Studies of the Chemical Selectivity of Hapten, Reactivity, and Skin Sensitization Potency. 1. Synthesis and Studies on the Reactivity toward Model Nucleophiles of the ^{13}C-Labeled Skin Sensitizers Hex-1-ene- and Hexane-1,3-sultones

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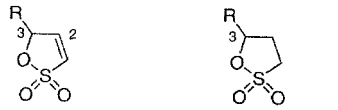
The potent skin sensitizers hex-1-ene- and hexane-1,3-sultone have been synthesized isotopically labeled with ^{13}C at reactive sites. The reactivity of 2-[^{13}C]- and 3-[^{13}C]hex-1-ene-1,3-sultones and of 3-[^{13}C]hexane-1,3-sultone toward a series of model nucleophiles for protein amino acid residues, i.e., butylamine, diethylamine, imidazole, propanethiol, and phenol, was followed by ^{13}C NMR spectroscopy. The reactivity in water of hex-1-ene-1,3-sultone toward model nucleophiles follows the hard and soft acid and base theory with the hard nucleophiles (primary and secondary amine and phenate) mainly reacting at position 3 by S_N substitution, and the soft nucleophiles (thiolate and imidazole) mainly reacting at position 2 by a Michael addition reaction. Hexane-1,3-sultone reacts with model nucleophiles at position 3 by S_N substitution. Both saturated and unsaturated sultones are sensitive to hydrolysis when reacted in water.

Introduction

Allergic contact dermatitis (ACD)[1] is a common disease produced by the modification of skin proteins by haptens (*1*). These low-molecular weight chemicals, usually rather lipophilic, are able to penetrate the skin where, either directly or after metabolism, they react with nucleophilic residues of amino acids through an electrophile−nucleophile mechanism or a radical mechanism (*2*). Subsequent processing of these modified proteins by Langerhans cells, the main antigen-presenting cell of the epidermis, leads to the selection and activation of T-lymphocytes with receptors able to selectively bind antigenic hapten-modified peptides (*3*). In the past few years, quantitative structure−activity relationships (QSAR) have been developed to explain the sensitizing potential of several haptens, and key parameters, such as lipophilicity and reaction rate, have been identified (*4*, *5*). Furthermore, it has been shown that, in most cases, haptens exhibit chemical selectivity for nucleophilic amino acids (*6*, *7*), although the effect of such selectivity on sensitization potential is not understood. This paper is intended to be the first of a series of studies aimed at investigating the relationship between the chemical selectivity of haptens with the potency of their skin sensitization potential. The first two papers in the series concern hex-1-ene-1,3-sultone and hexane-1,3-sultone.

Chart 1



1 R = C_3H_7
1a 3-[^{13}C]
1b 2-[^{13}C]

2 R = C_3H_7
2a 3-[^{13}C]

Alk-1-ene-γ-sultones (Chart 1) have been shown, in several animal models, to be particularly strong skin sensitizers (*8*, *9*), exhibiting sensitization potential down to levels of approximately 1 ppm, while alkane-γ-sultones were found to be moderate sensitizers. Attention was focused on these chemicals in the mid-1970s, when the cause of a 1968 outbreak of contact dermatitis in Scandinavia was traced to 2-chloro-γ-sultones and α,β-unsaturated γ-sultones, formed as contaminants in a batch of ether sulfate used to formulate dishwashing liquids (*10*). The high sensitizing ability of alkene versus alkane sultones has been attributed to Michael acceptor properties of the electron-deficient double bond (*8*). In fact, alkenesultones exhibit two potential reactive electrophilic centers that are able to react with nucleophilic amino acids via two different mechanisms ("Michael type" addition at position 2 and S_N reaction at position 3), while alkanesultones have only one reactive electrophilic center at position 3, which is able to react with nucleophilic amino acids via an S_N reaction. A comparison of the chemical behavior of these two molecules could be valuable for obtaining new insights into the relationship

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[1] Abbreviations: ACD, allergic contact dermatitis; DIBA-H, diisobutylaluminum hydride; HSA, human serum albumin; HSAB, hard and soft acid and base; NOE, nuclear Overhauser effect; QSAR, quantitative structure−activity relationships; RAI, relative alkylation index.

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between sensitization potential and mechanisms of protein modification.

In this paper, we report the synthesis of 3-[^{13}C]- and 2-[^{13}C]hex-1-ene-1,3-sultones **1a** and **1b**, respectively, and of 3-[^{13}C]hexane-1,3-sultone **2a** (Chart 1) and their reactivity toward model nucleophiles studied using ^{13}C NMR. The results of these experiments are used in the following paper (*11*) to analyze the reaction of these chemicals in water with human serum albumin (HSA), used as a model protein.

Materials and Methods

Caution: *Skin contact with sultone derivatives must be avoided. Since these are sensitizing substances, they must be handled with care.*

Chemistry. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 MHz spectrometer in $CDCl_3$ unless otherwise specified. Chemical shifts are reported in parts per million (δ) with respect to TMS, and $CHCl_3$ was used as an internal standard (δ = 7.26 ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), and m (multiplet). Infrared spectra were recorded on a Perkin-Elmer FT-IR 1600 spectrometer, the peaks being reported in reciprocal centimeters. Melting points were determined on a Buchi Tottoli 510 apparatus and are uncorrected. Dried solvents were freshly distilled before use. Tetrahydrofuran and ethyl ether were distilled from sodium benzophenone. Triethylamine was distilled from powdered calcium hydride. Methylene chloride was dried over P_2O_5 before distillation. All air- or moisture-sensitive reactions were conducted in flame-dried glassware under an atmosphere of dry argon. Chromatographic purifications were performed on silica gel columns according to the flash chromatography technique.

Ethyl (*E*)-3-[^{13}C]Hex-2-enoate (4a). To a solution of $Na^{13}CN$ (328 mg, 6.43 mmol) in water (1 mL) were added tributylamine (23 mg) and 1-bromopropane (807 mg, 6.43 mmol). The reaction mixture was stirred and heated under reflux for 12 h, and then extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over $MgSO_4$ and filtered under an atmosphere of argon, and then a solution of DIBA-H in dichloromethane (7.69 mL, 7.69 mmol, 1.0 M) was added at −78 °C. After 1 h, the reaction mixture was hydrolyzed at 0 °C and for 1.5 h with a tartaric buffer [26 mL, prepared from tartaric acid (54 g), sodium hydroxide (4.5 g), and water (360 mL)] in the presence of dichloromethane (12 mL). The aqueous layer was again extracted with dichloromethane (2 × 15 mL), and the combined organic layers were washed successively with saturated solutions of $NaHCO_3$ (15 mL) and NaCl (15 mL), dried over $MgSO_4$, and filtered in a reaction flask. A solution of (ethoxycarbonylmethylene)triphenylphosphorane (2.35 g, 6.4 mmol) in dichloromethane (10 mL) was added, and the reaction mixture was stirred at room temperature for 2 h. Solvents were removed under vacuum, and the crude product was purified by chromatography over silica (pentane, 6% Et_2O) to give 433 mg (3.02 mmol, 47% yield) of **4a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 [t, 3H, J = 7.3 Hz, $C\underline{H}_3(CH_2)_2$], 1.26 (t, 3H, J = 7.1 Hz, $C\underline{H}_3CH_2O$), 1.36−1.57 (m, 2H, $CH_3C\underline{H}_2CH_2$), 2.08−2.22 (m, 2H, $CH_3CH_2C\underline{H}_2$), 4.16 (q, 2H, J = 7.1 Hz, $O-C\underline{H}_2$), 5.78 (dt, 1H, J = 15.7 Hz, J = 1.5 Hz, $^{13}CH{=}C\underline{H}$), 6.93 (ddt, 1H, J_{H-C} = 153.9 Hz, J = 15.7 Hz, J = 6.9 Hz, $^{13}C\underline{H}{=}CH$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6 (d, J_{C-C} = 3.3 Hz), 14.3, 21.3, 34.2 (d, J_{C-C} = 41.2 Hz), 60.1, 121.4 (d, J_{C-C} = 69.3 Hz), 149.1, 166.8.

