boiling.[44] After the addition was complete, the mixture was heated at reflux for 3.5 hr. during which time it became light yellow. The cooled mixture was poured into 150 ml. of water and the organic phase was washed repeatedly with 20% aqueous sodium hydroxide, until the washings were no longer colored. The organic phase was washed with 50 ml. of 15% hydrochloric acid, dried over anhydrous magnesium sulfate, concentrated, and distilled. The distillate, b.p. 103–105° (15–17 mm.), weighed 4.5 g. (81%). Gas–liquid chromatography on a 4-ft. di-n-decyl phthalate column at 155° revealed a single peak with retention time equal to that of an authentic mixture of m- and p-chloronitrobenzenes.

Two *ca.* 1-g. samples of this mixture were combined with *ca.* 4 ml. of piperidine in sealed tubes and heated 12 hr. at 50°. Each resulting mixture was transferred to a separatory funnel quantitatively, benzene was added, and the mixture was extracted four times with distilled water. The combined aqueous extracts were heated on the steam bath to drive off traces of benzene, acidified by addition of nitric acid, and diluted quantitatively to 50 ml. Aliquots were titrated potentiometrically with silver nitrate, in duplicate. On the assumption that only p-chloronitrobenzene yielded chloride ion under these conditions, the titer from each run indicated that the chloronitrobenzene mixture was 81.3% *para* isomer.

Reaction of m-Dichlorobenzene with Potassium Amide. The procedure was the same as with p-dichlorobenzene; 21.5 g. of m-dichlorobenzene and 5.4 g. of potassium were used. There was obtained 6.17 g. (33%) of a

chloroaniline mixture, b.p. 97–98° (15–17 mm.). No attempt was made to recover unreacted starting material. Gas–liquid chromatography on a 4-ft. Carbowax 6000 column at 165° revealed two peaks, whose retention times were the same as those of o-chloroaniline and of a mixture of m- and p-chloroaniline. The area under the o-chloroaniline peak indicated 0.7% of this isomer; the same analysis was obtained on the product of a duplicate run from m-dichlorobenzene.

Analysis of Chloroaniline Mixture from m-Dichlorobenzene. The oxidation procedure described above was employed. The product was collected from distillation, b.p. 103–105° (15–17 mm.), in two fractions. The first, 0.6 g., showed several peaks by gas–liquid chromatography. The second, 5.0 g., froze to a solid of m.p. 43–44°. The reported melting point of m-chloronitrobenzene is 44°.[45] The total yield was 74% of theory.

Each fraction was allowed to react with excess piperidine for 21 hr. at 40°, much as described above, and chloride ion in the products was determined in substantially the same way. The yield of chloride ion from the first fraction was 3.65% and from the second, 2.3%. Similar determinations on the products from a similar but independent sequence of reactions from m-dichlorobenzene gave 3.39 and 3.42% chloride ion. We have taken 3.0% as a basis for yield calculations. If this represents the combined yields of o- and p-chloronitrobenzene, and there was no change of isomer ratio on oxidation of the chloroanilines, the composition of the mixture of chloroanilines from reaction of m-dichlorobenzene with potassium amide was 0.7% *ortho*, 97.0% *meta*, and 2.3% *para*.

(44) This procedure is adapted from W. D. Emmons, *J. Am. Chem. Soc.*, 79, 5528 (1957).

(45) V. v. Richter, "The Chemistry of the Carbon Compounds," Vol. III, Elsevier Publishing Co., New York, N. Y., 1946, p. 62.

