The Markedly Enhanced Basicity of Selenenamides vs Sulfenamides and the Mechanism of the Methanolysis of *o*-Nitro- and 2,4,6-Tri-*tert*-butylbenzeneselenenamides[1]

John L. Kice* and Andrei G. Kutateladze

Department of Chemistry, University of Denver, Denver, Colorado 80208

Received September 8, 1992

Measurement in acetonitrile–methanol of the basicity of selenenamides shows that they are approximately 3 pK units more basic than the corresponding sulfenamides. Since other explanations do not seem tenable, this apparently results from the fact that selenium is less electronegative than sulfur, although it is somewhat surprising that the small difference in the electronegativity of the two elements should lead to such a large difference in basicity. In the same solvent the kinetics of the acid-catalyzed methanolyses (eq 2) of *o*-nitro- and 2,4,6-tri-*tert*-butylbenzeneselenenamides are similar (large dependence of rate on [MeOH], unusual dependence of rate on [H^+]) to those for the methanolysis of the corresponding *o*-nitrobenzenesulfenamides. In the latter case the kinetics have been shown[6] to be indicative of a mechanism where a sulfuranide (**3**, eq 5) is the key intermediate on the reaction coordinate; as a consequence, a similar kind of mechanism (eq 6) involving a hypervalent selenium intermediate (**4**) is proposed for eq 2. The unusual dependence on [H^+] is because acid-catalyzed reversion of **4** to protonated selenenamide (**2**-H^+) and methanol (step k_{-6}) is faster under certain conditions than cleavage of **4** to give the final products (step k_7). Comparison of the methanolysis kinetics of *o*-nitro (**2a**) and 2,4,6-tri-*tert*-butylbenzeneselenenamides (**2c**) shows that the coordination of an *o*-nitro group to selenium that stabilizes **2a** and **2a**-H^+ does not appear to change the mechanism for methanolysis although it does cause the partitioning of **4** ($k_{-6}[H^+]/k_7$) to be much less favorable to the formation of products (step k_7).

Previous studies[2-4] have examined the mechanisms of a number of acid-catalyzed substitution reactions of *o*-nitrobenzeneselenenic acid (ArSeOH, Ar = *o*-$O_2NC_6H_4$–) and its derivatives. The choice of this particular selenenic acid as substrate was because at that time the only areneselenenic acids known to have more than a transitory existence were those, like *o*-benzoyl- and *o*-nitrobenzeneselenenic acid, where a strong electron-withdrawing group capable of coordination with the selenium was present ortho to the SeOH group. At the same time it was recognized that coordination of the ortho substituent to the selenium might introduce changes in the detailed mechanism of some of the reactions from what would have been obtained in its absence.

In 1988 Reich and Jasperse[5] showed that 2,4,6-tri-*tert*-butylbenzeneselenenic acid [ArSeOH, Ar = 2,4,6-(*t*-Bu)$_3C_6H_2$], where the selenenic acid functionality is shielded by two bulky alkyl groups, is also a relatively "stable" areneselenenic acid, thus providing an areneselenenic acid without a coordinating *o*-substituent as an alternative areneselenenic acid substrate.

A recent investigation[6] in this laboratory focused on the acid-catalyzed methanolysis (eq 1) of *o*-nitrobenzenesulfenamides (**1**, Ar = *o*-$O_2NC_6H_4$–) in acetonitrile–methanol and found evidence that this substitution at dicoordinate sulfur takes place by a mechanism where a hypervalent sulfur species (sulfuranide) is present as an intermediate on the reaction coordinate.

$$\underset{\mathbf{1}}{\mathrm{ArSNR_2}} + \mathrm{MeOH} + \mathrm{H^+} \rightarrow \mathrm{ArSOMe} + \mathrm{R_2NH_2^+} \quad (1)$$

Since we found that both *o*-nitro- (**2**, Ar = *o*-$O_2NC_6H_4$–) and 2,4,6-tri-*tert*-butylbenzeneselenenamides (**2**, Ar = 2,4,6-(*t*-Bu)$_3C_6H_2$–) also undergo quite facile methanolysis (eq 2) in acid solution we decided to investigate this

$$\underset{\mathbf{2}}{\mathrm{ArSeNR_2}} + \mathrm{MeOH} + \mathrm{H^+} \rightarrow \mathrm{ArSeOMe} + \mathrm{R_2NH_2^+} \quad (2)$$

reaction, and in the present work we have examined its detailed kinetic behavior under the same type of reaction conditions used for methanolysis of the sulfenamides. We were particularly interested in the following questions: (a) Were there significant differences in the behavior of the *o*-nitrobenzeneselenenamide (eq 2, Ar = *o*-$O_2NC_6H_4$) and the *o*-nitrobenzenesulfenamide (eq 1, Ar = *o*-$O_2NC_6H_4$) methanolyses, and if so, what might they contribute to our understanding of substitution at selenium as compared to sulfur? (b) What differences were there in the behavior of the methanolyses of *o*-$O_2NC_6H_4SeNR_2$ vs 2,4,6-(*t*-Bu)$_3C_6H_2SeNR_2$, and what, if anything, might they indicate about the impact on mechanism of the presence of the *o*-nitro group with its potential for coordination to the selenium. The present paper describes the results of that investigation.

Results

Basicity of Selenenamides in Acetonitrile–Methanol. As an adjunct to study of the kinetics of the methanolysis of arenesulfenamides (eq 1) the equilibrium constants (K_b) for the protonation (eq 3) of **1a** (Ar = *o*-$O_2NC_6H_4$, R = Me) and **1b** (Ar = *o*-$O_2NC_6H_4$, R_2 =

(1) This research supported by the National Science Foundation, Grant CHE-9000175.

(2) Kice, J. L.; McAfee, F.; Slebocka-Tilk, H. *J. Org. Chem.* **1984**, *49*, 3100.

(3) Kice, J. L.; McAfee, F.; Slebocka-Tilk, H. *J. Org. Chem.* **1984**, *49*, 3106.

(4) Kang, S.-I.; Kice, J. L. *J. Org. Chem.* **1986**, *51*, 295.

(5) Reich, H. J.; Jasperse, C. P. *J. Org. Chem.* **1988**, *53*, 2389.

(6) Kice, J. L.; Kutateladze, A. G. *J. Org. Chem.* **1992**, *57*, 3298.

