Mechanisms of Formation and Rearrangement of Benziodoxole-Based CF$_3$ and SCF$_3$ Transfer Reagents

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ABSTRACT: Togni’s benziodoxole-based reagents are widely used in trifluoromethylation reactions. It has been established that the kinetically stable hypervalent iodine form (I−CF$_3$) of the reagents is thermodynamically less stable than its acyclic ether isomer (O−CF$_3$). On the other hand, the trifluoromethylthio analogue exists in the thermodynamically stable thioperoxide form (O−SCF$_3$), and the hypervalent form (I−SCF$_3$) has been elusive. Despite the importance of these reagents, very little is known about the reaction mechanisms of their syntheses, which has hampered the development of new reagents of the same family. Herein, we use density functional theory calculations to understand the reasons for the divergent behaviors between the CF$_3$ and SCF$_3$ reagents. We demonstrate that they follow different mechanisms of formation and that the metals involved in the syntheses (potassium in the case of the trifluoromethyl reagent and silver in the trifluoromethylthio analogue) play key roles in the mechanisms and greatly influence the possibility of their rearrangements from the hypervalent (I−CF$_3$, I−SCF$_3$) to the corresponding ether-type form (O−CF$_3$, O−SCF$_3$).

1. INTRODUCTION

Organofluorine compounds are widely used as pharmaceuticals and agrochemical products and in medical diagnostics. One of the most important reasons for the widespread application of these compounds is their high metabolic stability, which, among other things, leads to smaller doses necessary to achieve the desired bioactivity compared to the nonfluorinated analogues. However, organofluorine compounds have different chemical and metabolic stabilities depending on the chemical environment of the C−F bond. Some of the most stable aliphatic species involve trifluoromethyl/perfluoroalkyl and trifluoromethylthiol derivatives.

The large demand for fluorinated compounds, in particular perfluoroalkylated ones containing CF$_3$ and SCF$_3$ groups, has stimulated the development of new synthetic methodologies for the selective preparation of fairly complex organofluorine species. In this context, one of the most important developments in the last 10−15 years has been the appearance of new reagents that can be employed for synthesis of organofluorines with high levels of selectivity. An important example of these reagents is Togni’s hypervalent iodine reagent I (Scheme 1), which can be used for the transfer of a trifluoromethyl group to a wide range of organic substrates. Although the Togni reagent was first reported in 2006, surprisingly few hypervalent iodine-based benziodoxole reagents have been reported that are suitable for the transfer of other fluorinated functional groups. Some of the few examples are fluorine and perfluoroalkyl transfer reagents $^{2,3}$ as well as the CF$_2$SO$_2$Ph analogue $^{4,12}$ On the other hand, the synthesis of benziodoxole-based SCF$_3$ transfer reagent S was unsuccessful and yielded the thioperoxide isomer $^{7,13,14}$ Most probably, many failed attempts for the synthesis of reagents with hypervalent iodine bound $^{−}$CF$_3R$ (R ≠ F, CF$_3$, CF$_2$SO$_2$Ph) have not been reported.

Schaefer and co-workers $^{15}$ pointed out that many hypervalent iodine-based reagents, such as I and S, are thermodynamically much less stable than their corresponding ether-type analogues, such as 6 and 7, which could explain the synthetic difficulties in accessing the hypervalent iodine reagents. Yet, I can be easily prepared, while S has never been observed. This suggests that certain benziodoxole-based reagents, such as I, are kinetically stable, while others rearrange to the thermodynamically most stable isomer or never form under the applied conditions of the synthesis. One may therefore pose the following question: What is the reason for the high kinetic stability of the hypervalent form of I as compared to S? The answer to this question and the details involved in the mechanism of the synthesis of this class of reagents would certainly be highly valuable in the design of new fluoroalkyl group-based hypervalent benziodoxole reagents for...
selective synthesis of new organofluorine compounds for the pharmaceutical industry and medical diagnostics.

