154. Stabilizing Effect by Geminal Dioxy Substitution and Anomeric Effect in 3,6-Dihydro-6-methoxy-1,2-oxathiin 2-Oxides

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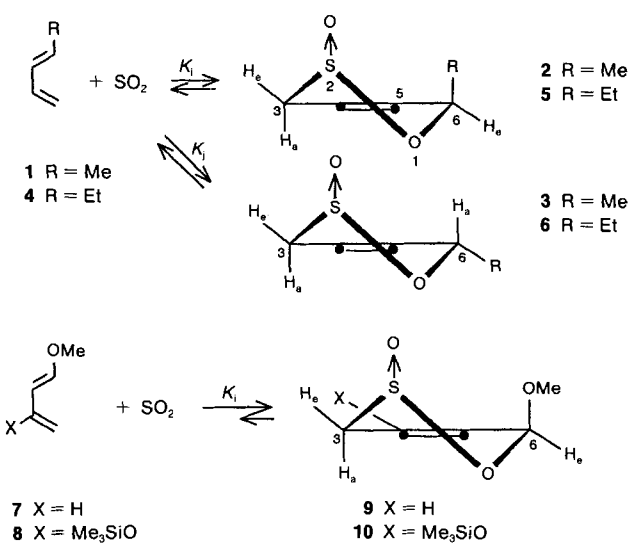
(25.V.93)

The hetero-*Diels-Alder* addition of SO_2 to (*E*)-hexa-1,3-diene (**4**) gives first 6-ethyl-3,6-dihydro-1,2-oxathiin 2-oxide (= 6-ethylsultine) with the Et group occupying a pseudoaxial position, and then the more stable stereoisomer **6** with the Et substituent in a pseudoequatorial position. The SO_2 additions to 1-methoxybuta-1,3-diene (**7**) and to 1-methoxy-3-[(trimethylsilyl)oxy]buta-1,3-diene (**8**) give the 6-methoxysultines **9** and **10**, respectively, with the MeO groups in pseudoaxial positions and which do not equilibrate with sultines having pseudoequatorial MeO substituents (anomeric effect). A lower limit of $\Delta\Delta G$ = 3.9 kcal/mol was evaluated at −60° for the stabilizing effect arising from the geminal vicinity of a MeO and sulfinate moiety in 3,6-dihydro-6-methoxy-4-[(trimethylsilyl)oxy]-1,2-oxathiin 2-oxide.

At low temperature and in the presence of a suitable catalyst, simple 1,3-dienes add reversibly to SO_2 giving the corresponding 3,6-dihydro-1,2-oxathiin 2-oxides (= sultines) [1]. In the case of (*E*)-piperilene (**1**), sultine **2** with a pseudoaxial Me group is formed at −80° (*Alder endo* rule); at −60°, **2** is decomposed into **1** + SO_2, and the more stable sultine **3** with the Me substituent in a pseudoequatorial position is formed [1] (*Scheme*).

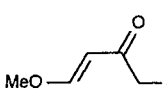
Scheme



We report here our studies on the hetero-*Diels-Alder* addition of SO_2 to (*E*)-hexa-1,3-diene (**4**), (*E*)-1-methoxybuta-1,3-diene (**7**), and 1-methoxy-3-[(trimethylsilyl)oxy]buta-1,3-diene (**8**). They allow one to establish the existence of a stabilizing effect by geminal dioxy substitution [2] and of an anomeric effect [3] [4] in MeO-substituted sultines.

