Apical and Equatorial Methoxy Ligands on Sulfuranes: Effect on Rates of Pyridine Methylation

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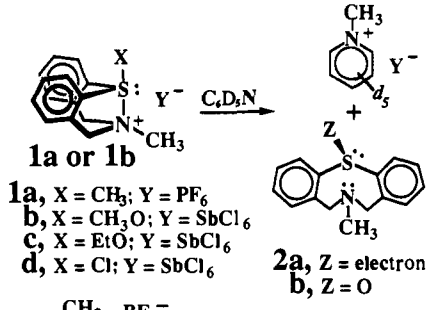
Abstract: The demethylation of a series of sulfur compounds by pyridine-d_5 is examined. Work done on the previously reported cationic 6,7-dihydro-*N*-methyl-5*H*-dibenzo[*b*,*g*][1,5]thiazocinium system **1a**, with an apical methyl group opposite to the other apical ammonium group, has been expanded to include the demethylation rate of the apical methoxy group on the cationic sulfur atom and the incorporation of ^{15}N into this series of compounds, **1a-d**, for ^{15}N NMR as well as ^{13}C NMR. The apical methoxy ligand of compound **1b** is demethylated faster in pyridine-d_5 ($k_{25°C}$, 4.54×10^{-5} s^{-1}) than is the apical methyl ligand of **1a** ($k_{25°C}$, 1.48×10^{-6} s^{-1}). The other compounds used, including the equatorial methyl ligand of sulfurane oxide **6**, the equatorial methoxy ligand of sulfurane **7**, and the 1-aryl-1-trifluoromethyl-2,2,2-trifluoroethyl methyl ether with a neighboring sultine group of **8**, are all demethylated in pyridine-d_5 with a wide range of methylation rates [$k_{25°C}$: **7**, 1.00×10^{-2} s^{-1}; **6**, 6.29×10^{-6} s^{-1}; **8**, 2.26×10^{-7} s^{-1}]. Compounds **6**, **7**, and **8** all react with pyridine to form *N*-methylpyridinium 4-(1,1-dimethylethyl)-6,8-dihydro-8-oxo-2,2,6,6-tetrakis(trifluoromethyl)-2*H*-[1,2]oxathiolo[4,3,2-*hi*][2,1]benzoxathiole (**10b**). The methoxysulfurane compounds have more negative ΔS^* values (**1b**, -18.5 eu; **7**, -19.7 eu) relative to the analogous methylsulfurane compounds (**1a**, -7.82 eu; **6**, -11.53 eu), but the ΔH^* values are much lower for **1b** (17.8 kcal/mol) and **7** (14.3 kcal/mol) than for **1a** (23.1 kcal/mol) and **6** (21.1 kcal/mol). These methoxy species are therefore more easily demethylated than the compounds with methyl groups coordinated to the sulfurane's sulfur. Sultine **8**, with the methoxide group coordinated to C rather than to S, methylates pyridine-d_5 at the slowest rate measured (ΔH^*, 18.5 kcal/mol; ΔS^*, -25.11 eu). Methoxysulfurane **7** methylates pyridine-d_5 much more quickly than all the other compounds. The hypervalent bonding is an important factor affecting the methylation reaction.

Introduction

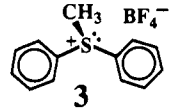
Earlier reports[1] described the reactions of methylsulfonium hexafluorophosphate with pyridine-d_5 showing the rate of demethylation of **1a** by pyridine-d_5 to be 1300 times slower than that for diphenylmethylsulfonium tetrafluoroborate (**3**). The decrease in rate is attributed to the cleavage of the N-S bond of the three-center four-electron (3c-4e) hypervalent bond of **1a**, as the S-CH_3 bond is cleaved forming **2a** with no hypervalent bond. Since both bonds of **1a** are broken, the transition-state



1a or 1b

1a, X = CH_3; Y = PF_6
b, X = CH_3O; Y = $SbCl_6$
c, X = EtO; Y = $SbCl_6$
d, X = Cl; Y = $SbCl_6$

2a, Z = electron pair
b, Z = O



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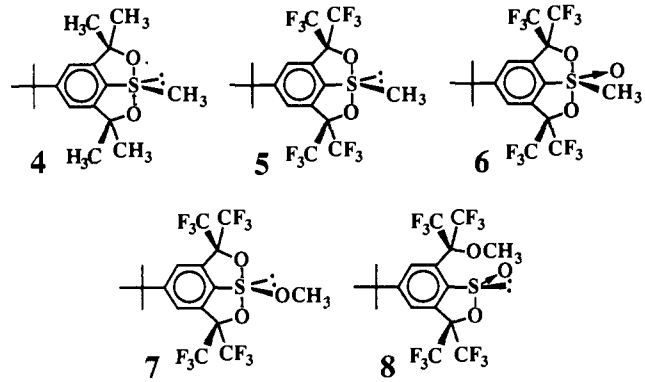
barrier is a higher one than for **3**, where only the S-CH_3 bond is broken in the attack by pyridine. The analogous species with an apical methoxy group (**1b**), an apical ethoxy group (**1c**), or an apical chlorine (**1d**) were prepared to study various reactions, including the methylation of pyridine by **1b**.

We also examined methylation by equatorial methyl groups on a sulfurane (**4** or **5**) or on a sulfurane oxide (**6**). We then prepared a sulfurane with an equatorial methoxy group on the sulfur (**7**), as well as a sulfurane with a methoxy group on the carbon adjacent to the sulfinate sulfur in **8**.

The formation and reaction of hypervalent molecules resulting from transannular interactions is a topical subject in high-coordinate species.[1] In the preceding papers, we reported the formation of a novel sulfurane, featuring an apical methyl group and an apical ammonium cation together with related sulfuranes.[1a] The structural features and ^1H and ^{13}C NMR chemical shifts for the ammonium methyl group varied with the electronegativity of the other apical group. Now we report further NMR spectral characteristics of the ^{15}N-enriched samples (**1a-d-^{15}N**). Nucleophilic methyl displacement reactions of **1b-d** and **4-8** are discussed.



4 **5** **6**

7 **8**

Experimental Section

All chemical shifts are reported as ppm downfield from tetramethylsilane (^1H and ^{13}C) or $CFCl_3$ (^{19}F), and the reported ^{15}N chemical shifts were measured by using aniline-^{15}N as the external reference (δ 56.5 ppm), evaluated from the $^{15}NH_3$ external standard. The ^1H, ^{15}N, ^{19}F, and ^{13}C NMR spectra were determined with a Hitachi R-90H at 300 MHz. All NMR spectra were taken in $CDCl_3$ unless otherwise noted. Elemental analysis values were within 0.4% of calculated values. The

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sulfoxide (**2**) and its derivatives (**1a–d**) were prepared by a previously described method.[1a] Methyldiphenylsulfonium hexachloroantimonate (**3**) was obtained by an ordinary method.[2] Ethyl ether was purified by distillation from sodium metal/benzophenone. Pyridine-d_5, CH_3OH, and CH_2Cl_2 were purified by distillation from CaH_2. Methyl triflate, from the Aldrich Chemical Co., was not purified. The syntheses of sulfurane oxide **6**,[3] the Et_4N^+ salt of sulfuranide oxide **10a**,[4] and 8-chloro-4-(1,1-dimethylethyl)-6,8-dihydro-2,2,6,6-tetrakis(trifluoromethyl)-2*H*-[1,2]-oxathiolo[4,3,2-*hi*][2,1]benzoxathiole (chlorosulfurane **11**)[5] have been previously reported. The kinetic runs at 25 °C for **6** and **8** were performed in a Polyscience Series 9500 refrigerated constant temperature circulator.

