morpholine for chlorine, but no elimination.

Thus the sought methyl abstraction was not found for these three well-disposed electrophiles. Whether this novel reaction is viewed as a S_N2 reaction on the methyl group with an unusual carbon leaving group or as a E2 reaction with methyl abstraction, the conditions seemed strong enough to allow this reaction if it were kinetically feasible. Nor should thermodynamics have prevented reaction. For example, at 25 °C, enthalpy favors cyanide abstracting a methyl group from 1-chloropropane over cyanide abstracting hydrogen from chloroethane (ΔH^0 = –9.4 vs –0.7 kcal/mol by heats of formation).

The reason for failed methyl abstraction is open to speculation. Either a hydrogen or a methyl group on a β carbon is sterically open to nucleophilic attack. Neither holds significant positive charge to attract a nucleophile. But a β hydrogen does have an advantage in being able to form a kind of hydrogen bond with the nucleophile in the transition state of a normal elimination reaction. In contrast, a methyl carbon cannot hydrogen bond and must rehybridize in its transition state. Such handicaps evidently prevent abstraction of a β-methyl group in elimination reactions even under otherwise favorable conditions. Probably the same handicaps deter strong nucleophiles, which can abstract alcohol hydrogens, from attacking ethers. Despite many similarities between the reactivities of hydrogen and a methyl group, another significant difference has now been established.

Experimental Section

DMF was purified by stirring with KOH for a few hours and then distilling from CaO onto 4A molecular sieves under aspirator vacuum. Morpholine was purified by stirring with $CaSO_4$ overnight and then fractionally distilling. Bu_3N was purified by stirring with KOH overnight and then distilling at 3 mmHg. LiCl and NaCN were dried in the oven. NMR spectra were recorded on a Varian EM360A proton spectrometer and are reported in δ units. The IR spectrum was recorded on a Perker-Elmer 1320 spectrometer.

Reaction of 1a with LiCl. A mixture of 3.37 g (20.0 mmol) of **1a**, 1.27 g (30.0 mmol) of LiCl, and 4.65 mL of DMF was refluxed for 4 days. NMR (DMF) δ 7.42 (br s, 5 H, Ar), 6.47 (br s, 1 H, HC=C), 2.15 (br s, 6 H, Me), very like the spectrum of authentic 2-methyl-1-phenyl-1-propene.

Reaction of 1a with NaCN. A mixture of 3.37 g (20.0 mmol) of **1a**, 0.98 g (20 mmol) of NaCN, and 4.65 mL of DMF was refluxed for 4 days. NMR (DMF) δ 7.39 (m, Ar), 1.47 (m, Me + CH_2), consistent with 3-methyl-3-phenylbutanenitrile; no vinyl protons; also peaks for starting materials.

Reaction of 1a with Morpholine or Bu_3N. A solution of 3.37 g (20.0 mmol) of **1a** and either 3.48 g (40.0 mmol) of morpholine or 6.19 g (33.4 mmol) of Bu_3N was heated at 123–129 °C for 2 days. NMR showed no reaction.

Reaction of 1b with LiCl or NaCN. A mixture of 2.66 g (25.0 mmol) of **1b** and either 2.00 g (47.2 mmol) of LiCl or 0.50 g (10 mmol) of NaCN in 11.62 mL of DMF was heated at 200 °C in a sealed bomb for 2 days. NMR showed no reactions.

Reaction of 1b with Morpholine. A solution of 5.32 g (50.0 mmol) of **1b** and 8.72 g (100 mmol) of morpholine was heated at 200 °C in a sealed bomb for 3 days. A reddish brown liquid and a white solid resulted: NMR (of liquid) δ 3.80 (t, 4 H, H_2CO), 2.67 (t, 4 H, $OCCH_2N$), 2.26 (s, 2 H, neopentyl CH_2), 1.13 (s, 9 H, Me), consistent with *N*-neopentylmorpholine; also peaks for starting materials.

