Computational Investigation of the Role of Fluoride in Tamao Oxidations

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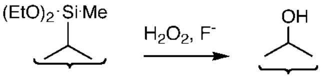
Abstract: The Tamao oxidation of alkoxysilanes was investigated computationally to determine the role of fluoride, a key additive, in this reaction. A sequence of fluoride equilibria as well as possible transition states, mediated by basic and neutral peroxide, respectively, were examined, and a potential energy surface was calculated which was consistent with the typical synthetic methods required for the conversion of alkoxysilanes to alcohols.

Keywords: alcohols · density functional calculations · oxidation · reaction mechanisms · silicates

Introduction

The oxidation chemistry of silanes has been exploited in natural products syntheses, as silicon's ability to act as a "masked" hydroxyl group allows it to be used in situations, in which the presence of an alcohol is unfavorable.[1] The oxidation requires that at least one of the silicon substituents is an electronegative heteroatom. Thus, the Tamao oxidation employs an alkoxysilane[2] [Eq. (1)], whereas the Fleming protocol[3] converts a phenylsilane to a fluoro- or carboxysilane before the actual oxidation [Eq. (2)]. The reactions have a similar, yet unique utility, as the silyl substituent effects can be critical in the success of the oxidation within the context of a complex molecule. In the synthesis of the antifungal natural product (+)-pramanicin, for example, a key step is the Tamao oxidation of a diethoxyphenylsilane; attempts to oxidize phenyldimethylsilane at the same point of attachment under Fleming conditions failed.[4] In other cases, the selection of silyl substituents can be influenced by the number of synthetic steps between the introduction of the silane and its subsequent oxidation, with the phenylsilanes being somewhat more robust than the alkoxysilanes to multiple synthetic manipulations.[5] Other aryl, heteroaryl, and allyl substituents on silicon can play the same role as the phenyl group and also are typically replaced by fluoride prior to oxidation.[1, 6]



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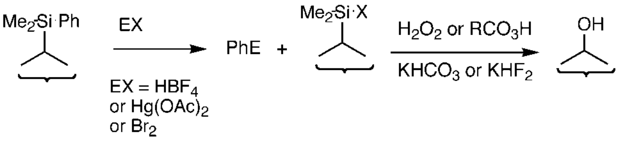

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The oxidizing agents most frequently used are hydrogen peroxide, *m*-chloroperbenzoic acid, or peracetic acid. Additional fluoride (KF and/or KHF_2) is required in many, but not all, existing protocols. Examples demonstrating the variety of alkoxysilane substrates and four protocols commonly employed to oxidize them are listed in Table 1. Tamao describes the "standard" oxidation conditions for an alkoxysilane as 30% H_2O_2, $KHCO_3$, and KF in a mixed solvent system of 1:1 THF:MeOH, typically at 0.1 to 0.5 M for each reagent.[7, 8] Although the "standard" conditions require 1.2 equiv H_2O_2 per Si–C bond oxidized,[8] in practice larger excesses of oxidant are often used. Strongly basic conditions (entry 8) are rarely cited, but they find use in cases in which silyl ether protection would be cleaved by fluoride.

We have demonstrated by ab initio methods that the mechanism of fluorosilane oxidation is dependent on the basicity of the reaction medium.[16] As in the cases listed in Table 1 for alkoxysilanes, fluorosilanes can also be oxidized to alcohols in aqueous H_2O_2 buffered with $KHCO_3$ in the presence of excess fluoride in the form of KF or KHF_2. The key rearrangement step, then, could be effected by either HOO^- or HOOH, and both paths were considered (Scheme 1, X = F). Attack of HOO^- upon an alkylfluorosilane **1** results in a stable pentacoordinate intermediate **3**, which then under-