When mixtures of **4** (0.13–0.35M), SO_2 (4–15M), CF_3COOH (0.18–0.28M), and toluene (0.08–0.18M; internal NMR reference) in CD_2Cl_2 (0.2–0.4 ml) were allowed to react at −80° (5-mm *Pyrex* NMR tubes, sealed *in vacuo*), the sultine **5** was formed in a few h. Raising the temperature to −60° led to cycloreversion of **5** into **4** + SO_2 and the formation of the more stable sultine **6**. Equilibrium constants $K_5 = (3–4)\cdot 10^{-3}$ $mol^{-1}dm^3$ and $K_6 = (1.8–6)\cdot 10^{-2}$ $mol^{-1}dm^3$ were measured by ^{1}H-NMR signal integration (toluene as internal reference) for equilibria **4** + SO_2 ⇄ **5** and **4** + SO_2 ⇄ **6**, respectively, at −60°. The equilibrium constant did not depend on the amount and concentration of catalyst (CF_3COOH) present. Under similar conditions, equilibrium constants $K_2 = (0.4–1.2)\cdot 10^{-3}$ $mol^{-1}dm^3$ and $K_3 = (0.4–2)\cdot 10^{-2}$ $mol^{-1}dm^3$ were evaluated at −60° for equilibria **1** + SO_2 ⇄ **2** and **1** + SO_2 ⇄ **3**, respectively. The structure of sultines **5** and **6** were deduced from their ^{1}H- and ^{13}C-NMR spectra (see *Exper. Part*) which were very similar to those of **2** and **3**, respectively [1]. The pseudoequatorial position of H–C(6) in **5** and the pseudoaxial position of H–C(6) in **6** were established by their vicinal coupling constants with H–C(5) and their homoallylic coupling constants with CH_2(3) [5].

The 1-methoxybutadienes **7** and **8** were more reactive than **1** and **4** toward SO_2 and did not require any acidic catalyst to undergo the hetero-*Diels-Alder* additions. In the presence of a 70-fold excess of SO_2, 0.1–0.2M **7** in CD_2Cl_2 (toluene reference, 0.09M) led to the quantitative (> 98% by ^{1}H-NMR) formation of sultine **9** after 12 h at −60°. The latter was stable up to −20°, temperature at which it was transformed slowly and irreversibly into a mixture of polymeric material. Neither concurrent cycloreversion into **7** + SO_2 nor formation of a stereoisomeric sultine (with pseudoequatorial MeO group) could be detected at this temperature. An equilibrium constant $K_9 > 3$ $mol^{-1}dm^3$ was estimated for equilibrium **7** + SO_2 ⇄ **9**. In the presence of a 5–6 fold excess of SO_2, the *Danishefsky* diene **8** gave (> 98% by 360-MHz ^{1}H-NMR) sultine **10** at −60° (after 5 h). In this case, an equilibrium constant $K_{10} > 40$ $mol^{-1}dm^3$ was evaluated for the hetero-*Diels-Alder* reaction **8** + SO_2 ⇄ **10**. Neither cycloreversion, nor isomerization to a sultine with a pseudoequatorial MeO substituent at C(6) could be detected after prolonged staying of **10** at −40°. In the presence of a large excess of SO_2, **10** was rearranged into **11** which was then slowly decomposed into (*E*)-4-methoxybut-3-en-2-one above −60°.



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The structures of sultines **9** and **10** were deduced from their ^{1}H- and ^{13}C-NMR spectra and with the help of double-irradiation experiments including ^{1}H,^{1}H NOE measurements. As for **5**, the pseudoequatorial position of H–C(6) in **9** and **10** was given by its vicinal coupling constant with H–C(5) and its homoallylic coupling constants with CH_2(3). The axial position of the S→O moiety [4b] was not established unambiguously[1]).

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[1]) Commercial (*E*)-1-methoxybuta-1,3-diene contains 5–10% of the (*Z*)-isomer. This reacted also with SO_2 giving sultine **9**, whereas (*Z*)-hexa-1,3-diene did not add to SO_2 between −80 and 20°.

On comparing equilibrium constants K_{10} and K_5 ($K_{10}/K_5 > 10^4$), a lower limit $\Delta\Delta G = 3.9$ kcal/mol was calculated at −60° for the stabilizing effect resulting from the geminal vicinity of a MeO and a sulfinate moiety. Assuming that there are no significant differential entropy or/and solution effects on equilibria **4** + SO_2 ⇄ **5** and **8** + SO_2 ⇄ **10**, the geminal dioxy substitution effect evaluated above is comparable to that found for the following isodesmic reaction on comparing the standard heats of formation of products and reactants [6].

$$2\ Me_2CH(OMe) \rightleftarrows Me_3CH + (MeO)_2CHMe \quad \Delta H_r^\circ = -5.4\ \text{kcal/mol}$$

The anomeric effect in sultines **9** and **10** (preference for the pseudoaxial rather than pseudoequatorial position for the MeO substituent) can be compared with the well-known *Edward-Lemieux* anomeric effect [3] in methyl pyranosides [4].

