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Reaction Mechanisms

Synthesis of a Stable Selenoaldehyde by Self-Catalyzed Thermal Dehydration of a Primary-Alkyl-Substituted Selenenic Acid**

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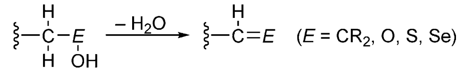
Abstract: *The unprecedented dehydration of a selenenic acid (RCH_2SeOH) to a selenoaldehyde (RCH=Se) has been demonstrated. A primary-alkyl-substituted selenenic acid was synthesized for the first time by taking advantage of a bulky cavity-shaped substituent. Upon heating in solution, the selenenic acid underwent thermal dehydration to produce a stable selenoaldehyde, which was isolated as stable crystals and crystallographically characterized. Investigation of the reaction mechanism revealed that this β dehydration reaction involves two processes, both of which reflect the characteristics of a selenenic acid: 1) dehydrative condensation of two molecules of selenenic acid to generate a selenoseleninate intermediate [$RCH_2SeSe(O)CH_2R$], an isomer of a selenenic anhydride, and 2) subsequent β elimination of the selenenic acid from this intermediate to form a C=Se double bond, which establishes the self-catalyzed β dehydration of the selenenic acid.*

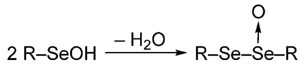
Dehydrative β elimination to form a double bond is one of the most fundamental transformations in organic chemistry as represented by dehydration of alcohols to form alkenes (Scheme 1, $E = CR_2$).[1] In contrast, there have been only a limited number of reports on the formation of aldehydes through dehydration of hydroperoxides (Scheme 1, $E = O$).[2] Furthermore, there has been no example of the formation of heavier congeners, such as thio- and selenoaldehydes, by dehydration of sulfenic acids and selenenic acids, respectively (Scheme 1, $E = S$, Se).



Scheme 1. Dehydrative β elimination to form a C=*E* bond ($E = CR_2$, O, S, Se).

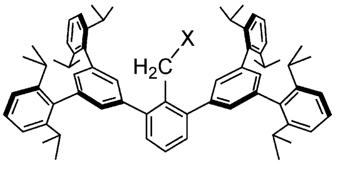
Herein, we report the first example of the synthesis of a selenoaldehyde (RCH=Se) through thermal dehydration of a primary-alkyl-substituted selenenic acid (RCH_2SeOH). Investigation of the reaction mechanism revealed that the intrinsic properties of a selenenic acid play a crucial role in this transformation, where a substrate selenenic acid functions as a self-catalyst for β dehydration.

Selenenic acids have received considerable attention in view of their importance in biological functions. They are deeply involved in the redox chemistry of selenocysteine residues in enzymatic reactions such as the catalytic cycle of glutathione peroxidase.[3] It is well known that selenenic acids are usually very unstable because of their propensity to undergo facile dehydrative self-condensation to form the corresponding selenoseleninate [RSeSe(O)R], an isomer of a selenenic anhydride (RSeOSeR; Scheme 2).[4–6] While isolation of some aryl-substituted selenenic acids[7] and a tertiary-alkyl derivative[4] has been achieved by taking advantage of appropriate bulky groups, the synthesis of a primary-alkyl-substituted counterpart has not yet been reported.[8] As a model compound of naturally occurring selenenic acids derived from selenocysteines,[9] a primary alkyl derivative is the most relevant. However, it is a common idea that the steric demands of primary alkyl groups are too small to protect such reactive species.



Scheme 2. Facile dehydrative self-condensation of a selenenic acid to form a selenoseleninate.

In the course of our studies on biologically relevant highly reactive species containing sulfur and selenium,[7,10] we have recently developed a sterically encumbered primary alkyl group with the cavity-shaped framework shown in Figure 1 (denoted as a $BpqCH_2$ group hereafter).[11] We found that the



$BpqCH_2X$

Figure 1. A bulky primary alkyl group with a cavity-shaped framework.

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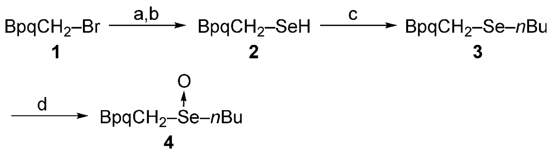
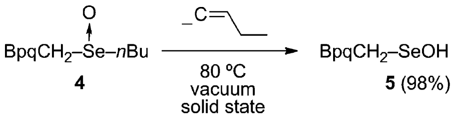
$BpqCH_2$ group is effective for kinetic stabilization of reactive species which otherwise undergo facile bimolecular decomposition such as a sulfenyl iodide (X = SI). In this context, we set out to prepare a primary-alkyl-substituted selenenic acid by utilizing this substituent.

