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Mechanism of the Aromatic Hydroxylation of Thiophene by Acid-Catalyzed Peracid Oxidation

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Received March 29, 2002

The oxidation of thiophene (**1**) with peracids in a strongly acidic environment yielded thiophen-2-one (**4**) as the product of an apparent direct hydroxylation of the thiophene aromatic ring together with the anticipated thiophene-*S*-oxide dimers, **2a,b**, as the main products. Formation of the latter dimers can be rationalized in a straightforward manner by initial oxidation at the sulfur atom of thiophene (**1**) to yield thiophene-*S*-oxide followed by subsequent dimerization in a Diels−Alder type reaction. Trapping experiments in the presence of a competing dienophile indicated that thiophen-2-one (**4**) did not originate from the monomeric thiophene-*S*-oxide but was the product of an independent reaction pathway. The extent of thiophen-2-one (**4**) formation correlated with the acidity of the reaction medium and was suppressed in the presence of water, the latter presumably acting as a competing base. As evidenced by the use of 2,5-dideuterated thiophene (**1-D**), its mechanism of formation involved a 1,2-hydride shift, a feature commonly described in the peracid-mediated epoxidation of aromatic hydrocarbons and indicative for the occurrence of cationic intermediates. In agreement with all these observations we propose a mechanism involving initial protonation of thiophene followed by nucleophilic attack of the peracid in position 2 of the thiophene ring. Intramolecular epoxidation may lead to the formation of thiophene 2,3-epoxide as a highly reactive intermediate that then undergoes heterolytic ring opening and a 1,2-hydride shift to yield thiophen-2-one (**4**) after a final, acid-catalyzed, isomerization of the double bond.

Introduction

The oxidation of organic sulfides to the corresponding sulfoxides and sulfones is a well-understood process[1−3] for which a large variety of synthetic methods exists.[4−9] In contrast, the analogous transformation of thiophenes in which the sulfur atom is an integral part of the aromatic system is much less explored, though numerous attempts toward a selective synthesis of thiophene-*S*-oxides have been reported during the past 4 decades.[10−17] The chemical access to thiophene-*S*-oxides is complicated by the intrinsically high reactivity of this class of compounds. While organic sulfides can be selectively oxidized to the corresponding sulfoxides by simple kinetic control, i.e., limitation of the amount of oxidant and/or low reaction temperatures, this method completely fails for the oxidation of thiophenes. As a consequence of the involvement of the sulfur lone pair in the aromatic system, the two oxidation potentials (S−SO and SO−SO_2) are too close to allow control at the stage of the thiophene-*S*-oxide. Therefore, thiophene-*S*,*S*-dioxides are the usual products isolated from oxidations of thiophenes with peracids,[10−13] dimethyldioxirane,[15] or oxodiperoxymolybdenum (MoO_5−HPMT).[14] The rare examples of stable thiophene-*S*-oxides comprise systems with bulky substituents in positions 2 and 5.[18−19] This steric encumbrance is necessary to suppress another common reaction pathway of thiophene-*S*-oxides, i.e., their dimerization in a Diels−Alder-type fashion.[10,20] However, thiophene-*S*-

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(1) Srinivasan, C.; Chellamani, A.; Kuthalingam, P. *J. Org. Chem.* **1982**, *47*, 428−431.
(2) Henbest, H. B.; Khan, S. A. *J. Chem. Soc., Chem. Commun.* **1968**, 1036.
(3) Oae, S.; Takata, T. *Tetrahedron Lett.* **1980**, *21*, 3213−3216.
(4) Modena, G.; Todesco, P. E. *J. Chem. Soc.* **1962**, 4920−4926.
(5) Curci, R.; Modena, G. *Tetrahedon Lett.* **1963**, 1749−1752.
(6) Beckenbauer, R.; Smart, B. E. *J. Org. Chem.* **1995**, *60*, 6186−6187.
(7) Colonna, S.; Gaggero, N. *Tetrahedron Lett.* **1989**, *111*, 6233−6236.
(8) Riley, D. P.; Smith, M. R.; Correa, P. E. *J. Am. Chem. Soc.* **1988**, *110*, 177−180.
(9) Holland, H. L. *Chem. Rev.* **1988**, *88*, 473−485.
(10) Davies, W.; Gamble, N.; James, F.; Savige, W. *Chem. Ind.* **1952**, 804.
(11) Melles, J. L.; Backer, H. J. *Trav. Rec. Chim.* **1953**, *72*, 316−328.
(12) Davis, W.; James, F. C. *J. Chem. Soc.* **1954**, 15−18.
(13) van Tilborg, W. J. M. *Synth. Commun.* **1976**, *6*, 583−589.
(14) Chien, C.-S.; Kawasaki, T.; Sakamoto, M. *Chem. Pharm. Bull.* **1985**, *11*, 5071−5074.
(15) Miyahara, Y.; Inazu, T. *Tetrahedron Lett.* **1990**, *31*, 5955−5958.
(16) Thiemann, T.; Li, Y.; Thiemann, C.; Sawada, T.; Ohira, D.; Tashiro, M.; Mataka, S. *Heterocycles* **2000**, *52*, 1215−1230.
(17) For some recent reviews see: (a) Thiemann, T. *Kyushu Daigaku Chuo Bunseki Senta Hokoku* **2001**, *18*, 1−7 (English). (b) Thiemann, T.; Arima, K.; Kumazoe, K.; Mataka, S. *Kyushu Daigaku Kino Busshitsu Kagaku Kenkyusho Hokoku* **2000**, *14*, 139−148 (English). (c) Nakayama, J.; Sugihara, Y. *Sulfur Rep.* **1997**, *19*, 349−375.
(18) Mock, W. L. *J. Am. Chem. Soc.* **1970**, *92*, 7610−7612.
(19) Pouzet, P.; Erdelmeier, I.; Ginderow, D.; Mornon J.-P.; Dansette, P. M.; Mansuy, D. *J. Chem. Soc., Chem. Comm.* **1995**, 473−474.

