723 (w), 463 (m) cm<sup>-1</sup>. Anal. Calcd for  $C_{24}H_{28}N_4$ : C, 77.38; H, 7.58; N, 15.04. Found: C, 77.48; H, 7.59; N, 15.02.

2-Benzyl-1,4-cyclohexanedione (2g) was prepared from 5 and benzyl bromide by the procedure given for 2e, method B. A white, crystalline product was obtained directly: 94% yield; mp 67.5-68.5 °C; NMR (CD<sub>2</sub>Cl<sub>2</sub>) δ 2.38 (dd, 2 H), 2.68 (br m, 4 H), 2.93 (m, 1 H), 3.20 (dd, 2 H), 7.18 (br m, 5 H); IR (cast film, CH<sub>2</sub>Cl<sub>2</sub>) 3028 (m), 2956 (m), 2916 (m), 2852 (m), 1707 (vs), 1496 (m), 1456 (m), 1418 (m), 1330 (m), 1309 (m), 1278 (m), 1142 (m), 1081 (m), 986 (m), 914 (m), 829 (m), 755 (s), 733 (s), 698 (s), 630 (m), 595 (m), 560 (m) cm<sup>-1</sup>. Anal. Calcd for C<sub>13</sub>H<sub>14</sub>O<sub>2</sub>: C, 77.20; H, 6.98; O, 15.82. Found: C, 77.17; H, 6.92; O, 15.90.

1,4-Bis(dicyanomethylene)-2-benzylcyclohexane (3g). A mixture of 2.13 g (0.011 mol) of 2g, 1.50 g (0.023 mol) of malononitrile, 0.08 g of  $\beta$ -alanine, 10 mL of THF, and 4 mL of water was stirred at room temperature for 7 h and then diluted with 25 mL of water, and the precipitate was collected and washed with 200 mL of water followed by 200 mL of ether, giving 1.76 g (56% yield) of a white, crystalline product: mp 218-219 °C dec; NMR (CD<sub>3</sub>CN) δ 2.8-3.3 (m, 7 H), 3.70 (m, 2 H), 7.32 (d, 2 H), 7.45 (m, 3 H); IR (KBr) 2959 (sh), 2924 (s), 2854 (m), 2232 (s, C=N), 1605 (s), 1497 (m), 1459 (m), 1442 (m), 1420 (m), 976 (m), 752 (s), 708 (m) cm<sup>-1</sup>. Anal. Calcd for  $C_{19}H_{14}N_4$ : C, 76.49; H, 4.73; N, 18.78. Found: C, 76.33; H, 4.76; N, 18.74.

Benzyl-TCNQ (4g) was prepared from 3g by the method given above for 4e. Rapid filtration through silica gel  $(CH_2Cl_2, some$ decomposition on column apparent) afforded an orange crystalline solid: 40% yield; mp 165.5–167 °C; NMR ( $CD_2Cl_2$ )  $\delta$  4.42 (s, 2 H), 7.04 (s, 1 H), 7.16 (d, 2 H), 7.4 (m, 4 H), 7.66 (d, 1 H); IR (KBr) 3060 (w), 2220 vs, C=N), 1609 (vw), 1552 (m), 1533 (s), 1493 (m), 1453 (m), 875 (m), 808 (s), 764 (m), 708 (s) cm<sup>-1</sup>. Anal. Calcd for  $C_{19}H_{10}N_4$ : C, 77.54; H, 3.42; N, 19.04. Found: C, 76.91; H, 3.48; N, 19.07.

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Registry No. 1e, 1199-08-2; 1h, 1201-38-3; 2e, 107616-65-9; 2f, 105314-19-0; 2g, 107616-67-1; 3e, 107616-66-0; 3f, 105314-20-3; 3g, 107616-68-2; 4e, 97221-64-2; 4f, 105314-21-4; 4g, 107616-69-3; 5, 2785-98-0;  $C_2H_5I$ , 75-03-6;  $C_{12}H_{25}I$ , 4292-19-7;  $C_6H_5CH_2Br$ , 100-39-0; NCCH<sub>2</sub>CN, 109-77-3.