0022-3263/93/1958-0917$04.00/0

$$\underset{1}{ArSNR_2} + MeOH_2^+ \overset{K_b}{\rightleftarrows} \underset{1\text{-}H^+}{ArSNH^+R_2} + MeOH \quad (3)$$

$(-CH_2CH_2)_2O]$ were measured[6] in acid solution in MeCN–methanol. In MeCN–8.2 M MeOH K_b (expressed in terms of *concentrations*, i.e., $K_b = [1\text{-}H^+]/[1][H^+]$, rather than activities) was 3.6 for **1a** and 0.33 for **1b**. In MeCN–5.0 M MeOH the k_b's for both sulfenamides were ~2 times larger (8.8 for **1a**, 0.65 for **1b**). This was shown[6] to be due to the proton activity of a solution containing a given $[H^+]$ increasing significantly as the concentration of methanol in the MeCN–MeOH mixture is decreased. The values of K_b for **1a** and **1b** were such that at the maximum strong acid concentration ($[H^+] = 0.016$ M) used for the kinetic studies of the sulfenamide methanolysis the fraction of 1 protonated to 1-H^+ at equilibrium in MeCN–8.2 M MeOH was less than 5.0%.

At the outset we thought that K_b for the *o*-nitrobenzeneselenenamides would probably be similar to K_b for the *o*-nitrobenzenesulfenamides. The equilibrium constant (K_b) for the protonation of selenenamides **2a** and **2b** (eq 4, Ar = *o*-$O_2NC_6H_4$, R = Me and R_2 = $(-CH_2CH_2)_2O$)

$$\underset{2}{ArSeNR_2} + MeOH_2^+ \overset{K_b}{\rightleftarrows} \underset{2\text{-}H^+}{ArSeNH^+R_2} + MeOH \quad (4)$$

could be evaluated easily by making use of the changes in the ultraviolet spectrum of the solution that accompany the protonation of **2** to 2-H^+. The values of K_b are tabulated in Table I. Selenenamides **2a** and **2b** are each *about 3.4 pK units more basic* than the corresponding sulfenamides **1a** and **1b**!

Measurements of K_b for *N,N*-dimethyl-2,4,6-tri-*tert*-butylbenzenesulfenamide (**1c**, Ar = 2,4,6-(*t*-Bu)$_3C_6H_2$, R = Me) and selenenamide (**2c**, Ar = 2,4,6-(*t*-Bu)$_3C_6H_2$, R = Me) revealed the following (Table I): (a) sulfenamide **1c** is approximately 3.8 pK units more basic than the corresponding sulfenamide with the *o*-nitro group (**1a**), presumably as a result of the marked difference in the inductive effect of the nitro group relative to the three *t*-Bu groups; (b) selenenamide **2c** is at least 2.8 pK units stronger base than sulfenamide **1c**, showing that, whether or not an *o*-nitro group is present, a selenenamide is much more basic than the corresponding sulfenamide.

Why selenenamides are much more basic than sulfenamides will be considered in the Discussion. For now the important practical consequence is that even the least basic selenenamide (**2b**) is effectively completely converted to its protonated form (**2b**-H^+) in solutions containing as little as 0.02 M H^+, and the more basic **2a** is completely protonated in media containing as little as 0.002 M strong acid. The same will be true for **2c**. Thus studies of the kinetics of the methanolysis of **2** in acid solution will be conducted under conditions where the selenenamide is present almost entirely as 2-H^+.

Methanolysis of *o*-Nitrobenzeneselenenamides. When trifluoromethanesulfonic acid (0.125 M) was added to a 0.06 M solution of either *N,N*-dimethyl-*o*-nitrobenzeneselenenamide (**2a**) or *N*-(*o*-nitrophenylselenenyl)morpholine (**2b**) in 2:1 acetonitrile–CD_3OD the ^1H NMR spectrum of the solution changed over the course of 15 min to that expected for the products of eq 2, i.e., $R_2ND_2^+$ plus *o*-$O_2NC_6H_4SeOCD_3$.

The kinetics of the methanolysis of **2a** and **2b** under such conditions could be most conveniently followed by observing the increase in the optical density (A) of the solution at 445 nm that accompanies the conversion of the protonated selenenamide to methyl *o*-nitrobenzeneselenenate,[4,7] *o*-$O_2NC_6H_4SeOMe$. The reactions were studied in MeCN–MeOH solvent mixtures containing either 3.0 or 8.0 M methanol. Experiments with added (0.05–0.30 M) lithium trifluoromethanesulfonate with $[CF_3SO_3H] = 0.01$ M showed no dependence of the rate on ionic strength. Consequently, no effort was made to keep the ionic strength constant. The concentration of added strong acid (CF_3SO_3H) was varied from 0.005 to 0.28 M. Plots of log $(A_\infty - A)$ vs time were nicely linear in all cases, and the experimental first-order rate constant (k_1) for each run was obtained from the slope of such a plot. The data are shown in the first two sections of Table II. Other experiments where no CF_3SO_3H was added showed that both **2a** and **2b** did *not* undergo methanolysis at a significant rate in the *absence* of added strong acid. The rates of "spontaneous" methanolysis of **2a** and **2b** in MeCN–8.0 M MeOH were 2×10^{-5} and $<0.1 \times 10^{-5}$ s^{-1}, respectively, which is from 0.01 (**2a**) to 0.00003 (**2b**) as fast as k_1 in the presence of 0.057 M CF_3SO_3H. The difference between the "spontaneous" rate and that in acid solution is even greater for both selenenamides in MeCN–3.0 M MeOH.

In considering the kinetic results it is important to remember that the basicity of **2a** and **2b** is such (see preceding section) that the selenenamides will be completely protonated (to 2-H^+) at $[H^+] > 0.02$ M. Increases in strong acid concentration in the region $[H^+] = 0.05$ to 0.30 M used for the majority of the kinetic studies will therefore not lead to an increase in $[2\text{-}H^+]$, since the selenenamide is already completely converted to 2-H^+. With this consideration in mind the following aspects of the kinetics are worth noting: (1) For $[H^+] \geq 0.05$ M k_1 decreases with increasing $[H^+]$, the effect being more marked in 3.0 M MeOH and for **2a** than **2b**, but conforming in each case to that expected for a dependence of k_1 on $[H^+]$ of the form: $(1/k_1) = (1/k)[k'[H^+] + 1]$; (2) the rate of methanolysis is markedly dependent on [MeOH], being 15 (**2a**) to 30 (**2b**) times faster in MeCN–8.0 M MeOH than it is in MeCN–3.0 M MeOH; (3) the morpholinoselenenamide (**2b**) undergoes methanolysis in the presence of 0.057 M CF_3SO_3H from 7 (MeCN–3.0 M MeOH) to 13 (MeCN–8.0 M MeOH) times faster than the *N,N*-dimethylselenenamide **2a**.