10.1021/jo0202177 CCC: $22.00
Published on Web 09/24/2002

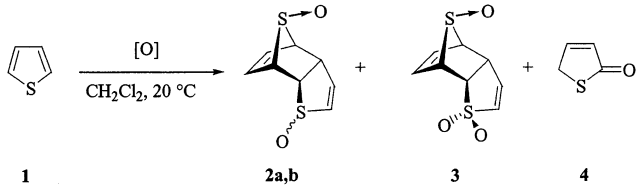


FIGURE 1. Product distribution in the TFA-catalyzed peracid oxidation of thiophene (**1**).

oxides, either isolated or generated in situ, have been used for the synthesis of thiophene-containing cephalosporines and for studies on the effects of the stereoelectronic control of Diels−Alder reactions with substituted cyclopentadienes.[21] More recently, they have been identified as the primary reactive metabolites in the cytochrome P450-catalyzed oxidation of thiophene-containing drugs in vitro[22,23] and in vivo.[24,25] In an earlier communication, we have shown that thiophene itself is metabolized in vivo in rats and in vitro with rat liver microsomes to the corresponding thiophene-*S*-oxide, which underwent subsequent Diels−Alder dimerization.[26] The H_2O_2/trifluoroacetic acid system was introduced as a synthetic tool for the selective mono-oxygen transfer to thiophene allowing for preparation of sufficient material to elucidate the exact chemical structure of these dimers. In this report, we describe another feature of this particular oxidation system, i.e., the direct hydroxylation of the thiophene aromatic ring via an independent reaction pathway presumably bypassing the stage of a highly unstable thiophene epoxide.

Results

The oxidation reactions with thiophene (**1**) were carried out in methylene chloride at ambient temperature using 0.2 equiv of the respective oxidant except for the reaction with dimethyldioxirane, for which acetone was used. The various substituted peracetic acids were prepared in situ by adding 30% H_2O_2 to a solution of the respective acetic acid in methylene chloride in a ratio of about 1:3. The initially biphasic reaction systems homogenized upon vigorous stirring and oxidation reactions were carried out after complete homogeneity was attained.

The oxidation of thiophene (**1**) yielded two different types of oxidation products, i.e., a mixture of two diastereoisomeric thiophene-*S*-oxide dimers, **2a** and **2b**, and a so-called sesquioxide **3** on one hand and on the other hand thiophen-2-one (**4**) (Figure 1). The isolation and structural characterization of the water-soluble thiophene-*S*-oxide dimers **2** and sesquioxide **3** was described in detail in an earlier communication.[26] Product ratios and yields were calculated after quantification with HPLC−UV using external calibration with authentic samples of all three products. In addition to these Diels−Alder dimers, thiophen-2-one (**4**) was detected in the organic phase of the crude extract. Thiophen-2-one (**4**) was identified by comparison of its NMR and IR characteristics with those of an authentic sample prepared by acid-catalyzed pyrolysis of 2-*tert*-butoxythiophene[27] after initial purification by silica gel chromatography.

TABLE 1. Influence of Variation of Reaction Conditions on Product Distribution in the Oxidation of Thiophene[a]

entry	oxidant	cat. acid	time[b] [h]	**2** + **3**[c,d] [%]	**4**[e] [%]	(**2** + **3**)/**4**
1	*m*-CPBA	none	192	76[f]	nd[g]	
2	*m*-CPBA	CF_3CO_2H	15	48	14	77:23
3	30% H_2O_2	CF_3CO_2H	11	58	7	89:11
4	30% H_2O_2	CCl_3CO_2H	30	57	4	93:7
5	30% H_2O_2	$CHCl_2CO_2H$	41	32	1	97:3
6	30% H_2O_2	CH_2ClCO_2H	90	22	0.5	99:1
7	30% H_2O_2	CH_3CO_2H	456	6[f]	nd	
8	30% H_2O_2	none	192	nr[h]		
9	DMD[i]	none	0.5	23	nd	
10	100% H_2O_2	CF_3CO_2H	2.5	54	18	75:25
11	85% H_2O_2	CF_3CO_2H	21	71	18	80:20
12	15% H_2O_2	CF_3CO_2H	17	55	6	90:10
13	8% H_2O_2	CF_3CO_2H	20	83	2	98:2