^{15}N-Labeled 6,7-Dihydro-6-methyl-5*H*-dibenzo[*b*,*g*][1,5]thiazocine 12-Oxide (2-^{15}N). To a suspension of bis[*o*-(bromomethyl)phenyl] sulfoxide (1.19 g, 3.06 mmol) and ^{15}N-labeled methylamine hydrochloride[2] (190 mg, 2.79 mmol) in $CHCl_3$ (40 mL) was added dropwise 1.4 mL (10 mmol) of Et_3N at room temperature.[1a,6a] The mixture was heated at reflux for 4 h. The mixture was washed with H_2O and a 10% K_2CO_3 solution prior to drying and evaporation. Purification to a colorless solid was achieved by column chromatography on silica gel (elution with ethyl acetate *n*-hexane 7:3 and ethyl acetate). Recrystallization of the solid from benzene/hexane gave 500 mg (70%) of **2** as a pure sample: mp 135–136 °C; ^1H NMR ($CDCl_3$) δ 2.57 (s, 3 H), 3.89 (s, 4 H), 7.0–7.5 (m, 6 H), 8.0–8.3 (m, 2 H); ^{13}C NMR (CD_3CN) δ 41.6 (d, $^1J_{CN}$ = 7.7 Hz), 58.4 (d, $^1J_{CN}$ = 6.8 Hz), 124.8, 126.9 (d, $^2J_{CN}$ = 1.9 Hz), 129.4, 130.2, 140.0 (d, $^3J_{CN}$ = 2.9 Hz), 145.3; ^{15}N NMR (CD_3CN) δ 35 ppm; mass spectrum, *m/e* 258 (M^+).

^{15}N-Labeled 6,7-Dihydro-6,12-dimethyl-5*H*-dibenzo[*b*,*g*][1,5]thiazocinium Hexafluorophosphate (1a-^{15}N). The ^{15}N-labeled sample (1a-^{15}N) was prepared by the method described above.[1a] **1a-^{15}N**: mp 195–197 °C (from acetonitrile/ether); ^1H NMR (CD_3CN) δ 2.53 (s, 3 H), 3.31 (s, 3 H), 4.06 (s, 4 H), 7.4–7.9 (m, 8 H); ^{13}C NMR (CD_3CN) δ 23.7 (d, $^2J_{CN}$ = 4.8 Hz), 40.0 (d, $^1J_{CN}$ = 8.7 Hz), 56.5 (d, $^1J_{CN}$ = 7.7 Hz), 126.8 (d, $^2J_{CN}$ = 1.9 Hz), 127.9, 130.2, 130.8, 133.4, 141.0 (d, $^3J_{CN}$ = 1.9 Hz); ^{15}N NMR (CD_3CN) δ 34 ppm.

^{15}N-Labeled 12-Chloro-6,7-dihydro-6-methyl-5*H*-dibenzo[*b*,*g*][1,5]-thiazocinium Hexachloroantimonate (1d-^{15}N). By the predescribed method,[1a] **1d-^{15}N** was obtained from **2-^{15}N**: mp 170–173 °C; ^1H NMR (CD_3CN) δ 3.12 (s, 3 H), 4.63 (s, 4 H), 7.4–7.8 (m, 6 H), 8.4–8.6 (m, 2 H); ^{13}C NMR (CD_3CN) δ 44.4 (d, $^1J_{CN}$ = 5.8 Hz), 60.4 (d, $^1J_{CN}$ = 4.8 Hz), 128.0, 131.1, 131.8, 132.1, 134.8, 138.0; ^{15}N NMR (CD_3CN) δ 103 ppm.

^{15}N-Labeled 6,7-Dihydro-12-methoxy-6-methyl-5*H*-dibenzo[*b*,*g*]-[1,5]thiazocinium Hexachloroantimonate (1b-^{15}N). To a sample of **1d-^{15}N** (200 mg, 0.32 mmol) was added 5 mL of dry methanol dropwise at 0 °C. The solution was then stirred at room temperature for 30 min before removal of solvent. The residual material was recrystallized from acetonitrile and ether to furnish 96 mg (50%) of **1b-^{15}N**: mp 146–149 °C; ^1H NMR (CD_3CN) δ 2.76 (s, 3 H), 3.92 (s, 3 H), 4.25 (s, 4 H), 7.3–7.8 (m, 6 H), 7.9–8.1 (m, 2 H); ^{13}C NMR (CD_3CN) δ 41.6 (d, $^1J_{CN}$ = 6.8 Hz), 57.4 (d, $^1J_{CN}$ = 5.8 Hz), 57.9, 128.2, 128.5, 130.8 (d, $^2J_{CN}$ = 2.9 Hz), 131.4, 133.6, 138.1 (d, $^3J_{CN}$ = 1.9 Hz); ^{15}N NMR (CD_3CN) δ 69 ppm.

^{15}N-Labeled 12-Ethoxy-6,7-dihydro-6-methyl-5*H*-dibenzo[*b*,*g*][1,5]-thiazocinium Hexachloroantimonate (1c-^{15}N). A sample of **1d-^{15}N** (104 mg, 0.17 mmol) was treated with 2.5 mL of dry ethanol at 50 °C for 30 min prior to evaporation. The residue was recrystallized from acetonitrile and ether to afford **1c-^{15}N** as a pure sample: mp 167–169 °C; ^1H NMR (CD_3CN) δ 1.49 (t, *J* = 7.0 Hz, 3 H), 2.75 (s, 3 H), 4.23 (s, 4 H), 4.23 (q, *J* = 7.0 Hz, 2 H), 7.3–7.8 (m, 6 H), 8.0–8.2 (m, 2 H); ^{13}C NMR (CD_3CN) δ 15.9, 41.2 (d, $^1J_{CN}$ = 6.8 Hz), 57.3 (d, $^1J_{CN}$ = 5.8 Hz), 67.9, 128.3 (×2), 131.3 (×2), 133.5, 138.0 (d, $^3J_{CN}$ = 1.9 Hz); ^{15}N NMR (CD_3CN) δ 66 ppm.

Kinetic Measurements on Transmethylation. General Procedure. A sample of **1b** (3.2 mg, 0.0054 mmol), with Me_4Si (TMS) in pyridine-d_5 (0.3 mL) in a 5-mm NMR tube, was placed at the NMR instrument probe (±0.3 °C). The ^1H NMR spectra of the *N*-methyl (δ 2.77) and TMS were used to calculate the percent composition. The values of the pseudo-first-order rate constant, k_{obsd}, for the transmethylation were calculated by using the method of least squares for ca. 3 half-lives to determine the apparent values of ΔH^* and ΔS^*. The results are summarized in Table I.