Ethyl 2-[^{13}C]-2-Bromoacetate (6). Bromine (0.82 mL, 15.9 mmol) was slowly added to $^{13}CH_3COOH$ (431 mg, 6.92 mmol) and PBr_3 (1.93 g, 6.92 mmol) and the reaction mixture stirred at room temperature for 15 min and then heated under reflux for 3 h. Ethanol (0.8 mL) was slowly added at room temperature and the mixture stirred for 12 h, and then more ethanol (2 mL) was added before extraction with water (10 mL) and ether (20 mL). The combined organic layers were successively washed with saturated solutions of $NaHCO_3$ (2 × 10 mL) and $Na_2S_2O_3$ (10 mL) and then with water (10 mL) and dried over $MgSO_4$. Solvent evaporation under reduced pressure gave **6** (779 mg, 4.64 mmol, 67% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.0 Hz, CH_3), 3.82 (d, 2H, J_{H-C} = 153.1 Hz, CH_2Br), 4.23 (q, 2H, J = 7.1 Hz, CH_2O); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 25.9, 62.3, 167.3 (d, J_{C-C} = 63.9 Hz); IR ($CHCl_3$) ν 1285 (C−O), 1738 (C═O).

2-[^{13}C](Ethoxycarbonylmethyl)triphenylphosphonium Bromide (7). Ethyl 2-[^{13}C]-2-bromoacetate **6** (779 mg, 4.64 mmol) in ethyl acetate (2.5 mL) was slowly added to a solution of triphenylphosphine (1.22 g, 4.64 mmol) in ethyl acetate (2.5 mL). The reaction mixture was then stirred at room temperature for 12 h and the white precipitate filtered off, washed with ether (3 × 10 mL), and dried under vacuum at 40 °C for 5 h to give **7** (1.73 g, 4.03 mmol, 87% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (t, 3H, J = 7.1 Hz, CH_3), 3.97 (q, 2H, J = 7.1 Hz, CH_2O), 5.39 (dd, 2H, J_{H-C} = 134.6 Hz, J_{H-P} = 13.8 Hz, CH_2P), 7.58−7.88 (m, 15H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 33.0 (d, $^1J_{C-P}$ = 56.1 Hz), 62.8, 117.8 (d, $^1J_{C-P}$ = 87.4 Hz), 130.2 (d, $^3J_{C-P}$ = 13.2 Hz), 133.8 (d, $^2J_{C-P}$ = 11.5 Hz), 135.1 (d, $^4J_{C-P}$ = 3.3 Hz), 164.2 (d, J_{C-C} = 59.4 Hz); IR ($CHCl_3$) ν 1733 (C═O).

2-[^{13}C](Ethoxycarbonylmethylene)triphenylphosphorane (8). A solution of sodium hydroxide (1.0 M, 15 mL) was added to a solution of 2-[^{13}C](ethoxycarbonylmethyl)-triphenylphosphonium **7** (1.73 g, 4.03 mmol) in dichloromethane (15 mL) and the reaction mixture stirred vigorously for 15 min. The organic layer was removed and the aqueous layer extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to give 1.38 g (3.96 mmol, 98% yield) of phosphorane **8**: ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.8, 30.1 (d, J_{C-P} = 125.3 Hz), 57.8, 128.0 (d, $^1J_{C-P}$ = 90.6 Hz), 128.7 (d, $^3J_{C-P}$ = 11.9 Hz), 131.9, 133.0 (d, $^2J_{C-P}$ = 9.9 Hz); IR ($CHCl_3$) ν 1610 (C═O).

Ethyl (*E*)-2-[^{13}C]Hex-2-enoate (4b). To a solution of butyraldehyde (434 μL, 4.77 mmol) in dichloromethane (15 mL) was added 2-[^{13}C](ethoxycarbonylmethylene)triphenylphosphorane **8** (1.38 g, 3.96 mmol) in dichloromethane (15 mL) and the reaction mixture stirred for 1.5 h. The solvent was evaporated under reduced pressure and the crude product purified by column chromatography over silica (pentane, 6% Et_2O) to give 465 mg (3.25 mmol, 82% yield) of **4b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 [t, 3H, J = 7.4 Hz, $C\underline{H}_3(CH_2)_2$], 1.27 (t, 3H, J = 7.1 Hz, $C\underline{H}_3CH_2O$), 1.47 (tq, 2H, J = 7.3 Hz, $CH_3C\underline{H}_2CH_2$), 2.09−2.23 (m, 2H, $CH_3CH_2C\underline{H}_2$), 4.17 (q, 2H, J = 7.1 Hz, $O-C\underline{H}_2$), 5.80 (ddt, 1H, J_{H-C} = 161.7 Hz, J = 15.7 Hz, J = 1.5 Hz, $CH{=}^{13}C\underline{H}$), 6.94 (ddt, 1H, J = 15.7 Hz, J = 6.9 Hz, J_{H-C} = 1.7 Hz, $C\underline{H}{=}^{13}CH$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 14.3, 21.3 (d, J_{C-C} = 3.3 Hz), 34.2, 60.1, 121.4, 149.1 (d, J_{C-C} = 70.9 Hz), 166.8 (d, J_{C-C} = 74.2 Hz).

(*E*)-3-[^{13}C]Hex-2-en-1-ol (9a). A solution of DIBA-H in dichloromethane (6.60 mL, 6.60 mmol, 1.0 M) was added at −78 °C to a solution of ethyl 3-[^{13}C]-2-bromoacetate (433 mg, 3.0 mmol) **4a** in dichloromethane (8 mL). After 1 h at 0 °C, the reaction mixture was hydrolyzed, at 0 °C for 1.5 h, with vigorous stirring with a tartaric buffer [13 mL, made from tartaric acid (54 g), sodium hydroxide (4.5 g), and water (360 mL)] and dichloromethane (6.5 mL). The aqueous phase was again extracted with ether (3 × 30 mL), and the combined organic layers were washed with saturated solutions of $NaHCO_3$ (10 mL) and NaCl (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography over silica (pentane, 30% Et_2O) to give 242 mg (2.39 mmol, 79% yield) of **9a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.4 Hz, $C\underline{H}_3$), 1.29−1.49 (m, 2H, $CH_3C\underline{H}_2$), 1.56 (s, 1H, O$\underline{H}$), 1.94−2.08 (m, 2H, $CH_3CH_2C\underline{H}_2$), 4.07 (m, 2H, $C\underline{H}_2OH$), 5.62 (dttd, 1H, J = 15.3 Hz, J = 6.0 Hz, J = 1.5 Hz, J_{H-C} = 1.5 Hz, $^{13}CH{=}C\underline{H}$), 5.67 (ddtt, 1H, J_{H-C} = 150.9 Hz, J = 15.3 Hz, J = 6.7 Hz, J = 1.4 Hz, $^{13}C\underline{H}{=}CH$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6 (d, J_{C-C} = 3.3 Hz), 22.3, 34.3 (d, J_{C-C} = 41.2 Hz), 63.8, 128.9 (d, J_{C-C} = 72.6 Hz), 133.2; IR ($CHCl_3$) ν 1671 (C═C), 3608 (OH).

