TABLE V

EFFECT OF SOLVENT DIELECTRIC ON SAPONIFICATION RATE

Ester	$\frac{\mathrm{d} \log k_2}{\mathrm{d}\ 1/D^a}$	Cor. coeff.	$\frac{\mathrm{d} \log k_2}{\mathrm{d}\ 1/D^b}$
CH_3CO_2Et	2.0	0.996	1.8
$CH_3CH_2CO_2Et$	1.6	0.999	1.4
$CH_3CH_2CH_2CO_2Et$	1.9	0.992	2.0
$(CH_3)_2CHCO_2Et$	2.5	0.997	2.5
$C_6H_5C(CH_3)_2CH_2CO_2Et$	3.3	0.996	3.3
$(CH_3CH_2)_2CHCO_2Et$	3.9	0.993	3.9

[a] Calculated by simple regression of log k_2 *vs.* $1/D$. [b] Calculated by use of eq. 4; $(\mathrm{d}\ N_{\mathrm{DMSO}})/(\mathrm{d}\ 1/D) = 1.20$ with correction coefficient = 0.994 (data obtained from ref. 9).

0.50 mole fraction solvent composition, are necessary for the straight-chain esters, while one set of linear equations satisfactorily correlates the rate data for the branched esters.

If the medium effect on rate is entirely due to dielectric effects, the following relationship should be valid. The values of $(\mathrm{d} \ln k)/(\mathrm{d}\ 1/D)$ obtained by simple regression analysis and by use of eq. 4 are

$$\frac{\mathrm{d} \ln k}{\mathrm{d}\ 1/D} = \frac{\mathrm{d}\ N_{\mathrm{DMSO}}}{\mathrm{d}\ 1/D} \frac{\mathrm{d} \ln k}{\mathrm{d}\ N_{\mathrm{DMSO}}} \tag{4}$$

recorded in Table V. The agreement between the two sets of values is good and indicates that electrostatic interaction energies are of the correct order of magnitude to account for the observed rate changes over the entire solvent-composition range for the branched esters and over the 0.20 to 0.50 mole fraction of DMSO range for the linear esters.

The rate enhancement in the region of excess DMSO for the straight-chain esters can then be attributed to specific solvation effects, *i.e.*, to short-range nonelectrostatic forces sensitive to steric bulk. Presumedly, this would involve primarily the DMSO molecules which is in accord with the enhanced ability of DMSO to stabilize extended charged structures such as transition states.[5,12]

Experimental Section

All boiling points are uncorrected for stem exposure. Purity of all distilled chemicals was established by gas chromatography.

Ethyl Esters.—Ethyl acetate, b.p. 77°, ethyl propionate, b.p. 99°, ethyl *n*-butyrate, b.p. 122°, and ethyl isobutyrate, b.p. 109–110°, were commercial samples fractionally distilled prior to use. Ethyl β-phenylisovalerate, b.p. 89° (0.4 mm.), was prepared according to published procedure.[1] Ethyl 2-ethylbutyrate was prepared in 85% yield from 2-ethylbutyryl chloride and ethanol, b.p. 149°, lit.[13] b.p. 148.7–150°.

Purification of Solvent.—Dimethyl sulfoxide was purified by distillation from calcium hydride and was stored over 4A Molecular Sieves. Analysis by g.l.p.c. did not reveal the presence of any significant amount of impurity.

Rate Measurements.—The technique and method used were those reported in previous investigations.[1,2]

Treatment of Kinetic Data.—The simple and multiple regression analyses were executed by an IBM 1620 computer.

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(12) D. J. Cram, B. Rickborn, C. A. Kingsbury, and P. Haberfield, *J. Am. Chem. Soc.*, **83**, 5835 (1961).

(13) F. C. Frostick and C. R. Hauser, *ibid.*, **71**, 1350 (1949).