# Leaving Group Rate Ratios in Solvolytic **Displacement Reactions.** The Effect of **Neighboring Sulfur**

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One of intriguing problems in the study of solvolytic reactivity of organic substrates in nucleophilic substitution is the choice of proper rate ratios for various leaving groups.<sup>1</sup> Although some authors claim<sup>2,3</sup> that leaving group effects in solvolytic reactions are not very sensitive to mechanistic changes, these effects often depend on various reaction characteristics such as a type of substrate,

Table I. Solvolysis Rate Constants of Various 2-(Methylthio)ethyl Substrates, CH<sub>3</sub>SCH<sub>2</sub>CH<sub>2</sub>Y

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Y	$solvent^a$	<i>t</i> , ℃	$k, s^{-1}$	$k_{97\mathrm{T}}/k_{80\mathrm{E}}$
OTs	80E	25	$(1.69 \pm 0.05) \times 10^{-4}$	
• • •	97T	25	$(2.74 \pm 0.05) \times 10^{-5}$	0.162
I	80E	25	$(2.70 \pm 0.07) \times 10^{-3}$	
	97T	25	$(2.63 \pm 0.05) \times 10^{-3}$	0.974
Br	80E	25	$(4.48 \pm 0.05) \times 10^{-4}$	
	97T	25	$(3.41 \pm 0.07) \times 10^{-4}$	0.761
		50	$(2.61 \pm 0.07) \times 10^{-3}$	
		65	$8.52 \times 10^{-3 b}$	
Cl	96E	25	$(1.02 \pm 0.02) \times 10^{-4}$	
	$80\mathbf{E}$	25	$(1.97 \pm 0.02) \times 10^{-4}$	
		50	$(1.39 \pm 0.06) \times 10^{-3}$	
		70	$5.43 \times 10^{-3b}$	
	60A	25	$(1.69 \pm 0.05) \times 10^{-4}$	
	97T	25	$(1.69 \pm 0.01) \times 10^{-4}$	0.858
		50	$(1.36 \pm 0.01) \times 10^{-3}$	0.978
		65	$4.15 \times 10^{-3b}$	
	97H	25	$(1.91 \pm 0.07) \times 10^{-4}$	
ODNB	80E	70	$(4.05 \pm 0.06) \times 10^{-5}$	
	97T	65	$(3.58 \pm 0.11) \times 10^{-5}$	
OPNB	80E	70	$(1.43 \pm 0.07) \times 10^{-5}$	
	97T	65	$(1.36 \pm 0.03) \times 10^{-5}$	
			. ,	

<sup>a</sup>96E = 96 vol % ethanol/water; 80E similarly; 60A = 60 vol % acetone/water; 97T = 97 wt % 2,2,2-trifluoroethanol/water; 97H = 97 wt % 1,1,1,3,3,3-hexafluoro-2-propanol/water. <sup>b</sup>Extrapolated from lower temperatures.

solvent, temperature, etc.<sup>4</sup> For 2-adamantyl substrates the OTs/Br rate ratio of 240 for 97% CF<sub>3</sub>CH<sub>2</sub>OH (97% TFE)<sup>3</sup> is similar to the value of 231 for 80% EtOH.<sup>5</sup> On the contrary, the Br/Cl rate ratios for both tert-butyl halides and 2-adamantyl halides in 97% (CF<sub>3</sub>)<sub>2</sub>CHOH are<sup>3</sup> about 9, whereas these ratios for tert-butyl halides in 97% TFE<sup>6,7</sup> and EtOH<sup>8</sup> are 22 and 50, respectively, indicating that the rate ratios in  $\mathbf{S}_N \mathbf{1}$  reactions have smaller values in solvents of low nucleophilicity. Furthermore, while in  $S_{N1}$  reactions sulfonates are usually much better leaving groups than halides, in S<sub>N</sub>2 reactions sulfonates and halides have comparable leaving-group ability and the relative reactivities of the leaving groups are considered to be dependent on the nucleophile as well as on solvent.<sup>1a</sup> However, the OTs/Br rate ratio is often very low but variable (even smaller than unity) for both  $S_N1$  and  $S_N2$ reactions in various solvents.<sup>4</sup>