(*E*)-2-[^{13}C]Hex-2-en-1-ol (9b). The same procedure that was used for **9a** was used for **9b**, starting from ethyl 2-[^{13}C]-2-bromoacetate (465 mg, 3.25 mmol) **4b**, to give 258 mg (2.55 mmol, 78% yield) of **9b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.2 Hz, $C\underline{H}_3$), 1.39 (tq, 2H, J = 7.3 Hz, $CH_3C\underline{H}_2$), 1.59 (s, 1H, O$\underline{H}$), 1.94−2.08 (m, 2H, $CH_3CH_2C\underline{H}_2$), 4.07 (m, 2H, $C\underline{H}_2$OH), 5.62 (ddtt, 1H, J_{H-C} = 153.8 Hz, J = 15.3 Hz, J = 6.0 Hz, J = 1.5 Hz, CH=^{13}C$\underline{H}$), 5.67 (dttd, J = 15.3 Hz, J = 6.8 Hz, J = 1.5 Hz, J_{H-C} = 1.5 Hz, 1H, C$\underline{H}$=^{13}CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 22.2 (d, J_{C-C} = 3.3 Hz), 34.3, 63.7 (d, J_{C-C} = 46.2 Hz), 129.0, 133.3 (d, J_{C-C} = 72.6 Hz); IR ($CHCl_3$) ν 1671 (C=C), 3608 (OH).

(*E*)-3-[^{13}C]-1-Bromohex-2-ene (10a). PBr_3 (117 μL, 1.19 mmol) was added at −10 °C to (*E*)-3-[^{13}C]hex-2-en-1-ol **9a** (242 mg, 2.39 mmol) in diethyl ether (1.5 mL). The reaction mixture was stirred for 20 min at −10 °C and for 14 h at room temperature, and then hydrolyzed slowly, at 0 °C, with water (1.5 mL); the aqueous phase was then extracted with pentane (3 × 5 mL). The combined organic layers were washed with a saturated solution of NaCl (2 × 5 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by silica gel column chromatography (100% pentane) to give 298 mg (1.82 mmol, 76% yield) of **10a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.2 Hz, $CH_3C\underline{H}_2$), 1.32−1.50 (m, 2H, $CH_3C\underline{H}_2$), 1.97−2.11 (m, 2H, $CH_3CH_2C\underline{H}_2$), 3.95 (m, 2H, $C\underline{H}_2$Br), 5.69 (dttd, 1H, J = 15.0 Hz, J = 7.6 Hz, J = 1.4 Hz, J_{H-C} = 1.4 Hz, ^{13}CH=C$\underline{H}$), 5.77 (ddtt, 1H, J_{H-C} = 151.9 Hz, J = 15.0 Hz, J = 6.9 Hz, J = 1.0 Hz, ^{13}C$\underline{H}$=CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6 (d, J_{C-C} = 3.3 Hz), 22.0, 33.6, 34.1 (d, J_{C-C} = 46.2 Hz), 126.4 (d, J_{C-C} = 70.9 Hz), 136.5; IR ($CHCl_3$) ν 1656 (C=C).

(*E*)-2-[^{13}C]-1-Bromohex-2-ene (10b). The same procedure that was used for **10a** was used for **10b**, starting from (*E*)-2-[^{13}C]hex-2-en-1-ol **9b** (258 mg, 2.55 mmol), to give 313 mg (1.91 mmol, 75% yield) of **10b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.3 Hz, $C\underline{H}_3CH_2$), 1.41 (tq, 2H, J = 7.3 Hz, $CH_3C\underline{H}_2$), 1.97−2.11 (m, 2H, $CH_3CH_2C\underline{H}_2$), 3.95 (dd, 2H, J = 7.6 Hz, J_{H-C} = 4.2 Hz, $C\underline{H}_2$Br), 5.69 (ddtt, 1H, J_{H-C} = 152.1 Hz, J = 15.1 Hz, J = 7.6 Hz, J = 1.5 Hz, CH=^{13}C$\underline{H}$), 5.77 (dt, 1H, J = 15.3, J = 6.7 Hz, C$\underline{H}$=^{13}CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 22.0 (d, J_{C-C} = 4.9 Hz), 33.6 (d, J_{C-C} = 49.5 Hz), 34.1, 126.5, 136.5 (d, J_{C-C} = 70.9 Hz); IR ($CHCl_3$) ν 1656 (C=C).

2-Bromohexane-1,3-sultone (11). (*E*)-1-Bromohex-2-ene (400 mg, 2.45 mmol) was added to a solution of Na_2SO_3 (620 mg, 4.9 mmol), NaI (1.6 mg), and Bu_4PBr (3.7 mg) in water (1 mL). The reaction mixture was stirred at 40 °C for 16 h, then washed with ether (3 × 5 mL), and hydrolyzed with a solution of HCl (2 mL, 6 M) to give (*E*)-hex-2-ene sulfonic acid, and then bromine (200 mL, 3.92 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then extracted with ether (3 × 25 mL). The combined organic layers were washed successively with saturated solutions of $NaHCO_3$ (2 × 10 mL), $Na_2S_2O_3$ (10 mL), and NaCl (2 × 10 mL), dried over $MgSO_4$, and concentrated under vacuum to give 316 mg (1.30 mmol, 53% yield) of 2-bromohexane-1,3-sultone **11** as a pale yellow liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (t, 3H, J = 7.2 Hz, $C\underline{H}_3$), 1.35−2.08 (m, 4H, $CH_3C\underline{H}_2CH_2$ and part AB of an ABX system, $CH_3CH_2C\underline{H}_2$), 3.54 (part A of an ABX system, 1H, J_{AB} = 13.5 Hz, J_{AX} = 9.9 Hz, $SC\underline{H}_2$), 3.90 (part B of an ABX system, 1H, J_{AB} = 13.5 Hz, J_{BX} = 8.1 Hz, $SC\underline{H}_2$), 4.30 (dedoubled part X of an ABX system, 1H, J_{AX} = 9.9 Hz, J_{BX} = 8.1 Hz, J = 8.9 Hz, C$\underline{H}$Br), 4.65 (dedoubled part X of an ABX system, 1H, J_{AX} = 8.9 Hz, J_{BX} = 3.2 Hz, J = 8.9 Hz, C$\underline{H}$−O); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 18.7, 33.7, 40.3, 54.4, 88.0; IR ($CHCl_3$) ν 1170 (SO_2 asymmetric), 1371 (SO_2 symmetric). Anal. Calcd for $C_6H_{11}BrO_3S$: C, 29.64; H, 4.56. Found: C, 29.70; H, 4.60.

