Garlic Chemistry. Nitric Oxide Oxidation of *S*-(2-Propenyl)cysteine and (+)-*S*-(2-Propenyl)-L-Cysteine Sulfoxide

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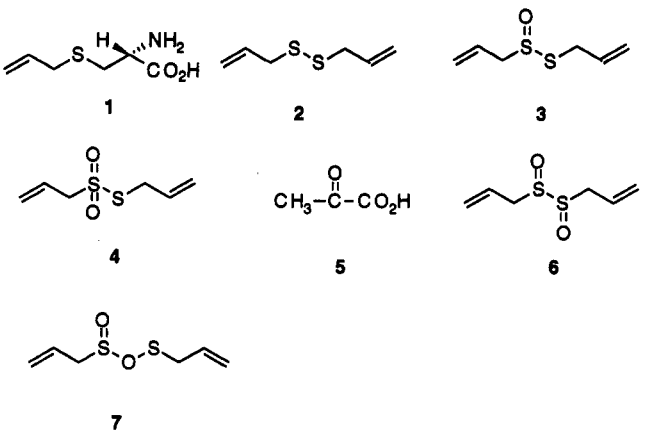
Nitric oxide (NO) is a component of air pollution and cigarette smoke. It is also an endogenous compound of the body and plays many roles in biological functions.[1-4] This important biochemical free radical is involved in a variety of biological processes including regulating immune functions,[2] physiological control of blood pressure,[3] and neurotransmission.[4] Thus, owing to the ubiquitous nature of nitric oxide,[5,6] to the limited fundamental chemistry of nitric oxide,[7] and to the widespread use of garlic in diets,[8-13] we are investigating the nitric oxide oxidation of some of the compounds found in garlic. Passage of pure nitric oxide gas through water at room temperature slowly leads to the oxidation of *S*-(2-propenyl)cysteine (**1**), which is found in garlic bulbs and extracts, to bis(2-propenyl) disulfide (**2**), *S*-(2-propenyl) 2-propene-1-sulfinothioate (allicin, **3**), *S*-(2-propenyl) 2-propene-1-sulfonothioate (pseudoallicin, **4**), and 2-oxopropanoic acid (**5**). A free radical mechanism involving sulfinyl radicals,[14] thioallyl radicals, vicinal disulfoxides (**6**), and *O*-sulfenyl sulfinates (**7**) is proposed (Schemes 1 and 2)[14-21] for the slow oxidation reaction (20% conversion after 24 h). Compounds **2** and **3** are formed when garlic is crushed or cut and compound **4** may be formed when **3** stands for some time.[13]



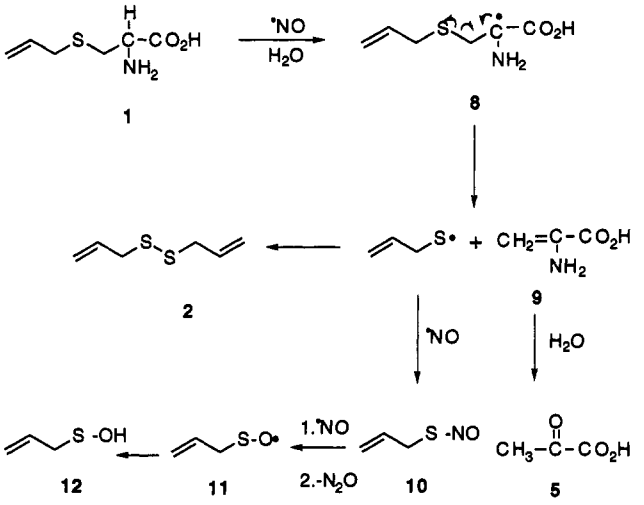
A reasonable first step in the nitric oxide oxidation of **1** could be hydrogen atom abstraction from the carbon bonded to the amino and carboxyl groups (Scheme 1). This leads to a particularly strongly stabilized radical (**8**) owing to the presence of both an electron-attracting and electron-donating substituent (captodative stabilization[22] or merostabilization[23]). Homolytic dissociation of the C-S bond in **8** affords the thioallyl radical[12] and the enamine **9** which hydrolyzes to 2-oxopropanoic acid (**5**).

