On the Stereochemistry of the Oxidation of 5-Phenyl-2-thiaadamantane

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We have previously studied the electronic factor in face selection during additions to trigonal carbon by means of 5-substituted adamantanones and their derivatives[1] and interpreted our results in terms of transition-state hyperconjugation.[2] The adamantane skeleton offers the dual advantages of two isosteric faces and conformational invariability; in addition, it avoids the possibility that a neighboring group may assist the reaction and thus influence selectivity. A stark example of this complication is offered by 7-norbornenone, which reacts with methylmagnesium iodide to give a 24:1 *E*/*Z* product ratio[3] but reacts with (pentafluoroethyl)magnesium bromide to give just the opposite result (1:24).[4] Involvement of the carbon–carbon double bond was suggested with some hesitation by Warkentin[5] and later supported by us when we found both of these reagents to attack 5-fluoro-2-adamantanone preferentially at the *zu* face, by about the same margin.[6]

This finding encouraged us to look for other instances in which face selection is apparently dependent on the nature of the reagent. Among the more interesting examples, we took note of the oxidation of sulfides to sulfoxides, previously, studied extensively by Johnson;[7-9] thus, 4-*tert*-butylthiane can be oxidized exclusively to the *Z* sulfoxide if *tert*-butyl hypochlorite is used, but the *E* sulfoxide is the preferred product with several other reagents.[7] An investigation of the oxidation of an appropriately 5-substituted 2-thiaadamantane enticed us additionally because it represents an extension of our studies of face selection at carbon.

Among the syntheses of the parent thiaadamantane previously reported, the one with the best prospects of allowing the same approach to a 5-substituted derivative was that reported by Suginome and Yamada.[10] We generally prefer to use a fluorine atom at the site of C5, this being the most strongly polarizing and sterically innocuous substituent; moreover, the nuclear spin of ^{19}F is very helpful in the assignment of the configuration of the two products. Unfortunately, the synthetic approach did not appear to be compatible with the presence of a tertiary fluoride, and hence, we settled for phenyl instead. The route to **1** is shown in Scheme 1.

Sulfoxides **2** could not be separated readily; however, the ^{13}C NMR signals could be assigned on the basis of additivity calculations.[11] The ^{13}C NMR chemical shifts for the $C_{4,9}$ and $C_{8,10}$ pairs in 2-thiaadamantane are known, and those in **1** were found where expected on the basis of the known phenyl effect in adamantane itself. In the parent sulfoxide, these peaks were readily assigned on the basis of APT experiments and of the effects of added Eu(fod)$_3$.[12] These data suffice to compute values for the shifts of these atoms in *E*- and *Z*-**2**, and indeed, signals are observed there. The effects of added Eu(fod)$_3$ on the signals in the mixture and an attached proton test further solidified our assignments. The ^1H NMR signals of the corresponding protons, in particular the strongly deshielded and well-separated protons "underneath" the oxygen atom, were located by means of proton–carbon correlation experiments; both they and the nearby $H_{1,3}$ proton signals were used for integration (see Figure 1). The product ratios so determined are shown in Table 1.

To understand the data of Table I, it should be realized that N_2O_4 produces an equilibrium mixture of the two sulfoxides;[7] indeed, when any of the other mixtures obtained was exposed to this reagent, the same 50/50 final composition resulted. The other oxidizing agents therefore react in processes that are not subject to thermodynamic control or to product stability considerations. Sodium periodate and *m*-chloroperbenzoic acid behave normally, *i.e.*, attack the face antiperiplanar to the more electron-rich vicinal bonds, but Oxone (effectively, peroxomonosulfate ion) and *tert*-butyl hypochlorite give exceptional results that need to be explained.