Methanolysis of *N,N*-Dimethyl-2,4,6-tri-*tert*-butylbenzeneselenenamide. *N,N*-Dimethyl-2,4,6-tri-*tert*-butylbenzeneselenenamide (**2c**) also undergoes methanolysis quite readily in acid solution in MeCN–MeOH. The product of the reaction was shown to be methyl 2,4,6-tri-*tert*-butylbenzeneselenenate [ArSeOMe, Ar = 2,4,6-(*t*-Bu)$_3C_6H_2$–] by comparison of its NMR spectrum with that reported for this ester by Reich and Jasperse.[5,16]

The kinetics of the methanolysis of **2c** could be followed in MeCN–MeOH by measuring the increase in optical density at 247 nm that accompanied the conversion of protonated **2c** to the methyl selenenate. In the runs with **2c** where $[CF_3SO_3H]$ was <0.2 M the ionic strength was kept constant (0.2) by the addition of CF_3SO_3Li, although there is no indication the rate of methanolysis of **2c** is any more sensitive to ionic strength than is the case for **2a** and **2b**. The concentration of added CF_3SO_3H was varied from 0.014 to 0.28 M. The experimental first-order rate

(7) Holzle, G.; Jenny, W. *Helv. Chim. Acta* **1958**, *41*, 331.

Table I. Basicity of Selenenamides or Sulfenamides

selenenamide or sulfenamide	solvent	K_b, M^{-1}	pK_a of 2-H$^+$	K_b for $ArSNR_2$	$K_b(ArSeNR_2)/K_b(ArSNR_2)$
2a	MeCN–8.2 M MeOH	1.2×10^4	4.1	3.6[6]	3.3×10^3
2b	MeCN–8.2 M MeOH	1.0×10^3	3.0	0.33[6]	3.1×10^3
	MeCN–5.0 M MeOH	1.9×10^3	3.3	0.65[6]	2.9×10^3
2c	MeCN–8.2 M MeOH	too large to measure accurately		2.6×10^4	
	t-BuOH	$>1 \times 10^5$	>5.0	185	$>5.4 \times 10^2$
1c	MeCN–8.2 M MeOH	2.6×10^4			
	t-BuOH	185			

Table II. Kinetics of the Methanolysis of Areneselenenamides at 25 °C in Acetonitrile–Methanol[a]

selenenamide	[MeOH], M	[CF_3SO_3H], M	$k_1 \times 10^3$, s^{-1}
2b	8.0	0.005	33
		0.01	37
		0.02	40
		0.033	40
		0.057	38
		0.17	29
		0.23	26
		0.28	25
	3.0	0.057	1.4
		0.113	0.98
		0.17	0.74
		0.28	0.48
2a	8.0	0.057	3.0
		0.113	2.3
		0.17	1.9
		0.28	1.5
	3.0	0.057	0.19
		0.113	0.13
		0.17	0.09
		0.28	0.057
2c	8.0	0.014	35
		0.028	43
		0.057	36
		0.113	40
		0.17	41
	3.0	0.057	0.86
		0.113	0.98
		0.17	1.14
		0.23	0.97
		0.28	1.03

[a] All runs with **2c** in 8.0 M MeOH at ionic strength = 0.2 (maintained by addition of CF_3SO_3Li). Other runs not at constant ionic strength, but separate experiments showed rate is not affected by a change in ionic strength. Initial concentration of **2**, 0.0001–0.000 14 M.

constants (k_1) for the methanolysis of **2c** under the various conditions are tabulated in the last section of Table II.

Like the methanolysis of **2a**, methanolysis of **2c** does not occur at a significant rate in the absence of CF_3SO_3H, so that a "spontaneous" reaction is not responsible for any part of the k_1 values shown in Table II. Like **2a** selenenamide **2c** is also so basic that it is present entirely as **2c**-H$^+$ under all of the conditions in Table II. In contrast to the behavior of the methanolysis of **2a** that of **2c** does *not* show a decrease in k_1 with increasing [H$^+$] under such conditions. The rate increases even more markedly with increasing [MeOH] than does the rate for the methanolysis of **2a**, being about 40 times faster in MeCN–8.0 M MeOH than it is in MeCN–3.0 M MeOH.

Discussion

Difference in Basicity of Sulfenamides and Selenenamides. An unexpected result of the present study was the finding that selenenamides, $ArSeNR_2$, are *much* more basic than the corresponding sulfenamides, $ArSNR_2$. Since this greater basicity is observed both with the tri-*tert*-butyl compounds (**1c** and **2c**) and in the cases (**1ab** and **2ab**) where an *o*-nitro group is present, it cannot have its origin in the coordination of the nitro group to the sulfur or selenium atom that is a feature of the structure of the *o*-nitro compounds.[8,9]

The difference in basicity of 3.4 pK units between selenenamide (**2a** or **b**) and sulfenamide (**1a** or **b**) corresponds to a difference in $\Delta G°$ of about 4.8 kcal/mol for the two equilibria. One factor that should make a selenenamide more basic than a sulfenamide is the fact that selenium is less electronegative than sulfur, although only by 0.1 unit (Se, 2.4; S, 2.5). How much of a difference in basicity will result from this difference in electronegativity? With the anions $HSeO_3^-$ and HSO_3^- the former is more basic by 0.8 pK unit.[10a] For $PhSeO_2^-$ vs $PhSO_2^-$, however, the difference is much larger, 3.5 pK units.[10b,c] Thus, there would appear to be some precedent that the small difference in electronegativity of Se and S could be responsible for the marked difference in basicity, surprising though it might otherwise seem.

Given the evidence from other studies[11] that overlap of the unshared pair on nitrogen with a vacant d orbital on the neighboring chalcogen atom is not important in sulfenamides and that n–σ^* hyperconjugation, while significant for trihalomethanesulfenamides, is not a factor for arenesulfenamides, it seems unlikely that either of these two phenomena are contributing significantly to the difference in basicity.