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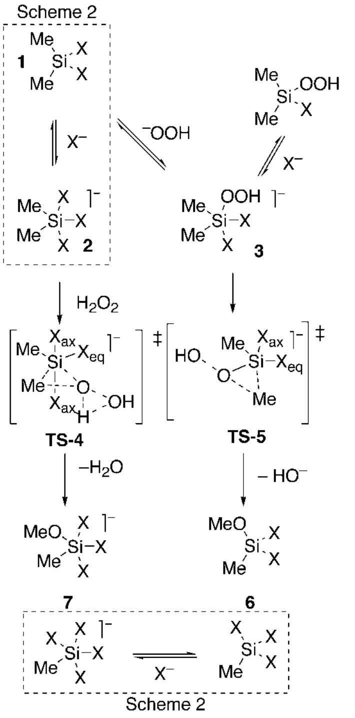
Table 1. Representative reaction conditions for the oxidation of alkoxysilanes.

	Substrate	Conditions	Temperature	Description	Reference
1	$RCH{=}CHCH_2SiPh_2OEt$	H_2O_2 (4.5 equiv), $KHCO_3$ (6 equiv), KF (4 equiv)	35–40 °C	standard	[9]
2	$RR'CHSiMe_2O\mathit{i}Pr$	H_2O_2 (5–20 equiv), $KHCO_3$ (3 equiv), KF (3 equiv)	RT	standard	[10]
3	$Ar_2CHSiPh_2(OAc)$	H_2O_2 (12 equiv), $KHCO_3$ (1 equiv), KF (4 equiv)	60 °C	standard	[11]
4	$RC({=}CH_2)CH_2SiMe_2O\mathit{i}Pr$	H_2O_2 (4.5 equiv), $KHCO_3$ (4 equiv), KF (7.5 equiv)	RT	standard	[12]
5	$RCH_2Si(OEt)_3$	H_2O_2, $KHCO_3$		basic	[13][a]
6	$RCH_2SiMe_2O\mathit{i}Pr$	H_2O_2 (9 equiv), $NaHCO_3$ (1 equiv)	reflux	basic	[14]
7	$RCH_2SiMe(OEt)_2$	H_2O_2 (12 equiv), $KHCO_3$ (1 equiv)	reflux	basic	[2]
8	$RR'CHSiMe_2OR'$	H_2O_2, 15 % KOH	50 °C	KOH	[15][a]
9	$RCH_2SiMe(OEt)_2$	H_2O_2 (12 equiv), KHF_2 (2 equiv)	60 °C	neutral	[2]

[a] No experimental details or stoichiometry reported.



Scheme 1. Reaction path for the oxidation of fluoro- and alkoxysilanes.

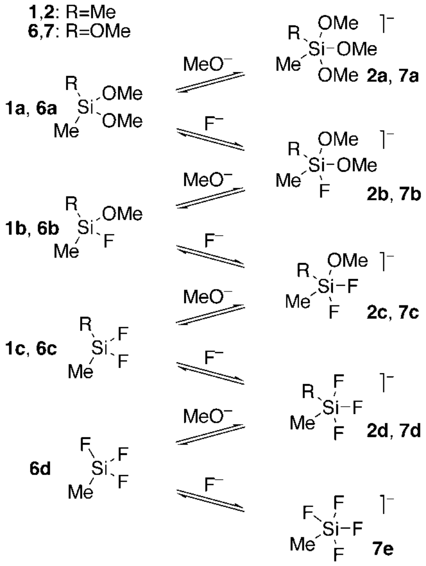
goes migration of an alkyl group to the oxygen atom (**TS-5**), with simultaneous loss of hydroxide to yield **6**.

Alternatively, addition of fluoride to **1** generates a pentacoordinate intermediate **2** that rearranges upon equatorial approach of HOOH with concomitant loss of water. The activation barrier for the rearrangement via HOO^- (**TS-5**) was found computationally to be 100–200 kJ mol^{-1} lower in energy than that for rearrangement via HOOH (**TS-4**); thus $\mathbf{1} \rightarrow \mathbf{3} \rightarrow [\mathbf{TS\text{-}5}] \rightarrow \mathbf{6}$ is the preferred path. Applying a solvent correction (MeOH) to the gas-phase structures was essential to obtaining results that were consistent with Tamao's kinetic studies on fluorosilanes.[1a] No kinetic studies have been reported by Tamao for the alkoxysilane substrates, and a priori a similar mechanism should not be assumed. Thus we wished to apply the same computational approach to the rearrangement of the Tamao-type substrates, the alkoxysilanes. Herein we demonstrate that the oxidation of alkoxysilanes is also likely to be mediated by basic peroxide rather than neutral hydrogen peroxide, and that fluoride shifts the equilibrium to more reactive fluorosilane species, which undergo oxidation.