Product Analysis of Transmethylation. A solution of **1b** (15 mg, 0.025 mmol) in 0.5 mL of pyridine-d_5 was heated at 50 °C for 60 h. The characteristic signals for **2** and *N*-methylpyridinium-d_5 salt were observed in the ^1H NMR spectrum. The solution was concentrated under reduced pressure, and the resulting suspension was subjected to preparative thin-layer chromatography on silica gel (elution with ethyl acetate). Sulfoxide **2** (5.2 mg, 85%) was isolated.

Methoxy-Exchange Reaction of 1b. A solution of **1b** (2.9 mg, 0.0049 mmol) in methanol-d_4 (2 mL) in a 5-mm NMR tube was immersed in a constant temperature bath maintained at 50.0 °C (±0.01 °C). After a measured time, the tube was removed from the bath and immediately cooled in an ice water bath. At each time interval, the ^1H NMR spectrum of the methyl region was recorded, and the relative integrated area of the peaks (MeO of **1b** and *N*-Me of **1b** and **2**) was used to calculate the percent composition of the starting material (**1b**) to the total concentration (**1b** and **2**). Values of the pseudo-first-order rate constant k_{obsd}, for the methoxy-exchange reaction were calculated by using the method of least squares. The value of k_{obsd} at 50 °C was 3.12×10^{-5} s^{-1} (r = 0.996); half-life, ca. 6 h. ^1H NMR spectrum of **1b-CD_3**: (CD_3OD) δ 2.82 (s, 3 H), 4.33 (s, 4 H), 7.4–7.8 (m, 6 H), 8.0–8.2 (m, 2 H).

Synthesis of 3,3-Bis(trifluoromethyl)-5-(1,1-dimethylethyl)-7-(1-methoxy-1-(trifluoromethyl)-2,2,2-trifluoroethyl)-3*H*-[2,1]benzoxathiole 1-Oxide (Sultine 8). To the Et_4N^+ salt of sulfuranide oxide **10a**[4] (200 mg, 0.312 mmol) in 4 mL of CH_2Cl_2 was added methyl triflate (0.256 g, 0.176 mL, 1.56 mmol) by microsyringe and stirred for 12 h. The solvent and excess methyl triflate were then removed in vacuo. The sample was redissolved in Et_2O and washed with 10% aqueous NaOH. The organic layer was separated and dried ($MgSO_4$). After filtration the sultine was recrystallized from Et_2O/hexane, giving a white crystalline solid, 156 mg (0.296 mmol, 95%) of **8**: mp 115–116 °C; ^1H NMR δ 7.93 (br, s, 1 H, ArH), 7.82 (br s, 1 H, ArH), 4.37 (br m, OCH_3, 11%) and 3.97 (br s, OCH_3, 89%) combined area for the last two peaks = 3 H, 1.37 (s, 9 H, *t*-Bu); ^{19}F NMR δ −68.44 (m, 1, CF_3), −71.12 (q, 0.11, CF_3, J_{FF} = 8.07 Hz), −71.33 (q, 0.89, CF_3, J_{FF} = 8.36 Hz), −74.66 (m, 1, CF_3), −76.11 (m, 1, CF_3). Anal. ($C_{17}H_{14}F_{12}O_3S$) C, H.

Synthesis of 4-(1,1-Dimethylethyl)-6,8-dihydro-8-methoxy-2,2,6,6-tetrakis(trifluoromethyl)-2*H*-[1,2]oxathiolo[4,3,2-*hi*][2,1]benzoxathiole (Methoxysulfurane 7). Chlorosulfurane **11**[5] (1.09 g, 2.05 mmol) in CH_3OH over dry Na_2CO_3 that had been heated to 110 °C at 0.05 Torr for 36 h was then stirred for 30 min and excess CH_3OH was removed under vacuum. The methoxysulfurane was dissolved in Et_2O, filtered, and then recrystallized from Et_2O/hexane, yielding 930 mg (1.77 mmol. 86%) of **7** as a white solid: mp 122–123 °C; ^1H NMR δ 7.94 (s, 2 H, ArH), 4.06 (s, 3 H, OCH_3), 1.43 (s, 9 H, *t*-Bu); ^{19}F NMR δ −75.45 (q, 6 F, J_{FF} = 9.21 Hz), −76.12 (q, 6 F, J_{FF} = 9.21 Hz). Anal. ($C_{17}H_{14}F_{12}O_3S$) C, H.

General Procedure for Demethylation of 6, 7, and 8. Samples of **6** and **7** were dissolved in dry pyridine-d_5 at room temperature, and **8** was dissolved in dry pyridine-d_5 cooled in a CCl_4/N_2 bath (−23 °C). The sample was then added to a heated (or cooled for **8**) NMR probe. Upon temperature equilibration, the rate of demethylation for a particular sample at a given temperature was measured.

Thermal Rearrangement of 7 and 10. Samples of **6** and **7** were added to separate NMR tubes. The tubes were then placed in an oil bath at 210 °C for 30 min. ^1H and ^{19}F NMR spectroscopy (in $CDCl_3$) showed the formation of sultine **8**. Removal of solvent and continued heating at 210 °C for 2 h gave **8** in quantitative yield. The identity of **8** was confirmed by an authentic sample.

Results

The sulfuranes (**1a–d**) and their ^{15}N-enriched samples (**1a–d-^{15}N**) were prepared[1a] by way of sulfoxides (**2** and **2-^{15}N**). Methylamine enriched with ^{15}N was prepared from ammonium sulfate-^{15}N by a known procedure.[2] The ^1H NMR data of **1a–d-^{15}N** are almost the same as those of **1a–d**. The ^{13}C NMR spectral data of **1a–d-^{15}N** and **2-^{15}N** are summarized in Table I. The ^{15}N NMR spectra of **1a–d-^{15}N** and **2-^{15}N** in CD_3CN solution displayed singlet signals at δ 34, 69, 66, 103, and 35 ppm from a $^{15}NH_3$ external standard for ^{15}N-enriched **1a**, **1b**, **1c**, **1d**, and **2**, respectively. As might be expected on the basis of increased positive charge around the nitrogen atom due to substitution for electron-withdrawing groups at the apical position of the sulfur

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Table I. ^{13}C and ^{15}N NMR Spectral Data of **1a–d-^{15}N** and **2-^{15}N** in CD_3CN

	^{13}C NMR (δ, ppm)[a]	^{15}N NMR (δ, ppm)[b]
1a-^{15}N	23.7 (d, J = 4.8 Hz), 40.0 (d, J = 8.7 Hz), 56.5 (d, J = 7.7 Hz), 126.8 (d, J = 1.9 Hz), 127.9, 130.2, 130.8, 133.4, 141.0 (d, J = 1.9 Hz)	34
1b-^{15}N	41.6 (d, J = 6.8 Hz), 57.4 (d, J = 5.8 Hz), 57.9, 128.2, 128.5, 130.8 (d, J = 2.9 Hz), 131.4, 133.6, 138.1 (d, J = 1.9 Hz)	69
1c-^{15}N	15.9, 41.2 (d, J = 6.8 Hz), 57.3 (d, J = 5.8 Hz), 67.9, 128.3 (×2), 131.3 (×2), 133.5, 138.0 (d, J = 1.9 Hz)	66
1d-^{15}N	44.37 (d, J = 5.8 Hz), 60.4 (d, J = 4.8 Hz), 128.0, 131.1, 131.8, 132.1, 134.8, 138.0	103
2-^{15}N	41.6 (d, J = 7.7 Hz), 58.4 (d, J = 6.8 Hz), 124.8, 126.9 (d, J = 1.9 Hz), 129.4, 130.2, 140.0 (d, J = 2.9 Hz), 145.3	35

