generation of the tricationic species (**1**), and we found both cyclization and arylation reactions for this reactive intermediate.[4] More highly charged organic ions are known, however, these have generally been highly stabilized systems and no synthetic chemistry has been demonstrated with them. These ions include, for example, the adamantyl and tetraarylmethane tetracations (**2**–**3**).[5] In this report, we describe attempts to generate and observe tetra- and pentacationic species. This includes isolation of products from their chemistry and discussions of their states of ionization.



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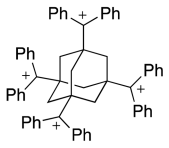

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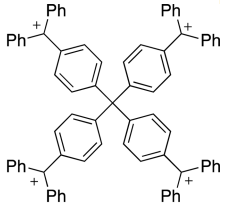

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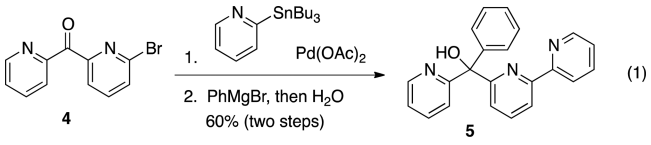
RESULTS AND DISCUSSION

The substrates for ionization were prepared by Stille coupling and Grignard chemistry. Starting from the known dipyridyl ketone **4**, substrate **5** was isolated in 60% yield following the Stille coupling and Grignard addition (eq 1). By analogyto the



4 **5** (1)

tricationic system (**1**), we reasoned that alcohol **5** should ionize in superacid to provide a tetracationic species. A precursor to a pentacation was obtained from bis(5-bromo-2-pyridyl)ketone (**6**, eq 2). Our initial approach was through thebis(dipyridyl)-ketone (**7**), however this compound could not be converted to

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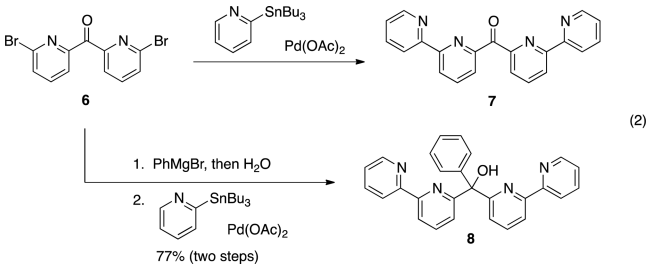

the desired alcohol product through organometallic chemistry. Despite numerous attempted reactions with PhLi and PhMgBr and various solvents, no adduct could be obtained. The poor reactivity may have been due to the low solubility of ketone **7**. The desired alcohol **8** was obtained by first preparing the Grignard reagent adduct and then subjecting the intermediate alcohol to double Stille coupling. The resulting alcohol was isolated in 45% yield from the two-step procedure.

When the alcohol substrates were subjected to superacid-promoted reactions, products were formed from arylation and cyclization (Figure 1). In the case of alcohol **5**, a reaction with CF_3SO_3H and benzene provides the arylation product **9**. However, a significant amount of the cyclization product **10** is also obtained. Without benzene, the cyclization product **10** is formed as the exclusive product in good yield. Although cyclization could potentially involve either the 2-pyridyl or the 2,6-pyridyl ring, only one product is obtained—that involving cyclization at the 2,6-pyridyl ring to give **10**.[6] When the stronger acid CF_3SO_3H-SbF_5 is used in the reaction with benzene, the arylation product **9** is formed exclusively. Similar results were obtained with alcohol **8**. However, an increasing proportion of the cyclization product **12** is formed in the CF_3SO_3H-promoted reaction with benzene, compared to the reaction with alcohol **5**. A modest increase in the amount of arylation product **11** is obtained with the use of benzene and the stronger superacid, CF_3SO_3H-SbF_5 (32% → 41%). Compounds **11** and **12** were very difficult to separate from these mixtures by column chromatography. Despite good mass recovery of the crude product mixture (ca. 65%), the purified products **11** and **12** could only be isolated as pure compounds in about 5% yield from these mixtures. Cyclization product **12** is the exclusive product from **7** in the absence of benzene, isolated in 82% yield.

The conversions above suggest a mechanism involving highly charged organic ions. In the case of alcohol **5**, protonation of the nitrogen base-sites and the hydroxyl group leads to the tetracationic oxonium ion **14** (Figure 2). Both spectroscopic

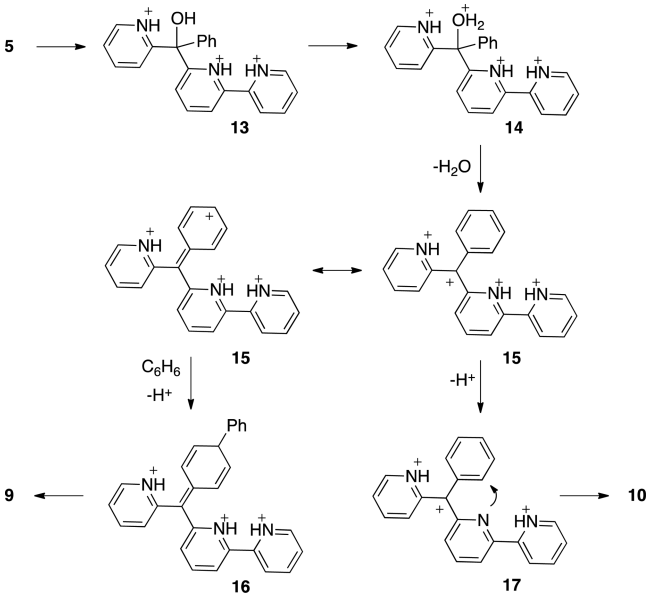

Figure 2. Proposed mechanism for the reactions of alcohol **5** in superacid.