Cumulative Influence of Methylthio Groups on the π-System Properties of Aromatic Hydrocarbons[1]

Arnold Zweig and John E. Lehnsen

Contribution from the Chemical Department, Central Research Division, American Cyanamid Company, Stamford, Connecticut. Received November 30, 1964

Charge-transfer maxima, polarographic oxidation potentials, and n.m.r. spectral data are reported for methylthio-substituted benzenes, anisoles, and N,N-dimethylanilines. Relative energy levels for 25 compounds are found to agree with polarographic oxidation potentials with a standard deviation of as little as 0.03 v. with six Hückel heteroatom parameters. Either the p- or d-orbital model for sulfur may be employed, but the parameters permissible for a good linear correlation fall in a narrow range, as shown by a nonlinear, least-squares estimation study. The parameters show that none of the other 46 planar combinations and permutations of dimethylamino, methylthio, and methoxy groups on a benzene nucleus can approach the low ionization potential of N,N,N',N'-tetramethyl-p-phenylenediamine. Correlation of aromatic proton chemical shifts with Hückel calculated charge densities is found to be less

satisfactory; however, the results decidedly favor use of the p-orbital model for sulfur.

Introduction

In previous papers[2–6] we have shown that some π-electronic properties of benzene derivatives containing

(1) Cumulative Influence of Conjugated Substituents on the π-system Properties of Aromatic Hydrocarbons. Part X. Part IX: A. Zweig and W. G. Hodgson, *Proc. Chem. Soc.*, 417 (1964).

(2) Part VIII: A. Zweig, J. E. Lancaster, M. T. Neglia, and W. H. Jura, *J. Am. Chem. Soc.*, 86, 4130 (1964).

(3) A. Zweig, W. G. Hodgson, and W. H. Jura, *ibid.*, 86, 4124 (1964).

(4) A. Zweig, J. E Lehnsen, J. E. Lancaster, and M. T. Neglia, *ibid.*, 85, 3940 (1963).

(5) A. Zweig, J. E. Lehnsen, and M. A. Murray, *ibid.*, 85, 3933 (1963).

(6) A. Zweig, *J. Phys. Chem.*, 67, 506 (1963).

the methoxy and dimethylamino substituents can be predicted by the Hückel molecular orbital theory. With the proper selection of two heteroatom parameters for each type of substituent, molecular orbital properties may be calculable for any multisubstituted aromatic when these substituents contain only a single orbital likely to interact strongly with the ring. As "internally consistent" Hückel heteroatom parameters were found which uniquely predicted energy levels of molecules containing *both* the methoxy and dimethylamino groups, a study of the corresponding sulfur derivatives, the methylthio aromatics, was of particular interest as the next area of investigation.

One reason for this is the continuing interest in the nature of the sulfur orbitals which interact in conjugated systems.[7-9] A further reason is the relatively low electronegativity of sulfur. The valence state ionization potential of divalent sulfur is about that of carbon.[10,11] On this basis Pullman and Pullman have suggested that $\alpha_S \cong \alpha_C$ in the Hückel approximation, and have made extensive calculations using this relationship.[12] Contrariwise, and on the basis of the close similarity of ionization potentials of ammonia and hydrogen sulfide (10.52 and 10.47 e.v., respectively), Streitwieser[13] suggested that $\alpha_S \cong \alpha_N$ in the Hückel method. As dimethylamino substituents sharply lower the ionization potentials of aromatic molecules, and as the steric requirement for coplanarity of a methylthio group with an aromatic nucleus is less than for a dimethylamino group (*vide infra*) multiple methylthio substitution could result in aromatic molecules with unusually low ionization potentials.
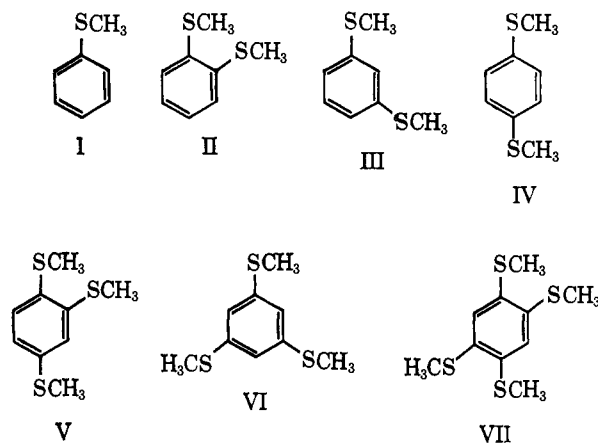
Factors other than the relative electronegativities of substituents will also influence the ionization potentials of conjugated systems. The ordering of the π-basicities of some N,N-dimethylamino-, methylthio-, and methoxy-substituted benzenes[14] was found to be similar to the orderings of the intensities and the positions of the 0–0 bands of aniline, thiophenol, and phenol in the near ultraviolet.[15] As had been pointed out,[15] the resonance integral for π-bonding between sulfur and the benzene ring is probably considerably smaller than for similar interaction between nitrogen or oxygen and the benzene ring. Although this fact is generally recognized,[16] a more quantitative description of the relative coulomb and resonance integrals for nitrogen, sulfur, and oxygen has not been made.