[a] The chemical shifts were referenced relative to TMS as an internal standard in ppm. [b] The chemical shifts were measured by using aniline-^{15}N as an external reference (δ 56.5 ppm) and were evaluated from a $^{15}NH_3$ external standard.

atom, increasing electronegativity of the apical group (Me, EtO, MeO, and Cl: σ_m = −0.07, 0.1, 0.12, and 0.37) in **1a–d** is accompanied by ^{15}N deshielding. Examination of ^{15}N NMR chemical shifts of **1a–e-^{15}N** revealed the existence of an excellent linear relationship of the signals, $\delta_N(^{15}N)$, against Hammett's substituent constants of the apical groups: $\delta_N(^{15}N) = 154.7\sigma_m + 47.9$, r = 0.994, n = 4. The corresponding signal for **2** was calculated to be δ 29 on the basis of the linear relationship by using $\sigma_I(O^-) = -0.12$.[3] In the ^{13}C NMR spectrum of **1a**, the *S*-methyl carbon is seen as a doublet ($^2J_{CN}$ = 4.8 Hz) with a chemical shift of δ 23.7, while the ipso carbon appears as a doublet ($^2J_{CN}$ = 1.9 Hz) at δ 126.8. The existence of a N–S bond in solution is supported by the observation of substantial N–S–CH_3 coupling $^2J_{CN}$, even in the weak transannular interaction in **1a** (N–S distance: 2.466 Å in the solid state).[1a] Furthermore, the decrease of the $^1J_{CN}$ coupling constant ($^1J_{CN}$ = 5.8 Hz) of the amino methyl group of **1d** relative to those ($^1J_{CN}$ = 8.7 and 7.7 Hz) of **1a** and **2** suggests the changing of hybridization of the nitrogen atom to a more pyramidal structure compared with the counterparts of **2** and **1a**.[7]

Although the physical data (NMR spectra and X-ray crystallographic analysis) of **1a** indicated a very weak transannular interaction relative to the other sulfuranes (**1b–d**), the chemical behavior of **1a** definitely confirmed the presence of considerable attractive interaction between the sulfur and nitrogen atoms in solution on the basis of the deceleration in transmethylation of **1a** to pyridine-d_5. In fact, the rate constant of methyl transfer from the sulfur of **1a** to pyridine at 25 °C was 1300 times slower than the analogous reaction of the methyldiphenylsulfonium salt.[1] Reaction of **1b** with pyridine-d_5 afforded the sulfoxide **2** along with methylpyridinium-d_5 salt in a spectroscopically quantitative yield. Reaction of **1c** under the same conditions proceeded more slowly to give **2** together with ethanol generated by hydrolysis from a trace of water in pyridine-d_5. Rate determinations for the reaction were carried out by ^1H NMR in pyridine-d_5 solution at various temperatures under pseudo-first-order conditions in which the nucleophile was present in ca. 50 times excess of the solvent, as described previously.[1] The transmethylation (S_N2) was found to follow first-order kinetics nicely for more than 3 half-lives in all cases. Pseudo-first-order rate constants (k_{obsd}) at different temperatures and one extrapolated for 25 °C are collected in Table II. Attempts to determine the rate of the methylation reaction of methoxydiphenylsulfonium hexachloroantimonate [$(Ph_2SOCH_3)^+(SbCl_6)^-$] were very difficult due to the high reactivity even at low temperature (−20 °C).

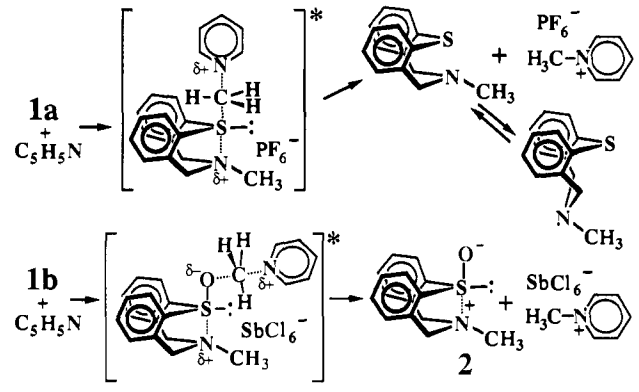
The low reactivity of **1b**, revealed by comparison with **3**, was attributed mainly to the ground-state stabilization due to the N–S attractive interaction or electron transfer from the nitrogen to the sulfonio moiety. This fact notwithstanding, the observed deceleration effect in **1b** was not as large as the value (1/1300) expected from the case of **1a**. This may be ascribed in part to the reason why N–S attractive interaction remains considerable, even at the transition state of the methyl transfer reaction that shows the greater stability of the sulfoxide **2** compared to the corresponding sulfide (Scheme I).

Table II. Rates for Transmethylation of Solvent Pyridine-d_5 by the Sulfuranes

compd	T (K)[a]	k_{obsd} (s^{-1})	corr coeff	ΔH^* (kcal/mol)	ΔS^* (eu)
1b	324.9	6.04×10^{-4}	0.997		
	319.1	3.23×10^{-4}	0.995		
	312.9	1.95×10^{-4}	0.995	17.8 ± 0.3	−18.5 ± 1.1
	304.4	8.49×10^{-5}	0.999		
	304.1	8.28×10^{-5}	0.999		
	298.2[b]	4.54×10^{-5}			
5	375.0	1.12×10^{-3}	0.999		
	358.0	2.98×10^{-4}	0.998	18.5 ± 1.8	−23.26 ± 0.8
	343.0	9.92×10^{-5}	0.997		
	298.2[b]	1.45×10^{-6}			
6	353.0	1.78×10^{-3}	0.992		
	339.0	7.74×10^{-4}	0.993	21.1 ± 0.7	−11.3 ± 0.7
	298.2[c]	6.29×10^{-6}	0.999		
7	284.0	2.99×10^{-3}	0.991		
	273.0	1.00×10^{-3}	0.997	14.3 ± 0.8	−19.7 ± 0.2
	251.0	9.48×10^{-5}	0.991		
	298.2[b]	1.00×10^{-2}			
8	375.0	1.44×10^{-4}	0.994		
	345.0	4.29×10^{-5}	0.998	18.5 ± 1.7	−25.1 ± 1.9
	298.2[c]	2.26×10^{-7}	0.974		

[a] Measured at the probe of the NMR (±0.3 °C). [b] Values were calculated from the higher temperature of measured activation parameters to provide rates at room temperature (~25 °C). [c] These rates were measured at 298.2 K rather than by the calculation done in *b*.