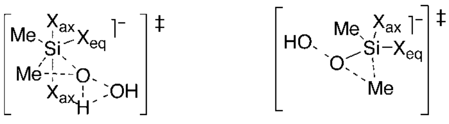
Computational Methods

Dimethoxydimethylsilane **1a** (X = OMe) was employed as the model in this study, as the model substrate employed in the development of the Tamao reaction possessed two alkoxy substituents.[2] Based on our earlier work, we focused on reaction under Tamao's "standard" conditions of fluoride, hydrogen peroxide, weak base, and methanol, and again assumed formation of pentacoordinate intermediates. In the buffered conditions of a Tamao oxidation, at least three anions (fluoride, methoxide, and hydroperoxide) are typically present, and attack of these three on the silane **1a** were considered in the equilibrium. Stable complexes formed by addition of neutral species (HOOH or MeOH) to the tetravalent silanes **1** could not be located computationally. The alkoxysilane reaction sequence is additionally complicated by the series of equilibria depicted in Scheme 2, in which fluoride and methoxide are exchanged via the pentavalent species **2** and **7**. The naming scheme for alkoxysilanes (X = OMe and/or F) at each point on Scheme 1 and 2 begins with the neutral, nonfluorinated starting material **1a** and continues by letter for each fluoride added (a: $n = 0$ fluoride; b: $n = 1$ fluoride; c: $n = 2$ fluoride, etc.). Thus, pentavalent species **2** are formed by sequential addition of fluoride or methoxide to a tetravalent **1**. Products of type **6** are neutral, tetravalent silanes, and the pentavalent anions of type **7** can be formed directly from **TS-4** or upon addition of fluoride to **6**.

For pentavalent intermediates, all structural isomers were calculated, and the lowest energy isomer was employed in calculating the relative energy differences for the equilibria and PES. The preferred structural isomers for the rearrangement TS are depicted in Scheme 3; the Tamao-type transition states **TS-4** are generated by approach of HOOH to **2**, and transition



Scheme 2. Anion-exchange equilibria between alkoxy-, fluoro-, and fluoroalkoxysilanes.



TS-4a $X_{ax} = X_{eq} = OMe$
TS-4b $X_{ax} = F, OMe\ X_{eq} = OMe$
TS-4c $X_{ax} = F, OMe\ X_{eq} = F$
TS-4d $X_{ax} = X_{eq} = F$

TS-5a $X_{ax} = X_{eq} = OMe$
TS-5b $X_{ax} = F, X_{eq} = OMe$
TS-5c $X_{ax} = X_{eq} = F$

Scheme 3. Structural isomers of rearrangement transition states.

states **TS-5** arise from rearrangement of pentavalent silylhydroperoxides **3** (vide supra). Initial transition state (TS) geometries were located by the linear synchronous transit, coordinate driving, or direct construction of a plausible geometry, and conformational searches were conducted at low levels of theory, with a coarse selection at AM1 in Spartan 5.13.[17] Having previously demonstrated that B3LYP/6-31 + G* provides energetic trends comparable with those obtained by MP2/6-311 + G** for these silanes,[13] the geometries were then optimized at B3LYP/6-31 + G*[18] using Jaguar.[19] Thermodynamic contributions were calculated from normal-mode analysis at B3LYP/6-31 + G* without scaling, using a temperature of 298 K. Transition states and minima were verified to have exactly one and zero negative eigenvalues, respectively. Solvation effects in a typical solvent, MeOH, were estimated at the gas-phase B3LYP/6-31 + G* geometries by using the continuum solvation method PB-SCRF together with the B3LYP/6-31 + G* wavefunction.[20]

Results

Four general observations can be made, and will be expanded upon in turn.