[a] In methylene chloride at 20 °C, thiophene/acid/oxidant ratio ca. 1:3:0.2. [b] Time until complete consumption of the oxidant was indicated by using KI/starch. [c] Diels−Alder dimers **2** and sesquioxide **3** were quantified by using HPLC−UV (for conditions, see Experimental Section), error ca. 3% of given values. [d] Yields of sesquioxide **3** were, if not otherwise stated, usually below the detection limit. [e] Thiophen-2-one (**4**) was quantified by ^{1}H NMR spectroscopy using 1,2-dichloroethane as internal standard. [f] The only detected compound was sesquioxide **3**. [g] Not detected. [h] No reaction. [i] Dimethyldioxirane.

The experimental conditions, product ratios, and yields of the various oxidation reactions of thiophene (**1**) are summarized in Table 1. The oxidation of **1** with *meta*-chloroperbenzoic acid (*m*-CPBA) yielded sesquioxide **3** as the only product in 76% yield (based on the oxidant; entry 1). When the oxidation with *m*-CPBA was carried out in the presence of 3 equiv of trifluoroacetic acid under otherwise identical experimental conditions, formation of sesquioxide **3** was no longer observed. Instead, the reaction yielded a mixture of the two thiophene-*S*-oxide dimers, **2a** and **2b**, together with thiophen-2-one (**4**) in 62% overall yield and a normalized product ratio **2**/**4** of 77:23 (entry 2).

To gain a better understanding of the molecular mechanisms determining the formation of Diels−Alder products **2** and **3** or thiophen-2-one (**4**), the influence of the strength of the oxidant, pH of the reaction medium, and the presence of water or a competing Diels−Alder dienophile on the product distribution was systematically studied. The effect of the strength of the oxidizing agent is reflected by the changes in the reaction times (entries 3−9, Table 1) with the expected inverse correlation between oxidizing power and reaction time. In contrast, product distributions in this series of experiments did not

(20) Thiemann, T.; Ohira, D.; Li, Y.; Sawada, T.; Mataka, S.; Rauch, K.; Noltemeyer, M.; de Meijere, A. *J. Chem. Soc. Perkin Trans. 1* **2000**, *17*, 2968−2976.
(21) Naperstkow, A. M.; Macauley, J. B.; Newlands, M. J.; Fallis, A. G. *Tetrahedron Lett.* **1989**, *30*, 5077−5080.
(22) Mansuy, D.; Valadon, P.; Erdelmeier, I.; Lopez-Garcia, P.; Amar, C.; Girault, J.-P.; Dansette, P. M. *J. Am. Chem. Soc.* **1991**, *113*, 7825−7826.
(23) Ha-Duong, N.-T.; Dijols, S.; Macherey, A.-C.; Goldstein, J. A.; Dansette, P. M.; Mansuy, D. *Biochemistry* **2001**, *40*, 12112−12122.
(24) Dansette, P. M.; Thang, D. C.; El Hamri, A.; Mansuy, D. *Biochem. Biophys. Res. Commun.* **1992**, *186*, 1624−1630.
(25) Schlenk, D.; Bevers, R. J.; Vertino, A. M.; Cerniglia, C. E. *Xenobiotica* **1994**, *24*, 1077−1083.
(26) Treiber, A.; Dansette, P. M.; El Amri, H.; Girault, J.-P.; Ginderow, D.; Mornon, J.-P.; Mansuy, D. *J. Am. Chem. Soc.* **1997**, *119*, 1565−1571.
(27) Jakobsen, H. J.; Larson, E. H.; Lawesson, S.-O. *Tetrahedron* **1963**, *19*, 1867−1882.

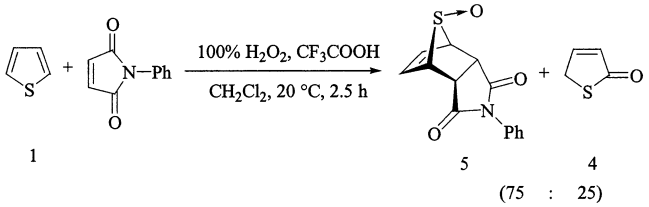


FIGURE 2. Product distribution in the TFA-catalyzed peracid oxidation of thiophene (**1**) in the presence of *N*-phenylmaleimide.