1-Chloro-2-methyl-2-(4-nitrophenyl)propane (1c). A mixture of 1.69 g (10.0 mmol) of **1a**, 1.27 mL (19.9 mmol) of 70% HNO_3, 2.21 mL (40.0 mmol) of concentrated H_2SO_4, and 6 mL of CH_2Cl_2 was stirred for 1 h. The organic layer was washed with saturated $NaHCO_3$ and NaCl solutions, dried with Na_2SO_4, and concentrated under vacuum. From 1.96 g of yellowish liquid crude **1c** was eluted at 1.0-g aliquot through 25 g of a silica gel column with 0–15% ether–hexane to yield 0.55 g of white **1c**: mp 29–33 °C; IR (melt) 1510 and 1340 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 7.86 (2 d, 4 H, Ar), 3.66 (s, 2 H, CH_2), 1.46 (s, 6 H, Me), consistent with **1c**.

Reaction of 1c with NaCN. A mixture of 0.213 g (1.00 mmol) of **1c**, 0.196 g (4.00 mmol) of NaCN, and 1.0 mL of DMF was refluxed for 1 day. NMR showed no reaction.

Reaction of 1c with Morpholine. A solution of 0.213 g (0.997 mmol) of **1c** and 0.90 g (10 mmol) of morpholine was refluxed for 3 days. NMR δ 2.64, perhaps a little substitution product; no vinyl protons; also peaks for starting materials.

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Registry No. **1a**, 515-40-2; **1b**, 753-89-9; **1c**, 99359-77-0; 2-methyl-1-phenyl-1-propene, 768-49-0; 3-methyl-3-phenylbutanenitrile, 17684-33-2; *N*-neopentylmorpholine, 67061-35-2.

Relative Ease of Transient Acyl Imine Formation via Selenoxide, Sulfoxide, and Sulfone β N–H Elimination. A Feasibility Study on the Preparation of Novel Peptide Analogues

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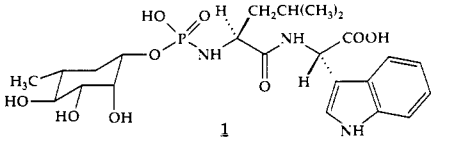
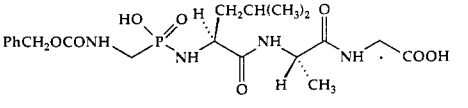
Received May 11, 1987

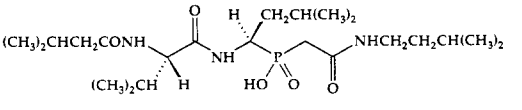
Many biomedically important naturally occurring and synthetic protease inhibitors have tetrahedral phosphorus functional groups as transition-state analogues or reactive-intermediate analogues. The microbial metabolite phosphoramidon **1**, long known as a potent competitive inhibitor of the bacterial zinc endopeptidase thermolysin,[1] has recently been shown to produce analgesia in rats, presumably via inhibition of the degradation of endogenous opioid peptides by the zinc protease enkephalinase.[2] Synthetic **2** and related compounds inhibit the human zinc peptidase neutrophil collagenase, which is believed to cause pathological connective tissue destruction in rheumatoid arthritis.[3] Synthetic **3** and related compounds inhibit the aspartic protease pepsin,[4] a model enzyme for the human blood pressure regulating enzyme renin.



1



2



3

It is reasonable to expect that tetrahedral selenoxide, sulfoxide, and sulfone functional groups should also possess

† Fellow of the Alfred P. Sloan Foundation, 1987–1989.

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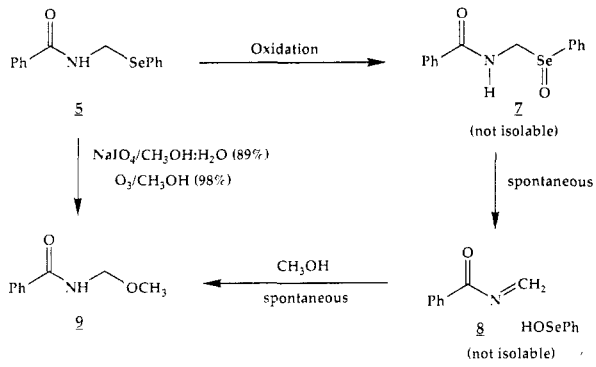
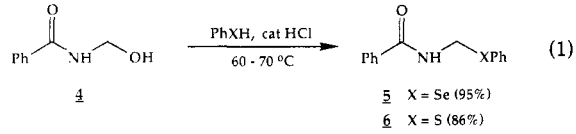
Scheme I



transition-state-analogue or reactive-intermediate-analogue protease-inhibitory properties. A potential problem with incorporating such functional groups into peptide analogues is β N–H elimination. To examine the β N–H elimination question in a model system, we studied the chemistry of *N*-[(phenylselenoxy)methyl]benzamide (**7**), the corresponding sulfoxide, *N*-[(phenylsulfoxy)methyl]-benzamide (**10**), and the corresponding sulfone, *N*-[(phenylsulfonyl)methyl]benzamide (**11**).