To this end, we have, in the present work, performed density functional theory (DFT) calculations to elucidate the mechanism of the formation of the Togni reagent 1 from the reaction of fluoro-benziodoxole 2 with the Ruppert–Prakash reagent 8 in the presence of KF (the second part of reaction I in Scheme 2). Quite surprisingly, knowledge about the mechanism of the synthesis of this important reagent has been missing. For comparison, we also studied the mechanism of the attempted synthesis of the trisfluoromethylthio analogue 5 from the reaction of chloro-benziodoxole 9 with AgSCF₃ 10 (reaction II in Scheme 2). In both cases, we studied the rearrangement possibilities of the hypervalent iodine species to the corresponding thermodynamically stable ether-type isomers.

2. RESULTS AND DISCUSSION

2.1. Mechanism of the Synthesis of the Togni Reagent.

The standard procedure for the synthesis of the Togni reagent 1 is shown in Scheme 2.⁹ It starts with chloro-benziodoxole 9, which is converted to fluoro-benziodoxole 2. Subsequently, 2 is reacted with the Ruppert–Prakash reagent 8 in the presence of potassium fluoride to obtain 1. We focus here on the second part of the synthesis, i.e., the conversion of 2 with 8 and KF. We considered two main possibilities under these conditions. Conversion of 2 to Togni reagent 1 and an alternative pathway involving the formation of the thermodynamically more stable ether form 6. In connection with these studies, we also investigated the possible formation of 6 from 1 under the above reaction conditions.

We start the computational investigation by examining the possible adducts that may form from various precursors present in the reaction mixture, i.e., 2, 8, and KF. The calculations show that the most stable complex is formed between 2 and KF (called 2-KF), in which the fluoride is associated with the iodine center and the potassium with the oxygen side, as displayed in Scheme 3 (optimized geometries of 2-KF and other possible complexes with higher energies are given in the Supporting Information).

From 2-KF, the reaction mechanism obtained on the basis of the current DFT calculations is shown in Scheme 3, and the associated energy profile is given in Figure 1. Optimized structures of key transition states (TSs) and intermediates are depicted in Figure 2, while other geometries are supplied in the Supporting Information. The first step of the reaction is the nucleophilic attack of the fluoride of KF on the silicon center of 8 via TS1. This step has a calculated barrier of 10.1 kcal/mol relative to 2-KF. In order for the nucleophilic attack to take place, the KF has to change its orientation relative to 1 such that the potassium points in the direction of the fluoride. This structure is called 2-KF’ and is 3.6 kcal/mol higher than 2-KF (Figure 1). At TS1, the F–Si bond distance is 2.72 Å, and the fluoride interacts also with the iodine with a distance of 2.49 Å (Figure 2). The nucleophilic attack results in Int1, which is 3.7 kcal/mol higher than 2-KF and which involves a hypervalent silicon center, with F–Si and Si–CF₃ bond distances of 1.84 and 2.01 Å, respectively (Figure 2). The negative charge in Int1 is...
distributed over the fluorine and trifluoromethyl group (see calculated charge distribution in the Supporting Information).

The next step involves a heterolytic dissociation of the Si–CF₃ bond. Direct dissociation at Int₁ has a barrier of 18.2 kcal/mol relative to 2-KF. Instead, we found that a prior reorientation of the anionic moiety in Int₁, such that the CF₃ group is positioned toward the potassium (Int'₁ in Figure 1), leads to a lower barrier for the (heterolytic) Si–CF₃ bond dissociation.

**Figure 1.** Calculated free energy profile (kcal/mol) for reaction I (black), the formation of the ether product (red), and the formation of a potential side product by reaction with an acetonitrile solvent molecule 11 (blue).