The thioallyl radical dimerizes to the disulfide **2** and reacts with nitric oxide to form the highly unstable *S*-nitroso compound (thionitrite) **10**.[19,24-26] Thionitrite **10** can undergo S-N bond cleavage to eventually afford disulfide **2** and nitric oxide[27] and/or react with nitric oxide to form an unstable intermediate which loses dinitrogen oxide[28-31] and rearranges to the sulfinyl radical **11** which abstracts a hydrogen atom to form 2-propenesulfenic acid (**12**). Cyclodehydration of **12** affords allicin (**3**).[32,33] Alternatively, allicin (**3**) may be formed from the thioallyl radical and the sulfinyl radical **11** (Scheme 2). The sulfinyl radical **11** may dimerize to the vicinal disulfoxide **6** and/or to the *O*-sulfenyl sulfinate **7**, either of which can rearrange to pseudoallicin (**4**). The disulfide **2** is not oxidized to **3** under these experimental conditions. Although under the experimental conditions allicin (**3**) is stable in water in the absence of nitric oxide at room temperature for 24 h,[34-37]

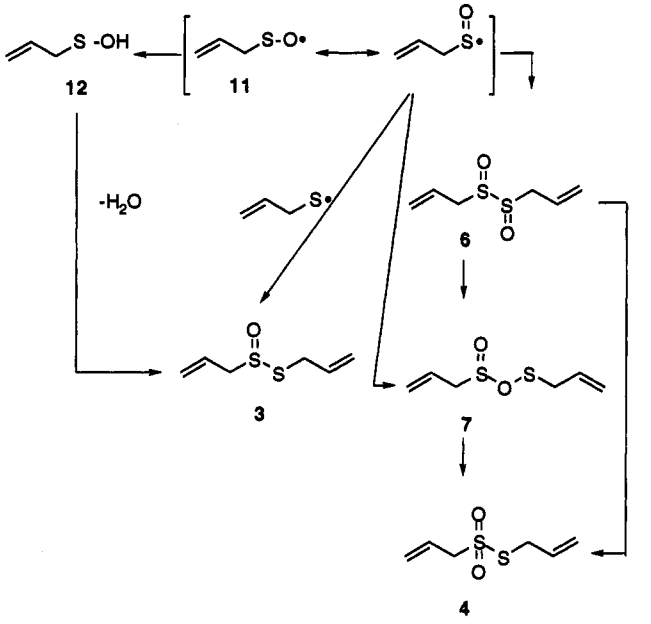
(1) (a) Lancaster, J. R., Jr. *Am. Sci.* **1992**, *80*, 248. (b) Stamler, J. S.; Singel, D. J.; Loscalzo, J. *Science* **1992**, *258*, 1898.
(2) Nathan, C. F.; Hibbs, J. B., Jr. *Curr. Opin. Immunol.* **1991**, *3*, 65.
(3) Moncada, S.; Palmer, R. M. J.; Higgs, E. A. *Pharmacol. Rev.* **1991**, *43*, 109.
(4) Bredt, D. S.; Snyder, S. H. *Neuron* **1992**, *8*, 3.
(5) Wink, D. A.; Kasprzak, K. S.; Maragos, C. M.; Elespuru, R. K.; Misra, M.; Dunams, T. M.; Cebula, T. A.; Koch, W. H.; Andrews, A. W.; Allen, J. S.; Keefer, L. K. *Science* **1991**, *254*, 1001.
(6) Calapai, G.; Squadrito, F.; Altavilla, D.; Zingarelli, B.; Campo, G. M.; Cilia, M.; Caputi, A. P. *Neuropharmacology* **1992**, *31*, 761.
(7) Janzen, E. G.; Wilcox, A. L.; Manoharan, V. *J. Org. Chem.* **1993**, *58*, 3597.
(8) Lin, R. I. *Garlic in Nutrition & Medicine*; Nutrition International Co.: 6 Silverfern Drive, Ivine, CA 92715, 1989.
(9) Block, E. In *Folk Medicine: The Art and the Sciences*; Steiner, R. P., Ed.; American Chemical Society: Washington, D.C., 1986; p 125.
(10) Block, E.; Ahmad, S.; Catalfamo, J. L.; Jain, M. K., Apitz-Castro, R. *J. Am. Chem. Soc.* **1986**, *108*, 7045, and refs therein.
(11) Block, E. *Phosphorus, Sulfur, Silicon, Relat. Elem.* **1991**, *58*, 3.