Results

Preparation of *N*-[(Phenylselenyl)methyl]benzamide (5) and *N*-[(Phenylsulfenyl)methyl]benzamide (6). Acid-catalyzed condensation of benzeneselenol with *N*-(hydroxymethyl)benzamide (**4**) produced crystalline **5** in 95% isolated yield (eq 1). Likewise, acid-catalyzed condensation of benzenethiol with **4** produced crystalline **6** in 86% isolated yield (eq 1).

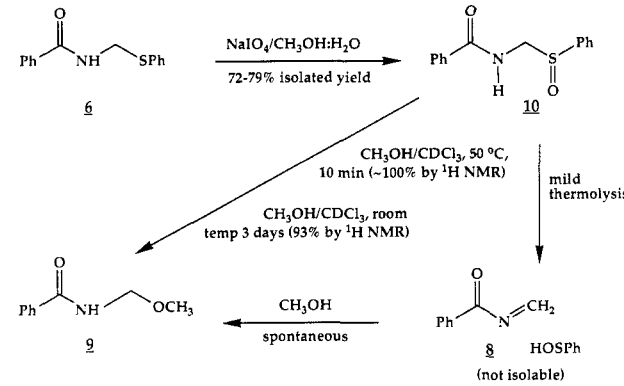


(1)

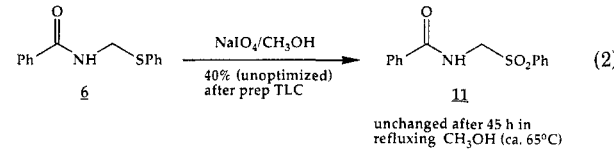
Oxidation of 5; Chemistry of 7. As summarized in Scheme I, oxidation of **5** with either $NaIO_4/CH_3OH/H_2O$ (room temperature) or O_3/CH_3OH (–78 °C to room temperature) produced *N*-(methoxymethyl)benzamide (**9**) in high yield. Since these are standard conditions for oxidizing selenides to selenoxides, it is essentially certain that selenoxide **7** was formed transiently in situ. The production of **9** can be rationalized by facile selenoxide β N–H elimination of **7** to spontaneously produce the highly reactive acyl imine *N*-benzoyl formaldehyde imine **8**. Rapid and efficient addition of CH_3OH solvent across the double bond of acyl imine **8** would then produce **9**.

Oxidation of 6; Chemistry of 10 and 11. As summarized in Scheme II, oxidation of **6** under conditions known to oxidize sulfides to sulfoxides produced stable, isolable sulfoxide **10** in good yields. Although **10** was sufficiently stable to isolate and characterize by ^1H NMR, sulfoxide β N–H elimination is a facile reaction. Mild thermolysis of **10** in the presence of CH_3OH produced **9** in high yield, presumably via formation of **8**. The same reaction occurred in high yield when **10** was allowed to stand for 3 days at room temperature in the presence of CH_3OH.

Scheme II



Oxidation of **6** with excess (>2 equiv) $NaIO_4/CH_3OH$–H_2O produced stable, isolable sulfone **11** in moderate yield (eq 2). Sulfone **11** was much more stable than sulfoxide **10**; thermolysis of **11** in refluxing CH_3OH (ca. 65 °C) for 45 h led to the recovery of unchanged **11**.