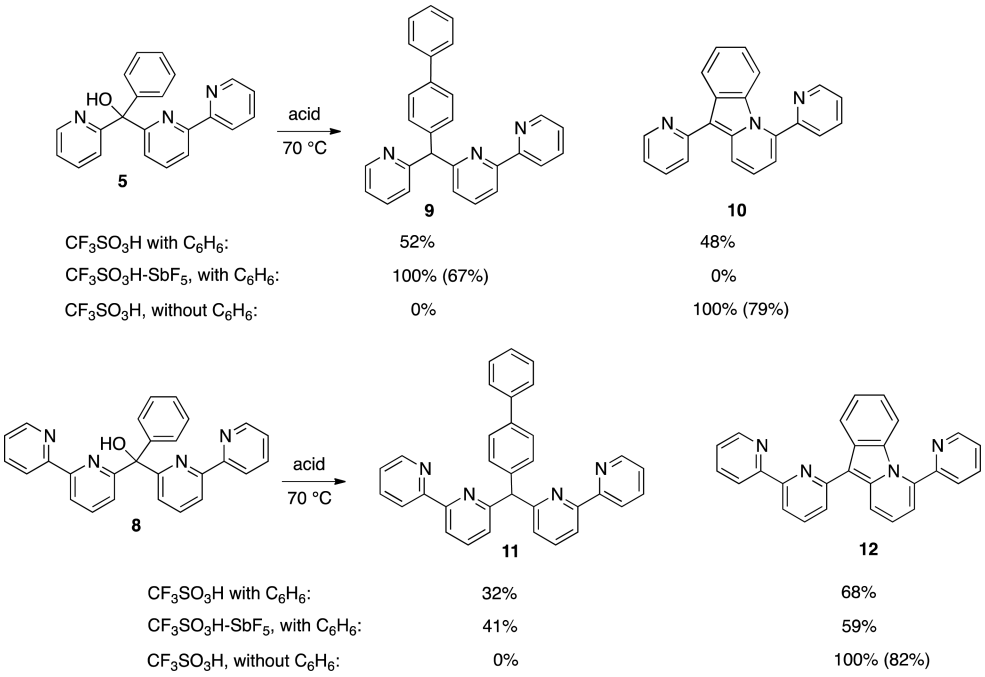

Figure 1. Products and relative yields from superacid-promoted reactions. Isolated yields are in parentheses; relative yields determined by NMR.

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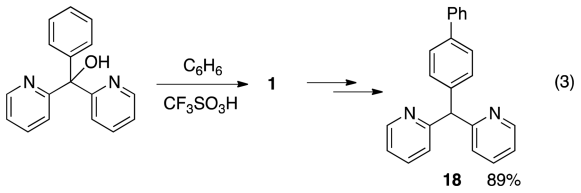
and computational experiments suggest that the oxonium ion **14** is a transient species leading to the carbocation **15** (*vide infra*). Cleavage of the C−O bond leads to the tetracationic species **15**, and the product water is immediately protonated in the excess superacid. It is proposed that **15** is the key intermediate in the arylation chemistry, as charge−charge repulsive effects lead to positive charge delocalization to the *para* position of the phenyl ring, a property confirmed by DFT calculations (*vide infra*). Nucleophilic attack by benzene then leads to **16** and subsequently to product **9**.

Based on previous theoretical calculations with the trication **1**,[4] we propose that the cyclization chemistry occurs through N-deprotonated species **17** (Figure 2). In order for this to occur, ion **15** must be protonating either the counterion triflate or benzene (if present in the mixture). This striking level of acidity of tetracation **15** arises from the large amount of cationic charge on the structure. It is notable that some cyclization is observed in the reaction of compound **5** with benzene in CF_3SO_3H. This did not occur in the case of the trication **1**, as benzene trapped the ion completely and the arylation product (**18**) was formed exclusively (eq 3).[4] This suggests the greater



amount of cationic charge in the tetracation **15** leads to an increased acidity of the N−H proton. This hypothesis is supported by the results fromthe CF_3SO_3H-SbF_5−benzene reaction. With use of CF_3SO_3H-SbF_5, cyclization is completely suppressed, presumably because CF_3SO_3H-SbF_5 has a significantly greater acidity (H_o −22) compared to CF_3SO_3H (H_o −14). This higher level of acidity prevents formation of the N-deprotonated species (**17**) and the cyclization product. If it is assumed that cyclization occurs rapidly with the deprotonated ion (**17**), then this further suggests the arylation chemistry involves the tetracationic species **15**.

The superacid-promoted reaction of substrate **8** likely involves an equilibrium between penta- and tetracationic species (Figure 3). In the superacid-promoted reactions, initial ionization leads to full protonation of the bipyridyl groups to give tetracation **19**. Further protonation at the hydroxyl group provides the pentacationic oxonium ion **20**, although spectroscopic and theoretical studies again suggest the oxonium ion is a low concentration, short-lived species (*vide infra*). It is proposed that the arylation product (**11**) arises from reaction of the pentacationic carbenium ion (**21**), while the cyclization product (**12**) is formed through the deprotonated tetracation (**22**). Interestingly, this system gives an even higher proportion of cyclized product **12** (68%)—in the presence of benzene—compared to the tricationic (**1**, 0% cyclization) and tetracation (**15**, 48%) systems. This suggests an equilibrium increasingly shifted toward the N-deprotonated species (i.e., **22**), as a result of the greater amount of cationic charge on the carbenium ion. While use of the stronger superacid CF_3SO_3H-SbF_5 did provide a measurable increase in the amount of arylation product (**11**), cyclization is still the major reaction path. This observation is an indication of the extraordinary N−H acidity of the pentacation species **21**.

These highly charged ions have been studied by low-temperature NMR using stable-ion conditions. When alcohol **5** is dissolved in FSO_3H with SO_2ClF at −30 °C, a ^{13}C NMR spectrum is obtained which is consistent with the tricationic alcohol (**13**, Table 1 and Figure 2). This includes a ^{13}C carbinol resonance at δ 78.3, which is close the ^{13}C carbinol signal of alcohol **5** (found at δ 80.6). This interpretation is also in accord with the calculated NMR spectra for ions **13** and **14** (*vide infra*). Evidently, the low-temperature FSO_3H ionization does not extensively protonate the hydroxyl group, and it does not promote cleavage of the C−O bond to form the carbocation, in contrast to the high-temperature CF_3SO_3H-promoted reactions of alcohol **5**. The ^1H NMR shows three distinct N−H ^1H resonances in the downfield region at δ 11.8−12.5, indicating that the pyridyl rings are completely protonated under these conditions. The acidity of FSO_3H (H_o −15) is comparable to CF_3SO_3H (H_o −14),[2] suggesting the pyridyl rings are largely protonated in the reactions of alcohol **5** in CF_3SO_3H.