Until now leaving group rate ratios for  $S_N 2$  solvolyses have been almost exclusively studied in reactions that include the nucleophilic attack of external nucleophile. For intramolecular displacement reactions such rate ratios were determined in very few cases.<sup>9-11</sup> In this work we report leaving group rate ratios for several common leaving groups (halides, sulfonates, and benzoates) in solvolyses of compounds with the methylthio group present as an internal nucleophile which can interact at the reaction center in the rate-determining step of solvolysis. For this

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Table II. Leaving Group Rate Ratios for Various Reactions

_	reaction	OTs/Br	I/Br	Br/Cl	Cl/OPNB	3,5-ODNB/ OPNB
	Aa	0.08 <sup>d</sup>	7.71 <sup>d</sup>	$2.02^{d}$	305°	2.63 <sup>e</sup>
	B <sup>o</sup>	0.384	6.03ª	2.27ª	380'	2.83'
	Cc	$2.6 \times 10^{3}$	6.4	14	$1.8 \times 10^{\circ}$	$10.5^{g}$

<sup>a</sup>Solvolysis of 2-(methylthio)ethyl substrates 1 in 97% TFE (this work). <sup>b</sup>Solvolysis of 2-(methylthio)ethyl substrates 1 in 80% EtOH (this work). <sup>c</sup>Solvolysis of 1-phenylethyl substrates 3 in 80% EtOH (for relative rates of solvolysis of these substrates with various leaving groups, see ref 21). <sup>d</sup>At 25 °C. <sup>e</sup>At 65 °C. <sup>f</sup>At 70 °C. <sup>e</sup>Estimated from the ratio of rates for 2-phenyl-2-propyl esters, C<sub>6</sub>H<sub>5</sub>C(CH<sub>3</sub>)<sub>2</sub>Y, in 80% EtOH at 70 °C (this work); for Y = 3,5-ODNB,  $k = (1.51 \pm 0.01) \times 10^{-3} \text{ s}^{-1}$ ; for Y = OPNB,  $k = (1.44 \pm 0.03) \times 10^{-4} \text{ s}^{-1}$ .

purpose 2-(methylthio)ethyl derivatives  $CH_3SCH_2CH_2Y$ (1; OTs, I, Br, Cl, 3,5-ODNB, OPNB) were synthesized from  $CH_3SCH_2CH_2OH$  (2) by standard procedures and fully characterized by spectral methods and in some cases also by elemental analysis. In order to study the solvent effect on rate ratios, these substrates were solvolyzed in 97% TFE and 80% EtOH, whereas the 2-(methylthio)ethyl chloride (1; Y = Cl) was also solvolyzed in various other solvents covering a wide range of ionizing power. Moderate solvolytic reactivities of these derivatives in comparison to analogous alkyl substrates<sup>12</sup> enabled rate measurements at convenient temperatures (25–70 °C).<sup>14</sup> The rate constants, obtained by titrimetric method, are listed in Table I.

In all solvolyses of 1 clear first-order kinetic behavior was observed, but the titer of the liberated acid was only ca. 30% confirming that the neighboring sulfur participation occurs during the ionization of *all these substrates*.<sup>15</sup> Obviously the high degree of neighboring group participation in solvolyses of these compounds was due to the excellent participating ability of sulfur<sup>16</sup> and occurs not only in 97% TFE but also in more nucleophilic 80% EtOH.

For all substrates 1 the ratios of rate constants for solvolyses in 97% TFE and 80% EtOH  $(k_{97T}/k_{80E})$  are small (Table I). 2-(Methylthio)ethyl chloride (1; Y = Cl) was solvolyzed in solvents with Y values<sup>17</sup> covering a range of almost 4 units, but the rate constant changed within this whole range for a factor of only 2. Using the modified form of the Grunwald–Winstein equation (1),<sup>17,18</sup> the values of

$$\log\left(k/k_0\right) = mY + lN \tag{1}$$

m = 0.13 and l = 0.06 were determined for this reaction<sup>19</sup> confirming its low sensitivity to solvent change due to the

neighboring sulfur assistance. For the aqueous ethanolysis of 2-(phenylseleno)ethyl chloride a plot of log k vs. Y values gave a significantly larger m value of 0.40, which was considered to be a typical value in nucleophilically assisted reactions.<sup>20</sup>