Mechanism of Methanolysis of 2a and 2b. It will be helpful first to summarize briefly the earlier findings[6] regarding the mechanism of the methanolysis of *o*-nitrobenzenesulfenamides (**1**, eq 1). The unusual nature of the dependence of the rate of methanolysis on [H$^+$], where $k_{exp} = k\alpha/(k'[H^+] + k'')$, with α, the fraction of **1** present as the protonated sulfenamide (**1**-H$^+$), equal to $K_b[H^+]/(K_b[H^+] + 1)$, was shown to be indicative of the mechanism in eqs 3 and 5. In this mechanism a sulfuranide inter-

$$1 + MeOH_2^+ \overset{K_b}{\rightleftharpoons} MeOH + 1\text{-}H^+ \quad (3)$$

$$2\ MeOH + 1\text{-}H^+ \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} MeOH_2^+ + \underset{\mathbf{3}}{MeO\text{–}S^-(Ar)\text{–}NH^+R_2} \quad (5a)$$

$$\underset{\mathbf{3}}{MeO\text{–}S^-(Ar)\text{–}NH^+R_2} \overset{k_b}{\rightarrow} ArSOMe + R_2NH \quad (5b)$$

(8) Austad, T. *Acta Chem. Scand. Ser. A* **1975**, *29A*, 895; *Ibid.* **1977**, *31A*, 93.

(9) Paulmier, C.; Lerouge, P.; Outurquin, F.; Chapelle, S.; Granger, P. *Magn. Reson. Chem.* **1987**, *25*, 955.

(10) (a) *Inorganic Chemistry*; Moeller, T., Ed.; John Wiley & Sons: New York, 1952; p 314. (b) McCullogh, J. D.; Gould, E. S. *J. Am. Chem. Soc.* **1949**, *71*, 674. (c) Ritchie, C. D.; Salteil, J. D.; Lewis, E. S. *Ibid.* **1961**, *83*, 4601.

(11) Kost, D.; Egozy, H.; *J. Org. Chem.* **1989**, *54*, 4909.

mediate **3** is present on the reaction coordinate, and reversion of **3** to **1**-H^+ (step k_{-a}) is comparable in rate for $[H^+] \geq 0.01$ M to the conversion of **3** to ArSOMe (step k_b). For this mechanism a plot of (α/k_{exp}) vs $[H^+]$ for the methanolysis of **1** is predicted (and found[6]) to be linear; its intercept is equal to $(1/k_a')$, and its slope to $(k_{-a}/k_b k_a')$, where k_a' includes any dependence of the rate of step k_a on methanol concentration. For **1a** in MeCN–8.2 M MeOH $k_a' = 0.035\ s^{-1}$ and $(k_{-a}/k_b) = 3.1 \times 10^2\ M^{-1}$, while in MeCN–3.0 M MeOH k_a' is over 50 times slower, 0.000 43 s^{-1}, and (k_{-a}/k_b) is about 5 times smaller, 59 M^{-1}. For **1b** $k_a' = 0.26\ s^{-1}$ and $(k_{-a}/k_b) = 3.3 \times 10^2\ M^{-1}$ in MeCN–8.2 M MeOH; as with **1a**, in MeCN–3.0 M MeOH k_a' is much smaller, 0.0048 s^{-1}, and (k_{-a}/k_b) is somewhat smaller, 56 M^{-1}.

Due to the basicity of the selenenamides being several pK units larger than that of the corresponding sulfenamides, both **2a** and **2b** are completely protonated to **2**-H^+, and $\alpha = 1.0$, for almost all of the kinetic runs in Table II (the exception being the two runs with **2b** in MeCN–8.0 M MeOH where $[H^+] \leq 0.02$ M). Plots of $(1/k_1)$ vs $[H^+]$ for these runs for **2a** and **2b** are linear, just as were[6] plots of (α/k_{exp}) vs $[H^+]$ for the methanolyses of sulfenamides **1a** and **1b**. The similar unusual dependence of rate on $[H^+]$ for the methanolyses of the corresponding sulfenamides and selenenamides suggests that the mechanism for the methanolysis of the selenenamides is analogous to that for the sulfenamides. Such a mechanism, with a hypervalent selenium intermediate (**4**) is shown in eq 6.

$$2\ MeOH + \textbf{2}\text{-}H^+ \underset{k_{-6}}{\overset{k_6}{\rightleftarrows}} MeOH_2^+ + \underset{\textbf{4}}{MeO\text{–}Se^-(Ar)\text{–}NH^+R_2} \quad (6a)$$

$$\underset{\textbf{4}}{MeO\text{–}Se^-(Ar)\text{–}NH^+R_2} \overset{k_7}{\rightarrow} ArSeOMe + R_2NH \quad (6b)$$

With such a mechanism for the methanolysis of **2a** and **2b**, the slope and intercept of a plot of $(1/k_1)$ vs $[H^+]$ become equal to $(k_{-6}/k_7 k_6')$ and $(1/k_6')$, respectively, where k_6' includes any dependence of the rate of step k_6 on methanol concentration. From such plots the following values are obtained for MeCN–8.0 M MeOH as solvent: **2a**, $k_6' = 0.0038\ s^{-1}$, $k_{-6}/k_7 = 5.7\ M^{-1}$; **2b**, $k_6' = 0.045\ s^{-1}$, $k_{-6}/k_7 = 2.9\ M^{-1}$. In MeCN–3.0 M MeOH the corresponding values are: **2a**, $k_6' = 0.000\,57\ s^{-1}$, $k_{-6}/k_7 = 32\ M^{-1}$; **2b**, $k_6' = 0.003\ s^{-1}$, $k_{-6}/k_7 = 18\ M^{-1}$.