If alcohol **5** is dissolved in the stronger superacid, FSO_3H-SbF_5 (1:1, H_o −23) with SO_2ClF at −30 °C, a ^{13}C NMR spectrum is obtained which is consistent with the tetracationic carbenium ion structure (**15**, Table 1 and Figure 4). The ^{13}C NMR resonances at δ 29 and 206 are attributed to the d_6-acetone external standard. The carbinol resonance is no longer present, and it is replaced by two downfield resonances at δ 171.9 and 174.8. These signals arise from the carbenium ion

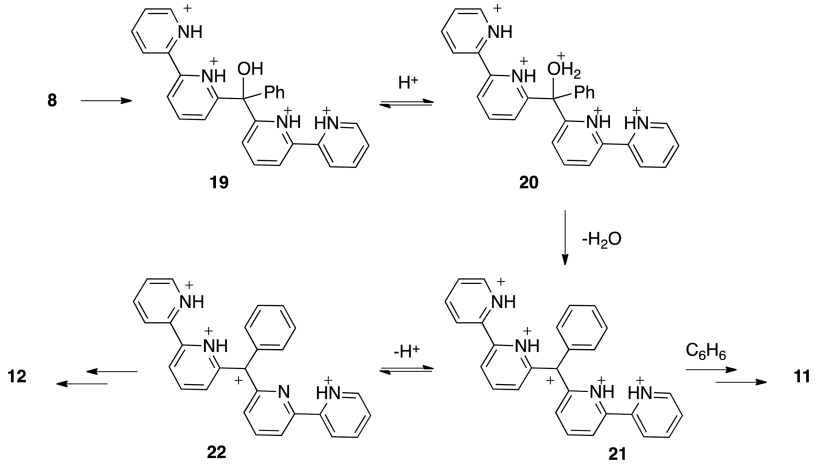


Figure 3. Proposed mechanism for the reactions of alcohol **8** in superacid.

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Table 1. NMR Spectral Data for Superacid-Ionization of Alcohol and Fluoride Substrates

substrate (acid)[a]	^{1}H NMR, δ	^{13}C NMR, δ
5 (FSO_3H)	4.9, 6.3, 6.7, 6.8, 7.3−7.4, 7.6−7.7, 7.9, 7.9, 8.1−8.14, 11.8, 12.3, 12.5.	78.3, 126.6, 127.4, 128.5, 128.6, 128.9, 129.0, 129.3,131.2, 131.6, 134.8, 139.1, 140.5, 141.0, 143.8, 148.6, 149.3, 149.7, 150.4, 154.8
5 (FSO_3H-SbF_5, 1:1)	7.6−7.7, 7.9, 8.0, 8.1−8.2, 8.3−8.4, 8.5, 8.6,11.9, 12.0,12.2	129.0, 131.6, 134.7, 135.9, 137.0, 137.6, 137.8, 139.3, 140.9, 142.6, 142.7, 145.4, 146.9, 148.7, 149.7, 150.2, 151.9, 152.1, 152.3, 171.9, 174.8
8 (FSO_3H-SbF_5, 1:1)	4.7, 6.1,6.5, 6.6, 7.4, 7.5, 7.9, 8.0, 11.4, 12.3	78.6, 123.6, 127.1, 128.4, 129.0, 129.7, 130.3, 132.0, 133.8, 138.4, 140.7, 143.8, 149.4, 151.0, 153.6
23 (FSO_3H-SbF_5, 1:1)	6.3, 6.7, 6.8, 7.3, 7.3, 7.5, 7.6, 7.7, 8.0, 8.2, 11.5, 12.0	96.1 (d, J_{C-F} 190.2 Hz), 126.6, 128.5, 129.1,129.7,130.1 (d, J_{C-F} 22.8 Hz), 130.7, 132.8, 132.8, 137.9, 142.6, 144.3, 149.1 (d, J_{C-F} 22.8 Hz), 149.7, 152.0

[a] SO_2ClF cosolvent, −30 °C.

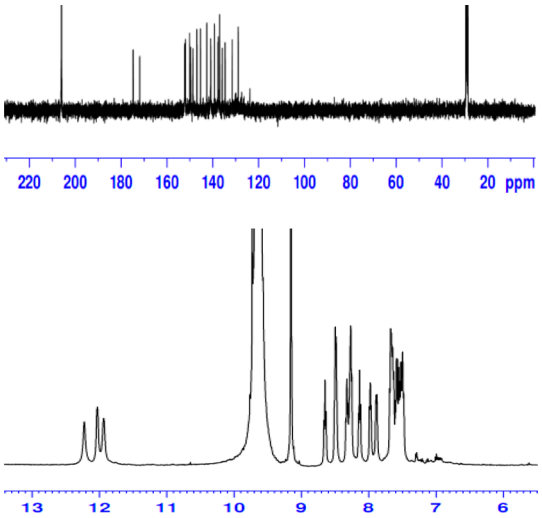
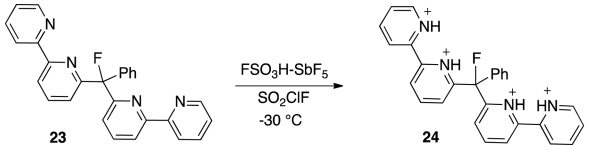


Figure 4. ^{13}C and ^{1}H NMR spectra of tetracation **15** in FSO_3H-SbF_5−SO_2ClF (1:1:1) at −30 °C (d_6-acetone external standard).

site and the *para* position on the phenyl ring. Comparison to the DFT calculated signals again supports this assignment (*vide infra*). In our previous studies of trication **1**, the carbenium ion resonance was observed and calculated to be around δ 176. In the FSO_3H-SbF_5 solution, ^{1}H NMR spectrum also shows three well-resolved N−H ^{1}H resonances in the range of δ 11.9−12.2 with approximately equal integrations, indicating full protonation of the pyridyl rings in the superacid. The ^{1}H NMR resonances at δ 9.1 is attributed to hydronium ion while the broad peak near δ 9.7 is from the superacid media.