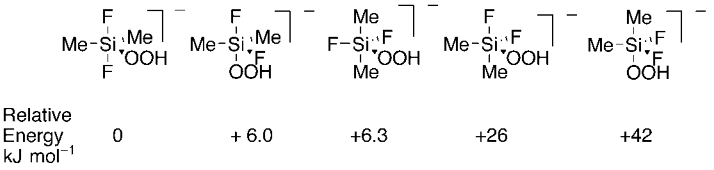
1) The role of solvation in the computational treatment is critical.
2) With increasing fluoride substitution, the attack of any of the three nucleophiles (F–, OR–, or OOH–) becomes increasingly exothermic, in both gas- and solvent-phase calculations.
3) The order for apicophilicity of attack is F > OR, and is consistent with literature reports for gas-phase reactions of silicates.
4) Berry pseudorotation of the pentavalent intermediates upon the rearrangement TS is common, and also is consistent with literature reports.

It has been shown both theoretically and experimentally that alkoxide tends to add to appropriately substituted, neutral silanes to form pentavalent silicates in the gas phase (computationally), and S_N2-like displacements by alkoxide are not observed.[21, 22] A representative series of competing equilibria for the formation of pentavalent intermediates is shown in Table 2, and a systematic trend is noted. As might be expected, the solvent- and gas-phase values differ. The F^-, OMe^-, and HOO^- anions are not well stabilized in the gas phase, and combination with neutral molecules yields anions with the charge distributed over a larger surface area. Application of a solvent model damps these effects, so that the reactions are significantly less exothermic with a solvent correction. The trends for the corrections are consistent because the magnitude of the correction correlates with the surface to charge ratio of the anion: the smaller the anion, the larger the correction, with the order F > OMe > OOH. With increasing fluoride substitution of the parent tetravalent species, the correction is less pronounced, and the difference for attack by the nucleophiles also becomes less pronounced (from approximately 50 kJ mol^{-1} for attack on **1a** to roughly 25 kJ mol^{-1} for attack on difluorodimethylsilane **1c**). The order of reactivity (fluoride forming more stable pentavalent species than methoxide or hydroperoxide) is predicted by gas-phase calculations at MP2/6-311 + + G**,[23] and is borne out here for B3LYP/6-31 + G* as well. It is notable that the formation of the pentavalent intermediates for all cases is exothermic in the gas phase, yet is endothermic with the solvent correction in some cases, notably for attack of *any* nucleophile on the dialkoxy starting material **1a** and for attack of OOH^- on any silane. Nonetheless, the key intermediate is $[F_3SiMe_2]^-$ **2d**, because under Curtin–Hammett conditions, it will be the barrier from this species, the most stable in the equilibrium, which determines the net rate of the reaction.[24]

The line formulae in Table 2 do not indicate the preferred structural isomers for each pentavalent intermediate; however, the energy of each isomer was determined. In all cases, the more electronegative substituents were found to be preferred in the axial position, and the apicophilicity of F > OOH > OMe was observed, presumably to provide the most stable isomer by optimal overlap in a diaxial relationship.[18, 25, 26] A representative case is shown in Scheme 4 for the five possible structural isomers of **3c**, $[F_2SiMe_2OOH]^-$, with the energy of each isomer indicated relative to the lowest energy structure, the diaxial difluoride.

Table 2. Representative equilibrium energies for formation of pentavalent silicates [kJ mol^{-1}].