Scheme I

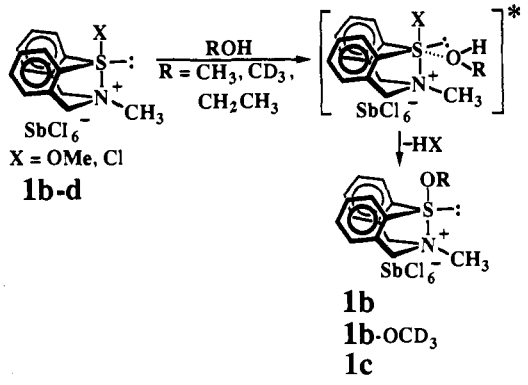


On the other hand, methanolysis of the chlorosulfurane (**1d**) in CD_3CN/MeOH solution at 0 °C immediately gave rise to the methoxysulfurane (**1b**), quantitatively. Ethanolysis of **1d** under the same conditions afforded the ethoxysulfurane (**1c**) in high yield. The methoxy-exchange reaction of **1b** in CD_3OD solution proceeded very slowly even at 50 °C (half-life of ca. 50 h) to give the deuterated methoxysulfurane (**1b**-OCD_3).

With respect to the nucleophilic displacement at the sulfur in the ammoniosulfuranes (**1b,d**), at least three types of mechanisms can be visualized. First, we can assume that the mechanism involved initial scission of the N^+–S bond in the sulfuranes to generate the corresponding sulfonium salts. This explanation can be easily ruled out since the fission in **1d** would be much more difficult than in **1b** because of the electron-withdrawing effect of the chloro group relative to the methoxy group. Secondly, we can assume that the mechanism might involve initial loss of the chloride ion in **1d** to generate a dication in a dissociative manner. This dissociative mechanism does not account for the fact that **1d** remains intact in acetic acid, trifluoroethanol, and trifluoroacetic

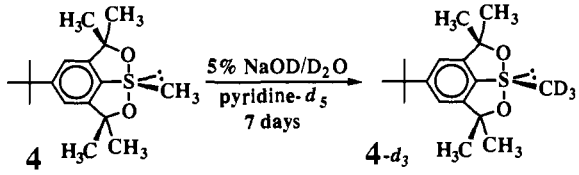
(7) Binsch, G.; Lambert, J. B.; Roberts, B. W.; Roberts, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 5564.

Scheme II

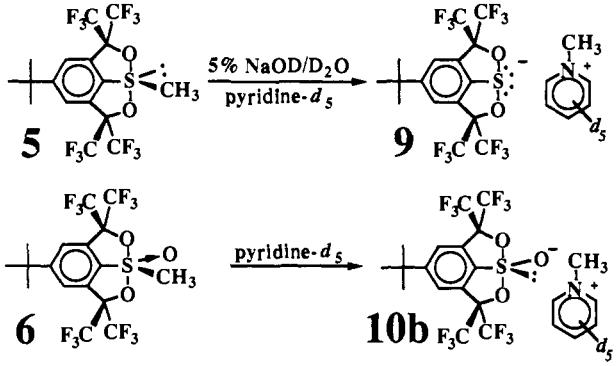


acid solutions, although the nucleophilicity of the acetate anion (n_{CH_3I}: 4.3) is comparable to that of the chloride anion (n_{CH_3I}: 4.37).[6] Furthermore, the methoxy exchange reaction can not be explained in terms of the dissociative mechanism due to the poor leaving ability of the methoxy group. The third possibility is associative nucleophilic displacement at the sulfur, proceeding through an octahedral sulfur transition state as proposed.[4] The nucleophilic displacements at the sulfur in **1b** and **1d** can be reasonably understood in terms of the associative mechanism (Scheme II).

At about the same time, a study was underway to compare the deuteration rates of **4** and **5**.[2,3] Sulfurane **4** had been shown by Lau[8] to undergo complete deuteration of the *S*-methyl group in pyridine-d_5 (~0.5 mL) with added 5% NaOD/D_2O (~50 μL, ~10 mg of **4**) over 7 days at room temperature with no methylation of the pyridine. Attempts to measure the deuterium



exchange rate for the CF_3-substituted **5** under the same conditions revealed the unexpected demethylation by pyridine-d_5 to form *N*-methylpyridinium-d_5 sulfuranide **9**. Further work showed sulfurane oxide **6** also to be demethylated by pyridine-d_5 to form sulfuranide oxide **10**.

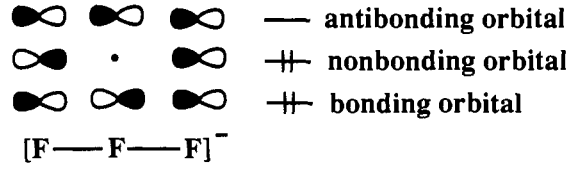


The methylation of the tetraethylammonium salt of sulfuranide oxide **10a** by methyl trifluoromethanesulfonate (methyl triflate, MeOTf) gave a high yield of sultine **8**.[7] With the formation of methoxysulfurane **7**, we examined the rates of demethylation of **6**, **7**, and **8** by pyridine-d_5 (Table II).

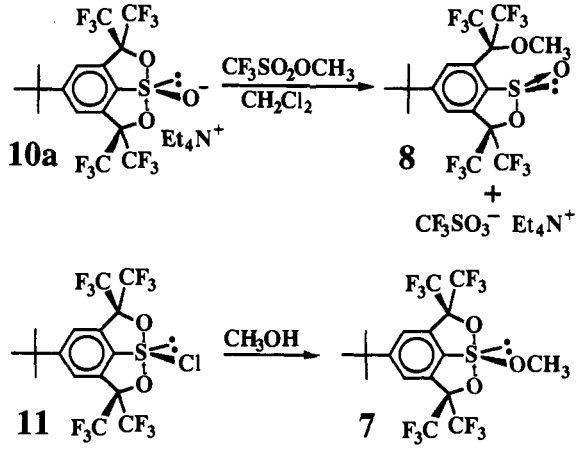
The subsequent determination of the rate of demethylation of the apical methoxy ligand of **1b** by pyridine-d_5 has further expanded the scope of this comparison.[6] The changes in rates of demethylation occurring at different positions around the central

(8) Lau, P. H. W.; Martin, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 5440.

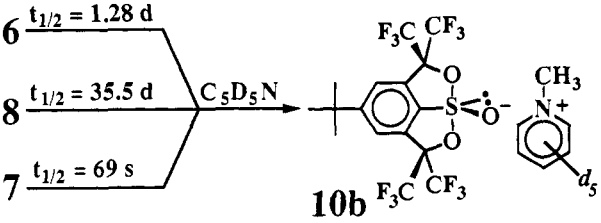
Scheme III. The Approximate Molecular Orbital Diagram for the Hypervalent Bond of F_3^-



sulfur atoms of these various geometries will later be presented and discussed.



Sultine **8** is rapidly formed by methyl triflate, and more slowly by methyl iodide, by methylations of sulfuranide oxide **10a**. Methoxysulfurane **7** is generated quickly by the reaction of CH_3OH with chlorosulfurane **11**.



Pyridine is methylated by methylsulfurane **5**, methylsulfurane oxide **6**, benzylmethoxy *o*-sultine **8**, and equatorial methoxysulfurane **7**. Compounds **6**, **7**, and **8** yield only *N*-methylpyridinium sulfuranide oxide **10b** in each case. Heating (>30 min at 210 °C) of either methylsulfurane oxide **6** or methoxysulfurane **7** provides rearrangements to sultine **8**.