(2)

Discussion

Our results demonstrate that the chemistry of a selenoxide, sulfoxide, or sulfone with a β amide N–H parallels the chemistry of alkyl selenoxides, sulfoxides, and sulfones with a β C–H. In each case, selenoxides spontaneously β-eliminate,[5] sulfoxides require heating to undergo β-elimination,[6] and sulfones are very stable to β-elimination even with heating.[6]

From our results on the oxidation of selenide **5**, and the ensuing chemistry of transient selenoxide **7**, it is clear that the preparation of peptide analogues containing the CONHCHRSe(=O) moiety is not feasible. In contrast, our results with **10** suggest that sulfoxide peptide analogues containing the CONHCHRS(=O) moiety should be feasible. The moderate instability of such compounds due to β N–H elimination may not necessarily be a disadvantage. Such reactions at an enzyme active site or peptide hormone receptor would generate highly reactive acyl imine ($RCON{=}CH_2$) and sulfenic acid (RSOH) functional groups, capable of covalent reaction with nearby nucleophilic residues, offering a new approach to affinity labeling[7] and the design of enzyme inactivators.

Acyl imines are very useful in organic synthesis, particularly for intramolecular imino Diels–Alder reactions.[8,9] The standard methods for acyl imine formation require thermolysis of *N*-(acetoxymethyl) amides at ca. 200–400 °C[8] or flash vacuum pyrolysis at 450 °C of *N*-acyl-2-azabicyclo[2.2.2]alk-5-enes.[9] Our finding that sulfoxide **10** is stable enough to isolate yet it undergoes β N–H elimination to form acyl imine **8** upon very mild thermolysis could be applied to the development of a synthetically useful new method for the generation of acyl imines under exceptionally mild conditions.

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Our finding that stable isolable sulfone **11** is not prone to β N–H elimination suggests that sulfone peptide analogues containing the $CONHCHRSO_2$ moiety should be feasible. Sulfone peptide analogues might be useful as transition-state-analogue or reactive-intermediate-analogue protease inhibitors. Alternatively, sulfone peptide analogues of peptide hormones might possess novel conformational properties that could be exploited for enhanced and/or more selective hormone receptor binding.

Experimental Section

Analytical thin-layer chromatography was performed on Merck aluminum-backed F_{254} silica gel 60 plates (product 5554). Visualization of TLC spots was done with 254-nm UV light, by dipping the plates in a vanillin solution (9.25 g of vanillin, 7.25 mL of glacial HOAc, 325 mL of absolute EtOH, 12.5 mL of concentrated H_2SO_4) followed by heating, or by dipping in an iodoplatinate solution (10 mL of 5% $PtCl_4/H_2O$, 5 mL of concentrated HCl, 240 mL of 2% KI/H_2O) followed by heating. Silica gel flash chromatography was performed with J. T. Baker 40-μm silica gel 7024-1. ^1H NMR spectra were recorded on a General Electric QE-300 spectrometer (300 MHz). ^{13}C NMR spectra were measured on the QE-300 instrument at 75.5 MHz. Melting points were taken on a Mel-Temp apparatus (Laboratory Devices) and are uncorrected. IR spectra were measured on a Beckman IR 4240 and are reported in cm^{-1}. Mass spectra (EI) were run on a CEC21-110B instrument. Elemental microanalyses were performed by Desert Analytics in Tucson, AZ.

Preparation of *N*-(Hydroxymethyl)benzamide (4). Via a general procedure for the preparation of *N*-(hydroxymethyl) amides,[10] a suspension of benzamide (10.0 g, 82.6 mmol) in 11 mL of 4% K_2CO_3/H_2O and 9 mL of 37% CH_2O/H_2O was warmed for 5 min in a 50 °C water bath to form a homogeneous solution. The water bath was removed, and the reaction was allowed to cool to room temperature. After 2 h, the white crystals that formed were collected by suction filtration and then washed with 20 mL of 5% $NaOH/H_2O$ and then with 50 mL of cold H_2O. Recrystallization from toluene lead to 6.23 g (50%) of **4**: mp 106–108 °C (lit.[11] mp 104–106 °C); ^1H NMR ($CDCl_3$) δ 3.4 (t, 1 H, J = 7.8 Hz), 4.98 (dd, 2 H J_{CH_2-OH} = 7.5 Hz, J_{CH_2-NH} = 6.4 Hz), 7.1 (br m, 1 H), 7.4–8.0 (m, 5 H).