When alcohol **8** is dissolved in FSO_3H-SbF_5 (1:1) with SO_2ClF at −30 °C, NMR spectra are obtained which are consistent with the formation of the tetracationic alcohol **19**. The ^{13}C NMR exhibits the carbinol ^{13}C resonance at δ 78.3 and no resonances beyond δ 156. The ^{1}H NMR shows two N−H ^{1}H resonances at δ 11.4 and 12.3. The peak integration is 1:1, indicating that all four pyridyl nitrogens are protonated. Despite being solvated in one of the strongest known acids, the alcohol does not appear to form significant concentrations of the pentacationic oxonium ion (**20**), and it does not cleave to the carbocation **21** at −30 °C. This may be understood to be a consequence of the low concentration of the oxonium ion **20** and the superelectrophilic character of the pentacationic carbenium ion **21**. In order for C−O bond cleavage to occur, water must separate from a highly reactive carbocation center (**21**, one that is part of a pentacationic system). Even though the water would immediately be solvated by superacid—a very favorable step—the oxonium ion remains intact at low temperature. Presumably, the oxonium ion **20** is formed and cleaves at the higher reaction temperatures used in the CF_3SO_3H-promoted conversions described above.

In an effort to generate the pentacationic species (**21**), the organofluorine compound **23** was also ionized in FSO_3H-SbF_5 (1:1). Olah and co-worker have utilized this method of ionization to generate numerous carbocationic structures, as the formation of the antimony fluoride bond is a powerful driving force for ionization.[7] Upon ionization at −30 °C however, only the tetracationic species (**24**) is observed by NMR (eq 4). The



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characteristic methine ^{13}C−^{19}F doublet is observed atδ 90.5 in the ^{13}C NMR spectrum. The doublets of the adjacent quaternary ring carbons are also observed. The four pyridinum cations evidently lead to an extraordinarily robust benzylic C−F bond, and ionization of this bond does not occur.

In order to further characterize these superelectrophilic species, theoretical calculations were done. The intermediates and transition states were studied using density functional theory (DFT). Geometries for these structures were optimized in the gas-phase at the M06/6-31G(d) level of theory[8] using Jaguar.[9] Gibbs' free energy corrections (ΔG) were calculated, and structures were verified to be minima or transition states by inspection of the number of imaginary frequencies. In a second step, single-point energies of the optimized structures were calculated using M06/cc-pVTZ(-f),[10,11] giving a basis set correction term (ΔBS). In a final step, solvent phase calculations were done using a Poisson−Boltzmann solver as implemented in Jaguar.[12] Electrostatic solvation effects from the surroundings were calculated using the SCRF method with CF_3SO_3H as a solvent (dielectric constant = 77.4, probe radius = 2.5985274).[13] The free energy (ΔG) and basis set correction terms (ΔBS) were added to the solution-phase energy. NMR chemical shifts were calculated using B3LYP/IGLO-II as implemented in Gaussian 09,[14−16] on M06/6-31G(d) gas-phase optimized structures with benzene set to the experimental value of 128.37 ppm as the NMR reference. NBO charges were calculated using NBO 6.0 as implemented in Jaguar.[17]

As noted above, the calculated ^{13}C NMR chemical shifts provide insights to the degree of ionization and the chemistry of the alcohols **5** and **8** in the stable ion conditions (Table 2). Ionization of alcohol **5** in FSO_3H−SO_2ClF provides a ^{13}C NMR spectrum with the methine ^{13}C signal found at δ 78.3. This compares favorably with the calculated value of δ 81.4 for the carbinol carbon of ion **13**. This suggests that low-

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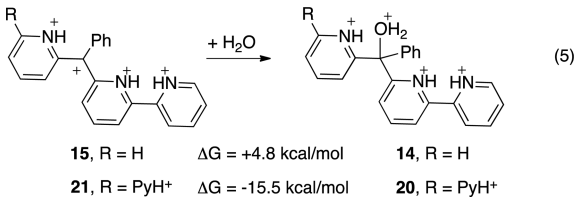
Table 2. DFT Calculated ^{13}C NMR Chemical Shifts for Ions 13−15, 19, and 20

structure	C-methine	C-*ipso*	C-*ortho*	C-*meta*	C-*para*	charge
13	81.4 (C−OH)	132.3	125.5	137.2	142.6	3
14	117.9 (C-$\overset{+}{O}H_2$)	117.2	130.6	141.7	155.2	4
15	174.9 (C+)	142.1	147.4	145.1	185.5	4
19	81.4 (C−OH)	123.5	124.3	137.6	142.9	4
20	114.9 (C-$\overset{+}{O}H_2$)	124.5	125.5	137.2	151.4	5

temperature ionization of **5** in superacidic FSO_3H gives primarily the tricationic alcohol **13**, with little protonation of the hydroxyl group. In the stronger superacid FSO_3H-SbF_5 (1:1), new resonances are observed at δ 171.9 and 174.8, indicating that the carbocation (**15**) is formed in the stronger superacid system. These signals are reasonably close to the calculated values for the carbocation center (δ 174.9) and the *para* carbon of the phenyl ring (δ 185.5). Again, there is no evidence in the ^{13}C NMR for the tetracationic oxonium ion **14** FSO_3H-SbF_5. We believe this is an indication of the short-lived nature of the highly charged oxonium ion **14**, and loss of water leads directly to the observed carbocation (**15**). There have been very few reports of primary oxonium ions in stable ion solution. Olah and co-worker have reported the experimental observation of protonated methanol in FSO_3H-SbF_5 solution,[18] but there have been no reports of primary oxonium ions observed from benzylic alcohols. In the case of alcohol **8**, low-temperature ionization in FSO_3H-SbF_5 provides the tetracationic alcohol **19**. The observed methine ^{13}C NMR resonance (δ 78.6) compares reasonably well with the calculated value (δ 81.4) for this ion. In contrast, the oxonium ion for this substrate is expected to provide a methine ^{13}C NMR resonance at δ 114.9. These observations again suggest that the expected oxonium ion **20** is a low concentration, unstable intermediate in the superacid-promoted reactions leading to phenylation and cyclization.