(12) Block, E. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1135, and refs cited therein.
(13) Block, E.; Naganathan, S.; Putnam, D.; Zhao, S.-H. *J. Agric. Food Chem.* **1992**, *40*, 2418.
(14) Freeman, F.; Keindl, M. C. *Sulfur Rep.* **1985**, *4*, 231.
(15) Freeman, F. *Chem. Rev.* **1984**, *84*, 117.
(16) Freeman, F.; Angeletakis, C. N.; Pietro, W. J.; Hehre, W. J. *J. Am. Chem. Soc.* **1982**, *104*, 1161.
(17) Freeman, F.; Angeletakis, C. N. *J. Am. Chem. Soc.* **1983**, *105*, 4039, and ref therein.
(18) Freeman, F.; Ma, X.; Lin, R. I. *Sulfur Lett.* **1993**, *15*, 253.
(19) Oae, S. *Organic Sulfur Chemistry: Structure and Mechanism*; CRC Press Inc.: Boston, 1991.
(20) Folkins, P. L.; Harpp, D. N. *J. Am. Chem. Soc.* **1993**, *115*, 3066.
(21) Block, E.; Bayer, T. *J. Am. Chem. Soc.* **1990**, *112*, 4584.
(22) Viehe, H. G.; Merenyi, R.; Stella, L.; Janousek, Z. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 917.
(23) Baldock, R. W.; Hudson, P.; Katritzky, A. R.; Soti, F. *J. Chem. Soc., Perkins Trans. 1* **1974**, 1422.
(24) The potent chemical and biological properties of the unstable and difficult to purify *S*-nitroso compounds are of interest owing to their powerful nitrosating and sulfenylating properties.[25,26]
(25) Oae, S.; Shinhama, K. *Org. Prep. Proc. Int.* **1983**, *15*, 165.
(26) Hart, T. W. *Tetrahedron Lett.* **1985**, *26*, 2013.
(27) Oae, S.; Kim, Y. H.; Fukushima, D.; Shinhama, K. *J. Chem. Soc., Perkin Trans. 1* **1978**, 913.
(28) Kuhn, L. P.; Doali, J. O.; Wellman, C. *J. Am. Chem. Soc.* **1960**, *82*, 4792.
(29) Pryor, W. A.; Church, D. F.; Govindan, C. K.; Crank, G. *J. Org. Chem.* **1982**, *47*, 156.
(30) Reihlen, H.; Friedolsheim, A.; Oswald, W. *Liebigs Ann. Chem.* **1928**, *465*, 72; see p 92.
(31) Ignarro, L. J.; Greutter, C. A. *Biochem. Biophys. Acta* **1980**, *631*, 221.
(32) Davis, F. A.; Jenkin, Jr., R. H. *J. Am. Chem. Soc.* **1980**, *102*, 7967.
(33) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3921.
(34) There may be a stabilizing effect by water on allicin (**3**) through hydrogen bonding.[12,35-38]
(35) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3929.
(36) Lawson, L. D.; Wood, S. G.; Hughes, B. G. *Planta Med.* **1991**, *57*, 263.
(37) Freeman, F.; Kodera, Y. *J. Agric. Food Chem.*, in press.