We postulate that in these cases, the sulfide reacts *via* a mechanism that involves bond *cleavage* in the product-forming step, releasing the sulfoxide from a tetravalent sulfurane intermediate. Scheme 2 describes an example in which the initial step is the displacement of *tert*-butoxide with the sulfur's favored *zu* face. In support of this contention, we note that alkoxysulfonium salts have been stated[7] to be intermediates. While such species could in principle result from the displacement of chloride, this seems quite unlikely; *tert*-butyl hypochlorite is isoelectronic and effectively isosteric with neopentyl chloride. The hindered sulfur atom in **1** and the low temperature at which the reaction readily occurs are further arguments against that pathway. It is also noteworthy that *vis-à-vis* 2-methylthiolane, this oxidizing agent is the only one that gives more (65/35) than the equilibrium amount (62/38) of the *cis* sulfoxide, while 2-propyl hypochlorite is the most extreme (6/94) among the reagents producing the *trans* isomer. The mechanism of oxidation by Oxone is unknown, but a pathway involving a product-determining bond cleavage in a cyclic intermediate is readily conceived.

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(12) In both **1** and **2**, the order of the signals parallels that of thiane and its sulfoxide. See: Lambert, J. B.; Netzel, D. A.; Sun, H.-n.; Lilianstrom, K. K. *J. Am. Chem. Soc.* **1976**, *98*, 3778.

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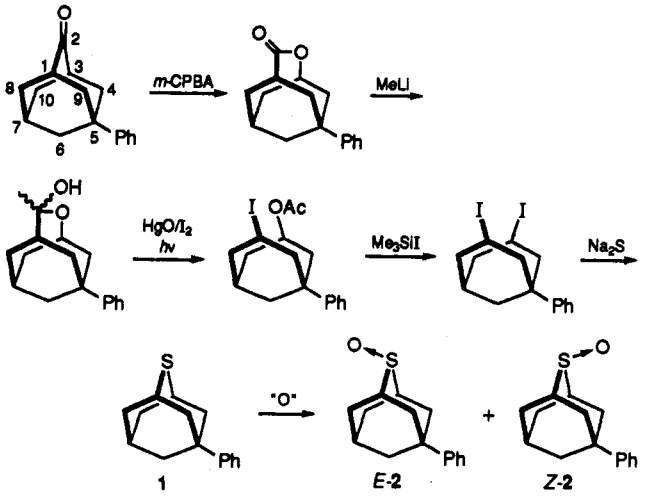
Scheme 1



In conclusion, either stereoisomeric sulfoxide can be made the dominant product in the oxidation of 1 by the appropriate choice of oxidation agent. Since the equilibrium composition is exactly 50/50, at least two types of mechanisms must be operative in these reactions. We suggest that the product-controlling step in some instances ($NaIO_4$ and *m*-CPBA) is the formation of the S–O bond and in others (*t*-BuOCl), it is the cleavage of a bond releasing the sulfoxide from a sulfurane intermediate.[13,14] In either case, this step is assumed to be assisted by the antiperiplanar vicinal bonds.

Experimental Section

2-Thiaadamantane was prepared as reported.[10] A solution of this sulfide (62 mg, 0.40 mM) in a mixture of acetone (2 mL) and methanol (3 mL) was treated with a solution of oxone (130 mg, 0.20 mM of $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in water (2.5 mL) at 0 °C for 10 min. After the solution was stirred for 0.5 h, 10% aqueous $NaHSO_3$ (5 mL) was added; extraction with CH_2Cl_2 and drying led to a pure white solid (>95%): mp >200 °C dec; MS (rel intensity) *m/z* 170.1 (M^+, 21), 153.1 (100), 143.0 (22), 121.1 (13); HRMS *m/z* calcd 170.079, obsd 170.082; ^1H NMR δ 3.028 (s, 2H, $H_{1,3}$), 2.765 (d, 2H, $H_{4,9ax}$, J = 15.0 Hz), 2.20–1.60 (m, 10H); ^{13}C NMR δ 48.19 ($C_{1,3}$, 2.2), 35.15 (C_6, 1.5), 32.71 ($C_{8,10}$, 1.0), 25.70 ($C_{4,9}$, 4.0), 24.70 (C_5, 2.4), 24.58 (C_7, ≃0). The ^{13}C NMR assignments were based on an APT and on the effect of repeated additions of small amounts of a solution of Eu(fod)$_3$ on the spectrum; the relative slopes are given in the parentheses. The ^1H NMR signals assigned were deduced from a ^1H–^{13}C NMR correlation experiment as well as from the Eu(fod)$_3$ effects.