Preparation of *N*-[(Phenylselenyl)methyl]benzamide (5). Benzeneselenol was freshly prepared according to a literature procedure.[12] Benzeneselenol (1.1 g, 7 mmol), **4** (1.0 g, 6.6 mmol), and 1 Pasteur pipet drop of concentrated HCl were heated under N_2 to 60–70 °C for 45 min until the solid was almost completely dissolved.[13] After cooling of the mixture to room temperature, the reaction mixture was dissolved in 60 mL of Et_2O. The Et_2O solution was washed with saturated $NaCl/H_2O$ and then dried over anhydrous Na_2SO_4. Removal of volatiles on a rotary evaporator left a yellow solid, which was washed with petroleum ether to produce 1.82 g (95%) of white crystals of **5**: mp 86–88 °C, mp 88–89 °C after recrystallization from Et_2O; ^1H NMR ($CDCl_3$) δ 4.96 (d, 2 H, J = 7.5 Hz), 6.54 (br m, 1 H), 7.0–8.0 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 37.33, 126.91, 127.78, 128.49, 128.77, 129.19, 131.68, 133.83, 134.25, 166.96; MS, m/e 291 (22, M^+ for ^{80}Se isotope), 289 (12, M^+ for ^{78}Se isotope), 157 (26, $^{80}SePh$), 155 (18, $^{78}SePh$), 134 (100, $PhCONH{=}CH_2$), 105 (93, PhCO), 77 (35, Ph). Anal. Calcd for $C_{14}H_{13}NOSe$: C, 57.94; H, 4.52; N, 4.83. Found: C, 57.91; H, 4.41; N, 4.67.

Preparation of *N*-[(Phenylsulfenyl)methyl]benzamide (6). Benzenethiol (0.50 mL, 536 mg, 4.88 mmol), **4** (160 mg, 1.059 mmol), and concentrated HCl (2 Pasteur pipet drops) were heated under N_2 to 60–70 °C for 1 h and then kept at room temperature for 2 h.[13] The reaction mixture was dissolved in 60 mL of $CHCl_3$ and washed with 20 mL of 10% $NaOH/H_2O$ and then saturated $NaCl/H_2O$, and then it was dried with anhydrous Na_2SO_4. Removal of volatiles with a rotary evaporator left a dark yellow liquid, which was purified by flash silica gel column chromatography, eluting with petroleum ether and then Et_2O to provide 220 mg (86%) of crystalline **6**: mp 61–63 °C, mp 65–66 °C after recrystallization from Et_2O (lit.[14] mp 67 °C); ^1H NMR ($CDCl_3$) δ 4.91 (d, 2 H, J = 6 Hz), 6.45 (br m, 1 H), 7.20–7.75 (m, 10 H); MS, m/e 243 (7, M^+), 134 (51, $PhCONH{=}CH_2$), 105 (100, PhCO), 77 (66, Ph).

$NaIO_4$ Oxidation of 5. To a solution of **5** (300 mg, 1.03 mmol) in 50 mL of CH_3OH was added dropwise by Pasteur pipet at room temperature saturated $NaIO_4/H_2O$ (440 mg, 2.05 mmol). After an additional 20 min, silica gel TLC indicated that no starting material remained. Removal of volatiles on a rotary evaporator was followed by extraction of the residue with 100 mL of Et_2O for 30 min with magnetic stirring. After suction filtration to remove solids, removal of the volatiles on a rotary evaporator produced a yellow solid, which was washed with petroleum ether and then recrystallized from petroleum ether/Et_2O to produce 151 mg (89%) of crystalline *N*-(methoxymethyl)benzamide **9**: mp 67–69 °C, mp 69–70 °C after recrystallization from Et_2O (lit.[15] mp 73–74 °C and 72.5 °C); ^1H NMR ($CDCl_3$) δ 3.39 (s, 3 H), 4.90 (d, 2 H, J = 7 Hz), 7.2 (br m, 1 H), 7.4–7.9 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 56.00, 71.80, 126.99, 128.50, 131.77, 132.50, 167.92; MS 165 (1, M^+), 150 (39, M – CH_3), 135 (7, M – CH_2O), 134 (8, $PhCONH{=}CH_2$), 105 (100, PhCO), 77 (47, Ph). IR ($CDCl_3$) 3460, 1678 (s), 1515 (s).

O_3 Oxidation of 5. O_3 was bubbled through a solution of **5** (19.5 mg, 0.067 mmol) in 1 mL of CH_3OH and cooled in a dry ice/acetone bath until the solution turned slightly blue. Ar was blown through the solution to expel the excess O_3, and then the solution was allowed to warm to room temperature. Removal of the volatiles on a rotary evaporator produced **9** (98% by ^1H NMR integration against a known quantity of cumene added as an internal standard).