correlate with the strength of the oxidant. Though within the series of substituted peracetic acids there was a decrease of the relative yields of thiophen-2-one (**4**) ranging from 11% with trifluoroperacetic acid to 1% with chloroperacetic acid, this correlation did not hold with dimethyldioxirane. Dimethyldioxirane is one of the strongest known oxidants,[28] as suggested by the short reaction time of 0.5 h (entry 9), but did not yield any thiophen-2-one (**4**). These results suggest the presence of the acid as a prerequisite for thiophen-2-one (**4**) formation. The extent of thiophen-2-one (**4**) formation clearly correlated with the acidity of the reaction medium in the order trifluoroacetic acid ($pK_a = 0.23$, 11% of **4**)[29] > trichloroacetic acid ($pK_a = 0.70$, 7%) > dichloroacetic acid ($pK_a = 1.48$, 3%) > chloroacetic acid ($pK_a = 2.85$, 1%) > acetic acid ($pK_a = 4.75$, no formation of **4**). Accordingly, no thiophen-2-one (**4**) was found in the oxidations with *m*-CPBA and dimethyldioxirane (entries 1 and 9). In control experiments, it was shown that **4** did not undergo further oxidation with *m*-CPBA and dimethyldioxirane under the applied experimental conditions. The importance of acid catalysis for the formation of **4** was also demonstrated by the addition of water as a competing base. Whereas the relative yields of **4** were about 25% in the apparent absence of water in the oxidations with *m*-CPBA/trifluoroacetic acid and 100% H_2O_2/trifluoroacetic acid (entries 2 and 10) they decreased steadily with increasing amounts of water present in the reaction system down to 2% when 8% H_2O_2 was used (entry 13).

Further mechanistic insight was gained by the use of *N*-phenylmaleimide as a competing dienophile. Oxidation of thiophene (**1**) with 0.2 equiv of water-free H_2O_2 in the presence of trifluoroacetic acid yielded the literature-known Diels–Alder adduct of thiophene-*S*-oxide and *N*-phenylmaleimide **5**[26] and thiophen-2-one (**4**) as the only products. The product distribution was determined as 75:25 in favor of **5** by quantitative ^{1}H NMR spectroscopy on the crude reaction mixture (Figure 2). In the chemistry of arene oxides, a characteristic 1,2-hydride shift, the so-called NIH-shift,[30,31] was established as a mechanistic feature of the spontaneous isomerization of arene epoxides to the corresponding phenols.[32,33] The oxidation of 2,5-dideuterated thiophene (**1-D**)[34] was performed with

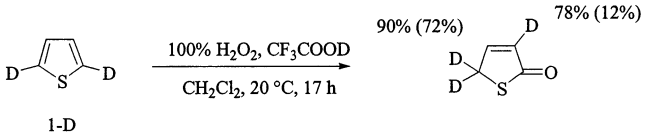


FIGURE 3. Oxidation of 2,5-dideuterated thiophene (**1-D**) with trifluoroperactic acid. Percentages indicate the degree of deuteration in the respective positions. Percentages in parentheses indicate the degree of deuteration in a control experiment monitoring the rate of H/D exchange of thiophen-2-one.

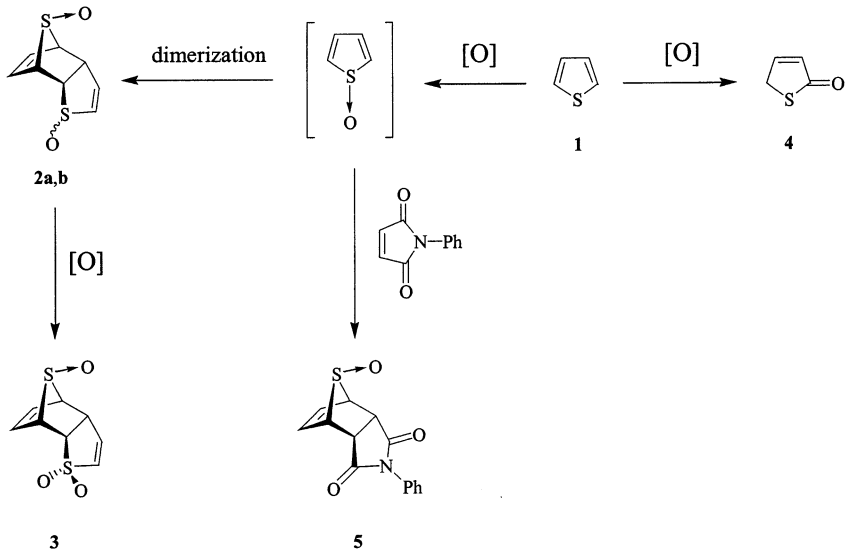
water-free H_2O_2 and deuterated trifluoroacetic acid under experimental conditions identical to those used for the oxidation of unlabeled thiophene (**1**) (Figure 3). The extent of deuterium incorporation in the different positions of thiophen-2-one (**4**) was determined by quantitative ^{1}H NMR spectroscopy directly from the crude reaction mixture to avoid postexperimental H/D exchange upon workup. In this experiment, 78% and 90% of deuteration was determined in positions 3 and 5 of thiophen-2-one (**4**). In a control experiment, the rate of H/D exchange in thiophen-2-one (**4**) was determined by ^{1}H NMR spectroscopy in $CDCl_3$ in the presence of 50 equiv of deuterated trifluoroacetic acid. After 17 h, i.e., the reaction time of the thiophene oxidation experiment, deuteration was 12% and 72% in positions 3 and 5, respectively. The yield of deuterated thiophen-2-one (**4**) was 15%, i.e., comparable to that obtained in the oxidation of nonlabeled thiophene (**1**).