1-Phenyl-4-oxatricyclo[4.3.1.1^{3,8}]undecan-5-one. *m*-CPBA (1.47 g, 8.5 mM) was added to a solution of 5-phenyladamantanone[1b] (1.70 g, 7.5 mM) in CH_2Cl_2 (50 mL), and the mixture was stirred at rt overnight. After the mixture was filtered, washed with 1 N NaOH, and dried over $MgSO_4$, 1.81 g of a white solid product was obtained (97%): mp 90–91 °C; ^1H NMR δ 7.3–7.1 (m, 5H), 4.56 (s, 1H), 3.18 (s, 1H), 2.35–1.75 (m, 11H); ^{13}C NMR δ 177.65 (C_5), 148.46 (C_i), 127.94 (C_m), 125.85 (C_p), 124.03 (C_o), 72.75 (C_3), 41.31 (C_2), 41.09 (C_6), 37.86 (C_9), 36.63 (C_{10}), 34.37 (C_{11}), 34.25 (C_1), 29.67 (C_7), 26.69 (C_8) (assignments by APT).

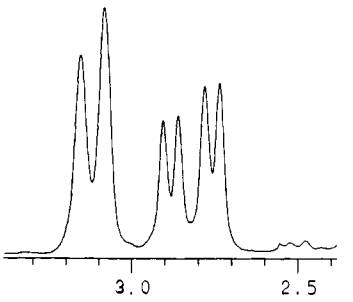
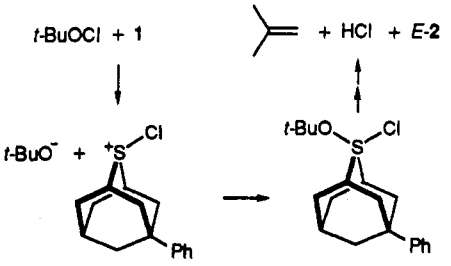


Figure 1. Portion of the 300-MHz ^1H NMR spectrum of a mixture of *E*- and *Z*-2. From left to right, the signals are s, $H_{1,3}$ (*Z*); s, $H_{1,3}$ (*E*); d, $H_{4,9ax}$ (*Z*); and d, $H_{8,10ax}$ (*E*).

Table 1. *E/Z* Product Ratios in the Oxidation of 1

oxidizing agent	solvent	*T* (°C)	*E*:*Z*
$NaIO_4$	aqueous MeOH	0	38:62
m-CPBA	CH_2Cl_2	0	43:57
N_2O_4	CH_2Cl_2	0	50:50
Oxone	aqueous Me_2CO	25	55:45
t-BuOCl	MeOH–CH_2Cl_2	−78	67:33

Scheme 2



1-Phenyl-3-*endo*-acetoxy-7-*exo*-iodobicyclo[3.3.1]nonane. To a solution of the lactone (700 mg, 2.9 mM) in dry TMF (40 mL) at −78 °C was added methyllithium (1.5 M, 4.5 mL) in 15 min. The mixture was stirred for 2 h and then poured into 0 °C water. Normal workup provided a solid mixture of the two diastereomeric pairs (640 mg, 85%) which was purified but not separated with silica gel chromatography and 20% ethyl acetate in hexanes. The ^1H NMR spectrum showed a singlet at δ 1.25 (CH_3). A solution of 200 mg (0.78 mM) of this mixture in dry benzene (60 mL) and pyridine (1 mL) was treated under nitrogen at rt with yellow HgO (1 g) and iodine (1 g) in a 100-mL flask and then irradiated with a 450-W medium-pressure mercury lamp for 2 h. After the mixture was washed with aqueous $Na_2S_2O_3$, routine workup gave 250 mg (85%) of the iodo ester: mp 101–103 °C; ^1H NMR δ 8.0–7.0 (m, 5H), 5.15–5.0 (m, 1H), 5.3–5.2 (m, 1H), 2.4–1.4 (m, 12H); ^{13}C NMR δ 169.84, 150.38, 128.47, 126.22, 124.56, 67.30, 52.93, 45.31, 43.55, 40.71, 35.12, 32.32, 30.48, 23.76, 21.56.