3-[^{13}C]-2-Bromohexane-1,3-sultone (11a). The same procedure that was used for **11** was used for **11a**, starting from (*E*)-3-[^{13}C]-1-bromohex-2-ene (298 mg, 1.82 mmol), to give 227 mg (0.93 mmol, 51% yield) of **11a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (t, 3H, J = 7.3 Hz, $C\underline{H}_3$), 1.38−2.10 (m, 4H, $CH_3C\underline{H}_2CH_2$ and $CH_3CH_2C\underline{H}_2$), 3.54 (part A of an ABX system, 1H, J_{AB} = 13.5 Hz, J_{AX} = 9.8 Hz, 1H, $SC\underline{H}_2$), 3.83−3.97 (m, 1H, $C\underline{H}_2$S), 4.20−4.38 (m, 1H, C$\underline{H}$Br), 4.65 (dedoubled part A of an ABX system, 1H, J_{H-C} = 157.9 Hz, J = 8.9 Hz, J_{AX} = 8.8 Hz, J_{BX} = 3.1 Hz, ^{13}C$\underline{H}$O); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5 (d, J_{C-C} = 4.9 Hz), 18.7, 33.8 (d, J_{C-C} = 39.6 Hz), 40.3 (d, J_{C-C} = 36.3 Hz), 54.4, 88.0; IR ($CHCl_3$) ν 1170 (SO_2 asymmetric), 1371 (SO_2 symmetric).

2-[^{13}C]-2-Bromohexane-1,3-sultone (11b). The same procedure that was used for **11** was used for **11b**, starting from (*E*)-2-[^{13}C]-1-bromohex-2-ene (313 mg, 1.91 mmol), to give 234 mg (0.96 mmol, 50% yield) of **11b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (t, 3H, J = 7.3 Hz, $C\underline{H}_3$), 1.35−2.08 (m, 4H, $CH_3C\underline{H}_2CH_2$ and $CH_3CH_2C\underline{H}_2$), 3.46−3.63 (m, 1H, $C\underline{H}_2$S), 3.83−3.97 (m, 1H, $C\underline{H}_2$S), 4.30 (dm, J_{H-C} = 159.4 Hz, 1H, ^{13}C$\underline{H}$), 4.65 (m, 1H, C$\underline{H}$−O); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 18.7 (d, J_{C-C} = 3.3 Hz), 33.8, 40.3, 54.4 (d, J_{C-C} = 36.3 Hz), 88.0 (d, J_{C-C} = 34.6 Hz); IR ($CHCl_3$) ν 1170 (SO_2 asymmetric), 1371 (SO_2 symmetric).

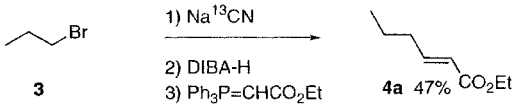
Hex-1-ene-1,3-sultone (1). To a solution of triethylamine (3.2 mL) was added at 0 °C a solution of 2-bromohexane-1,3-sultone **11** (316 mg, 1.30 mmol) in ether (8 mL). The reaction mixture was stirred at room temperature for 2 h, and the white precipitate that formed was filtered and washed with ethyl acetate. The organic solvents were concentrated under reduced pressure, and the residue was taken up in ethyl acetate (30 mL) and washed with water (7 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated under vacuum to give a crude product which was purified by column chromatography over silica (hexane, 40% AcOEt) to give 197 mg (1.21 mmol, 93% yield) of hex-1-ene-1,3-sultone as a pale yellow liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (t, 3H, J = 7.1 Hz, $C\underline{H}_3$), 1.50 (tq, 2H, J = 7.1 Hz, $CH_3C\underline{H}_2$), 1.75−1.87 (m, 2H, $C\underline{H}_2$CHO), 5.28 (part X of an ABX system, 1H, C$\underline{H}$−O), 6.73 (part A of an ABX system, 1H, J_{AB} = 6.4 Hz, J_{AX} = 2.2 Hz, CH=C$\underline{H}$−S), 6.87 (part B of an ABX system, 1H, J_{AB} = 6.4 Hz, J_{BX} = 1.6 Hz, C$\underline{H}$=CH−S); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 17.9, 35.8, 85.2, 124.6, 140.4; IR ($CHCl_3$) ν 1183 (SO_2 asymmetric), 1343 (SO_2 symmetric); EIMS 163 (M + 1), 145, 134, 120, 102, 81, 71, 56. Anal. Calcd for $C_6H_{10}O_3S$: C, 44.43; H, 6.22. Found: C, 44.54; H, 6.30.

3-[^{13}C]Hex-1-ene-1,3-sultone (1a). The same procedure that was used for **1** was used for **1a**, starting from [3-^{13}C]-2-bromohexane-1,3-sultone (227 mg, 0.93 mmol), to give 142 mg (0.87 mmol, 94% yield) of **1a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (t, 3H, J = 7.3 Hz, $C\underline{H}_3$), 1.42−1.62 (m, 2H, $CH_3C\underline{H}_2$), 1.75−1.88 (m, 2H, $C\underline{H}_2$CHO), 5.27 (dedoubled part X of an ABX system, J_{H-C} = 155.9 Hz, 1H, ^{13}C$\underline{H}$−O), 6.73 (part A of an ABX system, 1H, J_{H-C} = 9.6 Hz, J_{AB} = 6.6 Hz, J_{AX} = 2.2 Hz, CH=C$\underline{H}$−S), 6.86 (part B of an ABX system, 1H, J_{H-C} = 9.3 Hz, J_{AB} = 6.6 Hz, J_{BX} = 1.7 Hz, C$\underline{H}$=CH−S); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5 (d, J_{C-C} = 4.9 Hz), 18.0, 35.8 (d, J_{C-C} = 37.9 Hz), 85.1, 124.9, 140.1 (d, J_{C-C} = 37.9 Hz); EIMS 164 (M + 1), 146, 135, 121, 103, 82, 72, 57.

2-[^{13}C]Hex-1-ene-1,3-sultone (1b). The same procedure that was used for **1** was used for **1b**, starting from 2-[^{13}C]-2-bromohexane-1,3-sultone (234 mg, 0.96 mmol), to give 146 mg (0.90 mmol, 94% yield) of **1b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (t, 3H, J = 7.3 Hz, $C\underline{H}_3$), 1.50 (tq, 2H, J = 7.4 Hz, $CH_3C\underline{H}_2$), 1.76−1.89 (m, 2H, $C\underline{H}_2$CHO), 5.28 (part X of an ABX system, 1H, C$\underline{H}$−O), 6.74 (part A of an ABX system, 1H, J_{AB} = 6.6 Hz, J_{H-C} = 2.5 Hz, J_{AX} = 2.5 Hz, ^{13}CH=C$\underline{H}$−S), 6.87 (part B of an ABX system, 1H, J_{H-C} = 176.0 Hz, J_{AB} = 6.6 Hz, J_{BX} = 1.7 Hz, ^{13}C$\underline{H}$=CH−S); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 18.0, 35.9, 85.0 (d, J_{C-C} = 37.9 Hz), 124.9 (d, J_{C-C} = 72.6 Hz), 140.1; EIMS 164 (M + 1), 146, 135, 121, 103, 82, 71, 57.