	Equilibrium	ΔE_{rxn}, gas phase	ΔE_{rxn}, MeOH
1	$Me_2Si(OMe)_2$ (**1a**) + OMe^- ⇔ $[SiMe_2(OMe)_3]^-$ (**2a**)	– 71	75
2	$Me_2Si(OMe)_2$ (**1a**) + F^- ⇔ $[FSiMe_2(OMe)_2]^-$ (**2b**)	– 156	27
3	$Me_2Si(OMe)_2$ (**1a**) + OOH^- ⇔ $[SiMe_2(OMe)_2OOH]^-$ (**3a**)	– 88	80
4	$FSiMe_2OMe$ (**1b**) + OMe^- ⇔ $[FSiMe_2(OMe)_2]^-$ (**2b**)	– 103	32
5	$FSiMe_2OMe$ (**1b**) + F^- ⇔ $[F_2SiMe_2(OMe)]^-$ (**2c**)	– 180	– 10
6	$FSiMe_2OMe$ (**1b**) + OOH^- ⇔ $[FSiMe_2(OMe)OOH]^-$ (**3b**)	– 121	38
7	F_2SiMe_2 (**1c**) + OMe^- ⇔ $[F_2SiMe_2(OMe)]^-$ (**2c**)	– 145	– 19
8	F_2SiMe_2 (**1c**) + F^- ⇔ $[F_3SiMe_2]^-$ (**2d**)	– 201	– 34
9	F_2SiMe_2 (**1c**) + OOH^- ⇔ $[F_2SiMe_2OOH]^-$ (**3c**)	– 153	8



Scheme 4. Structural isomers and relative energies of **3c** [kJ mol^{-1}].

Lastly, our examination of all of the structural isomers of the pentavalent intermediates **3** formed by attack of hydroperoxide reveals that Berry pseudorotation in the rearrangement TS was common, and that the most stable isomer of the intermediate did not necessarily have the lowest activation barrier (vide infra). However, these energy differences were small and consistent with Gordon's observations of low barriers to Berry pseudorotation.[21] For this case, specifically the rearrangement of anion **3c**, the activation barriers were calculated as the difference between the most stable conformer and the lowest energy TS, in accord with the Curtin–Hammett principle.[24]

Discussion

Role of fluoride: The solvated (MeOH) PESs for the conversion of **1a** to product(s) in the presence of fluoride, methoxide, and hydroperoxide are depicted in Figure 1. Three general observations can be made: first, that starting material **1a** is converted to progressively more stable species by sequential addition of fluoride followed by elimination of alkoxide; second, that fluoride also influences the equilibria of products; lastly, that the activation barrier to rearrangement is significantly lower via pentavalent **TS-5** species than via Tamao-type, pseudohexacoordinate transition states **TS-4**. The lowest TS overall, **5c**, is depicted in Figure 2 (the isoenergetic **5b** is very similar). The fairly flat pre-equilibrium conforms with experimental observations of an exothermic reaction only upon the addition of the last component to the reaction mixture, H_2O_2. At that point, the reaction temperature reportedly rises to approximately 60 °C, whereas no exothermicity is noted at room temperature in the absence of the oxidant.[8] Slight exothermicity from trialkoxy **6a** → **7b** is supported by the experimental observations of DeShong in his development of siloxanes as alternatives to the Stille substrates. In these reactions, addition of a single equivalent of fluoride to phenyl triethoxysilane occurs in situ in THF with mild heating at 50–60 °C for 12–48 h to form a hypervalent fluorosilicate anion, and polyfluorination is not reported.[27]

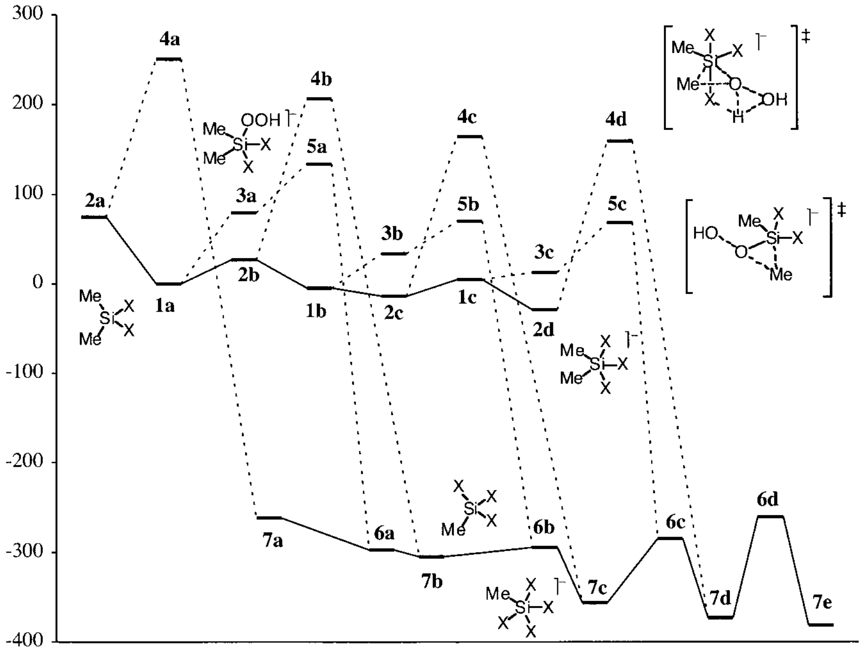


Figure 1. Solvated (MeOH) free energy profile for the oxidation of dimethoxydimethylsilane (**1a**) [kJ mol^{-1}].

The PES is consistent with the empirical use of at least three equivalents of fluoride. Fluoride will quickly convert all of dialkoxysilane **1a** in a slightly exothermic reaction to $[F_3SiMe_2]^-$ **2d**, with the experimental conditions requiring excess fluoride. This is the low point on the pre-reaction PES. Although the activation barrier from **2d** → **[TS-5c]** is moderately high (98 kJ mol^{-1}), the barrier is much less than it would be without fluoride (e.g. **1a** → **[TS-5a]**, 134 kJ mol^{-1}). The energy of the reactants is higher without the fluoride, and Table 3 demonstrates that the TS energies are also higher in the absence of fluoride. In addition, the postreactive equilibrium consumes fluoride as well, up to a total of four equivalents. The final equilibrium of **7d** ⇔ **6d** ⇔ **7e** is probably in equilibrium with free fluoride, but if less than four equivalents are used, the reaction should slow appreciably at the end.

In practice, in the absence of fluoride, base is employed (either $KHCO_3$ or KOH), and then the paths of attack by methoxide to generate **2a** and hydroperoxide to generate **3a** are approximately comparable and energetically accessible (approx. 75 kJ mol^{-1} for the initial equilibrium in solvent). These equilibria would, of course, favor **1a**, but formation of

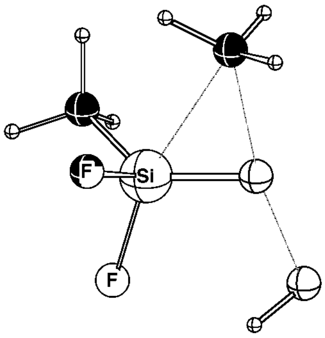


Figure 2. Transition state **5c**. In the almost isoenergetic **5b**, the equatorial fluoride is substituted by a methoxy group.

Table 3. Activation energies for formation of organosilicates [kJ mol^{-1}].

		E_{act}, gas	E_{act}, MeOH
1	$Me_2Si(OMe)_2$ (**1a**) + HOO^- → **[TS-5a]**	–18	134
2	$[F_3SiMe_2]^-$ (**2d**) + HOO^- → **[TS-5a]**	268	163
3	$[F_3SiMe_2]^-$ (**2d**) + HOO^- → **[TS-5b]**	207	99
4	$[F_3SiMe_2]^-$ (**2d**) + HOO^- → **[TS-5c]**	150	98
5	$Me_2Si(OMe)_2$ (**1a**) + HOOH → **[TS-4a]**	71	251
6	$[F_3SiMe_2]^-$ (**2d**) + HOOH → **[TS-4b]**	269	236
7	$[F_3SiMe_2]^-$ (**2d**) + HOOH → **[TS-4c]**	201	193
8	$[F_3SiMe_2]^-$ (**2d**) + HOOH → **[TS-4d]**	145	188

product **7a** is exothermic, driving the reaction to completion. Under these conditions, the rearrangement very likely occurs by an anionic transition state, and the activation barrier for this conversion (**1a** → **TS-5a**, via **3a**), 134 kJ mol^{-1}, would be accessible by heating the reaction mixture. It is not surprising that heating is required in the latter protocols, which have been employed when silyl ether protection could be competitively cleaved by fluoride.[12]