**Figure 2.** Optimized geometries of selected transition states and intermediates involved in the synthesis of the Togni reagent. Distances are given in Ångström (Å).
Such a reorientation is not associated with a high energy (see the Supporting Information), and the barrier for the Si–C bond cleavage from Int1 via TS2 is calculated to be 12.5 kcal/mol relative to 2-KF. This step releases the trimethylfluorosilane (CH$_3$)$_3$SiF side product and generates intermediate Int2. In Int2, the CF$_3$ anion interacts bidentately with the potassium cation (Figure 2). The lone pair of the CF$_3$ moiety in Int2 points in the direction of the iodine (see the Supporting Information), in anticipation of nucleophilic attack at the hypervalent iodine, which then takes place with the simultaneous loss of fluorine from the iodine to yield Togni reagent 1 in complex with KF (1-KF). This concerted step occurs through TS3, with a barrier of 14.7 kcal/mol relative to 2-KF, and constitutes thus the highest barrier of the reaction. At TS3, the 1–CF$_3$ bond distance is shortened to 2.47 Å, while the 1–F distance is elongated to 2.31 Å.

According to this mechanistic proposal, KF plays the role of not only an initiator in the reaction but also of a catalyst, donating a fluorine to the Ruppert–Prakash reagent 8 in the first step and receiving back a fluorine from fluoro-benziodoxole reagent 2 (Scheme 3). To complete the cycle, an exchange between 1 by 2 takes place to regenerate 2-KF, a step that is exergonic by 2.6 kcal/mol. The entire cycle is thus calculated to be exergonic by 16.4 kcal/mol.

The initial steps leading to the formation of the trifluoromethyl anion can be compared to the results of a computational study of a similar reaction in the context of the activation of the Ruppert–Prakash reagent with KCl as an initiator. In that case, no distinct hypervalent silyl intermediate corresponding to Int1 could be located, and the formation of CF$_3$ was found to take place through a 4-membered TS with concerted Si–Cl bond formation and Si–CF$_3$ bond cleavage.

Int2, which involves the potassium-bound CF$_3$ anion, is a key intermediate in the reaction. CF$_3$ is of course an excellent nucleophile that is able to displace the substituent on the hypervalent iodine. It is also a strong base (vide infra). It is known that CF$_3$ can readily undergo α-elimination by cleavage of one of the C–F bonds to give CF$_3$ carbene. A similar reaction may also take place with some metal complexes, such as in Cu–CF$_3$ strongly limiting the synthetic scope of CF$_3$-mediated nucleophilic trifluoromethylation reactions. The current mechanistic results show that coordination to the potassium cation effectively stabilizes CF$_3$ and prevents the formation of CF$_3$ carbene, allowing thus the formation of the Togni product 1. The calculations show that the CF$_3$ intermediate can also form in the absence of 2, i.e., in the reaction between the Ruppert–Prakash reagent and KF (see the Supporting Information for details).

It is interesting here to compare the mechanism shown in Scheme 3 with the one obtained by Schoenebeck and co-workers for the transmetalation of [Pd$_4$]–F complexes with the Ruppert–Prakash reagent 8 to yield [Pd$_4$]–CF$_3$ intermediates. In that case, the calculations showed that the reaction proceeds through a short-lived Pd-difluorocarbene intermediate.

We now turn to the question of why the trifluoromethyl ether isomer of 1, i.e., compound 6, is not observed experimentally under the above reaction conditions despite the fact that it is thermodynamically much more favored over the hypervalent iodine form, by more than 50 kcal/mol. As mentioned above, Schäfer and co-workers hypothesized that the synthetic pathway yields the hypervalent form, which is then kinetically blocked from converting to the ether form. Very similar to their results, we find that the direct isomerization of 1 to 6 is associated with a very high barrier, >45 kcal/mol (see the Supporting Information). We have also considered whether the potassium is able to catalyze the isomerization, but the involvement of KF was found to lower the barrier by only ca. 5 kcal/mol, which is not sufficient for observing 6 (see the Supporting Information).