Hexane-1,3-sultone (2). To a suspension of Pd/C (5%, 15 mg) in ethyl ether (10 mL) under hydrogen was added the sultone **1** (60 mg, 0.37 mmol) in ethyl ether (5 mL). The reaction mixture was stirred at room temperature for 30 min, degassed under vacuum, and filtered on Celite. The organic layer was dried over $MgSO_4$, filtered, and evaporated under vacuum to give 60.9 mg (0.37 mmol, 100% yield) of **2** as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H, CH_3), 1.36−1.94 (m, 4H, $CH_3C\underline{H}_2C\underline{H}_2$), 2.17−2.38 (m, 1H, $C\underline{H}_2CH_2$S), 2.51−

Scheme 1. Synthetic Pathway to Synthon 4a



3 **4a** 47%

2.67 (m, 1H, $C\underline{H}_2CH_2S$), 3.16−3.39 (m, 2H, CH_2S), 4.63 (m, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 18.5, 29.5, 37.1, 45.7, 82.6; IR ($CHCl_3$) ν 1163 (SO_2 asymmetric), 1346 (SO_2 symmetric); EIMS 165 (M + 1), 121, 82, 71, 65, 55. Anal. Calcd for $C_6H_{12}O_3S$: C, 43.88; H, 7.37. Found: C, 43.96; H, 7.48.

3-[^{13}C]Hexane-1,3-sultone (2a). The same procedure that was used for **2** was used for **2a**, starting from **1a** (59.9 mg, 0.37 mmol), to give 60.3 mg (0.37 mmol, 100% yield) of **2a** as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H, CH_3), 1.36−1.97 (m, 4H, $CH_3C\underline{H}_2C\underline{H}_2$), 2.17−2.00 (m, 1H, $C\underline{H}_2CH_2S$), 2.51−2.68 (m, 1H, $C\underline{H}_2C\underline{H}_2S$), 3.16−3.41 (m, 2H, $C\underline{H}_2S$), 4.63 (dm, J_{H-C} = 153.5 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6 (d, J_{C-C} = 4.9 Hz), 18.5, 29.5 (d, J_{C-C} = 31.3 Hz), 37.2 (d, J_{C-C} = 39.6 Hz), 45.6, 82.5; EIMS 166 (M + 1), 122, 83, 72, 65, 56.

Reactions of 1a, 1b, and 2a with *n*-Butylamine and Diethylamine in Chloroform. *n*-Butylamine or diethylamine (13.5 mg, 0.18 mmol, 30 equiv) in $CDCl_3$ (0.4 mL) was added to compound **1a**, **1b**, or **2a** (1 mg, 6 μmol), and the solution was filtered into an NMR tube and the reaction followed by ^{13}C NMR.

Reactions of 1a, 1b, and 2a with *n*-Butylamine and Diethylamine in Water. *n*-Butylamine or diethylamine (13.5 mg, 0.18 mmol, 30 equiv) in a mixture of H_2O and D_2O (0.35 and 0.05 mL, respectively) was added to compound **1a**, **1b**, or **2a** (1 mg, 6 μmol), and then the solution was filtered into an NMR tube, a trace of acetonitrile added as an internal reference, and the reaction followed by ^{13}C NMR.

Reactions of 1a, 1b, and 2a with Imidazole. Imidazole (12.6 mg, 0.18 mmol, 30 equiv) in a mixture of H_2O and D_2O (0.35 and 0.05 mL, respectively) was added to compound **1a**, **1b**, or **2a** (1 mg, 6 μmol) in 1 drop of acetone, and then the solution was filtered into an NMR tube, a trace of acetonitrile added as an internal reference, and the reaction followed by ^{13}C NMR.

Reactions of 1a, 1b, and 2a with Sodium Phenate. $PhONa\cdot 3H_2O$ (10.5 mg, 0.06 mmol, 10 equiv) in a mixture of H_2O and D_2O (0.35 and 0.05 mL, respectively) was added to compound **1a**, **1b**, or **2a** (1 mg, 6 μmol), and then the solution was filtered into an NMR tube, a trace of acetonitrile added as an internal reference, and the reaction followed by ^{13}C NMR.

Reactions of 1a, 1b, and 2a with Sodium Propanethiolate. A solution of propanethiolate (0.35 mL, 10 equiv) [prepared from sodium hydroxide (70 mg, 1.75 mmol), propanethiol (138 mg, 164 mL, 1.76 mmol), and water (10 mL)] and D_2O (0.05 mL) were added to compound **1a**, **1b**, or **2a** (1 mg, 6 μmol). The solution was filtered into an NMR tube, a trace of acetonitrile added as an internal reference, and the reaction followed by ^{13}C NMR.

Structure Assignment. Structures of the different adducts were assigned using a combination of {^1H}-decoupled ^{13}C NMR and ^{13}C DEPT 135 sequences. In DEPT $^{13}C\{^1H\}$ sequences with a Θ angle of 135°, up peaks correspond to methyl (CH_3) or methine (CH) signals while down peaks correspond to methylene (CH_2) signals. Moreover, this sequence allows us to increase the signal-to-noise ratio. The measured ^{13}C chemical shifts of the different adducts were compared with those calculated using the additivity principle and to NMR data of analogous compounds reported in the literature.

These assignments were further confirmed by ^1H chemical shifts obtained by heteronuclear correlations (*11*) and are in accordance with the sequence of adduct formation and hydrolysis.

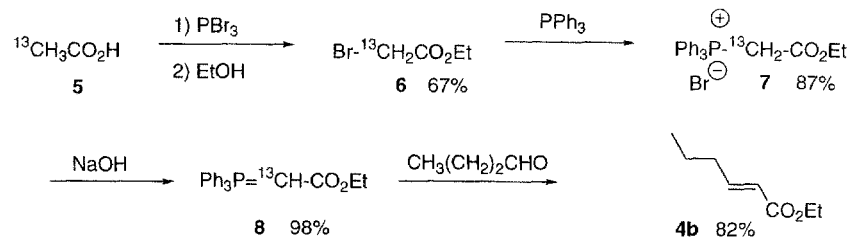
Results and Discussion

Synthesis. 3-^{13}C- and 2-^{13}C-labeled sultones (**1a** and **1b**, respectively) were synthesized from 3-[^{13}C]-(*E*)-ethyl hex-2-enoate **4a** and 2-[^{13}C]-(*E*)-ethyl hex-2-enoate **4b**, respectively, according to Scheme 3. Intermediate **4a** was directly prepared (Scheme 1) from propyl bromide **3** via a substitution reaction with $Na^{13}CN$ (*12*), followed by reduction of the intermediate cyanate to an aldehyde function with DIBAH (*13*) and its subsequent reaction with (ethoxycarbonylmethylene)triphenylphosphorane. These steps were carried out without purification due to the very low boiling point of intermediate compounds, and **4a** was obtained in an overall yield of 47%. 2-[^{13}C]-Acetic acid **5**, after bromination (PBr_3) and esterification, was transformed into its phosphonium salt **7** by reaction with PPh_3 (*14*) in quite good yield. The phosphonium salt was then treated with NaOH to give, in 98% yield, phosphorane **8**, which was condensed with butyraldehyde, giving the ^{13}C-labeled intermediate **4b** in 82% yield (Scheme 2).