We thank *F. Hoffmann-La Roche AG*, Basel, the *Fonds Herbette*, Lausanne, and the *Swiss National Science Foundation* for financial support.

Experimental Part

General. See [7].

NMR Sample Preparation. CD_2Cl_2 and toluene were distilled over anh. CaH_2, CF_3COOH over P_2O_5. SO_2 was filtered through a column of alcaline aluminium oxide *90* (act. I, *Merck*) before use. In a weighed, dry 5-mm NMR *Pyrex* tube, diene **4** (15.6 mg, 0.19 mmol), *e.g.*, toluene (9.2 mg, 0.1 mmol; internal ref.), CD_2Cl_2 (238 mg), and CF_3COOH (12.5 mg, 0.11 mmol; catalyst) were mixed under Ar. The soln. was degassed by several freeze-thaw cycles at 10^{-5} Torr. Degassed SO_2 (*ca.* 0.33 ml) was transferred to the above mixture on the vacuum line. The NMR tube was sealed under vacuum. The NMR tube, frozen in liq. N_2, was warmed up to −100° in EtOH/liq. N_2 and transferred into the *Bruker* (360 MHz) probe cooled to −90°. The first NMR spectrum was recorded at −80°, temp. at which **5** was formed. Raising the temp. to −60° induced a loss of **5** and formation of **6**. After 10 h at −60°, the equilibrium was reached: 4% of **5**, 19% of **6**, and 77% of **4**. The volume of the soln. (calibrated NMR tube) was 0.54 ml. After the NMR experiments, the NMR tube was allowed to reach r.t. and weighed together with the piece of tube left over after the sealing: thus, the exact amount of SO_2 introduced in the soln. was measured (480.5 mg, 7.5 mmol). In that experiment, $K_5 = 3 \cdot 10^{-3}$ mol^{-1}dm^3 and $K_6 = 1.8 \cdot 10^{-2}$ mol^{-1}dm^3 were evaluated at −60°. The equilibrium constants were evaluated for at least three different NMR samples and had reproducible values within experimental error.

*Data of (2*RS,*6*RS*)-6-Ethyl-3,6-dihydro-1,2-oxathiin 2-Oxide* (**5**). ^{1}H-NMR (360 MHz, CD_2Cl_2/SO_2, −80°): 6.20 (H–C(5)); 5.80 (H–C(4)); 4.45 (H–C(6)); 3.38 (H_e–C(3)); 3.28 (H_a–C(3)); 1.65, 0.83 (Et); ^2J(3a,3e) = 16.5, ^3J(3e,4) = 7, ^3J(3a,4) = 3, ^3J(4,5) = 11, ^3J(5,6e) = 2, ^3J(6e,MeCH_2) = 6, ^3J(MeCH_2,*Me*CH_2) = 7, ^4J(3e,5) < 0.5, ^4J(3a,5) = 2.5, ^4J(4,6e) = 3, ^5J(3e,6e) ≈ 0.5, ^5J(3a,6e) = 3.5. ^{13}C-NMR (100.63 MHz, CD_2Cl_2/SO_2, −80°): 135.5 (*d*, ^1J(C,H) = 157, C(5)); 114.1 (*d*, ^1J(C,H) = 171, C(4)); 79.2 (*d*, ^1J(C,H) = 153, C(6)); 44.8 (*t*, ^1J(C,H) = 140, C(3)); 29.3 (*t*, ^1J(C,H) = 125, CH_2); 9.3 (*q*, ^1J(C,H) = 120, Me).