1-Phenyl-3,7-*exo*,*exo*-diiodobicyclo[3.3.1]nonane. Iodotrimethylsilane (312 mg, 1.56 mM) was allowed to react with a solution of the iodo ester (240 mg, 0.62 mM) in dry CCl_4 (4 mL) at rt for 3 days. The reaction was monitored with TLC. Workup with water and ether provided the diiodo compound (210 mg, 75%) which was purified with silica gel chromatography (hexane): mp 117–119 °C; MS (rel intensity) *m/z* 325.0 (M^+, 68), 197.1 (M − I, 100), 155.1 (79), 141.1 (24), 115.1 (23), 91.1 (60), 77 (23); ^1H NMR δ 7.4–7.0 (m, 5H), 5.1–4.8 (dquin, 2H), 2.80–2.75 (dd, 2H), 2.5–2.0 (m, 9H); ^{13}C NMR δ 148.08, 128.53, 126.52, 124.37, 51.70, 45.21, 44.44, 37.47, 36.25, 25.15.

5-Phenyl-2-thiaadamantane (1). $Na_2S \cdot 9H_2O$ (950 mg, 4 mM) was added to a solution of the diiodo compound (210 mg, 0.45 mM) in ethanol (10 mL). After the mixture had refluxed for 10 h under nitrogen, routine workup gave 70 mg (65%) of 1 which was purified by silica gel chromatography (hexane): mp 78–79 °C; MS (rel intensity) *m/z* 230 (M^+, 100), 197 (26), 173 (10), 143

(13) In view of the possibility of multiple mechanisms, caution is advisable before accepting conclusions based on diastereoselectivities observed in sulfur oxidation. See: Fujita, M.; Suzuki, M.; Ogata, K.; Ogura, K. *Tetrahedron* **1991**, *32*, 1463. For further literature on this subject, see: Quallich, G. J.; Lackey, J. W. *Tetrahedron Lett.* **1990**, *31*, 3685 and papers quoted therein. Yuasa, H.; Takenaka, A.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3473. Yuasa, H.; Hashimoto, H. *Tetrahedron* **1993**, *40*, 8977 (in particular, see the closing sentence of this paper).

(14) Unbeknownst to the present authors until after the submission of this manuscript, proof of the postulated tetracovalent sulfurane intermediate was already in the literature: Johnson, C. R.; Rigau, J. J. *J. Am. Chem. Soc.* **1969**, *91*, 5398. We thank Professor Johnson for informing us.

(11), 95 (25), 77 (15); HMRS m/z calcd 230.1143, obsd 230.1128; ^{1}H NMR δ 7.5–7.1 (m, 5H), 3.05 (s, 2H), 2.5–2.0 (m, 11H); ^{13}C NMR δ 150.16, 128.30, 125.97, 124.71, 44.18 ($C_{4,9}$), 41.70 (C_6), 37.61 ($C_{8,10}$), 35.37 (C_5), 34.55 ($C_{1,3}$), 28.14 (C_7).