Comparison of these values with those for k_a' and k_{-a}/k_b for **1a** and **1b** reveals the following: (1) As was true for **1a** and **1b**, k_6' for the morpholino compound **2b** is larger than k_6' for the dimethylamino compound **2a** by a factor averaging about 10; (2) k_6' for either **2a** or **2b** decreases with decreasing methanol content of the solvent, but the magnitude of the decrease [factor of 7 (**2a**) to 15 (**2b**)] is somewhat smaller than the 50–80-fold decrease in k_a' found with the sulfenamides for the same change in solvent composition; (3) the difference in the behavior of k_{-6}/k_7 for **2** vs k_{-a}/k_b for **1** is also noteworthy. While k_{-6}/k_7 for **2a** (32 M^{-1}) and **2b** (18 M^{-1}) in MeCN–3.0 M MeOH are not too different from k_{-a}/k_b for **1a** (59) and **1b** (56) in the same solvent, there is an enormous difference in MeCN–8.0 M MeOH because k_{-a}/k_b for **1** increases by a factor of about 5 with the indicated increase in methanol concentration, while k_{-6}/k_7 for **2** *decreases* by about the same factor for such a solvent change; (4) despite the fact that rates for substitution at selenium are normally much faster than for substitution at an equivalent sulfur, k_6' for **2** are either about the same (MeCN–3.0 M MeOH) or 5–10-fold smaller (MeCN–8.0 M MeOH) than k_a' for **1**.

How can these various differences in behavior be explained and accounted for? Let us begin by considering why k_6' for **2a** and **2b** is either about the same, or somewhat smaller, than k_a' for **1a** and **1b**, given that normally[12] nucleophilic substitution at selenium is much *faster* than at sulfur. We have seen that the *o*-nitrobenzeneselenenamides are 3.4 pK units more basic than the corresponding *o*-nitrobenzenesulfenamides. This means *o*-$O_2NC_6H_4SeNH^+R_2$ is approximately 5 kcal/mol lower in energy relative to *o*-$O_2NC_6H_4SeNR_2$ than *o*-$O_2NC_6H_4SNH^+R_2$ is to *o*-$O_2NC_6H_4SNR_2$. It has generally been assumed that the reason nucleophilic substitution at selenium was so much faster than at sulfur was because in the substitution at selenium the transition state (or hypervalent intermediate) was considerably lower in energy relative to the energy of the starting selenium compound than in the corresponding substitution at sulfur. In the present situation, if we assume that $ArSeNR_2$ and $ArSNR_2$ are of approximately the same energy, then the fact that **4** is of significantly lower energy than **3** need not lead to k_6' for the protonated selenenamide being faster than k_a' for the protonated sulfenamide since, as noted above, the free energy of the protonated selenenamide (**2a**-H^+ or **2b**-H^+) is 5 kcal/mol lower relative to **2a** and **2b** than that of **1a**-H^+ or **1b**-H^+ is relative to the corresponding sulfenamide.

Second, let us consider why k_6' for the dimethylamino compound (**2a**) is less than k_6' for the morpholino compound (**2b**). Note that a similar reactivity pattern was observed[6] in the methanolysis of sulfenamides **1a** and **1b**. As the lower basicity (Table I) of **2b** shows, **2b**-H^+ is of higher energy relative to **2b** than **2a**-H^+ is to **2a**. Going from **2**-H^+ to **4** should increase the electron density on selenium (and presumably also on the adjacent nitrogen). This should make formation of **4** from **2**-H^+ easier (faster) for the morpholino compound.

Next we take up the difference in the effect of an increase in the methanol content of the solvent on k_6' vs k_a'. The reactions shown in eqs 5a and 6a are similar (except that each contains an extra molecular of methanol) to the acid dissociation equilibria for **1**-H^+ or **2**-H^+, respectively, i.e.:

$$\textbf{1}\text{-}H^+ \text{ (or } \textbf{2}\text{-}H^+) + MeOH \overset{1/K_b}{\rightleftharpoons} MeOH_2^+ + \textbf{1} \text{ (or } \textbf{2})$$

Equilibrium constants $K_6 = (k_6/k_{-6})$, eq 6a, and $K_a = (k_a/k_{-a})$, eq 5a, would therefore be expected to show a solvent effect similar to that for $1/K_b$ for eqs 3 and 4. This means that (k_6/k_{-6}) for eq 6a and (k_a/k_{-a}) for eq 5a would be expected to be, on average, about five times *larger* in MeCN–8.0 M MeOH than in MeCN–3.0 M MeOH. When combined with the difference in [MeOH] for those two media this means k_6' in the two solvents would be expected to be:

$$k_6'\ (8\ M)/k_6'\ (3\ M) = (K_6\ (8\ M)/K_6\ (3\ M))([8.0]/[3.0])$$
$$(k_{-6}\ (8\ M)/k_{-6}\ (3\ M)) \cong 5(2.66)(k_{-6}\ (8\ M)/k_{-6}\ (3\ M)) \cong 13\ (k_{-6}\ (8\ M)/k_{-6}\ (3\ M))$$

Both k_6' (8 M)/k_6' (3 M) for **2a**-H^+ (7) and **2b**-H^+ (15) are not too different from 13. This suggests that k_{-6} for **4** in eq 6a is not significantly dependent on solvent. This is

(12) Gancarz, R. A.; Kice, J. L. *J. Org. Chem.* **1981**, *46*, 4899. Kice, J. L.; Weclas-Henderson, L.; Kewan, A. *Ibid.* **1989**, *54*, 4198.

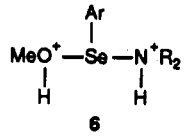
somewhat different from the situation for the analogous sulfuranide intermediate 3 in eq 5a.[6] There k_{-a} showed a dependence on solvent such that it was about 5 times faster in MeCN–8.0 M MeOH than in MeCN–3.0 M MeOH, and, as a result, k_a' was around 50 times larger in MeCN–8.0 M MeOH.

We do not know exactly why k_{-a} for 3 shows some dependence on methanol content whereas k_{-6} for 4 does not. The difference (a rate factor of ~5) corresponds, however, to less than 1 kcal/mol difference in $\Delta G^{\ddagger}$ with change in solvent, and because of the modest magnitude of this difference it is not surprising that pinpointing its exact origin is problematical.

Finally, we address the different solvent effects seen for (k_{-6}/k_7) vs (k_{-a}/k_b). In the sulfenamide system (k_{-a}/k_b) increases by a factor of ~5 on going from MeCN–3.0 M MeOH to MeCN–8.0 M MeOH. Since k_{-a} increases by a similar factor for this solvent change (see above), k_b must be essentially unaffected by solvent composition in MeCN–MeOH. In contrast (k_{-6}/k_7) decreases by a factor of about 5 on going from MeCN–3.0 M MeOH to MeCN–8.0 M MeOH. Since k_{-6} is not changed significantly by this change in solvent (see above), the observed decrease in (k_{-6}/k_7) must be the result of k_7 exhibiting a solvent effect such that it is about 5 times faster in the medium of higher methanol content.