One can envision that the formation of 6 is achieved prior to the formation of 1, i.e., starting from Int2. The first step from this intermediate would be through TS4, in which a nucleophilic attack of CF$_3$ the iodine center takes place concertedly with the cleavage of the I–O bond to yield the oxyanion Int3 (Figure 1). The calculated energy barrier for this step is +17.5 kcal/mol, and Int3, despite being an oxygen-based anion, is 3.9 kcal/mol higher than Int2. As discussed above, the interaction of the CF$_3$ anion with the potassium cation helps stabilizing this intermediate. Also, the F–I–C hypervalent bond in Int3 is less stable than the F–I–O in Int2, which involves two electronegative atoms.

Next, 6 can be obtained from Int3 through TS5, which is an electrophilic trifluoromethylation of the oxyanion, by a dissociation of the F–I and I–CF$_3$ bonds and the formation of the O–CF$_3$ bond (Figure 2). However, the energy barrier associated with this step was found to be high, 26.9 kcal/mol relative to 2-KF, i.e., 12.2 kcal/mol higher than the barrier for the formation of 1 through TS3. Thus, these results show that the high barrier associated with TS5 kinetically blocks the formation of 6, explaining why it is not observed experimentally under the above conditions for the synthesis of 1.

Interestingly, during the course of our investigations, we also discovered another reaction that can take place from Int2, namely, the CF$_3$ anion can act as a base, abstracting a proton from an acetonitrile solvent molecule 11 (Figure 1). Such reactivity has been reported previously for the reaction in the absence of 2. The barrier for this proton transfer (TS6) is calculated to be 14.3 kcal/mol, which is very close to the barrier found for the formation of 1 (TS3, 14.7 kcal/mol). From the resulting Int4, a concerted nucleophilic attack and fluoride loss through TS7 can take place to yield the hypervalent iodine Int5. Geometrically, this transition state resembles TS3, and the calculated barrier is 16.3 kcal/mol relative to Int4. Int5, which is 6.5 kcal/mol more stable than Togni reagent 1-KF, might of course rearrange and react further to yield other side products. This has not been studied explicitly here. The existence of this competitive mechanistic path might contribute to lowering the yields obtained in the synthesis of 1 in acetonitrile.

To summarize the results of this section, the calculations provide detailed insights into the mechanism of the formation of 1, which is demonstrated to be kinetically favored over the formation of its ether isomer 6. A plausible competitive pathway that involves the reaction with an acetonitrile solvent molecule is also shown to be possible.

### 2.2. Mechanism of Synthesis of 7

Having established the mechanism for the synthesis of the Togni reagent, we now turn our attention to the mechanism of the synthesis of 7 and the reasons why the thioperoxide isomer is obtained in this case and not the hypervalent iodine form 5. In the synthesis of 7, AgSCF$_3$ is employed as the source of SCF$_3$ (Scheme 2), and the complexation of this reagent with chloro-benziodoxole 9 to form 9-KF is found to be 7.7 kcal/mol more stable than the separate species. In this complex, the Ag ion interacts with the Cl center of 9 with a distance of 2.53 Å, while the SCF$_3$ group is arranged parallel to the benziodoxole ring. In what follows, the subscript...
Scheme 4. Proposed Mechanism of the Synthesis of Benziodoxole-Based SCF₃ Transfer Reagent 7 as Obtained from the Current DFT Calculations

Figure 3. Calculated free energy profiles (kcal/mol) for the synthesis of the benziodoxole-based SCF₃ transfer reagent 7. (a) Initial formation of the hypervalent iodine form 5. (b) Conversion of 5 into the thioperoxide form 7. Note that the energy associated with the precipitation of AgCl is not considered, and complex 5·10 is taken as the starting point of the second part of the reaction in (b).

“S” will be used in the names of the TSs and intermediates of this reaction to distinguish them from the ones involved in the synthesis of the Togni reagent discussed above.