Discussion

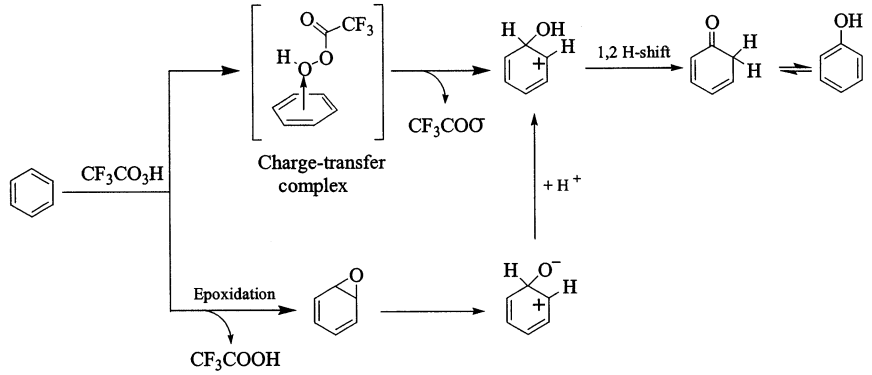
In an earlier communication we described for the first time the formation of thiophene-*S*-oxide dimers **2a,b** as the products of thiophene metabolism in vivo in rats and in vitro using rat liver microsomes.[26] The H_2O_2/trifluoroacetic acid system was introduced as a selective tool for the controlled mono-oxygen transfer to thiophene mimicking the enzymatic oxidation process of thiophene. Protonation of the sulfoxide under the acidic reaction conditions was proposed as the protective mechanism against a second electrophilic attack of the oxidant on the sulfur atom thus preventing the oxidation to the thiophene sulfone. The exact chemical structures of the two diastereoisomeric thiophene-*S*-oxide dimers, **2a** and **2b**, were elucidated by a combination of X-ray crystallography data and a sequence of chemical reactions. Furthermore, sesquioxide **3** was identified as a secondary oxidation product rather than the suspected product of a Diels–Alder reaction between thiophene-*S*-oxide and thiophene-*S*,*S*-dioxide (Scheme 1). Whereas the formation of all these products can be rationalized by an initial oxidation of the sulfur atom of thiophene (**1**), the mechanism behind the formation of thiophen-2-one (**4**) is less evident. Aromatic hydroxylations are commonly described in the cytochrome P450-catalyzed biotransformations of thiophene-containing drugs.[23,35–39] Their exact

(28) Adam, W.; Hadjiarapoglou, L.; Curci, R.; Mello, R. In *Organic Peroxides*; J. Wiley and Sons: New York, 1992; pp 195–217.
(29) pK_a values of the substituted acetic acids were taken from: *CRC Handbook of Chemistry and Physics*, 54th ed.; Weast, R. C.; CRC Press: Cleveland, 1973.
(30) Guroff, G.; Daly, J. W.; Jerina D. M.; Renson, J.; Witkop, B.; Udenfriend, S. *Science* **1967**, *157*, 1524–1530.
(31) Daly, J. W.; Jerina, D. M.; Witkop, B. *Experientia* **1972**, *28*, 1129–1164.
(32) Jerina, D. M.; Daly, J. W. *Science* **1974**, *185*, 573–582.
(33) Jerina D. M.; Daly, J. W.; Witkop, B.; Zaltzman-Nirenberg, P.; Udenfriend, S. *Biochemistry* **1970**, *9*, 147–155.
(34) Östman, B.; Olsen, S. *Ark. Kemi* **1960**, *15*, 275–282.
(35) Mansuy, D.; Dansette, P. M.; Foures, C.; Jaouen, M.; Moinet, G.; Bayer, N. *Biochem. Pharmacol.* **1984**, *33*, 1429–1435.
(36) Mori, Y.; Sakai, Y.; Kuroda, N.; Yokoja, F.; Toyoshi, K.; Hori, M.; Baba, S. *Drug Metab. Dispos.* **1984**, *12*, 767–771.
(37) Ishihara, S.; Tsuyuki, Y.; Tomisawa, H.; Fukasawa, H.; Nakayama, N.; Tateishi, M.; Joly, R. *Xenobiotica* **1984**, *14*, 727–739.

SCHEME 1. Mechanistic Pathways for Product Formation in the Acid-Catalyzed Peracid Oxidation of Thiophene (1)



SCHEME 2. Mechanistic Alternatives for the Oxidation of Aromatic Hydrocarbons with Trifluoroperacetic Acid