Solvent Effects in the Oxidation of Sulfur Compounds. The Base-Catalyzed Oxidation of Alkylthiophenes

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The base-catalyzed oxidation of several alkylthiophenes and toluene with molecular oxygen has been studied in the polar solvent, hexamethylphosphoramide (HMPA). 2-Methyl- and 2,5-dimethylthiophene were converted to thiophene-2-carboxylic acid under the reaction conditions employed. 3-Methylthiophene and toluene were oxidized to thiophene-3-carboxylic acid and benzoic acid, respectively. The initial rates of oxidation of these compounds were measured from the amount of oxygen consumed as a function of time and have been calculated relative to the rate observed for toluene in KO-*t*-Bu–HMPA at 80°. Of particular interest was the fact that 2-methylthiophene oxidized about 50 times faster than the 3 isomer and that $k_{\mathrm{ox}}^{\mathrm{KO}\text{-}t\text{-}\mathrm{Bu}}/k_{\mathrm{ox}}^{\mathrm{KOH}}$ for 2-methylthiophene at 80° was 25. Explanations for the observed results are presented and discussed. In addition, a brief study on the low-temperature anionic oxidation of thienylaldehyde and 2-thienyl methyl ketone was also carried out. Mechanistically, it would appear that the reaction proceeds by an anion-radical mechanism which leads to unstable hydroperoxide intermediates.

Previous studies on the anionic oxidation of sulfur compounds have shown that polar solvents have a marked effect on the rate of oxidation of mercaptans (thiols)[1-3] and hydrogen sulfide.[4] Similar observations have also been noted in the oxidation of acidic and nonacidic hydrocarbons,[5,6] the isomeric picolines,[7] and ketones.[8] An examination of the literature disclosed that anionic oxidation of weakly acidic sulfur compounds such as the alkylthiophenes has not been previously attempted. In fact, most studies on the oxidation of heterocyclic aromatic sulfur compounds have been concerned with the oxidation of thiophene or benzothiophenes in the presence of strong oxidizing agents

(1) T. J. Wallace and A. Schriesheim, *Tetrahedron Letters*, **No. 17**, 1131 (1963), and references therein.

(2) T. J. Wallace, H. Pobiner, and A. Schriesheim, *J. Org. Chem.*, **29**, 888 (1964).

(3) T. J. Wallace, N. Jacobson, and A. Schriesheim, *Nature*, **201**, 609 (1964).

(4) W. Fuchs, German Patent 895,539 (June 10, 1960).

(5) (a) Y. Sprinzak, *J. Am. Chem. Soc.*, **80**, 5449 (1958); (b) G. A. Russell, *et al.*, *ibid.*, **84**, 4154 (1962); (c) *ibid.*, **84**, 2652 (1962), and references therein; (d) G. A. Russell, "Peroxide Reaction Mechanisms," J. O. Edwards, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p. 107 ff; (e) G. A. Russell, *Chem. Eng. News*, **40**, 49 (April 20, 1964); (f) G. A. Russell and E. G. Janzen, Preprints, Petroleum Division, 148th National Meeting of the American Chemical Society, Detroit, Mich., Sept. 1964, Vol. 9, No. 4, p. D-129.

(6) T. J. Wallace, A. Schriesheim, and N. Jacobson, *J. Org. Chem.*, **29**, 2907 (1964).

(7) W. Bartok, D. D. Rosenfeld, and A. Schiresheim, *ibid.*, **28**, 410 (1963).

(8) W. E. Doering and R. M. Haines, *J. Am. Chem. Soc.*, **76**, 482 (1954).

such as hypochlorite,[9] vanadium pentoxide,[10] nitric acid,[11] and hydrogen peroxide.[12,13] These facts, coupled with the poor yields of thiophenecarboxylic acids obtained by the radical oxidation of methylthiophenes, suggested that an investigation on the feasibility of anionic oxidation of these species would be of considerable theroretical and synthetic value.

Results

The stability of several dipolar solvents toward attack by molecular oxygen has been investigated in the presence of various bases for the purpose of uncovering a solvent that could be used to study the base-catalyzed oxidation of weakly acidic sulfur compounds. The three dipolar solvents investigated were dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and hexamethylphosphoramide (HMPA). The results of this study are summarized in Table I. DMSO oxidized readily at room temperature and 80° in the presence of potassium hydroxide.[14] DMF, though stable at room temperature, decomposed at 80° in the presence of potassium hydroxide. HMPA was found to be highly stable to oxygen at room temperature and 80° even in the presence of potassium *t*-butoxide. For this reason, all alkylthiophene oxidations reported in this paper were carried out in HMPA.