Determination of preferred rearrangement transition state: Our previous work demonstrated that the rearrangement of difluorodimethylsilane in the presence of weak base occurs by means of attack by HOO− to form an anionic, pentavalent intermediate that undergoes rearrangement, rather than approach of neutral H_2O_2 to a pentavalent silicate. Thus, we hypothesized that with fluoride shifting the equilibrium from alkoxysilyl species to generate difluorodimethylsilane, **TS-5** is likely to be the preferred TS. Nonetheless, the activation barriers under both basic and neutral conditions were determined for all intermediates to confirm this hypothesis. We additionally sought to confirm that the TS induced by attack of HOO− would have lower activation barriers, regardless of substitution pattern, than that of the attack by HOOH. The preferred geometry for the pentavalent **TS-5** requires that there is an axial–equatorial relationship between the migrating methyl group and the hydroperoxide (Figure 2), and thus only structural isomers of this type were considered as rearrangement substrates. Given the low barrier to Berry pseudorotation, this seemed reasonable; indeed, attempts to locate TS from the other geometries also resulted in the geometry shown (Figure 2) anyway due to pseudorotation.

The activation barriers were calculated from the most stable fluoride species **2d** (Table 3), in accord with the Curtin–Hammett principle, although the species reacting with OOH$^-$ must re-equilibrate via the neutral silanes **1** and hydroperoxide silicates **3**. Uniformly, the barriers to the transition states **TS-5** are lower than the activation barriers to rearrangement mediated by neutral hydrogen peroxide, **TS-4** (Table 3, entries 1–4 vs. entries 5–8) in the solvated systems. The effect of the solvent correction differs with the nature of the reactants and the transition state. For **TS-5**, the solvent acts to decrease the activation barrier from **2d** because of increased stability of the anionic species in the solvent. The same principle is at work for entry 1, but with an opposite outcome: the gas-phase E_{act} is grossly underestimated. In the gas phase, the HOO$^-$ anion is not well stabilized, and combination with a neutral molecule **1a** yields an anion with the charge distributed over a larger surface area. In contrast, **TS-4** (entries 5–8) does not gain additional stability in solvent as the neutral leaving group (H_2O) is generated. **TS-4** also differs from **TS-5** by the presence of two intramolecular hydrogen bonds, providing a strong stabilization of the anionic charge in the gas phase, but a negligible contribution in solvent. The gas versus solvent differences between entry 5 and entries 6–8 are consistent with the HOO$^-$ case, and reflect the fact that entry 5 is the reaction of two neutral species, whereas entries 6–8 are the combination of an anion with a neutral. Regardless of the presence of additional fluoride, however, we submit that the mechanism of rearrangement for silylalkoxide starting materials is the same as that for fluorosilane starting materials:[16] rearrangement via a pentavalent intermediate formed by attack of HOO$^-$. Depending on the substrate, the barrier to anionic rearrangement is 50 to 120 kJ mol^{-1} lower in energy than rearrangement mediated by neutral HOOH. These differences are significant, and the trends should remain the same regardless of minor errors inherent in the basis set or solvation parameters.

Conclusion

It has been demonstrated that fluoride, while not essential for the oxidation of alkoxysilanes, lowers the activation barrier to the rearrangement step by shifting the equilibrium to more reactive silylfluorides. In the presence of a weak base that is typically used in the experimental protocols, the rearrangement step is likely to occur by means of attack by hydroperoxide to form a pentavalent intermediate that then undergoes rearrangement. An additional role for fluoride is the generation of stable fluorinated species **7** from the initial products of rearrangement, **TS-5**. The computational results are in accord with experimental observations and can provide insight into the development of reaction conditions and substituents for novel oxidizable organosilanes.

Acknowledgements

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