Methoxysulfurane **1b** is demethylated by pyridine-d_5 to form sulfoxide **2b** at a rate 30.7 times faster than **1a** at 25 °C. Attempts to measure the rate of reaction of diphenylmethoxysulfonium hexachloroantimonate ($Ph_2S^+OCH_3$ $SbCl_6^-$) were not successful due to its high reactivity with pyridine-d_5 even at low temperature (−20 °C).

Discussion

Demethylation Rates of Isomers 6, 7, and 8. The isomeric compounds **6**, **7**, and **8** exhibit a surprisingly wide range of rates, although each forms the same product, methylpyridinium sulfuranide oxide (**10b**). To understand this wide range of rates it is essential to first understand the electronic features of a 3-center 4-electron (3c–4e) bond.

Calculations[9] have shown that the two apical fluorines of the 10-F-2[10] species, F_3^-, develop a total negative charge of −1.03, more than the negative charge (−1.00) on the same two atoms of the precursor species (F_2 and F^-). A slight positive charge (+0.03) develops on the central fluorine atom. Replacing fluorines

(9) (a) Cahill, P. A.; Dykstra, C. E.; Martin, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 6359. (b) Musher, J. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 54.

(10) An *N*-X-*L* system formally involves *N* electrons in bonding *L* ligands to atom X. Perkins, C. W.; Martin, J. C.; Arduengo, A. J., III; Lau, P. H.; Alegria, A.; Kochi, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 7753.

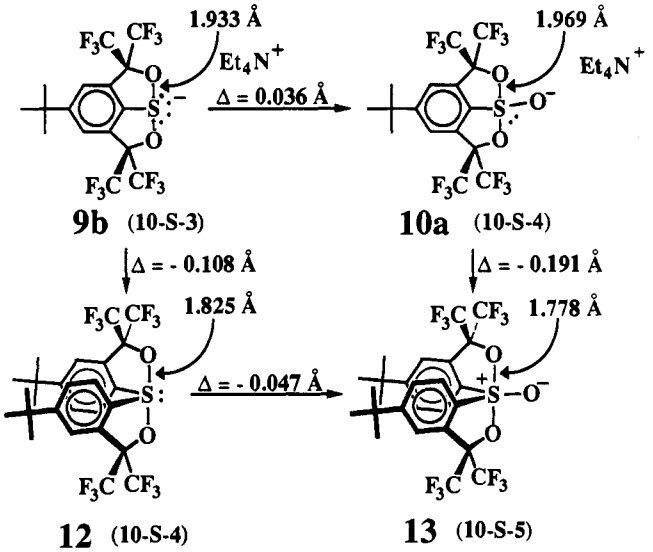
Table III. Rates for Methylation of Pyridine-d_5 by Sulfurane Species with OCH_3 or SCH Groups

compd	ΔH^* (kcal/mol)	ΔS^* (eu)	k (s^{-1}) at 298.2 K	rates relative to 8	rates relative to 1a
1a[a]	23.1	−7.82	1.38×10^{-6}	6.11	1
			1.58×10^{-6}	6.99	
1b	17.8	−18.5	4.54×10^{-5}	201	30.7
3	18.1	−10.3	1.90×10^{-3}	8.41×10^{3}	1.28×10^{3}
5[b]	18.5	−23.2	1.45×10^{-6}	6.42	0.98
8[b]	18.5	−25.1	2.26×10^{-7}	1	0.15
6[b]	21.1	−11.3	6.29×10^{-6}	27.8	4.25
7	14.3	−19.7	1.00×10^{-2}	4.42×10^{4}	6.76×10^{3}

[a] Reference 1a. [b] Reference 14.

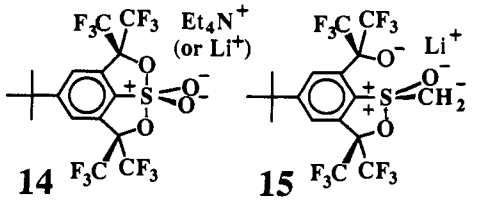
with an electropositive central atom and maintaining very electronegative apical ligands would stabilize the 3c–4e hypervalent bond (Scheme III).

Since the final product for the demethylation of **6**, **7**, and **8** is sulfuranide oxide **10b**, it is useful to compare the relative energy differences between **6**, **7**, **and 8**. Each demethylation transition state has the electropositive carbon as the central atom in the 3c–4e bond, making the S_N2 transition state lower in energy. One of the apical ligands is the nitrogen in the pyridine-d_5 ring. The

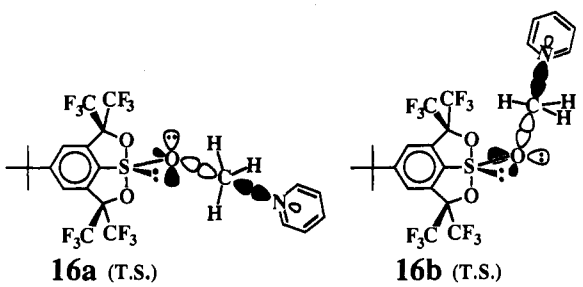


nitrogen is developing a positive charge during the transition state, which increases the apicophilicity of the nitrogen. The sulfur at the other apical position is also one with positive charge since it is the central atom of the O–S–O 3c–4e bond.

It has been shown that there is significant interaction between the two-electron p orbital on the equatorial oxygen parallel to the O–S–O antibonding hypervalent bond of anion **10a** or **10b**.[4,11] The lengthening of the apical S–O bond of sulfuranide oxide **10a** relative to **9b** (+0.036 Å)[4] is opposite to the bond length differences seen when one compares sulfurane oxide **13** to sulfurane **12**[11] (−0.047 Å). The apical O–S–O bond length decreases when sulfurane **12** is oxidized to sulfurane oxide **13**,[11] putting more positive charge on the sulfur. One electron pair of the p orbital of the equatorial oxygen of anion **10a** is parallel to the O–S–O hypervalent bond and lengthens the 3c–4e O–S–O bond by partial donation of this electron pair to the antibonding orbital of the O–S–O bond, weakening the apical S–O bonds.



Sulfuranide dioxide **14** is a symmetrical species as suggested by low-temperature ^{19}F NMR (−90 °C) and by its X-ray crystallographic structure.[4] Removal of a proton from the equatorial CH_3 of **6** to form the CH_2^- group of **15** replaces one of the equatorial oxygens of **14** to form the unsymmetrical species, **15**.[3] The filled p orbital of the CH_2^- carbon is higher in energy than a filled p orbital of an equatorial oxygen. The greater electron donation of the filled p orbital of the CH_2^- group, relative to the equatorial oxygen p orbital, to the empty antibonding orbital of the O–S–O bond explains the reason for the unsymmetrical geometry of **15**. Lower electron donation from the two equatorial O^- groups of sulfuranide dioxide **14** maintains symmetrical O–S–O bonds but causes the apical O–S bonds to be longer, by 0.036 Å, than for sulfuranide **9**.