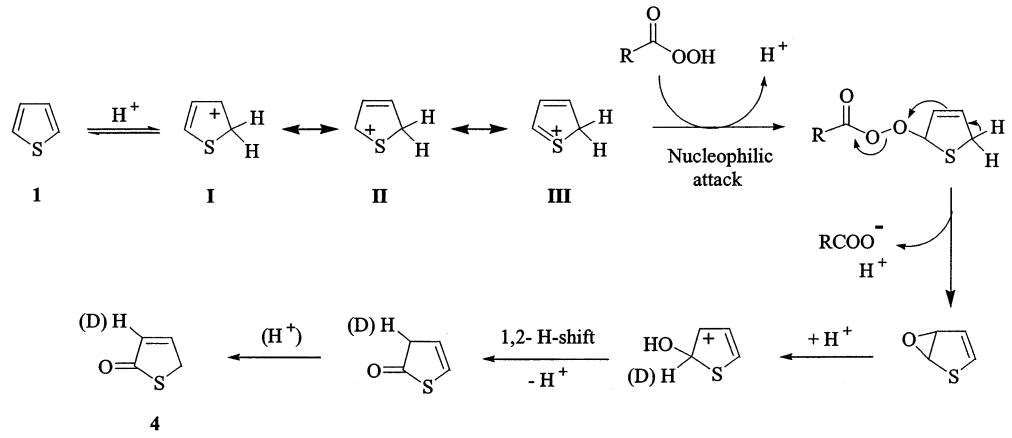


mechanism of formation and particularly the nature of the primary reactive intermediate are still a matter of scientific debate. Reports on the direct hydroxylation of thiophene derivatives by chemical means are rare. The formation of juglone was reported together with the expected 1,4-naphthoquinone in the oxidation of thiophene with perbenzoic acid in the presence of 1,4-benzoquinone as trapping agent.[40] Recently, the formation of thiophen-2-one was reported as the result of a Pummerer-like rearrangement of 2,5-bis(trimethylsilyl)-thiophene-*S*-oxide in the presence of trifluoroacetic anhydride.[41]

The product ratios in the oxidations of thiophene (**1**) with *m*-CPBA and H_2O_2 in the presence of an excess of trifluoroacetic acid (entries 2 and 10 in Table 1) were about 75:25 in favor of the Diels–Alder products and not affected by the use of N-maleinimide as a competing trapping agent. It appears therefore unlikely that the dimers **2a**,**b** and thiophen-2-one (**4**) are formed via the same primary intermediate, i.e., thiophene-*S*-oxide. In analogy to thiophene, the oxidation of alkyl-substituted benzene derivatives with trifluoroperacetic acid was also described to lead to phenolic products.[42–45] Mechanistic considerations postulated the initial formation of a charge-transfer complex[46] or a direct epoxidation of the aromatic ring[33] (Scheme 2). Common to both mechanisms is the occurrence of cationic intermediates that undergo a characteristic 1,2-hydride shift, the so-called NIH-shift,[30] on their way to the final phenol products. If either of these two mechanisms applied for the formation of thiophene-2-one (**4**) the extent of its formation should correlate with the electrophilicity of the oxidant. The results of the oxidation with dimethyldioxirane, however, clearly show that such a correlation does not exist since the strongest oxidant used in these experiments did not

(38) Nishikawa, T.; Nagata, O.; Tanbo, K.; Yamada, T.; Takahara, Y.; Kato, H.; Yamamoto, Y. *Xenobiotica* **1985**, *15*, 1053–1060.
(39) Lynch, M. J.; Mosher, F. R.; Levesque, W. R.; Newby, T. J. *Drug Metab. Rev.* **1987**, *18*, 253–288.
(40) Torsell, K. *Acta Chim. Scand.* **1976**, *B30*, 353–357.
(41) Sato, S.; Zhang, S.-Z.; Furukawa, N. *Heteroat. Chem.* **2001**, *12*, 444–450.
(42) Chambers, R. D.; Goggin, P.; Musgrave, W. K. R. *J. Chem. Soc.* **1959**, 1804–1807.
(43) Buehler, C. A.; Hart, H. *J. Am. Chem. Soc.* **1963**, *85*, 2177–2178.
(44) Waring, A. J.; Hart, H. *J. Am. Chem. Soc.* **1964**, *86*, 1454–1456.
(45) Hart, H.; Buehler, C. A. *J. Org. Chem.* **1964**, *29*, 2397–2400.
(46) Jerina, D. M.; Daly, J. W.; Witkop, B. *Biochemistry* **1971**, *10*, 366–372.

SCHEME 3. Proposed Mechanism for Formation of Thiophen-2-one (4)



yield any thiophen-2-one (**4**) at all. Moreover, these mechanisms do not explain the need for acid catalysis.

In agreement with all experimental observations we propose the mechanism depicted in Scheme 3.