Intermediates **4a** and **4b** were reduced with an excess of DIBAH to give alcohols **9a** and **9b**, respectively, which were brominated with PBr_3 (*15*). Compounds **10a** and **10b** were sulfonated with Na_2SO_3 (*16*) in water under phase transfer conditions and in the presence of a catalytic amount of NaI. Cyclization of the crude sulfonates was achieved via a bromation reaction (Br_2 in water) to give the 2-bromosultones, **11a** and **11b**, in an overall yield of approximately 50% (*17*); this rather poor yield is due to the formation, in 30% yield, of a byproduct resulting from the hydrolysis of the intermediate bromonium which competes with the cyclization reaction. The stereochemistry of compounds **11a** and **11b** was found to be trans as shown by NOE interactions observed between the H-2 (4.3 ppm) and both H-4 (2.0 ppm) and H-4′ (1.8 ppm) protons. The 2-bromosultones were finally transformed, in 94% yield, into labeled 3-[^{13}C]- and 2-[^{13}C]-sultones (**1a** and **1b**, respectively) by simple treatment with Et_3N in ethyl ether (Scheme 3). 3-[^{13}C]Hexane-1,3-sultone **2a** was quantitatively prepared by catalytic hydrogenation of 3-[^{13}C]sultone **1a**. The NMR data of the sultones were in accordance with those of previously reported unlabeled sultones (*17*).

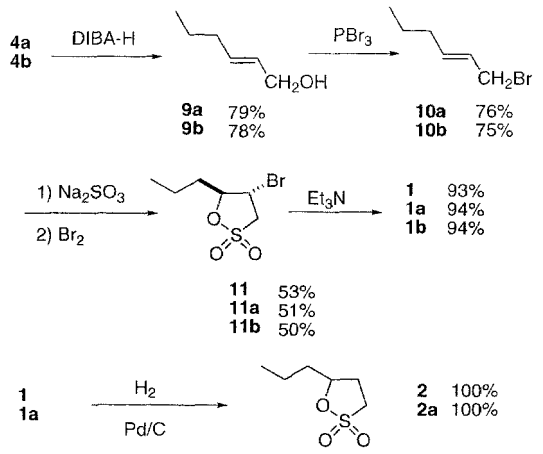
Reaction of 1a and 1b with Butylamine (Scheme 4). Both labeled unsaturated sultones **1a** and **1b** were reacted with butylamine, often considered a model for

Scheme 2. Synthetic Pathway to Synthon 4b

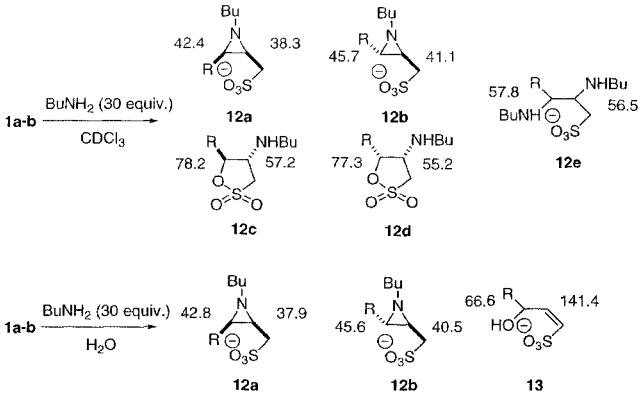


5 **6** 67% **7** 87% **8** 98% **4b** 82%

Scheme 3. Synthetic Pathway to Unsaturated Sultones 1, 1a, and 1b and Saturated Sultones 2 and 2a



Scheme 4. Reaction of 1a and 1b with Butylamine



the reactivity of lysine. This amine has, for example, been successfully used during the development of the relative alkylation index (RAI) to determine the relative reaction rate of different haptens (*18*, *19*). Reactions with 30 equiv of butylamine, to work under quasi-first-order conditions supposed to reflect an excess of protein over hapten, were followed by ^{13}C NMR in either $CDCl_3$ or water. The structures of the adducts that formed were assigned by comparison of the measured ^{13}C chemical shifts with those calculated using the additivity principle. In $CDCl_3$, the reaction was found to be rather slow, with most of the starting material remaining after 30 days, allowing the formation and/or disappearance of intermediates and/or products to be followed. Thus, after 5 h, aziridines **12a** and **12b** were already present, together with the trans "Michael" adduct **12c**. After 4 days (Figures 1A and 2A), the amount of **12a** (42.4 and 38.3 ppm), **12b** (45.7 and 41.1 ppm), and **12c** (78.2 and 57.2 ppm) increased, with the appearance of a tiny trace of cis Michael adduct **12d** (77.3 and 55.2 ppm) and of the diadduct, **12e** (57.8 and 56.5 ppm). After 30 days (Figures 1B and 2B), the main change was an increase in the content of the diadduct, **12e**, and aziridines **12a** and **12b** were present as a 1/1 mixture of cis and trans isomers.

The formation of the two minor Michael type adducts, **12b** and **12d**, was confirmed by reaction of **1a** and **1b** with pure butylamine for 40 min, evaporation of the amine under vacuum, and analysis of the products by ^{13}C NMR in water (Figure 3). Under these reaction conditions, formation of these Michael adducts seemed

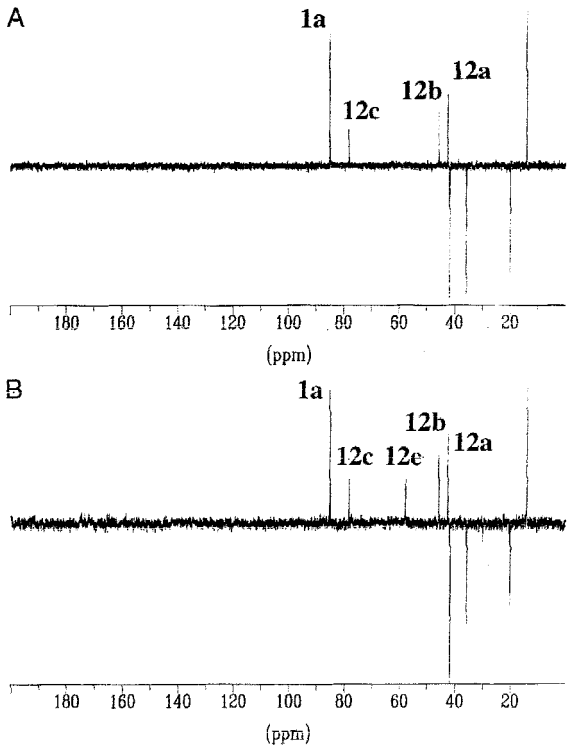


Figure 1. (A) DEPT 135 NMR spectrum of **1a** incubated with *n*-butylamine (30 equiv) in $CDCl_3$ after 4 days. (B) DEPT 135 NMR spectrum of **1a** incubated with *n*-butylamine (30 equiv) in $CDCl_3$ after 30 days.

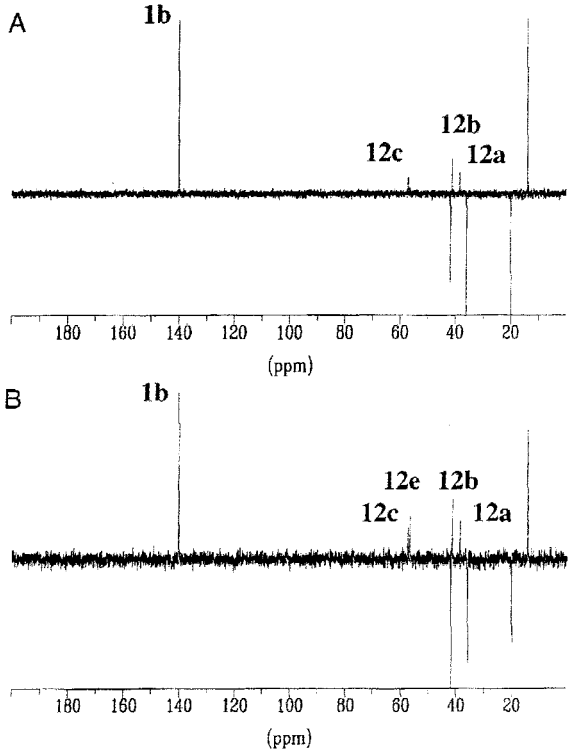


Figure 2. (A) DEPT 135 NMR spectrum of **1b** incubated with *n*-butylamine (30 equiv) in $CDCl_3$ after 4 days. (B) DEPT 135 NMR spectrum of **1b** incubated with *n*-butylamine (30 equiv) in $CDCl_3$ after 30 days.

to be favored, allowing us to obtain unambiguous chemical shifts. This experiment also confirmed that the anti addition, leading to the formation of the trans adduct **12c**, was highly favored for steric hindrance reasons (*20*).