Methoxysulfurane **7** is found to have lower energy toward the transition state for a demethylation reaction, much faster than demethylation of **6** or **8** (Table II). Transition state **16a** has two electrons in the equatorial oxygen's p orbital parallel to the apical O–S–O 3c–4e bond. This geometry allows more electron donation from the filled p orbital on the oxygen to the antibonding orbital of the O–S–O hypervalent bond than is thought for the geometry of **16b**. In the transition state for **16b**, the pair of electrons that could interact with the antibonding O–S–O orbital is not as parallel to the O–S–O bond as is **16a**, probably making **16b** a slower geometry. The electron donation from oxygen to the O–S–O bond of **16a** causes the equatorial oxygen to be more electronegative, making it a better second apical ligand in the O–C–N 3c–4e bond drawn as the transition state for the demethylation reaction of **16a**. The negative charge developing on the equatorial oxygen in the transition state provides electron donation to the O–S–O bond, as observed in sulfuranide oxide **10**. While transition state **16b** shows the O–CH_3 bond to be in the plane of the O–S–O hypervalent bond, the developing negative charge on the equatorial oxygen can be delocalized in the 3c–4e O–S–O bond, but perhaps not as much as in **16a**.

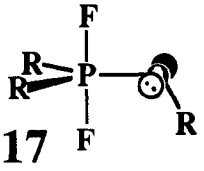
It was earlier suggested[12] that the equatorial oxygen electron pair attached to the sulfur would make a geometry like that of **16b** lower in energy than the twisted geometry of **16a**. The preferred geometry of the 10-P-5 species is that in which an equatorial substituent with a pair of electrons in a p orbital is found to have the filled p orbital perpendicular to the hypervalent 3c–4e bond, as in **17**.[13] Sulfurane **16b** has the two repulsive electron pairs on the sulfur and the oxygen of **16b**, making it easier to have

(11) Perozzi, E. F.; Martin, J. C.; Paul, I. C. *J. Am. Chem. Soc.* **1974**, *96*, 6735.

(12) Chen, M. M. L.; Hoffmann, R. *J. Am. Chem. Soc.* **1976**, *98*, 1647.

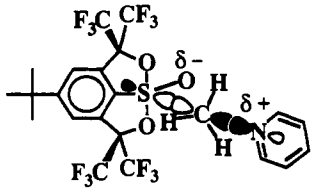
(13) (a) Peake, S. C.; Schmutzler, R. *J. Chem .Soc. A* **1970**, 1049. (b) Hoffmann, R.; Howell, J. M.; Muetterties, E. L. *J. Am. Chem. Soc.* **1972**, *94*, 3047.

the **16b** geometry with the two electron pairs twisted to 90°, with both providing some electron donation to the O–S–O or O–C–N antibonding orbitals.

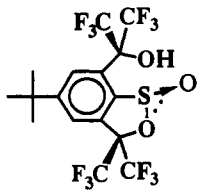


17

Methylsulfurane oxide **6** has the methyl group on sulfur rather than on the oxgyen as in methoxysulfurane **7**, but the 10-S-5 species **6** is demethylated at a much slower rate than its 10-S-4 isomer, **7**. The transition state (**18**) for attack of **6** by pyridine shows the equatorial oxygen donating electrons to the O–S–O antibonding orbital. Although the sulfur of **6** is partially positively charged as are all the sulfurs of sulfuranes or sulfurane oxides, it becomes less positively charged by being an apical ligand in the 10-C-5 S_N2 transition state, **18**. The equatorial oxygen of **18** is less negative than that of transition state **16a**. The 10-S-5 sulfurane oxide **6** is therefore demethylated more slowly than the 10-S-4 methoxysulfurane. Sulfurane oxide **6** was earlier found to be demethylated faster than methylsulfurane **5**.[14]



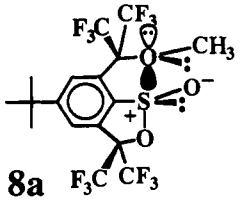
18 (T.S.)



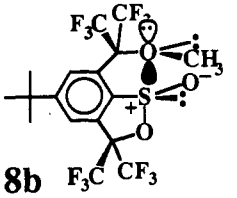
19

Benzylmethoxy *o*-sultine **8** is the most stable isomer of **6**, **7**, and **8**. Heating **6** or **7** above 250 °C leads to the formation of **8**. Adding acid to sulfuranide oxide **10** will give sultine **19** by protonation of an apical oxygen. The energy barrier between **10** and **8** is greater than that between **10** and **6** or **7**.

There is NMR evidence for interaction between the sultine sulfur and the benzylmethoxy oxygen of **8**. The very broad ^1H NMR peak at δ 4.37 and, in the ^{19}F NMR, the small quartet at δ −71.12, 11%, compared with the 89% CF_3 quartet at −71.33, suggest that two orientations, **8a** and **8b**, exist for **8** by interaction of the p orbital electrons with the S–O bond. This interaction would be increased during demethylation as the 3c–4e hypervalent O–S–O bond is formed.

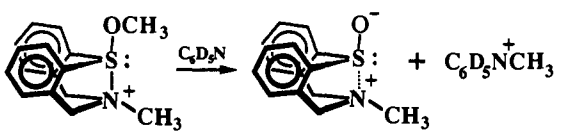


8a



8b

Methoxysulfuranes. Both methoxysulfuranes (**1b** and **7**) exhibit an increased rate of methylation of pyridine-d_5 relative to the SMe compounds (**6** vs **7** and **1b**[8] vs **1a**[1a]) although, in general, an S–C bond is weaker than an O–C bond. Both of these methoxysulfurane compounds are demethylated to give a similar geometry, forming **2b** and anion **10**. The methoxy compound **7** closely resembles sulfuranide oxide anion **10**, with little rearrangement necessary to go from **7** to either transition state (**16a** or **16b**) and then on to **10**.



1b **2b**

(14) Rongione, J. C.; Martin, J. C. Paper to be presented.

The same is true for methoxysulfurane **1b**. Upon demethylation of **1b**, neutral sulfurane **2b** is formed.[1a] The ^{15}N NMR evidence for **2b** suggests that there is significant S–N interaction, even though **2b** could be thought to be a simple sulfoxide without S–N bonding. The N–S bond length of **2b** (2.609 Å),[6c,d] although longer than for the species **1a–d**,[1a] is shorter than the sum of the van der Waals radii (3.35 Å)[15] and is therefore indicative of a weak S–N bond.

Methoxysulfurane **7** reacts at room temperature by methylating pyridine about 220 times faster than does **1b** (Table III), even though **1b** has a cationic species, which might be thought to be a faster methylating species. Demethylation of **7** forms an anion, **10b**, and demethylation of ionic **1b** yields the neutral **2b**. The removal of the methyl group of **1b** does make the apical ligand of the sulfur an anionic oxygen. The other apical ligand, the nitrogen of **1b**, has a much longer N–S bond putting less positive charge on the nitrogen of **1b**. The methylation by the methylsulfonium cation of **3** is about 42 times faster than by **1b** at room temperature. This is because **3** simply cleaves the S–C bond to form the sulfide. The methylation by **1b** is slower than **7** because it reduces the S–N bond strength when the O–C bond is cleaved. Methylation by neutral methoxysulfurane **7** is 5.3 times faster than by the sulfonium cation **3** at room temperature. This makes it clear that the interaction of the oxygen, from which the methyl group is transferred to pyridine, provides stabilization by having the electron pair on the oxygen in transition state **16a** parallel to the adjacent O–S–O antibonding orbital.