For sulfur, another effect that must be considered is that its unpaired electrons may exchange with the aromatic ring through the sulfur 3d-orbitals or through two hybrid orbitals on sulfur containing appreciable

d-character.[17] In such a situation, divalent sulfur would behave as a "double core." Because the electron pair contributed to the π-system by sulfur in such a situation would have to be spread over this double core, the ionization potentials of such aryl sulfides would not be particularly low, even though such orbitals might overlap with the ring and p-orbitals to a greater extent than comparable 3p-orbitals.

As the relative properties of the singly substituted aromatics can be explained by invoking many ambiguous combinations of the above effects, an attempt was made in this study to see if the properties of multiple-substituted methylthiobenzenes, anisoles, and N,N-dimethylanilines could be uniquely and unambiguously correlated with a particular model and set of Hückel parameters.

Selection of Compounds. Ultraviolet spectral studies[16] have indicated that the resonance interaction of the methylthio group with a benzene ring is not diminished by a single *ortho* substituent but is greatly affected when two substituents flank the methylthio group. Thus the (methylthio)benzenes have steric requirements similar to the methoxybenzenes.[5,6] It is therefore possible that unique values for α_S and β_{CS} could correlate some properties of the seven sterically unhindered (methylthio)benzenes (I–VII) with the seven corresponding methoxybenzenes. For further comparison, there are 16 possible unhindered com-

binations of methoxy and methylthio on a benzene nucleus. As we had previously obtained parameters for the N,N-dimethylamino group consistent with the methoxy group parameters in the Hückel approximation,[2] it is additionally possible to consider in the same over-all scheme five benzene derivatives that contain both the dimethylamino and methylthio groups and three compounds that contain all three types of substituents, methoxy, dimethylamino, and methylthio. All together, including the previously considered unhindered methoxy (7), dimethylamino (4), and mixed methoxy–dimethylamino (5) benzene derivatives, there are 47 substituted benzene derivatives which have π-electronic properties that might be characterized by parameters for α_O, α_N, α_S, β_{CO}, β_{CN}, and β_{CS} in the Hückel molecular orbital scheme.

In this paper, we report on calculations and some experimental properties of 12 of these compounds

(7) R. Breslow and E. Mohacsi, *J. Am. Chem. Soc.*, **85**, 431 (1963), and previous papers in this series.

(8) S. Oae, A. Ohno, and W. Tageki, *Tetrahedron*, **20**, 443 (1964), and previous papers in this series.

(9) R. Zahradnik, C. Parkanji, V. Horak, and J. Kautecky, *Collection Czech. Chem. Commun.*, **28**, 776 (1963).

(10) H. O. Prichard and H. A. Skinner, *Chem. Rev.*, **55**, 745 (1955).

(11) This treatment of sulfur as a weakly interacting carbanion has also been used by M. M. Kreevoy, *J. Am. Chem. Soc.*, **80**, 5543 (1958).

(12) B. Pullman and A. Pullman, "Quantum Biochemistry," Interscience Publishers, Inc., New York, N. Y., 1963.