The initial step of this sequence constitutes the protonation of thiophene (**1**), the protonated species being represented by the mesomeric structures **I**−**III**. The assumption of a primary protonation is in agreement with the fact that formation of thiophen-2-one (**4**) is favored in the presence of strong acids and with the observation that increasing concentrations of water, presumably acting as a competing base, suppressed its formation. As a result of the involvement of the sulfur lone pair in the delocalization of the positive charge, protonation of thiophene might also serve as a protective mechanism against the predominant oxidation on the sulfur atom. On the basis of isotope exchange studies, mesomeric structure **II** in Scheme 3 has been shown to be thermodynamically favored by a factor of 1000 compared to structure **I**[34] and thus represents the most likely target for nucleophilic attack of the peracid leading to a mixed acyl-allyl-peroxide. This peroxide intermediate may undergo intramolecular epoxidation, presumably supported by acid catalysis, yielding the highly unstable thiophene 2,3-epoxide. Opening of the epoxide, either spontaneously or acid-catalyzed, results in a cationic intermediate that might stabilize by a 1,2-hydride shift leading to the final thiophen-2-one (**4**) after acid-catalyzed isomerization of the double bond. Support for this hypothesis is given by the incorporation of deuterium into position 3 of thiophen-2-one (**4**) when the experiment is performed with the deuterated analogue **1-D**. Since the rate of deuterium exchange was much slower in the control experiment, the 1,2-hydride shift offers a reasonable explanation for the observed degree of deuteration in position 3. It is noteworthy that there was no obvious difference in the yield of thiophen-2-one (**4**) in the oxidation experiments of labeled and nonlabeled thiophene (**1**), indicating that the initial protonation equilibrium does not represent the rate-limiting step in the overall reaction sequence.

Conclusion

In summary, we have shown that the oxidation of thiophene (**1**) with peracids in the presence of an excess of acid leads to the formation of thiophene-*S*-oxide dimers **2a**,**b** and thiophene-2-one (**4**). The mechanism of formation for the dimers **2**, as well as for the secondary oxidation product **3**, can be rationalized by an initial oxidation at the sulfur atom to yield thiophene-*S*-oxide followed by a Diels−Alder-type dimerization. Thiophen-2-one (**4**) is most likely formed by an independent reaction pathway involving primary protonation and nucleophilic attack of the oxidant at the 2-position of the thiophene ring. Further intramolecular epoxidation, followed by ring opening of the highly strained thiophene epoxide, and a 1,2-hydride shift complete the reaction sequence.

Experimental Section

General Aspects. ^{1}H and ^{13}C NMR spectra were recorded at 250 and 63 MHz, respectively, the resonance of the solvent being used as internal standard. Column chromatography was done using silica gel (70−230 mesh) with an adsorbent/substrate ratio of about 100:1. Thin-layer chromatography was performed on silica gel coated aluminum plates. Products were visualized by using iodine vapor or by means of a 5% ethanolic solution of molybdophosphoric acid. Melting points are uncorrected. All starting materials and solvents were of highest commercially available quality and used without further purification. 30% and 85% hydrogen peroxide were of commercial origin; 8%, 15%, and 100% hydrogen peroxide were prepared either by dilution with water or by treatment of 30% hydrogen peroxide with trifluoroacetic anhydride. 2,5-Dideuterated thiophene (**1-D**)[34] and dimethyldioxirane[47] were prepared following literature procedures.

General Procedure for Peracetic Acid Oxidation of Thiophene (1). To a solution of thiophene (**1**, 533 mg, 6.63 mmol, 0.50 mL) in 10 mL of methylene chloride was added at ambient temperature 3 equiv (19.5 mmol) of the acetic acid derivative and 0.17 equiv (1.13 mmol) of the appropriately diluted H_2O_2. Upon stirring, the initially biphasic system became rapidly homogeneous. Stirring at ambient temperature was continued until no more peroxide could be detected using KI/starch. The crude reaction mixture was then extracted three times with 10 mL of water for the separation of the Diels−Alder products **2** and **3**. The aqueous phase was evaporated to dryness at 25 °C/0.1 Torr, and the residue was taken up in 5 mL of water and neutralized to pH 6 with saturated $NaHCO_3$ solution. The crude product containing a mixture of the two thiophene-*S*-oxide dimers, **2a** and **2b**, and the sesquioxide **3** was again evaporated to dryness (25 °C/0.1 Torr), and the individual components were quantified by HPLC on a Hypersil MOS column (5 μm, 250 × 4.6 mm) with an isocratic eluent

(47) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377−2380.

(98:2 H_2O/CH_3CN) and a flow rate of 1.0 mL/min. Authentic samples of all three analytes [26] were used for external calibration. Thiophen-2-one (**4**) was isolated from the organic phase by drying over $MgSO_4$ and evaporation of the solvent at 20 °C/15 Torr. The crude product was submitted to a short (5 cm) silica gel column and eluted with methylene chloride. Thiophen-2-one (**4**) was quantified from the crude eluate by ^{1}H NMR spectroscopy using 1,2-dichloroethane as internal standard. Thiophene-*S*-oxide dimers **2a** and **2b**, sesquioxide **3**, and thiophen-2-one (**4**) were structurally identified by comparison of their NMR and IR spectra with literature data[26,48] (for **2** and **3**) and those of an authentic sample (for **4**).[27] The results of the peracetic acid oxidations of thiophene are summarized in Table 1.

Oxidation of Thiophene (1) with *m*-CPBA. To a solution of thiophene (**1**, 533 mg, 6.33 mmol, 0.50 mL) in 10 mL of methylene chloride was added a solution of *m*-CPBA (233 mg, 1.35 mmol, 0.21 equiv) in 1.0 mL of methylene chloride. The mixture was stirred at ambient temperature for 192 h until no more peroxide could be detected by using KI/starch. After addition of 0.1 mL of trifluoroacetic acid, the crude reaction mixture was extracted three times with 10 mL of water. The separation and quantification of Diels−Alder products (**2** and **3**) and thiophen-2-one (**4**) was performed as described in the general method above and yielded sesquioxide **3** (136 mg, 76%) as the only detectable product.