Starting from complex 9·10, the energetically most favorable pathway obtained by the calculations is shown in Scheme 4, with the associated energy profile given in Figure 3 and selected optimized geometries in Figure 4. In the first step, the silver ion in AgSCF₃ abstracts the chloride from 9 to yield an ion-pair intermediate Int₁S that is 10.9 kcal/mol higher in energy (Figure 3a). No transition state could be obtained for the formation of Int₁S, and the energy of the ion pair can be considered as a good approximation of the barrier.24

At Int₁S, the SCF₃ group can then readily transfer to the iodine through TS₁S to yield 5, the hypervalent form of the reagent, in complex with AgCl (5·AgCl in Figure 3a). The barrier for this is very low, only 0.8 kcal/mol higher than Int₁S, i.e., 11.7 kcal/mol relative to 9·10. At this stage, AgCl is expected to precipitate fully or partially, making the process 9·10→5
involving hypervalent iodine reagents.25

been observed in a number of metal-catalyzed reactions facilitating the transfer of the SCF3 group to the oxygen at either complex also considered the possibility of the direct formation of

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How is then the thermodynamically more stable thioperoxide form of the reagent, takes place with a low barrier. Hypervalent hypervalent form of the reagent, takes place with a low barrier.

Namely, another AgSCF3 reagent can enter the solution can catalyze the cycle to form complex 5-10 or intermediate Int1S. The calculations show that the barriers for these scenarios are high, 25.3 and 27.8 kcal/mol, respectively, which are much higher than the energy of TS1S (see the Supporting Information for details).

Instead, we found that the presence of the AgSCF3 reagent 10 in the solution can catalyze the 5-7 isomerization with a reasonable barrier. Namely, another AgSCF3 reagent can enter the cycle to form complex 5-10 with the hypervalent benziodoxole-SCF3 5. Then, a trans-cis isomerization of the F3CS-I-O bond takes place through TS2S with a barrier of 16.7 kcal/mol, yielding Int2S, which is 9.1 kcal/mol higher in energy than 5-10. The silver ion acts here as a Lewis acid, facilitating the trans-cis isomerization, a mode of action that has been observed in a number of metal-catalyzed reactions involving hypervalent iodine reagents.

Next, the formation of complex 7-10 occurs through a five-membered S2,2-type transition state (TS3S), in which a nucleophilic attack of the SCF3 of 10 takes place on the oxygen center concerted with the dissociation of the I-O and I-SCF3 bonds (Figure 4). This step has an overall barrier of 27.1 kcal/mol relative to 5-10, which can be compared to the barrier of 36.7 kcal/mol calculated for the direct uncatalyzed isomerization from 5 to 7 (see the Supporting Information). The cycle closes by an exchange of 7 by 9 to regenerate 9-10, and this step is calculated to be exergonic by 0.4 kcal/mol. It should be mentioned that we also found a plausible pathway from 5 to 7 involving the silver ion of AgCl, if one assumes that it does not precipitate in the solution (see the Supporting Information for details).

The calculations thus show that the hypervalent iodine form of the reagent is formed initially, but the presence AgSCF3 provides a path to the thermodynamically more stable thioperoxide form 7. However, although the obtained barrier of 27.1 kcal/mol is energetically viable under the reaction conditions of the experiments, it is rather high, which indicates that it might be possible to isolate 5 by running the reaction at low temperatures.

Very recently, Zhang and co-workers succeeded in the synthesis of the hypervalent trifluoromethylthio iodine reagent 12 by modifying the benziodoxole ring in 9 into an N-acetylbenzodiazole one (13 in Scheme 5).30 Although the experimental procedure to synthesize 12 is very similar to the one used for 7, the hypervalent (I-SCF3) product could be obtained. We have also considered this reaction by calculations and found that the formation follows the same mechanism described above for 7. That is, a heterolytic dissociation of the Cl-I bond in 13 takes place first, followed by a nucleophilic attack of SCF3 at the iodine. Very importantly, however, the transformation of both 12 and 13 into the sulfenamide isomer 14 was found to be associated with very high barriers (>35 kcal/mol). Energy profiles and optimized geometries are given in the Supporting Information. These results thus demonstrate that the further isomerization of 12 is kinetically blocked, similarly to the Togni case, but in contrast to the situation with 5 that can convert to 7 with a reasonable barrier. The higher energy barrier in the case of 12 can be ascribed to the resonance effect of the acetyl substituent. Accordingly, when the acetyl group in 12 was replaced by a methyl in the calculations, the energy barrier for