The leaving group rate ratios determined in this work for substrates 1 were compared with the rate ratios for the same leaving groups observed in S<sub>N</sub>1 solvolyses of 1phenylethyl substrates 3 in 80% EtOH (Table II). The I/Br rate ratios are almost the same for all three reactions (A-C; Table II).<sup>22</sup> The rate ratios with all other leaving groups (OTs/Br, Br/Cl, Cl/OPNB, and 3,5-ODNB/ OPNB) for  $S_N2$  solvolyses of substrates 1 are almost identical in 97% TFE and 80% EtOH (reactions A and B) but significantly smaller than the analogous rate ratios for S<sub>N</sub>1 solvolyses of substrates 3 in 80% EtOH (reaction C, Table II). In some cyclizations larger Br/Cl rate ratios were observed,<sup>9-11</sup> falling within the range of values for intermolecular displacement reaction.<sup>10b</sup> Furthermore, for acetolysis of endo-7-norcaranyl halides (which solvolyze via the favored mode of disrotatory opening of the cyclopropane ring) the Br/Cl ratio is 28, whereas for the solvolysis of exo-7-norcaranyl halides (which are geometrically constrained against complete opening) this ratio is<sup>23</sup> only 1.7.

In conclusion, the results obtained in this work indicate that the leaving group rate ratios are for  $S_N^2$  reactions almost independent of solvent change, but they significantly differ within the  $S_N^{1-}S_N^2$  spectrum of mechanisms. However, we do not believe that these results enable reliable general conclusions to be drawn. Moreover, great caution should be exercised when the magnitudes of rate ratios for various leaving groups are used in assuming the reaction mechanism. Although such rate ratios are often reduced if a neighboring group participation occurs during the rate-determining step of solvolysis, the magnitude of rate ratios cannot serve as a criterion to determine the degree of participation.

## **Experimental Section**

Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer. <sup>1</sup>H NMR spectra of samples dissolved in tetrachloromethane were recorded on a Varian EM-360 spectrometer, with tetramethylsilane as internal standard. All reported yields are isolated yields.

The 2-(methylthio)ethyl chloride (1;  $Y = Cl)^{24}$  and 2-phenyl-2-propyl *p*-nitrobenzoate<sup>25</sup> were prepared as previously described.

**2-(Methylthio)ethyl tosylate (1; Y = OTs)** was prepared from alcohol **2** (460 mg, 5.0 mmol) and tosyl chloride (1.90 g, 10 mmol) in dry pyridine (20 mL) in a straightforward manner:<sup>26</sup> yield, 84.5%; IR (neat) 3090, 3055, and 3030 (Ar-H), 1598 (C==C), 1192 and 1180 cm<sup>-1</sup> (OSO<sub>2</sub>); <sup>1</sup>H NMR  $\delta$  2.35 (3 H, s, SCH<sub>3</sub>), 2.45 (3 H, s, ArCH<sub>3</sub>), 2.95 (2 H, t, J = 5 Hz, SCH<sub>2</sub>), 4.07 (2 H, t, J = 5 Hz, OCH<sub>2</sub>), 7.08-7.50 (4 H, AA'BB' pattern, J = 8 Hz, C<sub>6</sub>H<sub>4</sub>).

<sup>(12) 1-</sup>Butyl triflate, chosen as a suitable reference substrate, solvolyzes in 80% EtOH at 20 °C with the rate constant  $k = (8.32 \pm 0.06) \times 10^{-3} \, \mathrm{s}^{-1}$ . For its solvolysis in 97% TFE at 30 °C the rate constant  $k = (8.20 \pm 0.04) \times 10^{-5} \, \mathrm{s}^{-1}$  was obtained, which is comparable with the reported<sup>13</sup> value for 1-propyl triflate.