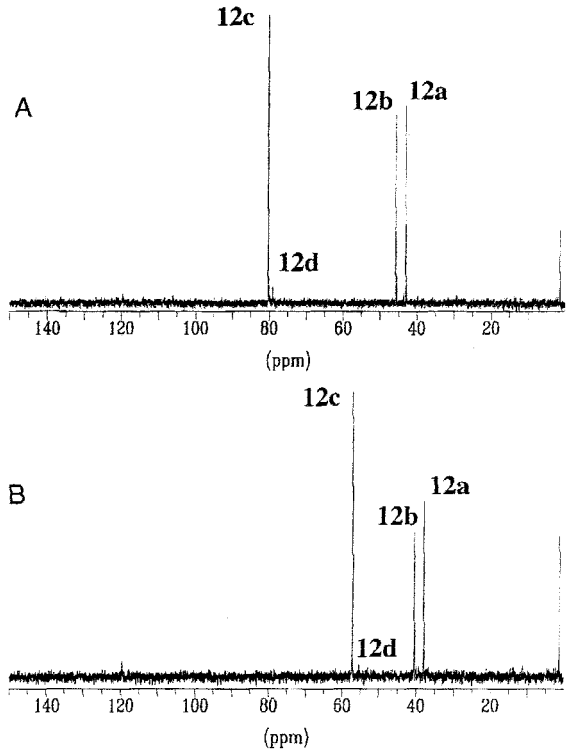


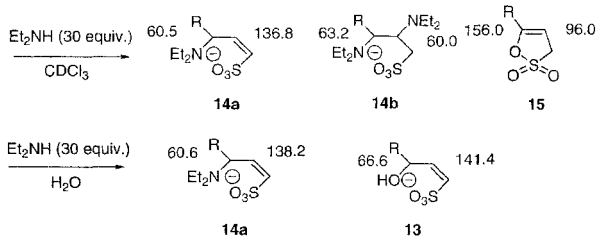
Figure 3. (A) ^{13}C NMR spectrum in water of *n*-butylamine adducts on **1a**. (B) ^{13}C NMR spectrum in water of *n*-butylamine adducts on **1b**.

Aziridines **12a** and **12b** were formed in a 1/1 ratio, and their cis and trans structure was assigned by comparison with other aziridine derivatives described in the literature (*21*).

In water, the reaction was much faster and found to be complete after 1 h. Only the two aziridines, **12a** and **12b**, were formed in a 1/1 mixture of cis and trans isomers, together with a new compound **13** resulting from hydrolysis of the starting sultone.

Mechanistic Interpretation of Aziridine Formation with Butylamine. In water, the reaction of **1a** and **1b** with butylamine was found to be rapid, and aziridines, **12a** and **12b**, were the only detected compounds. The problem of which mechanism is involved in the formation of these intermediates remains. Compounds **12a** and **12b** could conceivably arise either from a first Michael type addition followed by an intramolecular S_N reaction or from S_N reaction followed by an intramolecular Michael type addition on the intermediate α,β-unsaturated sulfonate. Instinctively, the first hypothesis would tend to be favored, but our data support the second. As seen using butylamine in $CDCl_3$, pure butylamine, or imidazole in water, Michael addition at position 2 of the sultones is very sensitive to steric hindrance, and anti addition, leading to the trans adduct, is highly favored. A subsequent intramolecular S_N reaction at position 3 would not change this ratio, and we should therefore obtain the trans aziridine **12b** as the major adduct. On the other hand, an S_N reaction at position 3 would lead to the formation of a racemic sulfonate intermediate with a freely rotating C2−C3 bond, allowing this 1/1 ratio to be maintained during the subsequent Michael cyclization. Moreover, the intramolecular aziridine formation seems to be very rapid, and a further argument in favor of an S_N reaction as the initial step is that no intermediate resulting from an S_N monoaddition was seen. In contrast, the Michael monoadducts observed in $CDCl_3$, or formed in pure butylamine and then observed in water, seemed to be rather stable for several days.

Scheme 5. Reaction of 1a and 1b with Diethylamine



Reaction of 1a and 1b with Diethylamine (Scheme 5). The same kind of experiment was carried out with 30 equiv of diethylamine as a model for secondary amines. As for *n*-butylamine, the reaction with **1a** and **1b** was found to be very slow in $CDCl_3$, most of the starting material still being present after 30 days, while that in water was rapid with no starting material left after 1 h. In $CDCl_3$, only one monoadduct (**14a**), resulting from an S_N reaction at position 3, was formed (the intermediate monoadduct is not able to react intramolecularly), but a second Michael type addition can occur on the intermediate sulfonate leading to the diadduct **14b**. A rearrangement product **15**, resulting from the abstraction of proton H-3 by diethylamine, was also seen.

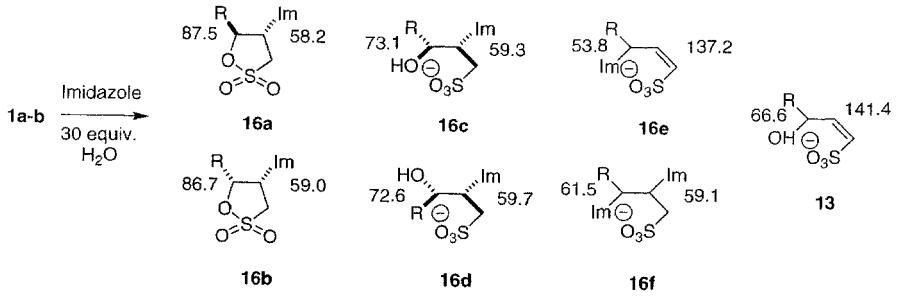
In water, only monoadduct **14a** was detected together with the hydrolysis compound **13**. Reaction with diethylamine confirmed our findings for butylamine with an S_N reaction being favored.

Reaction of 1a and 1b with Imidazole (Scheme 6). Imidazole was used as a simple model for histidine, which has been shown to be important in the induction of allergic contact dermatitis to certain haptens (*2*, *3*). As imidazole is much less reactive than *n*-butylamine or diethylamine, we decided to study its reactivity toward sultones in water. Even under these conditions, the reaction of labeled sultones **1a** and **1b** was much slower than with *n*-butylamine or diethylamine and some starting material was still present after 40 days. With imidazole, we observed the formation of monoadducts resulting both from Michael addition (**16a** and **16b**), the anti addition being favored, and from an S_N reaction (**16e**). The slow reaction also allowed the formation of several hydrolysis products: **13** resulting from the hydrolysis of the original sultone and a mixture of products **16c** and **16d** resulting from the hydrolysis of compounds **16a** and **16b**. The formation of a diadduct **16f** was also detected, although it is not known if it results from a second addition on intermediate **16a**, **16b**, or **16e**.