Oxidation of Thiophene (1) with *m*-CPBA in the Presence of Trifluoroacetic Acid. To a solution of thiophene (**1**, 533 mg, 6.33 mmol, 0.5 mL) in 10 mL of methylene chloride at ambient temperature was added trifluoroacetic acid (2.23 g, 19.5 mmol, 1.5 mL) and a solution of *m*-CPBA (229 mg, 1.33 mmol, 0.21 equiv) in 1.0 mL of methylene chloride. The reaction mixture was stirred for 15 h at ambient temperature until no more peroxide could be detected using KI/starch. The extraction and quantification of Diels−Alder products yielded the thiophene-*S*-oxide dimers (**2a,b**; 53.1 mg, 48%) but no sesquioxide **3**. The organic phase was dried over $MgSO_4$ and cooled to −40 °C to precipitate the *meta*-chlorobenzoic acid. After filtration, the solvent was removed at 15 Torr/20 °C, and thiophen-2-one (**4**, 15.9 mg, 14%) was quantified by ^{1}H NMR spectroscopy.

Oxidation of Thiophene (1) with Dimethyldioxirane. Thiophene (**1**, 53.3 mg, 0.633 mmol, 50 μL) was added to a solution of dimethyldioxirane (9.38 mg, 0.127 mmol, 0.20 equiv) in acetone. Stirring at room temperature was continued for 0.5 h until no more peroxide could be detected using KI/starch. The solvent was removed at 15 Torr/20 °C, and the crude reaction mixture was taken up in 10 mL of methylene chloride. Standard workup yielded sesquioxide **3** (6.3 mg, 23%) as the only detectable product.

(48) Merrill, R. E.; Sherwood, G. *J. Heterocycl. Chem.* **1977**, *14*, 1251−1253.

Oxidation of Thiophene (1) with Anhydrous H_2O_2 in the Presence of *N*-Phenylmaleimide and Trifluoroacetic Acid. A solution of water-free trifluoroperacetic acid was prepared by mixing 30% H_2O_2 (125 μL, 1.10 mmol), trifluoroacetic anhydride (1.02 g, 4.86 mmol, 686 μL), and trifluoroacetic acid (1.14 g, 10.0 mmol, 780 μL) in 10 mL of methylene chloride. To this mixture was added *N*-phenylmaleimide (190 mg, 1.10 mmol) and thiophene (**1**, 533 mg, 6.33 mmol, 0.5 mL). The solution was stirred at ambient temperature for 3 h until no more peroxide could be detected using KI/starch. The crude reaction mixture was then washed twice with 10 mL of water and once with 10 mL of a saturated $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$, and the solvent was removed at 15 Torr/20 °C. The product distribution of Diels−Alder adduct **5** [26] and thiophen-2-one (**4**) was determined as 75:25 directly from the crude reaction mixture by quantitative ^{1}H NMR spectroscopy using 1,2-dichloroethane as internal standard.

Oxidation of 2,5-Deuterated Thiophene (1-D) with Anhydrous H_2O_2 and Deuterated Trifluoroacetic Acid. To a solution of deuterated thiophene (**1-D**, 545 mg, 6.33 mmol, 0.5 mL) in 10 mL of methylene chloride was added at ambient temperature 30% H_2O_2 (125 μL, 1.10 mmol), trifluoroacetic anhydride (1.02 g, 4.86 mmol, 686 μL), and deuterated trifluoroacetic acid (1.14 g, 10.0 mmol, 780 μL). Stirring at ambient temperature was continued for 17 h until no more peroxide could be detected using KI/starch. The crude reaction mixture was three times extracted with 10 mL of water, the organic phase was dried over $MgSO_4$, and the solvent was evaporated at 15 Torr/20 °C. The residual oil was dissolved in 0.8 mL of $CDCl_3$, and the yield and the extent of deuteration in thiophen-2-one (**4**) were determined by quantitative ^{1}H NMR spectroscopy using 1,2-dichloroethane as internal standard.

Determination of H/D Exchange Rate of Thiophen-2-one (4). Thiophene-2-one (**4**, 5.00 mg, 49.9 μmol) was dissolved in 0.8 mL of $CDCl_3$, and 5.0 μL of 1,2-dichloroethane was added as internal standard. After a reference spectrum had been recorded, deuterated trifluoroacetic acid (285 mg, 2.50 mmol, 50 equiv) was added. H/D exchange in thiophen-2-one (**4**) was monitored at regular time intervals. After 17 h, 12% and 72% of H/D exchange was observed in positions 3 and 5, respectively.

Acknowledgment. The author thanks the Deutsche Forschungsgemeinschaft for a postdoctoral fellowship, Dr. Patrick Dansette from the CNRS (URA400), Université René Descartes, Paris for fruitful scientific discussions, and Dr. Thomas Weller for reviewing the manuscript.

JO0202177