SCH_3 vs $SOCH_3$. The methoxysulfuranes **1b** and **7** exhibited similar trends when compared to their respective SCH_3 compounds **1a** and **6**. While the methoxysulfuranes have larger negative entropies (ΔS^* for **1b**, −18.5 eu; **7**, −19.7 eu) than their SCH_3 counterparts (ΔS^* for **1a**, −7.82 eu;[1a] **6**, −11.3 eu), the ΔH^* values are smaller (**1b**, 17.8 kcal/mol; **7**, 14.3 kcal/mol) than for the SCH_3 compounds (**1a**, 23.1 kcal/mol;[1a] **6**, 21.1 kcal/mol). The methoxy groups of compounds **1b** and **7** were free to rotate around the S–O bond, and this randomness is removed after methylation of pyridine. The SCH_3 groups do not have this rotational freedom, thus providing larger negative ΔS^* values for the methoxysulfuranes.

Generally, an O–C bond (~86.5 kcal/mol) is stronger than the S–C bond (~69.7 kcal/mol).[16] The methoxysulfuranes are demethylated faster than the methylsulfuranes. One must consider the different interaction of the methoxy groups at the equatorial position of hypervalent sulfur or as part of the 3c–4e hypervalent bond, as in **17**. The methoxy group of **1b** methylates pyridine-d_5 30.7 times faster at 25 °C than does the SMe of **1a**. When methylsulfurane **1a** is demethylated, the C–S–N hypervalent bond has its S–N bond completely broken. Demethylation of methoxysulfurane **1b** does not provide complete cleavage of the O–S–N hypervalent bond, although the S–N bond length of **2b** (2.609 Å),[17] is longer than the S–N bond length of **1b** (2.206 Å).[1a]

Methoxysulfurane **7** (10-S-4 species) with an equatorial methoxy ligand is demethylated much faster than its 10-S-5 methylsulfurane oxide isomer, **6**, although both form the same sulfuranide oxide, **10**. The interaction of the filled p orbital of the oxygen with the antibonding O–S–O orbital of **7** and the electron–electron repulsion of the O and S p orbitals of **7**, the oxygen of the equatorial methoxy group, and the equatorial lone pair of electrons of the sulfur[12] raise the relative methylation rate of **7**, relative to **6** and to benzylmethoxy *o*-sultine **8**.

Conclusion

Methoxysulfuranes **7** and **1b** are demethylated faster by pyridine-d_5 than are SMe sulfuranes, **6** and **1a**, because the oxygens of **7** and **1b** remaining on the sulfur after demethylation help to stabilize the final sulfurane. Compound **7** provides a much faster methylation than **1b** and is also faster than **6** or **8**, although **6**,

(15) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.
(16) Pilcher, A.; Cox, J. D. In *Thermochemistry of Organic and Organometallic Compounds*; Academic Press: London, 1970.
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7, and 8 all form the same sulfurane oxide, 10. The demethylation transition state of 7 provides stabilization by having electrons donated to the antibonding O-S-O orbital, as the equatorial oxygen becomes more negatively charged as the CH_3 moves to pyridine from 7, via 16a. There is only a small (4.3) methylation rate increase for sulfurane oxide 6 relative to sulfurane 5 because the oxygen of 6 does not become much more negative as the CH_3 leaves, although the sulfur becomes less positive as the S-C bond is broken.

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Asymmetric Synthesis of Monosubstituted and α,α-Disubstituted α-Amino Acids via Diastereoselective Glycine Enolate Alkylations

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Abstract: The enolates derived from the optically active (5*S*,6*R*)- and (5*R*,6*S*)-4(*tert*-butyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (**1a,b**) and (5*S*,6*R*)- and (5*R*,6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-ones (**2a,b**) efficiently couple with alkyl halides to afford the corresponding anti-α-monosubstituted oxazinones (**3** and **4**). The enolate alkylation of the α-monosubstituted oxazinones (**3** and **4**) provides the corresponding α,α-disubstituted oxazinones (**7** and **8**). Dissolving-metal reduction of the homologated oxazinones allows the direct preparation of *t*-BOC-protected α-amino acids. In the case of a dissolving-metal-reducible functionality, hydrogenation over a Pd^0 catalyst furnishes the zwitterionic amino acids. By employing this protocol several amino acids or their corresponding *N*-*t*-BOC derivatives, such as allylglycine, alanine, phenylalanine, β-ethylaspartic acid, α-methylphenylalanine, *N*-(*tert*-butyloxycarbonyl)dimethallylglycine, *N*-(*tert*-butyloxycarbonyl)-2-(2′-propenyl)norvaline, *N*-(*tert*-butyloxycarbonyl)-2-(3′-methyl-2′-butenyl)alanine, *N*-(*tert*-butyloxycarbonyl)-2-(2′-propenyl)alanine, 2-(3′-phenylpropyl)alanine, 2-amino-6-(acetyloxy)hexanoic acid, and 2-(*tert*-butyloxycarbonyl)amino-6-[(*p*-methoxybenzyl)thio]hexanoic acid, are prepared in high enantiomeric excess.

Introduction

Nonproteinogenic, unnatural α-amino acids have increasingly attracted the attention of numerous disciplines in connection with the design and synthesis of enzyme inhibitors as potential constituents of pharmaceuticals, as optically active starting materials for a variety of synthetic applications, and for the study of enzymatic reaction mechanisms. As a consequence, numerous and versatile approaches to the synthesis of nonproteinogenic, natural and unnatural amino acids in optically active form have been reported in the past decade; several reviews have recently appeared on this subject.[1-3]

The established methods for the asymmetric synthesis of amino acids can be divided into roughly six categories:[1] (1) highly stereoselective hydrogenation of chiral, nonracemic dehydroamino acid derivatives or asymmetric hydrogenation of prochiral dehydroamino acid derivatives. Chiral glycine equivalents serve as useful α-amino acid templates undergoing homologation via carbon-carbon bond formation at the α-position through nucleophilic carbanion alkylation (2) or electrophilic carbocation substitution (3). In addition, both nucleophilic amination (4) and electrophilic amination (5) of optically active carbonyl derivatives have very recently been developed. (6) Enzymatic and whole cell-based syntheses have recently become more attractive in terms of substrate versatility, cost, and scale. All of these methods have their relative strengths and weaknesses; the optimum method for each individual application must still be considered on a case-by-case basis with respect to functionality, quantity desired, cost, and time.

We have previously reported on the utility of the diphenyloxazinones (**1** and **2**) as versatile templates from which both electrophilic[4] and nucleophilic[5a,6] C-C bond-forming strategies can be employed to access a variety of nonproteinogenic α-amino acids.[7] In this report, we detail our studies on the glycine enolate alkylations[5] of these systems for accessing a variety of α-monosubstituted and α,α-disubstituted α-amino acids. The α,α-disubstituted α-amino acids are particularly significant in that they

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