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<sup>(19)</sup> The analogous Grunwald-Winstein equation which includes  $Y_{\text{OTs}}$  and  $N_{\text{OTs}}$  constants<sup>16</sup> instead of Y and N, gives coefficients m = 0.16 and l = 0.11 with even a slightly better correlation coefficient (r = 0.900) than does eq 1, where r = 0.887.

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Anal. Calcd for C<sub>10</sub>H<sub>14</sub>S<sub>2</sub>O<sub>3</sub>: C, 49.16; H, 4.95; S, 26.25. Found: C, 49.52; H, 5.06; S, 25.94

2-(Methylthio)ethyl iodide (1; Y = I) was prepared by the standard halide exchange<sup>27</sup> from 2-(methylthio)ethyl chloride (1,  $Y = Cl)^{26}$  (2.21 g, 20 mmol) and NaI (4.80 g, 30 mmol) in anhydrous acetone (20 mL) in 61.3% yield: <sup>1</sup>H NMR δ 2.40 (3 H, s, SCH<sub>3</sub>), 3.07 (2 H, t, J = 6 Hz, SCH<sub>2</sub>), 3.87 (2 H, t, J = 6 Hz, ICH<sub>2</sub>).

2-(Methylthio)ethyl bromide (1; Y = Br) was prepared from alcohol 2 (4.60 g, 50 mmol), PBr<sub>3</sub> (4.52 g, 17 mmol), and pyridine (1.32 g, 17 mmol) in 42.4% yield by the standard procedure:<sup>28</sup> <sup>1</sup>H NMR  $\delta$  2.33 (3 H, s, SCH<sub>3</sub>), 2.78 (2 H, t, J = 6 Hz, SCH<sub>2</sub>), 3.88  $(2 \text{ H}, t, J = 6 \text{ Hz}, \text{BrCH}_2).$ 

2-(Methylthio)ethyl 2,5-dinitrobenzoate (1; Y = 3,5-ODNB) was prepared from alcohol 2 (460 mg, 5.0 mmol) and 3,5-dinitrobenzoyl chloride (3.45 g, 15 mmol) in dry pyridine (20 mL) in 86.7% yield by following the standard procedure:<sup>29</sup> IR (KBr) 3090 and 3075 (Ar-H), 1729 (CO-O-C), 1630 (C=C), 1542 and 1347 (NO<sub>2</sub>), 1285 (C–O), 733 and 725 cm<sup>-1</sup> (Ar–H); <sup>1</sup>H NMR  $\delta$ 2.47 (3 H, s, SCH<sub>3</sub>), 3.10 (2 H, t, J = 6 Hz, SCH<sub>2</sub>), 4.10 (2 H, t, J = 6 Hz, OCH<sub>2</sub>), 9.22 (3 H, s, C<sub>6</sub>H<sub>3</sub>). Anal. Calcd for C<sub>10</sub>H<sub>11</sub>NO<sub>2</sub>S: C, 57.41; H, 5.30; N, 6.70; S, 15.33. Found: C, 56.82; H, 5.24; N, 6.52; S, 15.07

2-(Methylthio)ethyl p-nitrobenzoate (1; Y = OPNB) was prepared from alcohol 2 (460 mg, 5.0 mmol) and p-nitrobenzoyl chloride (1.90 g, 10 mmol) in dry pyridine (20 mL) in 95.4% yield by following our literature procedure:<sup>30</sup> IR (KBr) 3110, 3085, and 3060 (Ar-H), 1722 (CO-O-C), 1612 (C=C), 1528 and 1352 (NO<sub>2</sub>), 1282 (C-O), 722 cm<sup>-1</sup> (Ar-H); <sup>1</sup>H NMR δ 2.37 (3 H, s, SCH<sub>3</sub>), 3.03  $(2 \text{ H}, \text{t}, J = 6 \text{ Hz}, \text{SCH}_2), 4.05 (2 \text{ H}, \text{t}, J = 6 \text{ Hz}, \text{OCH}_2), 8.18 (4 \text{ Hz})$ H, s,  $C_6H_4$ ). Anal. Calcd for  $C_{10}H_{10}N_2O_4S$ : C, 47.25; H, 3.97; N, 11.02; S, 12.61. Found: C, 46.77; H, 4.09; N, 11.21; S, 12.36.