0022-3263/94/1959-3227$04.50/0

Scheme 1

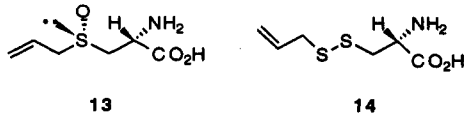


Scheme 2



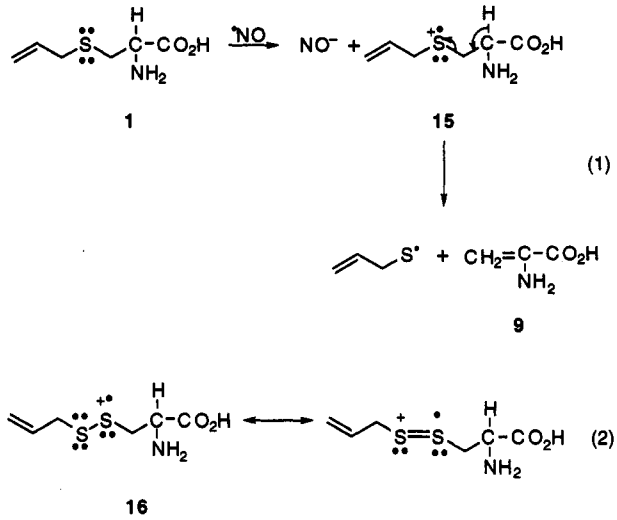
it is slowly oxidized by ṄO to pseudoallicin (4).[38-41] Thus, part of the pseudoallicin (4) formed during the ṄO oxidation of 1 may arise from 3. No disulfide (2) was isolated from the ṄO oxidation of 3.

(+)-*S*-(2-Propenyl)-L-cysteine sulfoxide (alliin, 13) was oxidized by ṄO to compounds 3–5, which is consistent with the proposed mechanisms (Schemes 1 and 2). The absence of the disulfide 2 from the oxidation of aliin (13) is also consistent with the proposed mechanism.



S-(2-Propenylthio)-L-cysteine (14) is not soluble in water but dissolves in acidic (CF_3CO_2H) aqueous solution. No reaction was observed with 14 after passage of ṄO through the solution for 24 h at room temperature. However, both 1 and 13 are oxidized by ṄO in this acidic aqueous solution. The stability of 2 and 14 under these experimental conditions is consistent with the report that disulfides, including cystine and glutathione disulfide, are prepared from the ṄO oxidation of the corresponding thiols.[29-31,42] These results suggest that the disulfide linkage is stable to nitric oxide under these experimental conditions.[29-31]

An alternate mechanism (eq 1) involving disulfide carbon radicals (15)[43-45] may account in part why sulfides 1 and 13 undergo cleavage when treated with ṄO but disulfide 14 does not. Interaction of ṄO with 1 or 13 at sulfur could lead to cation radical 15 (*cf.* 8, Scheme 1) which undergoes cleavage to 9 and the thioallyl radical. The corresponding cation radical 16 from 14 may not undergo similar cleavage owing to stabilization provided by the adjacent sulfur (eq 2). If 16, which is an oxidant, is so stabilized, it would simply wait around to regenerate 14 by an electron transfer with NO^- (i.e. reversal of eq 1).



Experimental Section

Melting points were obtained in open capillaries on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were obtained in CCl_4, as neat films, in Nujol, or as KBr disks. HRMS were obtained at 70 eV, CIMS (2-methylpropane) at 50, 70, or 100 eV, and EIMS at 100 eV. ^1H NMR and ^{13}C NMR (300 and 500 MHz) spectra were recorded in $CDCl_3$ unless specified otherwise. Analytical TLC was performed on Analtech Uniplate 10 × 20 cm (250 μm thick) silica gel GF prescored glass plates, which were developed with solvent A: 7:3:0.5 $CHCl_3/CH_3OH/H_2O$ or solvent B: 5:2 hexanes/ethyl acetate. The plates were analyzed with ninhydrin or UV light and/or developed in a diiodine chamber. Flash column chromatography was performed on 230–400 mesh silica gel.

Reagents and solvents were purified by standard procedures. N_2 was dried by passing it through a column of Drierite and 4-Å molecular sieves, and nitric oxide (Aldrich, 98.5%) was bubbled through 10 M NaOH and dried by passing through column containing NaOH pellets.[46]

Synthesis of *S*-(2-Propenyl)-L-cysteine (1).[47,48] To the ice-cooled solution of L-cysteine [(*R*)-2-amino-3-mercaptopropanoic

(38) Although thiosulfinates generally disproportionate to disulfides and thiosulfonates,[39] the corresponding products were not formed from allicin (3).[40,41]

(39) Kice, J. L.; Cleveland, J. P. *J. Am. Chem. Soc.* **1973**, *95*, 109.

(40) Iberl, B.; Winkler, G. Knobloch, K. *Planta Med.* **1990**, *56*, 202.

(41) Belous, M. A.; Postovskii, I. Y. *Zhur. Obshchei Khim.* (*J. Gen. Chem.*) **1950**, *20*, 1701; *Chem. Abstr.* **1951**, *45*, 2391.

(42) Longhi, R.; Ragsdale, R. O. S. *Inorg. Chem.* **1962**, *1*, 768.