*Data of (2*RS,*6*SR*)-6-Ethyl-3,6-dihydro-1,2-oxathiin 2-Oxide* (**6**). ^{1}H-NMR (360 MHz, CD_2Cl_2/SO_2, −60°): 5.80 (H–C(5)); 5.70 (H–C(4)); 4.55 (H_a–C(6)); 3.45 (H_a–C(3)); 3.00 (H_e–C(3)); 1.7, 1.6 (MeCH_2); 0.8 (*Me*CH_2); ^2J(MeCH_2) = 15, ^2J(3a,3e) = 17.5, ^3J(3e,4) = 6.0, ^3J(3a,4) = 2.5, ^4J(3e,5) = 1.0, ^4J(3a,5) = 2.5, ^5J(3a,6a) = 4.5, ^5J(3e,6a) = 3.0, ^3J(6a,MeCH_2) = 5.0, 7.5, ^3J(MeCH_2,*Me*CH_2) = 7, 7.5. ^{13}C-NMR (100.62 MHz, CD_2Cl_2/SO_2, −60°): 132.0 (*d*, ^1J(C,H) = 152, C(5)); 114.5 (*d*, ^1J(C,H) = 175, C(4)); 70.4 (*d*, ^1J(C,H) = 148, C(6)); 45.3 (*t*, ^1J(C,H) = 140, C(3)); 26.3 (*t*, ^1J(C,H) = 125, MeCH_2); 8.3 (*q*, ^1J(C,H) = 120, *Me*CH_2).

*Data of (2*RS,*6*SR*)-3,6-Dihydro-6-methoxy-1,2-oxathiin 2-Oxide* (**9**). ^{1}H-NMR (360 MHz, CD_2Cl_2/SO_2, −60°): 6.18 (H–C(4)); 5.95 (H–C(5)); 4.65 (H_e–C(6)); 3.65 (H_a–C(3)); 3.55 (H_e–C(3)); 3.46 (MeO); ^2J(3a,3e) = 17.5, ^3J(4,5) = 9.0, ^3J(3a,4) = 2.5, ^3J(3e,4) = 3, ^3J(5,6e) = 3.0, ^4J(3e,5) = ^4J(3a,5) = 2.5, ^4J(4,6e) = 1.5, ^5J(3a,6e) = 1.0, ^5J(3e,6e) ≤ 1. ^{13}C-NMR (100.62 MHz, CD_2Cl_2/SO_2, −60°): 129 (*d*, ^1J(C,H) = 177, C(4)); 126 (*d*, ^1J(C,H) = 174, C(5)); 97 (*d*, ^1J(C,H) = 164, C(6)); 58 (*q*, ^1J(C,H) = 145, MeO); 53.5 (*t*, ^1J(C,H) = 145, C(3)).

*Data of (2*RS,*6*SR*)-3,6-Dihydro-6-methoxy-4-[(trimethylsilyl)oxy]-1,2-oxathiin 2-Oxide* (**10**). ^{1}H-NMR (360 MHz, CD_2Cl_2/SO_2, −60°): 4.82 (H–C(4)); 4.75 (H_e–C(6)); 3.65 (H_a–C(3)); 3.40 (H_e–C(3)); 3.43 (MeO); 0.15

(Me_3Si); ^2J(3a,3e) = 16, ^3J(5,6e) = 3.0, ^4J(3e,5) = 1.5, ^4J(3a,5) = 2.0, ^5J(3a,6e) = 1.5, ^5J(3e,6e) < 0.5. ^{13}C-NMR (100.62 MHz, CD_2Cl_2/SO_2, −60°): 151 (*s*, C(4)); 99 (*d*, ^1J(C,H) = 170, C(5)); 97 (*d*, ^1J(C,H) = 160, C(6)); 59 (*q*, ^1J(C,H) = 145, MeO); 54 (*t*, ^1J(C,H) = 145, C(3)); 0.65 (*q*, ^1J(C,H) = 119, Me_3Si).

Data of Trimethylsilyl (E)-4-Methoxy-2-oxobut-3-enesulfinate (**11**). Oil. Unstable at 20°, can be stored in soln. at −20°. ^{1}H-NMR (250 MHz, $CDCl_3$): 7.5 (*d*, ^3J = 11, H–C(4)); 5.6 (*d*, ^3J = 11, H–C(3)); 3.72 (*s*, 2 H–C(1)); 3.69 (*s*, MeO); 0.9 (*s*, Me_3Si). ^{13}C-NMR (62.9 MHz, $CDCl_3$): 190 (*s*, C(2)); 166 (*d*, ^1J(C,H) = 175, C(4)); 107 (*d*, ^1J(C,H) = 157, C(3)); 69 (*t*, ^1J(C,H) = 140, C(1)); 57 (*q*, ^1J(C,H) = 140, MeO); 0 (*q*, ^1J(C,H) = 140, Me_3Si).

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