It is somewhat surprising that alcohol **5** leads to the carbocation **15** in FSO_3H-SbF_5, while alcohol **8** does not provide carbocation **21** under identical conditions. Assuming that the carbocations are formed by cleavage of the respective oxonium ions, this suggests the pentacationic oxonium ion intermediate (**20**, if formed) does not cleave to the carbocation **21** at a low temperature. These reactions have been studied by computational analyses, examining the reaction of water with the highly charged carbocations (eq 5). The transformations

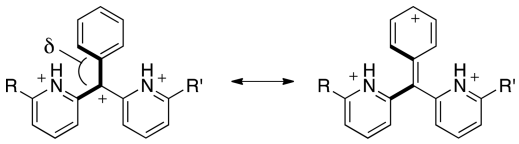


(5)

were modeled usingthe energies in the solvation field as described previously. When the tetracationic carbenium ion **15** reacts with water to give the corresponding oxonium ion **14**, the transformation is found to be endergonic by 4.8 kcal/mol. However, the same process with the pentacationic carbenium ion **21** leading to the oxonium ion **20** is exergonic by 15.5 kcal/mol. These data are consistent with the enhanced superelectrophilic character of the pentacationic carbenium ion (**21**) compared to the tetracationic system (**15**). The increased charge leads to a more energetically favorable reaction with the nucleophilic water. Conversely, these results are in accord with the observations from the NMR experiments that cleavage of pentacationic oxonium ion **20** does not occur at low temperature. This may be understood to be a result of the strongly endergonic character of oxonium C−O bond cleavage in the pentacationic oxonium **20**. While ionization at low temperature does not provide the pentacationic carbocation (**21**), reactions in superacid at elevated temperatures are thought to give this superelectrophilic carbocation.

From a structural perspective, highly charged carbocations are known to exhibit unusual conformations, distorted bond lengths, and delocalized charges.[19] Charge−charge repulsive effects are important in these types of ions, and this was examined by calculation of the natural bond order (NBO) charges at the methine carbon and the *para*-position ring carbon. We reasoned that increasing the amount of positive charge adjacent to the carbocation site should lead to greater charge migration and increasingly positive NBO charge at the *para*-position. As expected, calculations show a small albeit increasing positive charge at the *para*-position (0.00, 0.02, 0.04) for the ions **1**, **15**, and **21** (Table 3). For comparison, the NBO

Table 3. Calculated Properties of Ions 1, 15, and 21



		NBO charge			
structure	charge	C-methine	C-*para*	dihedral angle, δ	C−C bond length (methine-*ipso*), Å
1[a] R,R′ = H	3+	+0.12	0.00	24.0°	1.402
15 R = H,R′ = PyH^+	4+	+0.10	+0.02	22.5°	1.399
21 R = PyH^+, R′= PyH^+	5+	+0.09	+0.04	21.1°	1.396

[a]Data taken from ref 4.

charge is calculated to be −0.15 for the *para*-position on the trityl cation.[4] The NBO charge is also calculated to decrease at the carbocation center as the charge on the ion increases. Thus, for the ions **1**, **15**, and **21**, the NBO charge decreases from +0.12 to +0.10 to +0.09. This is a consequence of greater electron delocalization from the phenyl group to the methine carbon. For comparison, the NBO charge on the carbocation center of a trityl cation is calculated to be +0.24.[4]

As a consequence of the delocalization of π-electrons, there is increasing π-bond character between the methine and *ipso* carbons. This structural effect is seen in the C−C bond length between the methine and *ipso* carbons, a bond length that steadily decreases with increasing charge. Likewise, the dihedral angle between ring carbons exhibits a modest decrease in the series **1**, **15**, and **21**. This is consistent with greater π-bond character within the more highly charged ions.

The cyclization reactions were also examined computationally. In the case of alcohol **5** leading to the cyclization product **10**, cyclization is thought to involve the tricationic species **17** (Figure 5). A tautomeric species (**17t**) is possible in the acid

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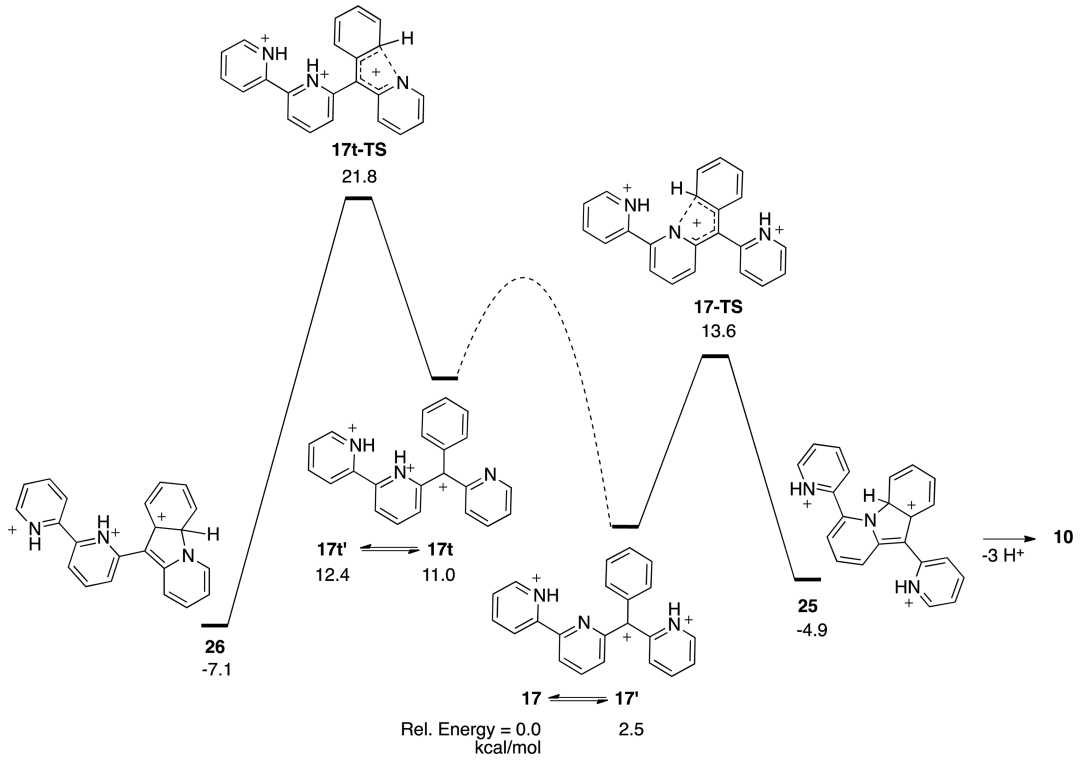