Can one offer an explanation for why step k_7 for 4 is sensitive to the concentration of the protic solvent when step k_b is not? Compounds of the type R–Se–Y– have been shown[13] to be stronger donors than R–S–Y– in hydrogen-bonding interactions. The transition state for step k_7, where ArSe–OMe is being formed, might well be stabilized by H-bonding of the ester oxygen to methanol, i.e., ArSe–O(Me)···H–OMe, to enough greater extent than for the analogous reaction (step k_b) where ArSOMe is being formed, for step k_7 to show an increase in rate with increase in concentration of protic solvent whereas step k_b does not.

The basic mechanisms for the methanolysis of the o-nitrobenzeneselenenamides (eqs 6a and 6b) and the o-nitrobenzenesulfenamides (eqs 5a and 5b) seem to be the same. Both go through a hypervalent intermediate. In this intermediate a proton has been removed from the incoming methanol molecule, so that the intermediate has structure 3 (from 1) or 4 (from 2), rather than 6. The

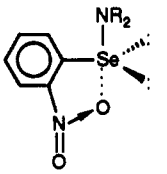


6

reason for this is that in 6 $MeOH^+$ is a so much better leaving group than R_2NH^+ that collapse of 6 with loss of the amine is not adequately competitive with collapse with loss of MeOH for a path through 6 to be a kinetically viable route to products.[14] With 4 (or 3) loss of amine, step k_7 (or k_b), is adequately competitive in rate with step k_{-6} (or k_{-a}).

As far as partitioning of the hypervalent intermediate is concerned, in MeCN–3.0 M MeOH it is not significantly different for selenium vs sulfur, k_{-6}/k_7 for 4 being about half as large as k_{-a}/k_b for 3. Because of the solvent effect on k_{-a} and k_7, and lack of same for k_b and k_{-6}, k_{-6}/k_7 for 4 is much smaller than k_{-a}/k_b in MeCN–8.0 M MeOH, meaning that in the more protic medium partitioning of the hypervalent intermediate to product is much more favorable in the case of the selenium intermediate.

Mechanism of Methanolysis of 2c. The o-nitrobenzeneselenenamides **2a** and **2b**, like other o-nitrobenzeneselenenyl derivatives,[8] are presumably stabilized by coordination of the *ortho* nitro group to the selenium:[9]



Does this have any important effect on the mechanism for methanolysis? For example, if the coordination were absent would the mechanism involve a simple S_N2 displacement by MeOH on $ArSeNH^+R_2$, rather than the mechanism going through the hypervalent intermediate 4 found with **2a** and **2b**?

One way to investigate this question is to determine the mechanism of methanolysis of **2c** [$ArSeNMe_2$, Ar = 2,4,6-$(t\text{-Bu})_3C_6H_2$]. In **2c** the o-*tert*-butyl groups provide steric hindrance to attack on the selenium, but they cannot stabilize either $ArSeNMe_2$ or $ArSeNH^+Me_2$ by coordination.

The reaction of a thiol (R'SH) with a protonated sulfenamide ($ArSNH^+R_2$) has been shown[6] to be a reaction where attack of a neutral molecule on 1-H^+ is rate-determining. In MeCN–MeOH solvent mixtures the rate of this reaction, in contrast to the rates of either eq 5a or 6a, shows no dependence on solvent composition. Given this behavior, if the methanolysis of **2c** were to proceed by a mechanism where there was a simple S_N2 displacement of Me_2NH^+ from **2c**-H^+ by MeOH, we would not expect to see a dependence of its rate on solvent composition, other than the 2.6-fold increase expected from the difference in [MeOH] between MeCN–8.0 M MeOH vs MeCN–3.0 M MeOH.

On the other hand, if the methanolysis of **2c** goes through a mechanism where there is formation of hypervalent intermediate 4 [Ar = 2,4,6-$(t\text{-Bu})_3C_6H_2$, R = Me], we would expect to see a significantly larger increase in rate than a factor of 2.6 on going from MeCN–3.0 M MeOH to MeCN–8.0 M MeOH.

Table II shows that k_1 for **2c**-H^+ is 40 times faster in MeCN–8.0 M MeOH than in MeCN–3.0 M MeOH. This large dependence of rate on methanol concentration

(13) Epshtein, L. M.; Zhdanova, A. N.; Dolgopyat, N. S.; Bochvar, D. A.; Gambaryan, N. D.; Kazitsyna, L. A. *Bull. Acad. Sci. USSR (Chem.)* 1979, 2302.

(14) As was also true in the methanolysis of sulfenamides,[6] formation of 4 in eq 6a may actually involve *two* steps, the first being addition of methanol to 2-H^+ to give 6, and the second transfer of a proton from 6 to the solvent:

$$2\text{-}H^+ + MeOH \rightleftharpoons 6$$

$$6 + MeOH \rightleftharpoons 4 + MeOH_2^+$$

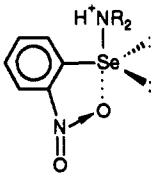
Regardless of whether 4 is produced in this way, or in a single step, the key point is that 4 is an intermediate that partitions to products with reasonable efficiency, whereas 6, because of $MeOH^+$ being a much better leaving group than R_2NH^+, does not.

suggests (although it does not require[15]) that methanolysis of **2c** also goes through a hypervalent intermediate **4** with the rate of formation of that intermediate from **2c**-H^+ showing an even more pronounced solvent effect than k_6' for **2a**-H^+.

If the mechanism for the methanolysis of **2c**-H^+ is as shown in eqs 6a and 6b [Ar = 2,4,6-(*t*-Bu)$_3C_6H_2$, R = Me] why isn't there a decrease in k_1 with increasing [H^+] as in the methanolyses of **2a**-H^+ and **2b**-H^+? The reason presumably is because (k_{-6}/k_7) for **4c** [**4**, Ar = 2,4,6-(*t*-Bu)$_3C_6H_2$, R = Me] is much smaller than (k_{-6}/k_7) for **4a** (**4**, Ar = *o*-$O_2NC_6H_4$, R = Me). For the mechanism in eqs 6a and 6b, where $1/k_1 = (1/k_6')[(k_{-6}[H^+]/k_7) + 1]$, an experimentally significant (i.e., >10%) decrease in k_1 with increase in [H^+] for [H^+] in the range 0.01–0.30 M will not observed *unless* (k_{-6}/k_7) ≥ 0.33. The behavior of k_1 for **2c** with increasing [H^+] therefore suggests that for **4c** (k_{-6}/k_7) ≤ 0.3.