$NaIO_4$ Oxidation of 6: Preparation of *N*-[(Phenylsulfinyl)methyl]benzamide (10). To a solution of **6** (12 mg, 0.049 mmol) in 0.5 mL of CH_3OH was added by Pasteur pipet at room temperature saturated $NaIO_4/H_2O$ (20.9 mg, 0.098 mmol). The reaction mixture was stirred 4 h until silica gel TLC showed that no starting material remained. Removal of volatiles on a rotary evaporator was followed by the addition of 30 mL of Et_2O and 10 mL of H_2O, followed by transfer to a separatory funnel. After separation of the layers, the organic phase was washed with 10 mL of saturated $NaCl/H_2O$, and then it was dried over anhydrous Na_2SO_4. Removal of the volatiles on a rotary evaporator produced 10 mg (79%) of **10**, which was analyzed directly by ^1H NMR ($CDCl_3$) δ 4.37 (dd, 1 H, J_{gem} = 12 Hz, J_{CH-NH} = 6 Hz), 4.87 (dd, 1 H, J_{gem} = 12 Hz, J_{CH-NH} = 6 Hz), 7.3–8.0 (m, 11 H, including NH). Attempts at purification by silica gel TLC led to decomposition.

To a $CDCl_3$ solution of **10** (0.0576 mmol, obtained in 72% isolated yield from $NaIO_4/CH_3OH/H_2O$ oxidation of 14 mg of **6**) in an NMR tube was added 1 Pasteur pipet drop of CH_3OH. After 3 days at room temperature, ^1H NMR analysis indicated 93% conversion to **9**. When a sample of **10** prepared identically with that described in the preceding sentence was warmed to 50 °C for 10 min, it resulted in an almost complete conversion of **10** to **9**, as judged by ^1H NMR spectroscopy.

O_3 Oxidation of 6. A solution of **6** (26 mg, 0.107 mmol) in 0.5 mL of CD_3OD in an NMR tube was treated with O_3 as described for **5**. After the mixture was warmed to room temperature, immediate ^1H NMR analysis indicated clean and quantitative conversion to $PhCONDCH_2S(=O)Ph$ (**10**): ^1H NMR (CD_3OD) δ 4.55 (d, 1 H, J_{gem} = 12 Hz), 4.65 (d, 1 H, J_{gem} = 12 Hz), 7.3–7.9 (m, 10 H). After the sample was warmed to 40 °C for 10 min, ^1H NMR analysis indicated that no sulfoxide **10** remained, and that it had been converted to $PhCONDCH_2OCD_3$ (**9**): ^1H NMR (CD_3OD) δ 4.67 (s, 2 H), 7.3–7.9 (m, 10 H). Silica gel TLC comparison of the product of this experiment with authentic

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$PhCONHCH_2OCH_3$ (9) showed them to be identical (R_f 0.3 with Et_2O).

In a separate experiment, a solution of 6 (30 mg, 0.12 mmol) in 1 mL of CD_2Cl_2 in an NMR tube was treated with O_3 as described for 5. After the mixture was warmed to room temperature, immediate ^1H NMR analysis indicated 66% conversion to sulfoxide 10: ^1H NMR (CD_2Cl_2) δ 4.40 (dd, 1 H, J_{gem} = 12 Hz, J_{CH-NH} = 6 Hz), 4.84 (dd, 1 H, J_{gem} = 12 Hz, J_{CH-NH} = 6 Hz), 7.3–8.1 (m, 11 H, including NH). After the sample was warmed to 40 °C for 10 min, ^1H NMR analysis indicated that no sulfoxide 10 remained; the decomposition products were not analyzed further.