Figure 5. Calculated structures and energies (kcal/mol) related to the cyclization of trication **17** to product **10**.

equilibrium, a structure with the terminal pyridyl ring deprotonated. Ion **17t** would lead to a cyclization product differing from **10**. Experimental observations indicate that only one cyclization product is formed in the superacid-promoted reaction of alcohol **5**. The results from the calculations are consistent with a preference for cyclization to product **10**. Thus, trication **17** is calculated to be 11.0 kcal/mol more stable than the tautomer **17t**. This significant energy difference may be the result of more closely oriented charge centers in trication **17t** compared to **17**. Both trication species (**17** and **17t**) are found to exist in equilibrium with conformational isomers (**17′** and **17t′**), which are characterized as minima on the potential energy surface. The two cyclization transition states (**17-TS** and **17t-TS**) were located and found to be 13.6 and 21.8 kcal/mol, respectively, above the global minimum structure (**17**). In the final cyclization steps, trications **25** and **26** are characterized as minima, both of which are significantly more stable than the starting trications **17** and **17t**. The final deprotonation steps provide the observed cyclization product **10**. During the characterization of product **10**, we realized that the cyclization product arising from **26** (upon deprotonation) is expected to have very similar NMR spectra with those from compound **10**. We were unable to grow X-ray quality crystals of the product **10**, but the calculations support our structural assignment, as intermediate **25** is on the kinetically preferred reaction path.

In the cyclization of alcohol **8** to product **12**, the tetracationic species **22** is thought to be involved. Two conformers were located for the tetracationic species (**22** and **22′**), structures calculated to be within 0.9 kcal/mol in energy (Figure 6). The cyclization transition state was located, and it is estimated to be 10.3 kcal/mol above the minimum structure **22**. This barrier is significantly less than that observed in the cyclization involving the tricationic species (**17**) generated from alcohol **5** (Figure 4). The lower cyclization barrier is likely a consequence of the

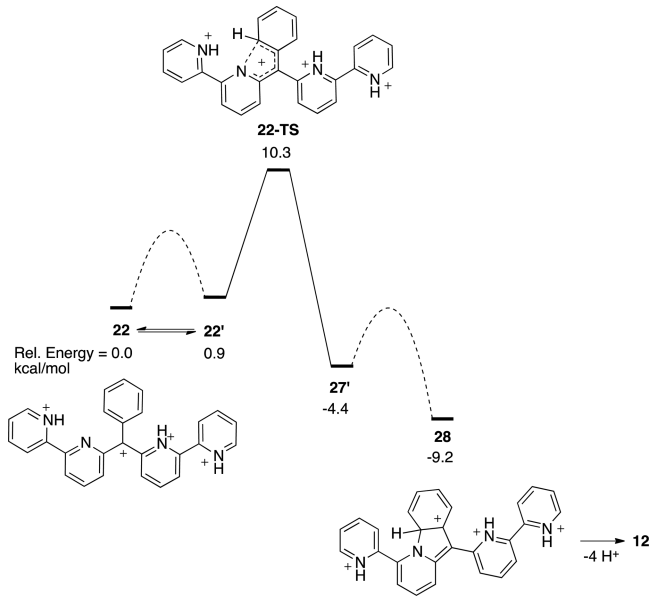

Figure 6. Calculated structures and energies (kcal/mol) related to the cyclization of tetracation **18** to product **11**.

increased charged and enhanced positive charge delocalization. Cyclization leads to intermediate **28**, calculated to be 9.2 kcal/mol more stable than carbocation **22**. Again, this energy value (−9.2 kcal/mol) differs considerably from that observed in the cyclization of the tricationic system (−4.9 kcal/mol). It has been previously noted that superelectrophiles and highly charged ions tend to favor reaction steps that disperse, spread out, or jettison positive charge.[3,19,20] In the tetracationic system, the carbocation center is in close proximity to three positive charge centers so it greatly benefits from the cyclization. The resulting cyclization intermediate **28** possesses a more highly

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dispersed carbocationic charge, and this is likely an important aspect of this exergonic reaction step. This effect is expected to be smaller in the tricationic cyclization, and consequently, the cyclization is found to be less exergonic compared to the tetracation.

CONCLUSIONS

We have examined the superacid-promoted chemistry of alcohols **5** and **8**. In the presence of benzene or CF_3SO_3H, the substrates give products from arylation or cyclization. The ratio of arylated and cyclization products varies with the strength of superacid, the result of equilibria involving highly ionized species including tricationic, tetracationic, and pentacationic intermediates. These synthetic transformations represent the first examples bond-forming reactions with such highly charged cationic electrophiles. In general, the more highly charged ions exhibited enhanced N−H bond acidities and greater π-electron delocalization.

EXPERIMENTAL SECTION

General. All reactions were performed using oven-dried glassware under an argon atmosphere. Trifluoromethanesulfonic acid (triflic acid) was freshly distilled prior to use. All purchased compounds and solvents were used as received. ^{1}H and ^{13}C NMR were done using either a 300 or 500 MHz NMR spectrometer. Low-temperature NMR spectra were done using acetone-d_6 as the external standard. Low-resolution mass spectra were obtained from a gas chromatography instrument equipped with a mass-selective detector, whereas high-resolution mass spectra were obtained from a commercial analytical laboratory (electron impact ionization; sector instrument analyzer type). Compounds **4**,[21] **5**,[22] **6**,[23] and **7**[24] were prepared by published methods.