2-Phenyl-2-propyl 3,5-dinitrobenzoate was prepared from 2-phenyl-2-propanol (680 mg, 5.0 mmol) and 3,5-dinitrobenzoyl chloride (2.30 g, 10 mmol) in dry pyridine (20 mL) in 72.1% yield by the standard procedure:<sup>29</sup> IR (KBr) 3100, 3070, and 3030 (Ar-H), 1730 (CO-O-C), 1630 and 1600 (C=C), 1545 and 1347 (NO<sub>2</sub>), 1290 (C–O), 772, 740, 730, and 702 cm<sup>-1</sup> (Ar–H); <sup>1</sup>H NMR  $\delta$  1.92 (6 H, s, CH<sub>3</sub>), 7.35 (5 H, s, C<sub>6</sub>H<sub>5</sub>), 9.23 (3 H, s, C<sub>6</sub>H<sub>3</sub>).

Kinetic Measurements. Reaction rates were measured by continuous automatic potentiometric titration of the liberated acid<sup>31</sup> by means of a pH-stat (Radiometer, Copenhagen). In each measurement ca. 0.03 mmol of the substrate was dissolved in 15 mL of solvent and the liberated acid titrated with 0.025 M NaOH solution in the same solvent.

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## **Revised Structure of Bursatellin**

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In 1980, F.J.S. and G.Y. reported the isolation of bursatellin,<sup>2</sup> a metabolite from the sea hare Bursatella leachii pleii, and proposed for it structure 1. Recently, the re-



search group at Naples collected two Mediterranean sea hares. Bursatella leachii leachii and Bursatella leachii savignyana, and isolated from them a compound that exhibited <sup>1</sup>H NMR spectral data nearly identical with that reported for bursatellin except for one additional low-field singlet observed between  $\sim$ 7.90 and 8.20 ppm, the precise position being solvent dependent. This led the Italian workers to suspect the identity of the two compounds but also to question the original structural assignment, an assessment in which the Oklahoma investigators concurred after review of their original spectra. In the original report, the molecular formula was assumed from high-resolution mass analysis of the highest observable ion; in retrospect, this highest mass peak must be assigned an  $M^+$  – 18 ion status. Similarly, highest mass ions of the derived diacetate 2 and manganese dioxide oxidation product 3 were interpreted, then seemingly plausibly but with hindsight incorrectly, as  $M^+$  – HCN and  $M^+$  ions. Operating with the incorrect molecular formula led the original workers to disregard a low-field singlet (8.08-8.20 ppm singlet) in 1-3 and also a very broad, medium-intensity infrared absorption from 1600 to 1700 cm<sup>-1</sup>. With the aid of higher field <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra plus some synthetic work, a revised structure of bursatellin is now reported.

#### **Results and Discussion**

Mantles and digestive glands of B. leachii leachii and B. leachii savignyana were extracted separately. Bursatellin was obtained from the mantles of both species, but from the digestive glands of only B. leachii savignyana. The 500-MHz <sup>1</sup>H NMR spectrum (CD<sub>3</sub>OD) of bursatellin from these sources was nearly identical with that reported earlier<sup>2</sup> with the exception of a slightly broadened singlet at 7.90 ppm. Reexamination of the spectra obtained in the earlier work confirmed a similar peak, which had been ignored as an artifactual peak due to the assumption of an incorrect molecular formula from high-resolution mass data. A <sup>13</sup>C NMR spectrum (not available in the earlier work) (Table I) revealed that this low-field proton singlet is due to a formamide group and that there is only one sp<sup>3</sup> carbon that is not deshielded by a heteroatom; hence, the structure of bursatellin had to be revised. In particular, the dihydroxybutyronitrile moiety of 1 was confirmed to be incorrect.

In light of the evidence for the presence of a formamide group, decoupling results combined with chemical shift considerations led the Naples group initially to consider the revised diastereomeric structures 4 or 5, based on the



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