5-Phenyl-2-thiaadamantane *S*-Oxides *E*- and *Z*-2. Oxidation of 1 by any of the means detailed below gave liquid mixtures of *E* and *Z*-2 would could not be separated: ^{1}H NMR δ 7.3–7.0 (m, 5H), 3.15 and 3.08 (2s, 2H, $H_{1,3}$ (*Z* and *E*, respectively)), 2.88 and 2.76 (2d, 2H, $H_{4,9ax}$ (*Z*) $H_{8,10ax}$ (*E*), respectively, J = 13.5 Hz), 2.25–1.60 (m, 9H); the assignments rest on a ^{1}H–^{13}C NMR correlation spectrum; ^{13}C NMR δ 148.56, 147.54, 128.38, 128.28, 126.37, 126.21, 124.47, 49.37 ($C_{1,3}$ (*Z*)), 48.65 ($C_{1,3}$ (E)), 40.54 and 40.04 (C_6 (*E*) and (*Z*)), 38.57 ($C_{8,10}$ (*E*), calcd 38.18, slope 4.5), 33.58 and 33.30 (C_5 (*E*) and (*Z*)), 31.83 ($C_{8,10}$ (*Z*), calcd 32.84, slope 1.1), 31.39 ($C_{4,9}$ (*Z*), calcd 31.16, slope 4.0), 25.78 and 25.61 (C_7 (*E*) and (*Z*)), 24.94 ($C_{4,9}$ (*E*), calcd 24.81, slope 1). The calculated values for $C_{4,9}$ and $C_{8,10}$ are based on those of thiaadamantane, 5-phenyl-2-thiaadamantane, and thiaadamantane *S*-oxide; the slopes are those of the responses to additions of Eu(fod)$_3$, in arbitrary units.

Oxidations of 1. With Oxone: a solution of this reagent (0.10 g, 0.32 mM) in water (2.5 mL) was added to a solution of 1 in acetone (2 mL) and methanol (3 mL) at 0 °C in 10 min. After 30 min, 5 mL of aqueous $NaHSO_3$ (10%) was added. After extraction with CH_2Cl_2 and evaporation of the solvent, a colorless liquid residue consisting of *E*- and *Z*-2 was obtained in 98% yield which was analyzed by ^{1}H NMR ($H_{1,3}$ signals). **With $NaIO_4$:** a solution of this reagent (20 mg, 0.093 mM) in water (5 mL) was added at 0 °C to a solution of 1 in methanol (1 mL) and kept at that temperature for 7 h. The yield was 80% after workup as above. **With N_2O_4:** this reagent (liquified, 2 mL) was added to 1 (20 mg, 0.09 mM) dissolved in CH_2Cl_2 (2 mL) at 0 °C. After 30 min, the solvent and the reagent were allowed to evaporate and the residue was analyzed as before. It was also verified that other mixtures reached the same composition upon treatment with this reagent. **With *m*-CPBA:** a mixture of *m*-CPBA (30 mg, 0.17 mM), CH_2Cl_2 (7 mL), and 1 (20 mg, 0.09 mM) was allowed to react at 0 °C for 12 h. After the mixture was quenched with $NaHCO_3$ and worked up, the product was analyzed as before. **With *tert*-butyl hypochlorite:** this reagent (1.2 equiv), dissolved in methanol (2 mL) and CH_2Cl_2 (2 mL), was added to 1 (30 mg, 0.14 mM) in methanol (3 mL) at −78 °C. The dry ice–acetone bath was allowed to warm to −40 °C, whereupon anhydrous Na_2CO_3 was added. When the mixture had reached rt, the solvent was removed and the residue worked up and analyzed in the usual way.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of the new compounds mentioned in this paper and plots of the effect of Eu(fod)$_3$ on the ^{13}C NMR chemical shifts of the sulfoxides (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Additions and Corrections

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Rui Tamura,* Masatoshi Kohno, Sei Utsunomiya, Kunihiko Yamawaki, Nagao Azuma, Akira Matsumoto, and Yasutaka Ishii. Synthesis of PBG_1 Analogues by Radical Chain Substitution Reaction.

Page 3953, column 1, lines 16–19. Introduction should read Its intriguing photochemical behavior shows that the single electron transfer reaction from $RNu^{\bullet-}$ to RX should be the rate-determining step in the dark.[3]