(43) Zwieg, A.; Hoffmann, A. K. *J. Org. Chem.* **1965**, *30*, 3997.

(44) Bonifacic, M.; Schäfer, K.; Mockel, H.; Asmus, K.-D. *J. Phys. Chem.* **1975**, *79*, 1496.

(45) Bonifacic, M.; Asmus, K.-D. *J. Phys. Chem.* **1976**, *80*, 2426.

(46) Drago, R. S.; Paulik, F. E. *J. Am. Chem. Soc.* **1960**, *82*, 96.

(47) Nishimura, H.; Mizutani, J. *J. Org. Chem.* **1975**, *40*, 1567.

(48) The crude alliin (13) was obtained from Mr. Yukihiro Kodera.

acid, 10.0 g, 82.6 mmol)] in NH_4OH (2 M, 240 mL) was added 3-bromopropene (15.0 g, 124 mmol) was vigorous stirring. The mixture was stirred at 0 °C for 40 min and filtered, and the filtrate was concentrated in vacuo (<40 °C) to a small volume, and filtered. The solid was washed repeatedly with ethanol, dried in vacuo, and recrystallized from 2:3 H_2O/C_2H_5OH to yield white needles (1, 10.7 g, 80.1%): mp 219–220 °C; (lit.[47] mp 208–210 °C (dec)]; IR (KBr, cm^{-1}) 2919, 2598 (m, C–H), 1610 (s, C=C), 1588, 1508, 1397 (s, COO^-), 760 (m, S–C); ^1H NMR (D_2O) δ 2.90–3.10 (m, 2 H, allyl-CH_2), 3.20 (d, 2 H, SCH_2) 3.85 (m, 1 H, $CHNH_2$), 5.20 (m, 2 H, CH_2=), 5.80 (m, 1 H, CH=); ^{13}C NMR (D_2O + CD_3OD) δ 168.30, 129.08, 113.90, 44.51, 29.50, 26.31; HRCIMS, *m/z* 162.0595 (calcd for $C_6H_{11}NO_2S$ 162.0582).

Purification of (+)-*S*-(2-Propenyl)-L-cysteine Sulfoxide (Alliin, 13). Crude racemic alliin (10 g)[48] was dissolved in H_2O (20 mL) at 50 °C and filtered, and the filtrate was added to 120 mL of aqueous acetone (20 mL of H_2O). The suspension was kept at 0 °C for 24 h and filtered. The solid (4.2 g) was dissolved in 14 mL of water at 50 °C. This solution was added to 62 mL of aqueous acetone (12 mL of H_2O). The suspension was kept at 0 °C for 20 h and filtered. The crystals (3.0 g) were dissolved in H_2O (8 mL) at 50 °C and the solution was added to 32 mL of aqueous acetone (6 mL of H_2O). The suspension was kept at 0 °C for 24 h and filtered, and the solid was dried to afford the optically pure alliin (13): mp 164–166 °C [lit.[49] mp 163–165 °C]; $[\alpha]^{20}$ = +63.0° (H_2O); (Nujol, cm^{-1}) 2921, 1649, 1460, 1377, 1304, 1133, 1018, 913; ^1H NMR [D_2O + $(CD_3)_2C$=O] δ 3.45–3.48 (m, 1 H), 3.72–3.79 (m, 1 H), 3.81–3.97 (m, 1 H), 4.16–4.18 (d, 1 H), 4.28–4.35 (m, 1 H), 5.54–5.69 (m, 2 H), 5.94–6.00 (m, 1 H); ^{13}C NMR δ 29.80, 48.83, 57.83, 105.13, 126.84, 171.15; HRFABMS *m/z* 178.0531 (calcd for $C_6H_{11}NO_3S$ + 1.0078, 178.0538).