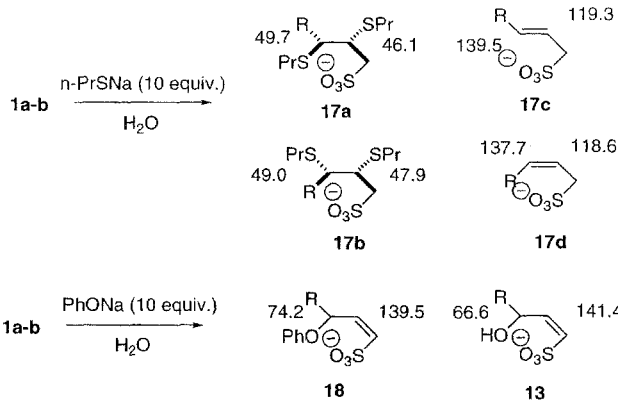
Thus, in contrast to the other two amines, with imidazole, Michael addition at position 2 predominated over S_N substitution at position 3.

Reaction of 1a and 1b with Propanethiol and Phenol (Scheme 7). Propanethiol, a model for cysteine, and phenol, a model for tyrosine, were found to be nonreactive toward alkenesultones **1a** and **1b** in water. Nevertheless, to obtain ^{13}C NMR reference values for further studies, we forced the reaction conditions using sodium salts of the thiol and phenol. Thus, the reaction of **1a** and **1b** with 10 equiv of sodium propanethiolate was rapid and led to the formation of diadducts **17a** and **17b**, but the major peaks were due to the elimination

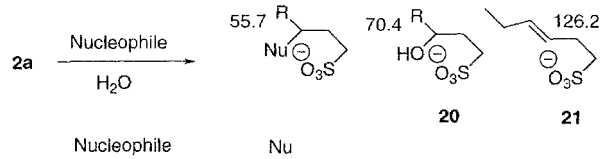
Scheme 6. Reaction of 1a and 1b with Imidazole



Scheme 7. Reaction of 1a and 1b with Propanethiol and Phenol



Scheme 8. Reaction of 2a with Model Nucleophiles



Nucleophile	Nu	
$BuNH_2$ (30 equiv.)	$BuNH^-$	**19**
Et_2NH (30 equiv.)	Et_2N^-	**22**
Imidazole (30 equiv.)	Im-	**23**
n-PrSNa (10 equiv.)	PrS-	**24**
PhONa (10 equiv.)	PhO^-	**25**

products **17c** and **17d**. The major product was the trans derivative **17c**, derived by cis dithio elimination of the intermediate diadduct **17a**. For mechanistic reasons, it therefore seems that the initial step is anti addition of propanethiolate at position 2, followed by an S_N substitution at position 3 which may possibly be assisted by the thio atom through the formation of an intermediate cyclic sulfonium.

The reaction of **1a** and **1b** with 10 equiv of sodium phenate was much slower and resulted in the formation of only one monoadduct (**18**) resulting from S_N substitution at position 3 and of the hydrolysis product **13**.

This difference in reactivity between thio and oxo nucleophiles is in agreement with the hard and soft acid and base (HSAB) theory (*22*), the thiolate being considered a "soft" nucleophile compared to the phenate.

Reaction of 2a with Model Nucleophiles (Scheme 8). Reaction of the labeled sultone **2a** with butylamine was followed using the previously described conditions. As opposed to sultones **1a** and **1b**, sultone **2a** was found to be nonreactive toward butylamine in chloroform even after 14 days. In water, the reaction was slow and the major product that was observed was the hydrolysis derivative **20** together with the monoadduct **19** resulting from an S_N reaction at position 3. A minor elimination product **21** was also detected in the reaction mixture. The structure of **21** was confirmed by the hydrolysis (H_2O, 100 °C) of sultone **2** which led to a mixture of cis and trans alcene, the trans isomer (J = 15.3 Hz) being the major one.

The reaction of sultone **2a** in water with ethylamine confirmed the low reactivity of this molecule toward amino groups with mainly the formation of the hydrolysis product **20**. The only adduct formed was **22**, resulting of an S_N reaction at position 3. Traces of **21** were also detected.

With imidazole, the low reactivity of sultone **2a** was confirmed. The reaction of **2a** in water led mainly to the formation of **20**, the hydrolysis product, together with **23**, an imidazole adduct at position 3.

Interestingly, the reaction of **2a** with propanethiolate was found to be faster than the hydrolysis reaction with the formation of a monoadduct **24** as the major reaction product.

The reaction of **2a** with sodium phenate was found to be competitive with the hydrolysis reaction. Thus, an almost equimolecular mixture of the monoadduct **25** and of the hydrolysis product **20** was formed.

Reactivity of Sultones. Electrophiles and nucleophiles can be regarded, respectively, as Lewis acids and bases, and their classification as hard or soft acids and bases can also be applied to their electrophilicity and nucleophilicity. Following the HSAB theory, if an electrophile is hard, its reactivity toward hard nucleophiles will be increased and its reactivity toward soft nucleophiles decreased. Conversely, if the electrophile is soft, its reactivity toward hard nucleophiles will be decreased and its reactivity toward soft nucleophiles increased. Hard electrophiles or nucleophiles react through low-energy vacant or occupied orbitals, respectively, and are less polarizable. Soft electrophiles and nucleophiles react through higher-energy orbitals and are more polarizable. Examples of hard nucleophiles are water, alkoxides, and primary and secondary amines, while examples of soft nucleophiles are thiol and thiolate anions, sulfides, or the thiosulfate anion.

On the basis of the above description, it seems clear that for sultone **1** the soft electrophilic center 2 (α,β-unsaturated system) should be more reactive toward S^- groups and the hard electrophilic center 3 (S_N center) more reactive toward RNH_2 and PhO^- groups. Interestingly, imidazole is border-line with a marked reactivity toward the soft electrophilic center 2, but still reacting with the hard electrophilic center 3.

Reactions with the alkanesultone are much simpler with only one reactive site, namely, position 3, which is able to react with nucleophiles through an S_N reaction.

Sultone **2** was found to have a very low reactivity toward amino groups even in water. In three cases (butylamine, diethylamine, and imidazole), the major product that was obtained was always the hydrolysis one resulting from a nucleophilic attack of water at position 3. The only significant addition reactions were observed with propanethiolate and sodium phenate which can significantly compete with the hydrolysis reaction.

The very potent skin sensitizing properties of alkyl-1-ene-1,3-sultones have been attributed to the presence of an electron-deficient double bond that allows the formation of protein adducts through Michael type nucleophilic additions (*8*). This explanation was mainly supported by the markedly lower sensitizing potential of saturated analogues of sultones.

The reactivity of sultones toward model nucleophiles does not support this hypothesis except in the case of histidine residues. If it seems obvious that introduction of a double bond increases the reactivity of sultone toward amino groups, the major reactive site remains position 3 and the major reaction a nucleophilic substitution. These results, obtained in water, but with model nucleophiles, need to be confirmed under more realistic conditions, i.e., with a large protein, such as human serum albumin.

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