Table I

Stability Studies on Polar Solvents in the Presence of Molecular Oxygen

Solvent (75 ml.)	Base (mole)	Temp., °C.	Time, hr.	Oxygen consumed, mmoles
DMSO	KOH (0.1)	23.5	68	6.29
DMSO	KOH (0.1)	80	28	50.42
DMF	KOH (0.1)	23.5	21	0
DMF[a]	KOH (0.1)	80	18	~0
HMPA	KOH (0.1)	23.5	69	0
HMPA	KOH (0.1)	80	54	1.29
HMPA	KO-*t*-Bu (0.15)	23.5	70	2.10
HMPA	KO-*t*-Bu (0.15)	80	26	8.00
HMPA	NaOMe (0.1)	23.5	22	0.10
DMF	NaOMe (0.1)	23.5	20	0

[a] This solvent undergoes some hydrolysis on prolonged contact with base at this temperature.

2-Methylthiophene, 3-methylthiophene, 2,5-dimethylthiophene, and toluene were oxidized to their corresponding carboxylic acids in 75 ml. of 2 *M* KO-*t*-Bu in HMPA at 80°. In addition, 2-methylthiophene was also oxidized to thiophene-2-carboxylic acid in 2 *M* KOH in HMPA at 80° and 2 *M* KO-*t*-Bu in HMPA at 23.5°. 3-Methylthiophene would not oxidize under the latter conditions and thiophene itself could not be oxidized in KO-*t*-Bu–HMPA at 80°. The individual reaction conditions employed and the product yields obtained are summarized in Table II. Further, the rates of oxidation obtained under these conditions are also listed in Table II and are calculated relative to the rate of toluene oxidation in KO-*t*-Bu–HMPA at 80°. All rates of oxidation were calculated from the initial moles of oxygen consumed as a function of time using the oxidation apparatus described in the Experimental Section. The rate plots shown in Figure 1 for 2-methylthiophene are typical of those obtained in all oxidations. The rate is fastest in the initial stages of the oxidation and gradually decreased with time. It is interesting to note that 2-methyl- and 2,5-dimethylthiophene are similar in reactivity and only slightly more reactive than toluene. However, under the same conditions, 2-methylthiophene is 50 times more reactive than the 3 isomer. The rate of oxidation of the 2 isomer was also dependent on temperature and base type; *i.e.*, KO-*t*-Bu (80°) > KO-*t*-Bu (23.5°) ≫ KOH (80°).

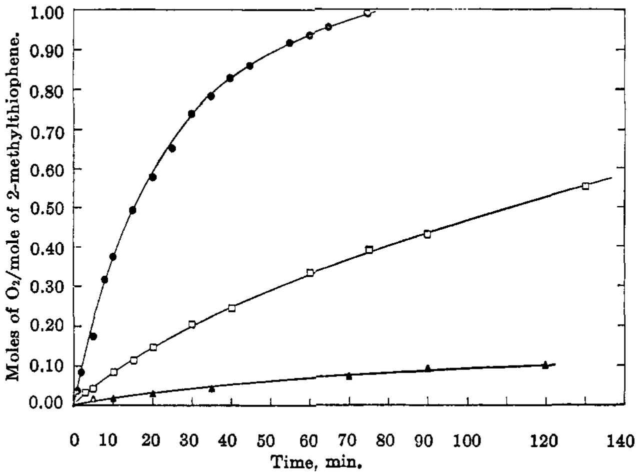

Figure 1.—Rate plots for the oxidation of 2-methylthiophene in HMPA: ●, KO-*t*-Bu–HMPA at 80°; □, KO-*t*-Bu–HMPA at 23.5°; and ▲, KOH–HMPA at 80°.

In the final phase of this work, a brief investigation on the base-catalyzed oxidation of 2-thienylaldehyde and 2-thienyl methyl ketone was undertaken in HMPA at 23.5°. The reaction conditions employed and results obtained under these conditions are summarized in Table III. Both the aldehyde and ketone oxidized readily in HMPA in the presence of either KOH or KO-*t*-Bu. However, even with these relatively acidic thiophene derivatives the rate of oxidation in HMPA was greater than that observed in the protic solvent, *t*-butyl alcohol.