Why might (k_{-6}/k_7) for **4c** be this much less than (k_{-6}/k_7) for **4a**? Two reasons suggest themselves. First, in **4** Me_2NH^+ should be a significantly bulkier ligand than MeO. Given that the *o*-*tert*-butyl groups lead to serious steric crowding in **4c** and that loss of Me_2NH^+ will relieve that crowding better than loss of MeO, the steric crowding in **4c** should make (k_{-6}/k_7) for **4c** smaller than for **4a**.

The second factor that could make (k_{-6}/k_7) for **4c** smaller than for **4a** is the following. We believe that **2a**-H^+, like **2a**, is stabilized by coordination of the *o*-nitro group to selenium:



Such coordination is presumably not present in **4**. The fact that step k_{-6} in eq 6a restores coordination to Se for **2a**-H^+, but not for **2c**-H^+, could cause k_{-6} for **4a** to be larger than k_{-6} for **4c**. This could also contribute to (k_{-6}/k_7) for **4c** being smaller than for **4a**.

In our opinion the combination of these two effects could easily be large enough to account for the factor of about 100 change in (k_{-6}/k_7) needed to account for the differing behavior of the methanolysis of **2c** relative to **2a**.

The fact that the mechanism for the methanolysis of **2c** appears to be the same, i.e., eqs 6a and 6b, as for the methanolysis of **2a** suggests that coordination of the *o*-nitro group to selenium in **2a** and **2b** does not lead to a fundamental change in the mechanism for the reaction. It does, however, lead to a less efficient (larger k_{-6}/k_7) partitioning of the hypervalent intermediate **4** to products.

Experimental Section

Preparation of *o*-Nitrobenzeneselenenamides. Both **2a** and **2b** were prepared by the general procedure outlined by Paulmier et al.[9] To 0.8 g (2 mmol) of di-*o*-nitrophenyl diselenide (Aldrich) dissolved in 30 mL of methylene chloride was added with stirring 0.32 g (2 mmol) of bromine. After 5 min 10 mmol of the appropriate amine was added, and the reaction mixture was allowed to stir for 30 min. The methylene chloride was then removed under reduced pressure, and the pure selenenamide was isolated in the following manner.

***N,N*-Dimethyl-*o*-nitrobenzeneselenenamide (2a).** The residue was treated with tetrahydrofuran. The insoluble material ($Me_2NH_2^+Br^-$) was filtered off, and the tetrahydrofuran was removed from the filtrate under reduced pressure to give **2a** as an oil in 90% yield. The crude **2a** was sublimed under reduced pressure to give 0.6 g (60%) of **2a**[9] as a red-brown crystalline solid, mp 58–60 °C: ^{1}H NMR ($CDCl_3$) δ 3.06 (s, 6 H), 7.33 (t, 1 H), 7.66 (t, 1 H), 8.23 (d, 1 H), 8.34 (t, 1 H); ^{13}C NMR ($CDCl_3$) δ 49.55, 125.53, 125.89, 127.28, 133.83; mass spectrum *m/e* 246 (M^+, ^{80}Se), 202 ($M^+ - Me_2N$), 186, 156, 133, 109, 106; UV (MeCN) λ_{max} 403 nm (ε, 3860).

***N*-(*o*-Nitrophenylselenenyl)morpholine (2b).** The residue was recrystallized twice from methanol giving 0.51 g (44%) of **2b** as a carrot-colored crystalline solid, mp 83–85 °C (lit.[9] mp 82 °C): ^{1}H NMR ($CDCl_3$) δ 3.25 (m, 4 H), 3.81 (m, 4 H), 7.36 (t, 1 H), 7.68 (t, 1 H), 8.36 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 56.84, 68.77, 125.86, 126.00, 126.99, 134.05, 139.40; mass spectrum *m/e* 288 (M^+, ^{80}Se), 202, 186, 156, 106, 86; UV (MeCN) λ_{max} 398 nm (ε, 3990).

Preparation of *N,N*-Dimethyl-2,4,6-tri-*tert*-butylbenzeneselenenamide (2c). Gaseous dimethylamine was passed through a solution of 0.120 g (0.3 mmol) of 2,4,6-tri-*tert*-butylbenzeneselenenyl bromide[5,16] dissolved in 10 mL of *dry* ether until the solution turned yellow and dimethylammonium hydrobromide no longer precipitated (approximately 10 min). The reaction mixture was filtered, and the ether was removed under reduced pressure to give 0.096 g (87%) of **2c** as a yellow brown oil that solidified upon standing in the refrigerator: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9 H), 1.55 (s, 18 H), 2.53 (s, 6 H), 7.38 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 31.29, 33.19, 34.07, 38.98, 48.64, 122.23, 129.19, 149.79, 154.8. Anal. Calcd for $C_{20}H_{34}NSe$: C, 65.19; H, 9.57. Found: C, 65.51; H, 9.38.

Preparation of *N,N*-Dimethyl-2,4,6-tri-*tert*-butylbenzenesulfenamide (1c). 2,4,6-Tri-*tert*-butylphenyl disulfide was prepared by a modification of the procedure of Davis et al.[17] To a solution of 20 mmol of 2,4,6-tri-*tert*-butylphenyllithium (prepared as described by Reich and Jasperse[5,16]) in 75 mL of dry tetrahydrofuran at −20 °C was added 0.7 g of sulfur powder in small portions. After the addition was complete the reaction mixture was allowed to warm to room temperature and was stirred overnight. Lithium aluminum hydride (0.4 g) was then added. The solution was refluxed for 1 h, cooled, hydrolyzed by the addition of saturated ammonium chloride solution, and then extracted with ether (2 × 150 mL). The ether extracts were washed with water. This was followed by the oxidation of the thiol to the disulfide by the dropwise addition of a saturated solution of potassium ferricyanide (10 g of $K_3[Fe(CN)_6]$ in 100 mL of 10% sodium hydroxide solution). The ether solution was dried over $MgSO_4$, and the ether was removed under reduced pressure to give a yellow solid that was recrystallized from ethyl acetate giving 3.0 g (54%) of 2,4,6-tri-*tert*-butylphenyl disulfide, mp 229–230 °C (lit.[17] mp 230–232 °C).