*Di([2,2′-bipyridin]-6-yl) (phenyl)methanol (**8**).* Compound **6** (107.7 mg, 0.317 mmol) is dissolved in THF (10 mL) and cooled to 0 °C. Phenylmagnesium bromide (0.20 mL, 0.475 mmol) solution is then added slowly, and the mixture is stirred at room temperature for 24 h. The reaction is subsequently quenched with 1 M HCl and partitioned between ethyl acetate and water. The aqueous phase is further extracted twice, and the combined organic extracts are washed with brine and dried over anhydrous sodium sulfate. The solvent is then removed, and the product is purified by column chromatography (R_f 0.22, hexane: ethyl acetate, 3:1). Bis(6-bromopyridin-2-yl) (phenyl)methanol is isolated (0.118 g, 0.28 mmol, 89%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (s, 1 H), 7.29−7.32 (m, 3 H), 7.39−7.44 (m, 3 H), 7.59 (t, J = 7.80 Hz, 3 H), 7.84 (d, J = 7.74 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.7, 122.1, 126.8, 127.6, 127.7, 128.2, 139.0, 139.7, 144.8, 163.9. Low-resolution MS (EI): 420 (M+), 402, 343, 262, 234, 184, 157, 127, 105, 77, 51. HRMS (EI) calcd for $C_{17}H_{12}ON_2Br_2$, 417.9317, found 417.9334.

Bis(6-bromopyridin-2-yl) (phenyl)methanol (69.7 mg, 0.167 mmol) is dissolved in 10 mL of toluene, and 2-pyridyltributyltin (0.2 mL, 0.349 mmol) is added, followed by addition of tetrakis-(triphenylphosphine)palladium (0) (35.2 mg, 0.025 mmol). The solution is refluxed for 24 h, after which, it is cooled and partitioned between chloroform and water. The aqueous phase is further extracted twice, after which the organic extracts are combined, washed with brine, and dried over anhydrous sodium sulfate. The solvent is removed, and the product purified by column chromatography (R_f 0.21, hexane: ethyl acetate, 1:1). Compound **8** is isolated (60.4 mg, 0.145 mmol, 87%) as a powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (s, 1 H), 7.26−7.35 (m, 5 H), 7.41−7.45 (m, 1 H), 7.76−7.82 (m, 2 H), 7.88 (s, 1 H), 7.90−7.92 (m, 2 H), 8.30 (d, J = 8.88 Hz, 2 H), 8.36 (s, 1 H), 8.39 (s, 1 H), 8.67−8.69 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 80.6, 119.5, 121.0, 123.5, 123.7, 127.3, 127.9, 128.0, 136.9, 137.4, 146.3, 149.1, 153.5, 155.8, 162.4. Low resolution MS (EI): 416 (M^+), 398, 339, 261, 233, 208, 155, 78. HRMS (EI) calcd for $C_{27}H_{20}ON_4$, 416.1637, found 416.1648.

*6-([1,1′-Biphenyl]-4-yl(pyridin-2-yl)methyl)-2,2′-bipyridine (**9**).* This chemistry is done in a thick-walled, glass tube reactor having a Teflon cap. Compound **5** (61.7 mg, 0.182 mmol) is dissolved in benzene (1 mL, 11.2 mmol) to which is added (slowly) a solution antimony pentafluoride, SbF_5 (ca. 50 mg, 0.231 mmol) in triflic acid, CF_3SO_3H (1 mL, 11 mmol). Following 24 h of stirring at 60−70 °C, the mixture is cooled to room temperature and poured over about 10 g of ice. The resulting mixture is neutralized with 10 M NaOH and then partitioned between chloroform and water. The aqueous fraction is further extracted twice with chloroform, after which the organic fractions are combined, washed with brine, and dried over anhydrous sodium sulfate. The solvent is removed by vacuum, and the product purified by column chromatography (R_f 0.31, hexane: ethyl acetate, 1:1). Compound **9** (49 mg, 0.122 mmol, 67%) is isolated as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (s, 1 H), 7.13−7.20 (m, 2 H), 7.37 (d, J = 2.40 Hz, 1 H), 7.39, (d, J = 1.35 Hz, 1 H), 7.45 (s, 2 H), 7.47 (d, J = 2.10 Hz, 2 H), 7.50−7.56 (m, 2 H), 7.60 (d, J = 2.01 Hz, 1 H), 7.74−7.84 (m, 2 H), 8.20−8.25 (m, 2 H), 8.36 (t, J = 8.91 Hz, 2 H), 8.63−8.65 (m, 1 H), 8.67−8.69 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.5, 118.8, 121.3, 121.6, 123.6, 124.1, 124.2, 127.2, 128.7, 129.8, 136.4, 136.8, 137.5, 139.6, 140.9, 141.1, 149.0, 149.3, 155.5, 156.4, 161.0, 162.4. High-resolution mass spectrum (EI): calcd for $C_{28}H_{20}N_3$ (M-1) 398.1657, found 398.1646.

*6,10-Di(pyridin-2-yl)pyrido[1,2-a]indole (**10**).* This chemistry is done in a thick-walled, glass tube reactor having a Teflon cap. Compound **5** (48.5 mg, 0.143 mmol) is dissolved in triflic acid (1 mL, 11 mmol) and stirred at 60−70 °C for 24 h. The reaction mixture is allowed to cool and then poured on ca. 10 g of ice, neutralized with 10 M NaOH, and partitioned between chloroform and water. The aqueous phase is further extracted twice with chloroform, after which the organic fractions are combined, washed with brine, and dried over anhydrous sodium sulfate. The solvent is removed by rotary evaporation, and the product purified by column chromatography (R_f 0.27, hexane: ethyl acetate, 1:1). Compound **6** (36.3 mg, 11.2 mmol, 79%) is isolated as brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (d, J = 8.70 Hz, 1 H), 6.48 (d, J = 6.27 Hz, 1 H), 6.85 (t, J = 7.77 Hz, 1 H), 7.00−7.07 (m, 2 H), 7.25 (t, J = 7.41 Hz, 1 H), 7.39−7.43 (m, 1 H), 7.50 (d, J = 7.65 Hz, 1 H), 7.70 (s, 2 H), 7.81 (t, J = 7.59 Hz, 1 H), 8.15 (d, J = 8.19 Hz, 1 H), 8.28, (d, J = 9.15 Hz, 1 H), 8.69 (d, J = 3.57 Hz, 1 H), 8.75 (d, J = 2.70 Hz, 1 H).^{13}C NMR (75 MHz, $CDCl_3$) δ 106.3, 112.8, 114.8, 119.46, 119.49, 119.7, 119.9, 123.2, 123.3, 123.6, 124.3, 124.4, 128.3, 130.3, 136.3, 136.8, 137.4, 138.8, 149.8, 150.2, 154.8, 155.2. High-resolution mass spectrum (EI): calcd for $C_{22}H_{15}N_3$, 321.1266, found 321.1264.