The synthesis of a primary-alkyl-substituted selenenic acid was achieved by thermal β elimination from a selenoxide.[12] The selenoxide precursor **4** was prepared from the bromide **1**[11] as outlined in Scheme 3. After scrutiny of the reaction conditions for thermolysis of **4**, we found that heating **4** in the solid state at 80 °C in vacuo cleanly produced the desired selenenic acid **5** (Scheme 4). The selenenic acid **5** was isolated as a colorless solid and characterized by NMR (^1H, ^{13}C, and ^{77}Se) and IR spectroscopies as well as elemental analysis. In the ^{77}Se NMR spectrum of **5**, a signal was observed at $\delta = 1261$ ppm, and is comparable with the ^{77}Se chemical shift of a selenenic acid bearing a triptycyl group ($\delta = 1108$ ppm).[4] The ^1H NMR spectrum showed a singlet at $\delta = 2.39$ ppm and is attributed to the hydroxy proton, which is readily exchangeable with D_2O.



$$\underset{\mathbf{1}}{BpqCH_2\text{–}Br} \xrightarrow{a,b} \underset{\mathbf{2}}{BpqCH_2\text{–}SeH} \xrightarrow{c} \underset{\mathbf{3}}{BpqCH_2\text{–}Se\text{–}nBu} \xrightarrow{d} \underset{\mathbf{4}}{BpqCH_2\text{–}\overset{O}{\overset{\uparrow}{Se}}\text{–}nBu}$$

Scheme 3. Synthesis of the selenoxide **4**. Reagents and conditions: a) KSeCN (1.4 equiv), THF, 86%; b) $NaBH_4$ (4.3 equiv), THF, 94%; c) *n*BuI (3.5 equiv), Et_3N (1.2 equiv), $CHCl_3$, 72%; d) *m*CPBA (1.0 equiv), $CHCl_3$, 56%. *m*CPBA = *m*-chloroperbenzoic acid, THF = tetrahydrofuran.



Scheme 4. Synthesis of the primary-alkyl-substituted selenenic acid **5**.

In spite of being a primary alkyl derivative, **5** was found to be stable enough to manipulate under laboratory conditions. It decomposed at 275–277 °C in the solid state and is almost persistent in a $[D_6]$benzene solution at ambient temperature. However, when heated in $[D_6]$benzene at 60 °C, **5** decomposed slowly with concomitant release of water, which was confirmed by ^1H NMR spectroscopy. After 230 hours, quantitative conversion of **5** into a dehydrated product was observed. Unexpectedly, the product was identified to be the selenoaldehyde **6** (Scheme 5), not the selenoseleninate that was supposed to be formed by the self-condensation of **5**.

$$\underset{\mathbf{5}}{BpqCH_2\text{–}SeOH} \xrightarrow[\substack{[D_6]\text{benzene, 60 °C} \\ 230\ h}]{-H_2O} \underset{\mathbf{6}\ (85\%)}{BpqCH{=}Se}$$

Scheme 5. Dehydration of **5** to form selenoaldehyde **6**.

The selenoaldehyde **6** was isolated as stable green crystals in 85 % yield.

Selenoaldehydes have attracted much attention because of their intriguing properties.[13] Because of their high reactivity, only a limited number of selenoaldehydes have been isolated by taking advantage of either kinetic stabilization by bulky substituents[14,15] or thermodynamic stabilization such as coordination to transition metals[14b,c,16] and mesomeric effects due to heteroatoms.[17] The selenoaldehyde **6** was identified based on its spectroscopic data [$\delta_H = 17.08$ ppm($HC{=}Se$), $\delta_C = 240.86$ ppm ($HC{=}Se$), $\delta_{Se} = 2321$ ppm, $\lambda_{max} = 784$ nm ($\varepsilon = 83$, $CHCl_3$)], all of which are comparable with those of kinetically stabilized selenoaldehydes reported to date.[14] The structure of **6** was finally established by X-ray crystallographic analysis (Figure 2).[18] The C=Se bond length in the kinetically stabilized **6** [1.739(3) Å] is significantly shorter than that in **7** [1.805(5) Å],[17b] which is stabilized by mesomeric effects due to the nitrogen atom, and that in the η^1-selenoaldehyde tungsten complex **8** [1.783(15) and 1.781(13) Å][14b,c] (Figure 3). These data indicate less electronic perturbation into the selenoformyl moiety in **6** by the substituent. Given that the kinetically stabilized selenoaldehydes reported to date are unstable at elevated temperatures,[14] clean formation of **6** under prolonged heated conditions (Scheme 5) is remarkable.