Discussion of Results

The results obtained from the stability studies with the dipolar solvents are fairly easy to interpret. The instability of DMSO is apparently due to formation of the DMSO anion ($CH_3SOCH_2^-$) which, in the presence of oxygen, can be oxidized to carbon dioxide and sulfonic acid. This is reasonable since the α-C–H bonds in DMSO are fairly acidic. Decomposition of DMF at 80° presumably occurs by base-catalyzed hydrolysis since a strong dimethylamine odor was present at the end of the reaction. The unique stability of HMPA under the present reaction conditions is probably due to two factors: steric hindrance to hydrolysis and no α-methyl groups. Hence, one can see the advantage of using this solvent in anionic oxidation reactions which require strong base and elevated temperatures.

The results obtained from the oxidation of the alkylthiophenes offer a new synthetic route to thiophene-

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[9] W. G. Ardagh, W. H. Bowman, and A. S. Weatherburn, *J. Soc. Chem. Ind.* (London), **59**, 27 (1940), and references therein.

[10] E. G. Werner, Dutch Patent 70,105 (June 16, 1952); *Chem. Abstr.*, **47**, 6439*g* (1953).

[11] L. S. Levitt and E. Howard, *J. Am. Chem. Soc.*, **76**, 1951 (1954).

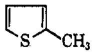
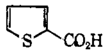
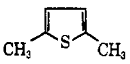
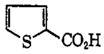
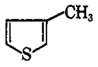
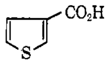
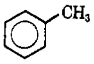
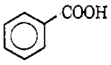
[12] H. Gilman and D. L. Esmay, *ibid.*, **74**, 2021 (1952).

[13] W. Davies, *et al.*, *Chem. Ind.* (London), 804 (1952).

[14] The oxidation products of DMSO are methanesulfonic acid and carbon dioxide.

TABLE II

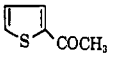
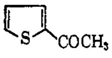
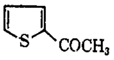
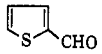
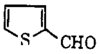
RESULTS FROM THE OXIDATION OF ALKYLTHIOPHENES IN HMPA

Reactant (0.5 moles)	Base (0.15 mole)	Temp., °C.	Product	% yield[a]	Reaction time, hr.	Rate[b] of oxygen consumption	Rate relative to toluene
	KO-*t*-Bu	80		75.8	70	0.0380 0.0320	1.50[b]
	KO-*t*-Bu	23.5		19.9	48	0.0075	0.32
	KOH	80		2.2	25	0.0013	0.06
	KO-*t*-Bu	80		13.4	23	0.0334	1.40
	KO-*t*-Bu	80		19.2	70	0.0008 0.0007	0.03[c]
	KO-*t*-Bu	80		47.8	24	0.0230	1.00

[a] All yields are based on the theoretical yield of product from starting material. [b] Rate of oxidation = mole of oxygen/mole of reactant, min. [c] Based on the average rate for two separate reactions.

TABLE III

RESULTS FROM THE BASE-CATALYZED OXIDATION OF THIENYLALDEHYDE AND THIENYL METHYL KETONE AT 23.5°

Reactant (mole)	Base–solvent (molarity, ml.)	% yield of thiophene-2-carboxylic acid	Reaction time, hr.	Rate of oxygen consumption × 10^2
 (0.059)	KO-*t*-Bu–HMPA (2, 50)	57.1	1	2.45
 (0.050)	KOH–HMPA (2, 50)	26.3	20	0.41
 (0.050)	KO-*t*-Bu–*t*-BuOH (0.75, 200)	28.8	23	0.25
	KOH–HMPA (2, 50)	80.6	91	0.25
 (0.045)	KO-*t*-Bu–HMPA (2, 50)	40.0	21	8.13

carboxylic acids. The fact that the oxidation of 2-methylthiophene occurred even in the presence of potassium hydroxide is another example of the unique ability of polar solvents to activate weakly acidic carbon–hydrogen bonds. Formation of thiophene-2-carboxylic acid from 2,5-dimethylthiophene is presumably due to decarboxylation of the diacid during the reaction. Mechanistically, the reaction probably involves formation of the anion and subsequent reaction of the anion with oxygen by one of two possible paths. One possi-

$$\text{ArCH}_3 + \text{RO}^- \rightleftharpoons \text{ArCH}_2^- + \text{ROH} \qquad (1)$$

bility is the direct addition of oxygen to the carbanion (eq. 2) followed by proton abstraction and decomposi-

$$\text{ArCH}_2^- + \text{O}_2 \longrightarrow \text{ArCH}_2\text{OO}^- \qquad (2)$$

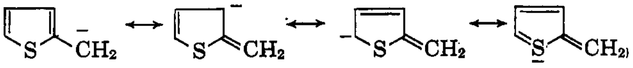
tion of the resulting hydroperoxide to aldehyde. Peroxide anions of this type have been postulated as possible intermediates in the anionic oxidation of 2-nitropropane.[15] A second possible mode of reaction would be direct transfer of an electron to oxygen (eq. 3), reaction of the resulting radical with oxygen (eq. 4), and subsequent abstraction of a hydrogen atom to form the hydroperoxide. In view of recent evidence that car-

$$\text{ArCH}_2^- + \text{O}_2 \longrightarrow \text{ArCH}_2\cdot + \bar{\text{O}}_2 \qquad (3)$$

$$\text{ArCH}_2\cdot + \text{O}_2 \longrightarrow \text{ArCH}_2\text{OO}\cdot \qquad (4)$$

banion oxidations of this general type often involve intermediate free radicals,[5f] the latter seems most reasonable. Under the present reaction conditions, the intermediate hydroperoxides would be unstable and decomposition by several competing reaction paths could occur. In either case, however, a deviation from the usual behavior in free-radical autoxidations of these systems would be expected. The initial rate of oxidation should be rapid. As can be seen in Figure 1, this does occur. Even in the presence of potassium hydroxide no induction period was observed with 2-methylthiophene. The decrease in rate with time is apparently due to consumption of the base and increasing concentrations of water and alcohol as the reaction proceeds. The hydroxylic species can inhibit carbanion formation and also deactivate the base and solvent by complex formation. A similar explanation was recently proposed to explain the decreased rate of oxidation of mercaptide ions in DMF.[1] The absence of dimeric products is apparently due to rapid reaction of the intermediate carbanions and radicals with oxygen which is present in excess concentration.

The difference in reactivity of the 2- and 3-methylthiophene is consistent with previous observations[16] and leads to information on the rate-determining step. One possible explanation for this is that the C–H bond in the 2 isomer is more acidic since the carbanion formed can be stabilized by complete delocalization of the negative charge throughout the aromatic ring. In the 3 isomer, delocalization is limited to a 1,3-π system.



This would indicate that ionization (eq. 1), and not reaction of the anion with oxygen, is rate limiting. The rate dependence on base type also supports the proposed rate-determining step since $k_{\text{ox}}^{\text{KO-}t\text{-Bu}}/k_{\text{ox}}^{\text{KOH}}$ for 2-methylthiophene was 25. This is consistent with proton magnetic resonance studies on these compounds[17] which indicated that the C–H bond in the 2

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(15) G. A. Russell, *J. Am. Chem. Soc.*, **76**, 1595 (1954).

(16) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," Interscience Publishers, New York, N. Y., 1960, Chapter III.

(17) C. S. Reddy and T. H. Goldstein, *J. Am. Chem. Soc.*, **83**, 5020 (1961).

isomer is more acidic than that in the 3 isomer but is contrary to the rate-determining step in the oxidation of mercaptide ions and highly resonance-stabilized carbanions where reaction of the anion with oxygen appears to be rate limiting.

The brief study on the oxidation of thienylaldehyde indicates that it is readily oxidized in HMPA. Thus, aldehydes may be unstable intermediates in the methylthiophene oxidations. In the case of the ketone, oxidation probably proceeds through the glycolic acid. It is interesting that the rate of oxidation of this relatively acidic species is also greatly affected by solvent. An extensive investigation on ketone oxidations in various base–HMPA systems will be the subject of a future publication from these laboratories. However, the present results do suggest that a base–alcohol agglomerate is responsible for the decreased rate of oxidation and yield of acidic product.

Experimental Section

Reagents.—Toluene (Matheson Coleman and Bell), 2-methylthiophene, 3-methylthiophene, and 2,5-dimethylthiophene (K & K Laboratories) were at least 99% pure based on gas chromatography. 2-Thienyl methyl ketone and 2-thienylaldehyde (K & K Laboratories) were purified by distillation through 18-in. column equipped with a tantalum-wire spiral. Their physical properties agreed with those reported in the literature. Potassium *t*-butoxide was purchased from the Mine Safety Appliance Co. and was 98% pure. The potassium hydroxide used (Baker Analyzed reagent) was assayed as 86% pure. Sodium methoxide (Matheson Coleman and Bell) was purchased as the reagent grade material. All bases and reagents were stored in a nitrogen drybox.

Purification of Solvents.—*t*-Butyl alcohol, DMF, DMSO (Matheson Coleman and Bell), and HMPA (Eastman Organic Chemicals) were distilled in an inert atmosphere under reduced pressure over 13X Linde Molecular Sieves to remove any water that was present and subsequently stored in a nitrogen drybox. The sieves were previously conditioned by heating them under nitrogen for 4 hr. at 400°C.

Oxidation Experiments.—All base–solvent systems were made up to the desired molarity in a specially adapted, heavy-walled Pyrex glass oxidation flask in a nitrogen dry box. The flask was sealed under nitrogen prior to removal from the drybox and transferred to the oxidation apparatus. The oxygen was stored in a polyethylene balloon under 1 atm. of pressure and passed through a wet-test meter and into a drying tower packed with indicating Drierite before entering the glass reaction vessel containing the reaction mixture. After purging the system with oxygen through the reaction flask side arm, the side arm was sealed with a glass cap, an equilibrium pressure was established, and the reaction was initiated by stirring with a large magnetic stirring bar at 1300 r.p.m. The volume of oxygen consumed at any given time was read off the wet-test meter which allowed estimation of ±1 cc. to be made. In this manner a constant oxygen pressure of 1 atm. was maintained throughout the entire oxidation reaction. A more detailed description of the apparatus can be found elsewhere.[18]

Determination of Products.—Quantitative data were obtained by a separation scheme followed by ultraviolet and infrared spectral measurements of unreacted starting materials and products. The separation scheme involved cyclohexane extraction of the basic oxidation mixture. The aromatic carboxylic acids remained as their salts in the oxidation solvent and were determined by ultraviolet spectroscopy. Unreacted starting materials in the cyclohexane phase were determined by both ultraviolet and infrared spectroscopy. One exception to this scheme was thiophene-3-carboxylic acid. Here the yield was based only on the material isolated by extraction and subsequently recrystallized. Thus, the yield reported represents a minimum value. In addition to the ultraviolet method of analysis, the acidic products were isolated by conventional methods, recrystallized, and characterized further. Benzoic acid (m.p. 122°) had an infrared spectrum identical with an authentic sample. Thiophene-2-carboxylic acid (m.p. 127–129°, lit.[19] m.p. 129°, m.m.p. 128–129°) also had an infrared spectrum identical with an authentic sample of the acid. The thiophene-3-carboxylic acid when isolated had m.p. 136–137° (lit.[19] m.p. 138°) and *m/e* 128, and its infrared spectrum was not identical with that obtained from the 2 isomer. All melting points are uncorrected.

Acknowledgment.—The authors are grateful to the Esso Research and Engineering Company, especially the Process Research Division, for the privilege of publishing this work, to Mr. Joel Haberman who performed much of the experimental work, and to Mr. H. Pobiner for technical assistance in the analytical aspects of the work.

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[18] T. J. Wallace, W. Bartok, and A. Schriesheim, *J. Chem. Educ.*, **40**, 39 (1963).

[19] I. Heilbron, "Dictionary of Organic Compounds," Vol. IV, Oxford University Press, New York, N. Y., 1953.