*6,6″-([1,1′-Biphenyl]-4-ylmethylene)di-2,2′-bipyridine (**11**).* This chemistry is done in a thick-walled, glass tube reactor having a Teflon cap. Compound **8** (201.4 mg, 0.484 mmol) is dissolved in benzene (1 mL, 11.2 mmol), and a solution of SbF_5 (ca. 50 mg, 0.231 mmol) in CF_3SO_3H (1 mL, 11 mmol) is slowly added. The tube reactor is closed, and the solution is stirred at 70 °C for 24 h. The solution is then poured over about 10 g of ice, neutralized with 10 M NaOH, and partitioned between chloroform and water. The aqueous phase is extracted twice, after which the organic fractions are combined, washed with brine, and dried over anhydrous sodium sulfate. Removal of the solvent leads to a product mixture (0.133 g) containing **11** and **12** in a 41:59 ratio (NMR). Chromatography is done with hexanes:ether (1:1), however only a small amount of pure **11** (R_f = 0.17) is obtained (ca. 0.005 g), as compound **11** is extremely difficult to separate from product **12**. Compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (s, 1H), 7.29−7.36 (m, 4H), 7.40−7.55 (m, 5H), 7.55−7.65 (m, 4H), 7.75−7.84 (m, 4H), 8.31−8.39 (m, 4H).8.69 (d, J = 0.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.5, 118.8, 123.6, 124.4, 127.0, 127.0, 127.2, 128.7, 129.8, 137.0, 137.3, 139.5, 140.9, 141.3, 148.8, 155.1, 156.3, 161.4. HRMS (TOF MS, ES+) calcd for $C_{33}H_{25}N_4$, 477.2079, found 477.2073.

*10-([2,2′-Bipyridin]-6-yl)-6-(pyridin-2-yl)pyrido[1,2-a]indole (**12**).* This chemistry is done in a thick-walled, glass tube reactor having a Teflon cap. Compound **8** (200 mg, 0.481 mmol) is dissolved in triflic acid, CF_3SO_3H (1 mL, 11 mmol), and the mixture is stirred 70 °C for 24 h. The resulting mixture is then poured over about10 g of ice,

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neutralized with 10 M NaOH, and then partitioned between chloroform and water. The aqueous phase is further extracted twice with chloroform, after which the organic extracts are combined, washed with brine, and dried over anhydrous sodium sulfate. The solvent is removed, and the product purified by column chromatography (R_f 0.46, hexanes:ethyl acetate, 1:1). Compound **12** is isolated in 82% yield as an off-white solid, MP 173−175 ° C (EtOAc-hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (d, J = 8.65 Hz, 1 H), 6.60 (d, J = 6.25 Hz, 1 H), 7.00 (t, J = 7.85 Hz, 1 H), 7.15−7.18 (m, 1 H), 7.32−7.35 (m, 1 H), 7.40 (t, J = 7.5 Hz, 1 H), 7.48−7.51 (m, 1 H), 7.59 (d, J = 7.65 Hz, 1 H), 7.85−7.91 (m, 3 H), 7.95 (t, J = 7.75 Hz, 1 H), 8.38 (t, J = 8.40 Hz, 2 H), 8.49 (d, J = 9.15 Hz, 1 H), 8.67 (d, J = 7.85 Hz, 1 H), 8.76 (d, J = 4.10 Hz, 1 H), 8.86 (d, J = 4.15 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 106.5, 112.9, 114.9, 117.0, 119.4, 119.7, 120.0, 121.1, 123.3, 123.4, 123.6, 123.7, 124.3, 124.4, 128.4, 130.5, 136.9, 137.0, 137.3, 137.4, 139.0, 149.1, 150.2, 154.5, 154.7, 155.8, 156.8. HRMS (EI) calcd for $C_{27}H_{18}N_4$, 398.1531, found 398.1513.

*6,6″-(Fluoro(phenyl)methylene)di-2,2′-bipyridine (**23**).* A solution of deoxo-fluor (5.4 mmol) in CH_2Cl_2 (2 mL) is cooled to −78 °C, and to this solution is added di([2,2′-bipyridin]-6-yl) (phenyl)methanol **8** (23.5 mg, 0.06 mmol in 3 mL CH_2Cl_2). The mixture is stirred for 2 h and then allowed to warm to 25 °C. After several hours, the products mixture is poured into 10 mL of saturated $NaHCO_3$ and stirred until the evolution of CO_2 is complete. The mixture is extracted twice with CH_2Cl_2, and the organic extracts washed with brine and then dried with anhydrous Na_2SO_4. The product is isolate by concentration and purified by column chromatography (R_f = 0.33, hexane:ethyl acetate, 3:1). Compound **23** is isolated as an oil (23.4 mg, 0.056 mmol, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22−7.28 (m, 1 H), 7.36−7.43 (M, 2 H), 7.63−7.71 (m, 3 H), 7.88 (t, J = 7.83 Hz, 1 H), 8.13 (d, J = 7.98 Hz, 1 H), 8.39 (d, J = 7.80 Hz, 1 H), 8.63−8.65 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.2 (J_{C-F} = 176.0 Hz), 119.7 (J_{C-F} = 1.10 Hz), 121.3, 122.0 (J_{C-F} = 6.39 Hz), 123.7, 127.3, 127.4, 127.6, 127.9 (J_{C-F} = 1.50 Hz), 137.1 (J_{C-F} = 37.3 Hz), 141.4 (J_{C-F} = 22.6 Hz), 148.9, 154.5, 156.0 160.2 (J_{C-F} = 26.1 Hz). Low-resolution MS (EI): 399 (M-19), 322, 244, 200, 167, 159, 78. HRMS (TOF MS, ES+) calcd for $C_{27}H_{20}FN_4$, 419.1672, found 419.1665.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02220.

NMR spectra for compounds **4**, **5**, **8**−**12** and computational results (PDF)

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Notes

The authors declare no competing financial interest.

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