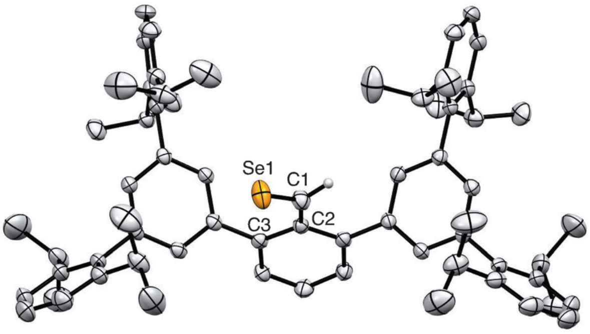
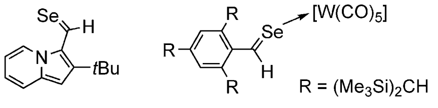


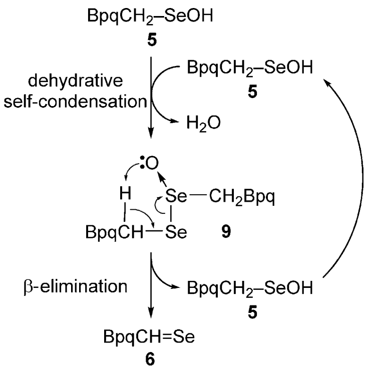
Figure 2. ORTEP drawing of **6** (thermal ellipsoid shown at 50% probability). Selected bond length (Å), bond angle (deg), and torsion angle (deg): Se(1)-C(1) 1.739(3); Se(1)-C(1)-C(2), 133.2(2); Se(1)-C(1)-C(2)-C(3), 20.8(4). In the crystalline state, there is a rotational disorder of the CHSe moiety along the C(1)-C(2) bond in the ratio of 0.77:0.23, and only the major component is shown.



7 **8**

Figure 3. Structures of selenoaldehydes characterized by X-ray crystallographic analysis.

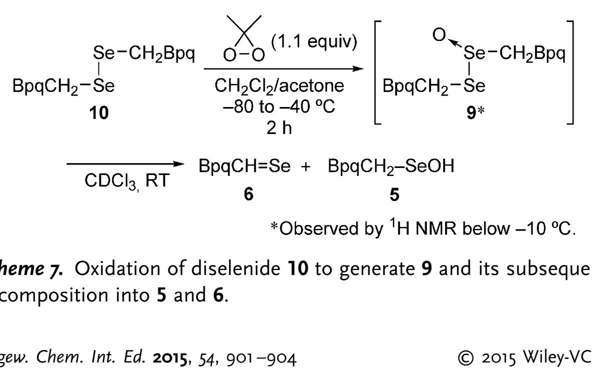
We next performed several experiments to clarify the mechanism of this intriguing β dehydration of a selenenic acid to form a C=Se bond. Examination of the concentration effect



Scheme 6. Plausible mechanism for conversion of **5** into **6**.