The disulfide (0.55 g, 1 mmol) was dissolved in 30 mL of carbon tetrachloride, and 0.2 mL (~4 mmol) of bromine was added to the solution at room temperature. The reaction mixture was stirred overnight, and solvent and excess bromine were removed under vacuum, giving 2,4,6-tri-*tert*-butylbenzenesulfenyl bromide: ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9 H), 1.65 (s, 18 H), 7.44 (s, 2 H). Without further purification, the sulfenyl bromide (0.36 g, 1 mmol) was *partially* dissolved in dry ether and gaseous dimethylamine was bubbled through the solution at −20 °C until the brown-red color of the solution changed to yellow and precipitation of $Me_2NH_2^+Br^-$ was no longer observed. The reaction mixture was stirred at room temperature for 1 h, the amine hydrobromide was filtered off, and the ether was removed under reduced pressure to give *N,N*-dimethyl-2,4,6-tri-*tert*-butylbenzenesulfenamide (**1c**), 0.29 g (90%), as a yellow oil that

(15) As a reviewer has pointed out, if the S_N2 mechanism for displacement of Me_2NH^+ for **2c**-H^+ by methanol were to involve a general-base catalyzed (by MeOH) displacement

gidJO1C2d

it might also show a sizeable dependence of rate on [MeOH]. We think such a mechanism is unlikely but can not entirely rule it out.

(16) Jasperse, C. P. Ph.D. Thesis, University of Wisconsin, 1987.
(17) Davis, F. A.; Jenkins, R. H., Jr.; Rizvi, S. Q. A.; Yocklovich, S. G. *J. Org. Chem.* 1981, *46*, 3467.

solidified upon standing in the refrigerator: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9 H), 1.53 (s, 18 H), 2.38 (s, 6 H), 7.35 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 31.33, 32.94, 38.68, 46.30, 122.82, 149.28, 154.11. Isolated **1c** contains a small amount of 2,4,6-tri-*tert*-butylbenzene as an impurity. This does not interfere with the measurement of its basicity, but did preclude getting a C, H analysis.

Methanolysis of Selenenamides. Products: From 2a or 2b. To 1.0 mL of a 0.06 M solution of the *o*-nitrobenzeneselenenamide (**2a** or **2b**) in 2:1 CD_3CN–CD_3OD contained in an NMR tube was added 20 μL of a 2.5 M solution of trifluoromethanesulfonic acid (Aldrich) in the same solvent. The ^{1}H NMR spectrum of the solution changed promptly from that for **2a** or **2b** to that for an equimolar mixture of methyl-d_3 *o*-nitrobenzeneselenenate[4] and the appropriate dialkylammonium salt ($Me_2ND_2^+$ for **2a**, $O(CH_2CH_2)_2ND_2^+$ for **2b**). The change was complete in a few minutes, and no further change in the spectrum was observed over a period of 1 h.

From 2c. The selenenamide (18.5 mg, 0.05 mmol) was dissolved in 10 mL of methanol, and, after standing for a short period of time, the solution was evaporated under reduced pressure. The residue was dissolved in $CDCl_3$ and the ^{1}H NMR measured: ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9 H), 1.53 (s, 18 H), 3.57 (s, 3 H), 7.45 (s, 2 H), in good agreement with the ^{1}H NMR for methyl 2,4,6-tri-*tert*-butylbenzeneselenenate reported by Jasperse.[16]

Kinetics. An acetonitrile–methanol solution (3 mL) containing the desired concentrations of trifluoromethanesulfonic acid and lithium trifluoromethanesulfonate (Aldrich) was placed in a 1-cm spectrophotometer cell in the thermostated cell compartment of a Beckman DU-50 spectrophotometer, and 10–20 μL of a stock solution of the selenenamide (0.015–0.03 M) in acetonitrile was injected into the cell to initiate the reaction. With **2a** or **2b** the progress of the reaction was followed by observing the increase in the absorbance of the solution at 445 nm. In the case of **2c** the wavelength used was 247 nm. In each instance plots of log ($A_\infty - A$) vs time were linear; the experimental first-order rate constant for each run was obtained from the slope of the plot.

Measurement of Basicity of Selenenamides. Addition of sufficient CF_3SO_3H to solutions of either **2a** or **2b** in MeCN–MeOH leads to an *immediate* decrease in the absorbance of the solution at 403 nm (**2a**) or 398 nm (**2b**). This change is due to the fact that the absorption spectrum for the protonated selenenamide is different from that for the selenenamide. If A_0 is the optical density for the particular solution with **2** unprotonated, A_∞ the optical density for the same solution with **2** completely protonated, and A the measured optical density for a particular concentration of added CF_3SO_3H then the fraction (α) of **2** present as **2**-H^+ is

$$\alpha = (A_0 - A)/(A_0 - A_\infty)$$

For each selenenamide and methanol concentration, measurements were made using solutions containing (5.0–8.0) $\times 10^{-5}$ M **2** and three to four different concentrations of added CF_3SO_3H sufficient to give a conveniently measurable spread of α values. The data for each selenenamide in a particular MeCN–MeOH mixture were then plotted according to the following equation:

$$1/\alpha = 1 + (1/K_b[H^+])$$

In each instance such plots were linear ($r \geq 0.99$) and had an intercept on the $1/\alpha$ axis of 1.0 ± 0.1. Their slope is equal to K_b.

Measurements of the basicity of sulfenamide **1c** were carried out in the same manner. Unprotonated **1c** has its λ_{max} of 244 nm, while **1c**-H^+ has its λ_{max} at 276 nm in MeCN–MeOH. In *tert*-butyl alcohol the optimum wavelength (maximum change in optical density upon complete protonation of **1c**) for measurement of α was 280 nm.

Selenenamide **2c** was so basic that protonation was complete in *t*-BuOH even at [CF_3SO_3H] as low as 0.001 M. This means that K_b for **2c** in this solvent must be greater than 1×10^5.