Synthesis of *S*-(2-Propenylthio)-L-cysteine (14). To an ice-cooled solution of bis(2-propenyl) disulfide (2, 15.0 g, 0.103 mol) in acetic acid (50 mL) was added dropwise during 1 h a solution of 30% hydrogen peroxide (17.8 g, 16 mL, 0.157 mol) in acetic acid (50 mL).[10,18] After addition, the mixture was stirred for 2 h at 0 °C, for 4 h at rt, and poured into ice–water (1 L). The aqueous solution was extracted with CH_2Cl_2 (4 × 300 mL), and the combined extracts were washed with aqueous Na_2CO_3 solution (3 × 100 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to give a residue (13 g) of crude *S*-(2-propenyl) 2-propene-1-sulfinothioate (allicin, 3). To the residue was added the solution of L-cysteine (7.0 g, 0.579 mol) in H_2O (200 mL) in small portions with vigorous stirring at rt. After stirring at rt for 40 min, the reaction mixture was kept at 0 °C overnight and filtered. The solid was washed successively with H_2O, C_2H_5OH, and ethyl acetate to yield white crystals (13, 9.2 g, 76.3%): mp 198–199 °C [lit.[50] mp 185 °C dec]; IR (Nujol, cm^{-1}) 2923, 2853, 1581, 1460, 1377, 847, 722; ^1H NMR (D_2O + CF_3COOH) δ 2.88–3.05 (m, 2 H, allyl-CH_2), 3.15 (d, 2 H, SCH_2), 3.80 (m, 1 H, $CHNH_2$), 5.15 (m, 2 H, CH_2=), 5.75 (m, 1 H, CH=); ^{13}C NMR (D_2O + CF_3COOH + CD_3OD) δ 168.0, 130.10, 113.80, 44.50, 30.20, 25.80; HRCIMS *m/z* 193.0257 (calcd for $C_6H_{11}NO_2S_2$ 193.0231).

Reaction of *S*-(2-Propenyl)-L-cysteine (1) with Nitric Oxide in Water. *S*-(2-Propenyl)cysteine (1, 810 mg, 5 mmol) was dissolved in H_2O (10 mL). The solution was deoxygenated with dry N_2 before NO was slowly bubbled through the solution at rt for 24 h. The excess NO was removed under vacuo and the remaining mixture was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), the solvent was evaporated, and the residue was chromatographed to give diallyl disulfide (2, 47 mg) and allicin (3, 36 mg) [IR (neat, cm^{-1}) 3084, 3014, 2910, 1635, 1426, 1403, 1230, 1087, 989; ^1H NMR ($CDCl_3$) δ 3.70–3.90 (m, 4 H, CH_2), 5.20–5.50 (m, 4 H, CH_2=), 5.86–6.02 (m, 2 H, -CH=); ^{13}C NMR ($CDCl_3$) δ 34.60, 59.40, 118.70, 123.65, 125.50, 132.60; HRCIMS *m/z* 163.0250 (calcd for $C_6H_{10}OS_2$ + 1.0078, 163.0251)], and *S*-(2-propenyl) 2-propene-1-sulfonothioate[41] (pseudoallicin, 4, 48 mg)[IR (neat, cm^{-1}) 1324, 1127; ^1H NMR ($CDCl_3$) δ 3.78 (d, 2 H, CH_2, *J* = 7.0 Hz), 3.98 (d, 2 H, CH_2, *J* = 7.5 Hz), 5.20–5.55 (m, 4 H, CH_2), 5.80–5.94 (m, 2 H, -CH=); ^{13}C NMR ($CDCl_3$) δ 39.20, 66.95, 119.92, 124.30, 125.80, 131.50; HRCIMS, *m/z* 179.0210 (calcd for $C_6H_{10}O_2S_2$ + 1.0078 = 179.0200)].

The aqueous solution was neutralized (pH paper) with 0.1 M NaOH, and the volume of the solution was reduced at rt and stored at 0 °C for 24 h and filtered. Unreacted 1 (650 mg, 19.8% conversion) was recovered. The filtrate was evaporated overnight in a flow of dry air and the residue recrystallized from H_2O to give sodium 2-oxopropanoate (45 mg): ^1H NMR (D_2O) δ 2.37 (s, 3 H); ^{13}C NMR [D_2O + $(CD)_3)_2CO$] δ 26.51 (CH_3), 170.16 (C=O), 205.11 (COO^-). Treatment of sodium 2-oxopropanoate with thionyl chloride followed by aniline gave the anilide derivative $CH_3COCONHC_6H_5$: mp 102–103 °C [lit.[51] mp 104 °C]; IR (neat, cm^{-1}) 1721, 1694, 1599, 1534, 909, 735; ^1H NMR ($CDCl_3$) δ 2.65 (s, 3 H, CH_3), 7.14–7.65 (m, 5 H, C_6H_5), 8.74 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 24.04 (CH_3), 119.80, 125.27, 129.22, 136.21, 157.52, 197.29; HRCIMS, *m/z* 163.0640 (calcd for $C_9H_9NO_2$, 163.0633).

Reaction of *S*-(2-Propenyl)-L-cysteine (1) with Nitric Oxide in Water and Trifluoroacetic Acid. *S*-(2-Propenyl)-L-cysteine (1, 322 mg, 2 mmol) was dissolved in 12 mL of H_2O containing 1 mL of trifluoroacetic acid. The solution was deoxygenated with dry N_2 before NO was slowly bubbled through the solution at rt for 5 h. The products were detected by TLC (solvent B, 2, R_f = 0.90, 3 R_f = 0.40, 4 R_f = 0.10); solvent A 2-oxopropanoic acid (5), R_f = 0.31].

Stability of Allicin (3) in Water. Allicin (3, 162 mg, 1 mmol) was added to 5 mL of H_2O. The two-phase mixture was stirred at rt for 24 h. No reaction was observed by TLC.

Reaction of Allicin (3) with Nitric Oxide. Allicin (324 mg, 2 mmol) was added to 10 mL of H_2O. Nitric oxide was slowly bubbled through the two-phase mixture at rt for 24 h as described above for the oxidation of 1. The reaction mixture became homogeneous during the passage of nitric oxide. The product solution was extracted with CH_2Cl_2 (3 × 10 mL), and the combined extract was dried (Na_2SO_4) and evaporated. The residue was chromatographed with cooled 8:1 hexanes/ethyl acetate to give an unstable product (6 mg), with 5:1 hexanes/ethyl acetate to give allicin (3, 250 mg, 24% conversion), and then with 1:1 hexanes/ethyl acetate to give pseudoallicin (4, 12 mg).

Attempted Reaction of Diallyl Disulfide (2) with Nitric Oxide. Diallyl disulfide (2, 292 mg, 2 mmol) was added to water (10 mL). Nitric oxide was bubbled slowly through the stirred two-phase mixture at rt for 24 h as described above for the oxidation of 1. No reaction was observed by TLC.

Reaction of (+)-*S*-(2-Propenyl)-L-Cysteine Sulfoxide (Alliin, 13) with Nitric Oxide in Water. (+)-*S*-(2-Propenyl)-L-cysteine sulfoxide (14, 531 mg, 3 mmol) was dissolved in 10 mL of water. Nitric oxide was slowly bubbled through the solution at rt for 24 h as described above for the oxidation of 1. Starting material (13, 400 mg, 24.7% conversion) and sodium 2-oxopropanoate (35 mg) were obtained from the aqueous layer. The organic layer afforded allicin (3, 50 mg) and pseudoallcin (4, 45 mg).

Reaction of (+)-*S*-(2-Propenyl)-L-Cysteine Sulfoxide (Alliin, 13) with Nitric Oxide in Water and Trifluoroacetic Acid. (+)-*S*-(2-Propenyl)-L-cysteine sulfoxide (13, 354 mg, 2 mmol) was dissolved in 12 mL of water containing 1 mL of trifluoroacetic acid. Nitric oxide was slowly bubbled through the solution at rt for 6 h. The products were detected by TLC [solvent B, 3R_f = 0.40, 4 R_f = 0.10); solvent A, 2-oxopropanoic acid (5), R_f = 0.31].

Attempted Reaction of *S*-2-(Propenylthio)-L-cysteine (14) with Nitric Oxide in Water and Trifluoroacetic Acid. *S*-2-Propenylthio)-L-cysteine (14, 579 mg, 3 mmol) was dissolved in 12 mL of H_2O containing 1 mL of trifluoroacetic acid. Nitric oxide was passed slowly through the solution at rt for 24 h as described above for the oxidation of 1. No reaction was observed by TLC.

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(49) Stoll, A.; Seebeck, E. *Helv. Chim. Acta* **1951**, *34*, 481.
(50) Cavallito, C. J.; Bailey, J. H. *J. Am. Chem. Soc.* **1944**, *66*, 1952.
(51) Carre, P.; Jullien, P. *Compt. Rend.* **1936**, *202*, 1521.