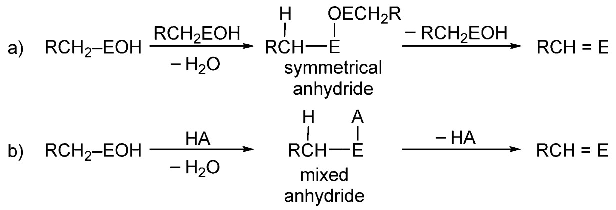
revealed that the decomposition of **5** was accelerated by increasing the initial concentration (see Table S2 in the Supporting Information). This feature suggests that an intermolecular process involving **5** should be involved in the reaction. The most probable mechanism, as we propose the reaction pathways shown in Scheme 6, involves 1) dehydrative condensation of two molecules of **5** to generate the selenoseleninate **9**, and 2) subsequent β elimination of **5** from **9** to generate **6**. Facile dehydrative self-condensation to a selenoseleninate is one of the most characteristic reactivities of a selenenic acid.[4,5] It is probable that **9**, thus formed, readily undergoes β elimination of **5** to form a C=Se double bond by a mechanism similar to that of selenoxide *syn* elimination. Formation of unsaturated bonds by β elimination of a sulfenic acid (RSOH)[19] and a selenenic acid[12] from sulfinyl and seleninyl derivatives, respectively, is well established. Although β elimination of a selenenic acid from a selenoseleninate has not been described in the literature, it has been reported that thermolysis of a thiosulfinate, a sulfur analogue of a selenoseleninate, forms a C=S bond through β elimination of a sulfenic acid.[20] It is of note that in the reaction sequence shown in Scheme 6, **5** behaves as a self-catalyst for the β dehydration to **6**.

Evidence in support of the intermediacy of a selenoseleninate was obtained from the following experiments. It has been known that a selenoseleninate can be prepared by oxidation of the corresponding diselenide.[4,5] When the diselenide **10** was carefully oxidized with dimethyldioxirane at low temperature, the selenoseleninate **9** was observed by ^{1}H NMR spectroscopy (Scheme 7).[21] Because of its thermal lability, **9** was observable only at temperatures below −10 °C. Upon warming the solution containing **9** in $CDCl_3$ to room temperature, **9** completely disappeared, which resulted in the formation of **6** and **5** in a 1:0.9 molar ratio. These results clearly demonstrate the ready β elimination of **5** from **9** to form **6**.



Scheme 7. Oxidation of diselenide **10** to generate **9** and its subsequent decomposition into **5** and **6**.

Thus, it can be concluded that the dehydration of **5** to **6** reflects two intrinsic properties of a selenenic acid: 1) the high propensity to undergo the dehydrative condensation between two molecules, and 2) the ability to undergo β elimination from seleninyl derivatives to form unsaturated bonds. The formation of aldehydes by dehydration of hydroperoxides (RCH_2OOH) is known to proceed only sluggishly and to compete seriously with other pathways, and the decomposition mechanism is rather complicated.[2] Sulfenic acids (RCH_2SOH)[22] could follow a reaction course similar to those of selenenic acids, that is, the self-condensation to $RCH_2SS(O)CH_2R$ followed by β elimination of sulfenic acid, but it is reasonable to expect that much harsher reaction conditions would be required for the β elimination step.[20a,23] In contrast with the lighter congeners, selenenic acids have the distinctive feature that both processes shown in Scheme 6 proceed smoothly under mild reaction conditions. In addition, it should be emphasized that the bulky cavity-shaped substituent, the Bpq group, exerts just the right effect in stabilizing each of the selenenic acid and the selenoaldehyde, thus enabling this unprecedented dehydration reaction to be accomplished. The Bpq group stabilizes a selenenic acid spaced by a CH_2 group so that it can be isolated as a stable solid, while it still allows the selenenic acid to undergo the dehydrative self-condensation when heated. Furthermore, the selenoaldehyde thus formed is robustly stabilized by the Bpq group to survive during prolonged heating.



Scheme 8. The β dehydration of organic acids (RCH_2EOH) to form a C=E bond via acid anhydride intermediates. a) Self-catalyzed β dehydration via a symmetrical anhydride. b) β dehydration catalyzed by other acids via a mixed anhydride.

The mechanism shown in Scheme 6 corresponds to a general sequence of a self-catalyzed β dehydration of an organic acid shown in Scheme 8a, that is, dehydration of an acid to generate a symmetrical anhydride (or its equivalent) followed by β elimination of an acid from the anhydride to form an unsaturated bond. When the acid is a carboxylic acid (E = CO), a ketene is formed by the reaction sequence. However, the elimination of a ketene from a carboxylic anhydride is a thermodynamically unfavorable process and usually requires very high temperatures.[24] In contrast, both processes of the reaction sequence for a selenenic acid (E = Se) proceed under thermally mild conditions, although the first step produces a selenoseleninate as an equivalent of a selenenic anhydride. In addition to a self-catalyzed system, a dehydration sequence catalyzed by other acids involving a mixed anhydride as an intermediate could be considered (Scheme 8b). Investigation of β dehydration of **5** using another acid as a catalyst is currently in progress.

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