$NaIO_4$ Oxidation of 6: Preparation of *N*-[(Phenylsulfonyl)methyl]benzamide (11). To a stirred solution of 6 (130 mg, 0.535 mmol) in 20 mL of CH_3OH was added a solution of $NaIO_4$ (1.145 g, 5.35 mmol) in 5 mL of H_2O by Pasteur pipet at room temperature. The reaction mixture was stirred at room temperature for a total of 60 h. Over the course of the reaction, additional $NaIO_4$ (3.45 g, 6.1 mmol) was added periodically until silica gel TLC showed no starting sulfide 6 and only a trace of sulfoxide 10. The white precipitate was suction filtered off with a fritted-glass funnel, and then the volatiles were removed on a rotary evaporator. The white solid residue was extracted with 2 × 40 mL of Et_2O, and then the combined Et_2O solution was dried over anhydrous Na_2SO_4. Filtration followed by evaporation provided crude product, which was purified by preparative silica gel TLC with 40:60 (v:v) EtOAc/Et_2O to provide 60 mg (40%) of sulfone 11. ^1H NMR analysis of the remainder of the preparative plate cut as a single sample revealed minor products as follows: 4 (5%), 9 (8%), and 10 (8%). Recrystallization of chromatographically purified 11 with Et_2O/EtOAc furnished white needles of 11: mp 127–129 °C (lit.[14] mp 129–131 °C); ^1H NMR ($CDCl_3$) δ 4.91 (d, 2 H, J = 7 Hz), 6.85 (br m, 1 H), 7.4–7.9 (m, 10 H); IR ($CDCl_3$) 1680 (s), 1511 (s), 1490 (s), 1322 (s, sulfone), 1148 (s) cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.09; S, 11.65. Found: C, 60.85; H, 4.66; N, 4.92; S, 11.63.

Thermolysis of 11. A solution of 11 (5 mg, 0.018 mmol) in 1 mL of CH_3OH was refluxed for 45 h with periodic monitoring by silica gel TLC. After 45 h, the solvent was removed with a rotary evaporator leaving 4.5 mg of residue. Silica gel TLC and ^1H NMR analyses of the residue showed that it was exclusively unchanged 11.

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Registry No. 4, 6282-02-6; 5, 110682-74-1; 6, 58379-67-2; 7, 110682-75-2; 8, 81793-17-1; 9, 13156-28-0; 10, 110682-76-3; 11, 76965-50-9; $PhCONH_2$, 55-21-0; HCHO, 50-00-0; PhSeH, 645-96-5; PhSH, 108-98-5.

Synthesis of Phospholipids Suitable for Covalent Binding to Surfaces

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Phospholipids are an important class of organic compounds and find extensive applicability in a variety of fields.[1] Their most important area of utility is in the study of biomembrane structure and function.[2-5] Synthetic as well as naturally occurring phospholipids are used as membrane model systems for investigating lipid–protein,[6-8] lipid–steroid,[9] lipid–receptor,[2] and other similar biochemical interactions that occur within the biological milieu. During the past decade, extensive work has been carried out to determine the effects on the nature and extent of these interactions of altering the head-group structure,[10] length of the acyl chain,[5] substituting the ester function by ether linkages,[11] and introducing polymerizable moieties into the lipid system.[12,13]

In our work[14,15] we have been concerned with the development of chemical sensors based on the use of the lipid membrane as a chemoreceptive transducer for bimolecular interactions. Present technology involves deposition of lipid layers on polymer and other surfaces by the Langmuir–Blodgett technique. However, it was found that lipid films prepared by this method lack durability and were also subject to undesirable perturbation which imposed limitations on their use as membranes for extended periods of time. Covalent binding of lipids to substrates offers an attractive route to overcome these problems. This type of attachment can be accomplished through the introduction of a reactive functional group such as a chlorosilyl moiety into the alkyl chains of the lipid skeleton and reacting it with the surface hydroxyl groups. The reactivity of simpler chlorosilanes with silicon and other metallic surfaces containing a thin oxide layer has been extensively examined previously,[16-18] and the chlorosilylated lipid is expected to behave analogously. The present paper describes the synthesis of two such [(chlorosilyl)oxy] acyl-substituted phosphatidylcholines (12 and 21) suitable for covalent attachment to a silica surface. Previous reports on the covalent binding of lipids[19] and lipid precursors[20] to silica surfaces made use of photoactivable heterobifunctional cross-linking agents and a prelinked alkylamino function carrying a reactive acid chloride moiety respectively.

The synthetic route to 3-hexanoyl-2-[9-((chlorodimethylsilyl)oxy)nonanoyl]-*sn*-glycerophosphatidylcholine (12) has been outlined in Scheme I. The methyl ester of 9-hydroxynonanoic acid (4) could be isolated in only 35% yield starting from nonanedioic acid monomethyl ester (5),

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