Figure 4. Optimized geometries of relevant transition states and intermediates involved in the synthesis of the benziodoxole-based SCF3 transfer reagent 7.
the isomerization to the analogue of 14 decreased by as much as 10.7 kcal/mol (see the Supporting Information).

3. CONCLUSIONS
We have in the present work employed the DFT methodology to unravel the reaction mechanisms for the formation of the benziodoxole-based CF₃ (1) and SCF₃ (7) reagents. The calculations show that the two reactions follow quite different mechanisms, as shown in Schemes 3 and 4.

In the case of the synthesis of 1, the mechanism involves the following steps: (i) nucleophilic attack by the fluoride of KF on the silicon center of the Ruppert–Prakash reagent 8 to generate a hypervalent silicon intermediate; (ii) heterolytic dissociation of the Si–CF₃ bond to yield the (CH₃)₃SiF side product and a CF₃ carbanion stabilized by the potassium cation; and (iii) nucleophilic attack of the CF₃ at iodine of fluoro-benziodoxole 2 to obtain the hypervalent iodine Togni reagent.

The calculations show that KF acts as a catalyst in this reaction, first donating a fluoride to activate 8 and generate CF₃ and later receiving a fluoride back from the fluoro-benziodoxole reagent 2 (Scheme 3). The calculations further show that the pathways leading to the thermodynamically stable ether form of the reagent, i.e., compound 6, are associated with high barriers, rationalizing the kinetic stability of the hypervalent iodine form 1.

In the case of the thioperoxide SCF₃ reagent, the mechanism suggested by the calculations comprises an initial step in which the silver ion of the AgSCF₃ reagent 10 assists the heterolytic dissociation of the CF₃I bond to form the CF₃SCF₃ dication and a CF₃ anion. Subsequent nucleophilic attack of the CF₃ at iodine of 2 to obtain the hypervalent iodine Togni reagent.

Following the experimental conditions, acetonitrile (ε = 35.69) was used in the study of the synthesis of the Togni reagent 1 (reaction I)⁹ and tetrahydrofuran (ε = 7.43) for the formation of 7 (reaction II).¹³

Vibrational frequencies were calculated at the same level of theory as the geometry optimization, and the Gibbs free energy corrections were calculated using the quasi-rigid-rotor-harmonic-oscillator (qRHO) approximation at room temperature.³⁷ Experimentally, the reactions were performed at 263 and 323 K for reactions I and II, respectively.⁵,¹² The effect of the reaction temperatures in the calculations was found to be small, as discussed in the Supporting Information.

Standard state corrections were added to account for the conversion from the 1 atm ideal gas to the 1 M standard state of the solutes and 19.1 M for the acetonitrile solvent. This implies that the term RT ln (24.5) = +1.9 kcal/mol was added to the energies of all complexes, except for the acetonitrile (in the case where it was considered explicitly, see above) for which the value RT ln (24.5 × 19.1) = +3.6 kcal/mol was added.

To improve the accuracy of the electronic structure calculations, single-point gas-phase energies using a larger basis set consisting of LANL2DZ for K and Ag, LANL2DZpd for I, and 6-311+G(2d,2p) for the other atoms were calculated on the basis of the optimized geometries. The final energies reported in the paper are thus these large basis set gas-phase energies corrected for Gibbs free energy, standard state change, and solvation, where the latter was calculated by comparing the energies obtained from the geometry optimization with the gas-phase values calculated with the same basis set.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02306.

Additional results discussed in the text; absolute energies and energy corrections; and Cartesian coordinates (PDF)

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Notes
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