(13) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961.

(14) A. Zweig, W. G. Hodgson, W. H. Jura, and D. L. Maricle, *Tetrahedron Letters*, No. 26, 1821 (1963).

(15) W. W. Robertson and F. A. Matsen, *J. Am. Chem. Soc.*, **72**, 5248 (1950).

(16) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962, p. 33.

(17) This has been used to explain the similarity of thiophene and benzene: V. Schoemaker and L. Pauling, *J. Am. Chem. Soc.*, **61**, 1778 (1939); H. C. Longuet-Higgins, *Trans. Faraday Soc.*, **45**, 173 (1949).

(previous papers[2,3] had discussed 16 others). These include six of the seven (methylthio)benzenes (omitting VI), and six (methylthio)anisoles and (methylthio)-N,N-dimethylanilines (cf. Table II). The latter were chosen to reflect the widest variety of group interactions through the benzene ring. In addition, one sterically hindered compound, o-(methylthio)-N,N-dimethylaniline, was examined, as it completes the set of disubstituted benzenes. Also included in this paper are some results of Hückel molecular orbital calculations made on the 19 sterically unhindered compounds in this series which were not experimentally investigated.

Results

Preparation of Compounds. The compounds were prepared by the methods described in the literature or by other synthetic techniques, the details of which are reported in the Experimental section.

Methylation of p-aminothiophenol, either with trimethyl phosphate or with alkaline dimethyl sulfate, gave at least five products, as determined by g.l.c. The n.m.r. spectrum of the major component of the mixture obtained with excess methylating agent showed three types of methyl protons and aryl protons in the ratio of 2:1:1:1. This evidence and an elemental analysis established that ring methylation had occurred. The low extinction coefficient of this new compound as compared to authentic p-(methylthio)-N,N-dimethylaniline (cf. Table I) leaves little doubt that ring methylation had occurred *ortho* to the dimethylamino group to give 2-methyl-4-(methylthio)-N,N-dimethylaniline. Under appropriate conditions (cf. Experimental) the desired p-(methylthio)-N,N-dimethylaniline was obtained as a major product of the methylation of p-aminothiophenol, and could be purified by g.l.c.
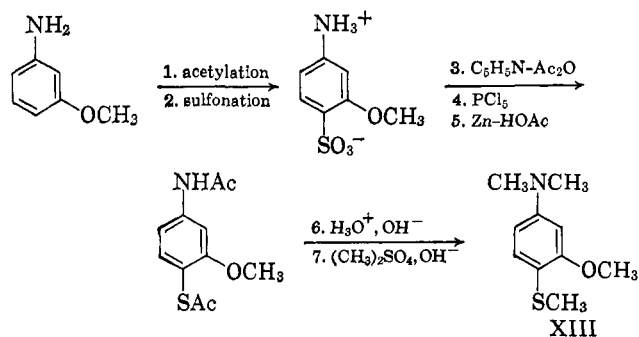
Table I. Ultraviolet Spectral Data Bearing on Tetramethylated p-Aminothiophenol

Compd.	Solvent	λ_{max}	ϵ
N,N-Dimethylaniline	Isooctane[a]	251	15,500
o-Methyl-N,N-dimethyl-aniline	Isooctane[a]	248	6,360
Thioanisole	Ethanol[c] or cyclohexane[b]	254	9,800
o-Methylthioanisole	Ethanol[c]	250	9,000
p-(Methylthio)-N,N-di-methylaniline	Cyclohexane[b]	272	20,500
Tetramethylated p-amino-thiophenol	Cyclohexane[d]	268	11,800

[a] J. Burgers, M. A. Hoefnagel, P. E. Verkade, H. Visser, and B. M. Wepster, *Rec. trav. chim.*, **77**, 491 (1958). [b] L. Ruzzier and A. Tundo, *Boll. sci. fac. chim. ind. Bologna*, **14**, 16 (1956). [c] G. Leandri, A. