Thiophene *S*-Oxides: Convenient Preparation, First Complete Structural Characterization and Unexpected Dimerization of One of Them, 2,5-Diphenylthiophene-1-oxide

Pascale Pouzet,[a] Irene Erdelmeier,[a] Daria Ginderow,[b] Jean-Paul Mornon,[b] Patrick Dansette[a] and Daniel Mansuy*[a]

[a] *Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques (URA 400), Université René Descartes, 45 Rue des Saints-Pères, 75270 Paris Cedex 06, France*
[b] *Laboratoire de Minéralogie et Cristallographie (URA 09), Université Pierre et Marie Curie, T16, 4 place Jussieu, 75252 Paris Cedex 05, France*

Oxidation of 2,5-disubstituted thiophenes and benzothiophenes by H_2O_2 in CF_3CO_2H–CH_2Cl_2 appears a convenient method to access the corresponding reactive sulfoxides; it is used to prepare 2,5-diphenylthiophene-1-oxide, which is the first thiophene oxide to be fully structurally characterised crystallographically and the nonplanar structure of the thiophene ring is established; formation of an unexpected dehydrogenated dimer of this sulfoxide is also observed.

Recent results suggest that thiophene *S*-oxides could often be formed as primary reactive metabolites of thiophene compounds *in vivo*. Actually, metabolites derived from the reaction of glutathione with thiophene *S*-oxide have been identified in the urine of rats treated with thiophene itself,[1] and an *S*-oxide derived from the cytochrome P450-catalyzed oxidation of a 3-acylthiophene compound in rat liver microsomes has been trapped by reaction with thiol nucleophiles.[2,3] Such thiophene *S*-oxides, which could play important roles in toxicology,[2–4] are unstable species which are poorly known in chemistry in general.[5] Only two of them bearing two bulky substituents at ring positions 2 and 5 have been prepared in low yields (5%) by chemical oxidation of the corresponding thiophenes and were characterized by UV and NMR spectroscopy in solution.[6] Other thiophene *S*-oxides have been produced as transient species[7] and only characterized at the level of their Diels–Alder products[5] or metal complexes.[8]

In order to understand the formation and biological consequences of thiophene *S*-oxides, it is necessary to better know the chemical structure and reactivity of these species, and, hence to find good preparative methods for their formation. This communication reports initial results in this direction including a preparation method of one of them by selective oxidation of the corresponding thiophene, the first complete X-ray structure determination of a thiophene *S*-oxide,[9] and the surprising formation of an unexpected dimer during the preparation of this *S*-oxide.

Treatment at 0 °C of 2,5-diphenylthiophene, **1**, with 4 equiv. of H_2O_2 (30% in H_2O) in CF_3CO_2H–CH_2Cl_2 (1 : 2) led, after stirring for 4 hours, neutralization by $NaHCO_3$, extraction by CH_2Cl_2 and flash chromatography on deactivated neutral alumina (CH_2Cl_2 as eluent), to the corresponding sulfoxide **2** (mp = 124–126 °C decomp.) in an isolated yield of 25%. Reaction conditions (time, temperature and amount of H_2O_2) are very important for obtaining **2** in a selective manner (maximum yield of 40% after 3 hours reaction under the above conditions with 70% conversion of **1**). Using longer reaction times led to increasing amounts of the corresponding sulfone **3**. It is noteworthy that other classical oxidizing systems, *e.g.* 3-chloroperbenzoic acid, dimethyl dioxirane[10] or the cytochome P450 model system using C_6H_5IO and [Mn(tdcpp)Cl] [H_2tdcpp = 5,10,15,20-tetrakis(2,6-dichlorophenyl)-porphyrin][11] failed to give **2** in significant amounts. The latter system gave *cis*-1,2-dibenzoylethylene in 90% yield, whereas the two former systems led to 2,5-diphenylthiophene sulfone, **3**, as a major product (Fig. 1).

Compound **2** is stable at −20 °C but slowly decomposes in solution over a few days at room temperature. Its high-resolution mass spectrum (Found: *m/z* 252.0611. Calc. for $C_{16}H_{12}OS$ 252.0609), ^{1}H NMR [δ, CD_2Cl_2: 6.94 (s, 2H), 7.30–7.50 (m, 6H) and 7.72 (m, 4H)], and IR (a strong band at 1050 cm^{-1}) spectra, are in complete agreement with the thiophene sulfoxide structure indicated in Fig. 1.

Interestingly, the oxidation method based on H_2O_2 and CF_3CO_2H was, in our experience, the only satisfactory one to prepare **2**. It also proved to be by far the best procedure for the preparation of the *S*-oxides of 2,3,4,5-tetraphenylthiophene, benzothiophene and 2-(4-chlorobenzoyl)benzo[b]thiophene (yields of 30, 90 and 40% respectively). Benzothiophene sulfoxide itself, which could not be obtained selectively by using other peracids, is only stable in dilute solution.[12]

The molecular structure of **2** as deduced from an X-ray analysis, and selected bond distances and angles, are shown in Fig. 2. The S atom presents pyramidalisation and lies outside the plane formed by the four thiophene C atoms by 0.278 Å, whereas the O atom lies outside this plane in the opposite direction by 0.746 Å. These data, as well as the C–C, C–S and S–O bond distances are globally in good agreement with those previously predicted for thiophene *S*-oxide from *ab initio* calculations.[13,14] These results definitively establish the nonplanarity of a thiophene *S*-oxide in the solid state, which was previously predicted by calculations[13,14] and deduced from ^{1}H NMR data for 2,5-di-*tert*-butylthiophene *S*-oxide in solution.[6] This pyramidal configuration of the S atom of **2** makes it unlikely to be aromatic. However, since the deviation from planarity of **2** is small, the S and O atoms being only slightly displaced out of the plane renders the possibility that some π-delocalization may still occur.

In general, thiophene *S*-oxides which do not contain substituents at ring positions 2 and 5, such as thiophene *S*-oxide itself, undergo facile Diels–Alder dimerization.[5] Thus, oxidation of thiophene, which is believed to produce thiophene *S*-oxide *in situ* eventually leads to formation of a Diels–Alder dimer.[5] The chemical reactivity of isolated **2** is under study. A surprising preliminary result was observed during the preparation of **2** in that whereas **2** was the major product formed at the beginning of the oxidation of **1** by the H_2O_2–CF_3CO_2H system,

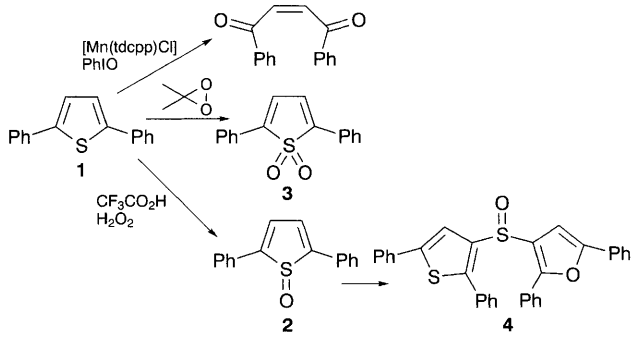

Fig. 1

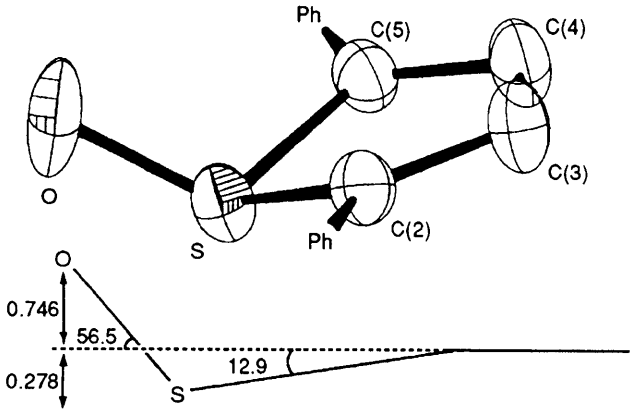

Fig. 2 ORTEP structure of 2,5-diphenylthiophene-1-oxide **2** with phenyl rings omitted for clarity. The molecule has a plane of symmetry with the S and O atoms in this plane. Main bond lengths (Å) and angles (°) of the thiophene sulfoxide ring: S–O 1.484(3), S–C(2) 1.781(2), C(2)–C(3) 1.345(4), C(3)–C(4) 1.433(5), O–S–C(2) 112.6(1), C(2)–S –C(5) 91.3(2), S–C(2)–C(3) 108.9(2), C(2)–C(3)–C(4) 114.5(2). Deviations (Å) of the S and O atoms from the thiophene C atom plane are indicated. A complete description of the structural data of **2** compared with those of 2,5-diphenylthiophene and its sulfone **3** will be reported elsewhere.

a secondary product **4** appeared to be formed at the expense of **2** at later stages. This product was characterized by mass spectrometry [CI, NH_3: m/z = 503 $(M + NH_4)^+$, 237, 221], ^1H NMR (δ, CD_2Cl_2: 7.88 (s, 1H), 7.76 (d, J = 3 Hz, 2H), 7.68 (d, J = 3 Hz, 2H), 7.57 (d, J = 3 Hz, 2H), 7.53–7.28 (m, 14H), 7.18 (s, 1H)], and IR (strong band at 1035–1050 cm^{-1}) spectroscopy, and by X-ray analysis.[15] It is an unexpected dimeric compound consisting of a 2,5-diphenylthiophene and a 2,5-diphenylfuran ring linked by a SO moiety at position 3 (Fig. 1). Formally, it is a dimer of **2** having lost two hydrogen atoms. The mechanism of this peculiar formation of **4** is under study.

The aforementioned results reports the first accurate structural determination of a thiophene sulfoxide.[9] It clearly shows a non-planar structure as previously proposed for thiophene sulfoxides from indirect evidence.[6,13,14] The method used for oxidation of **1** is convenient and was successful for the preparation of thiophene- and benzothiophene-*S*-oxides which are difficult to obtain otherwise. Its use for the preparation of other thiophene *S*-oxides which are biologically important reactive metabolites, and the determination of their reactivity is under study.

Received, 22nd July 1994; Com. 4/04515G

Footnote

† *Crystal data* for **2**: $C_{16}H_{12}OS$, M = 252.32, orthorhombic, Space group *Pnam*, a = 6.631(3), b = 7.270(3), c = 26.081(10) Å, V = 1257.3(9) Å^3, Z = 4, D_c = 1.33 g cm^{-3}, crystal dimensions: 0.2 × 0.3 × 0.5 mm^3, Cu-Kα radiation (λ 1.5418 Å), T = 293 K, Philips PW100 diffractometer. The structure was solved by the SHELXS86 program[16] and the data were refined using SHELXL 93 program.[17] Hydrogen atoms were located by Fourier difference methods and refined with isotropic thermal parameters; μ = 2.138 mm^{-1}, 3.39 < θ < 67.02°, 1347 unique reflexions, 1077 observed reflections with $F^2 > 2\sigma(F^2)$, full-matrix least squares on F^2, R = 0.049 [$wR(F^2)$ = 0.153]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors Issue No. 1.

References

1 P. M. Dansette, T. Do Cao, H. El Amri and D. Mansuy, *Biochem. Biophys. Res. Commun.*, 1992, **186**, 1624.
2 D. Mansuy, P. Valadon, I. Erdelmeier, P. Lopez-Garcia, C. Amar, J. P. Girault and P. M. Dansette, *J. Am. Chem. Soc.*, 1991, **113**, 7825.
3 P. Lopez-Garcia, P. M. Dansette, P. Valadon, C. Amar, P. Beaune, F. Guengerich and D. Mansuy, *Eur. J. Biochem.*, 1993, **213**, 223.
4 P. Lopez-Garcia, P. Dansette and D. Mansuy, *Biochemistry*, 1994, **33**, 166.
5 R. M. Kellog, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, vol. 4, p. 713; M. S. Raasch, in *Chemistry of Heterocyclic Compounds, Thiophene and its Derivatives*, ed. S. Gronowitz, Wiley, New York, 1985, **44**, 871.
6 W. L. Mock, *J. Am. Chem. Soc.*, 1970, **92**, 7610.
7 M. Prochazka, *Collect Czech Chem. Comm.*, 1965, **30**, 1158.
8 A. E. Skaugset, T. B. Rauchfuss and C. L. Stern, *J. Am. Chem. Soc.*, 1990, **112**, 2423.
9 Very recently, an X-ray structure determination was published for 2,3,4,5-tetraphenylthiophene *S*-oxide: F. Meier-Brocks and E. Weiss, *J. Organomet. Chem.*, 1993, **453**, 33. However, a precise determination of the ring conformation and of the S–O and S–C distances was not possible in that case because of structural disorder.
10 A. Waldemar, R. Curci and J. O. Edwards, *Acc. Chem. Res.*, 1989, **22**, 205.
11 B. Meunier, *Chem. Rev.*, 1992, **92**, 1411.
12 P. Geneste, J. Grimaud, J. L. Olivé and S. N. Ung, *Bull. Soc. Chim. Fr.*, 1977, 271.
13 J. A. Hashmall, V. Horak, L. E. Khoo, C. O. Quicksall and M. K. Sun, *J. Am. Chem. Soc.*, 1981, **103**, 289.
14 I. Rozas, *J. Phys. Org. Chem.*, 1992, **5**, 74.
15 D. Ginderow, J. P. Mornon, I. Erdelmeier, P. Dansette and D. Mansuy, *Acta Crystallogr., Sect. C*, 1992, **48**, 1808.
16 G. M. Sheldrick, SHELXS 86, Program for Crystal Structure Determination, University of Göttingen, Germany, 1986.
17 G. M. Sheldrick, SHELXL 93, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1993.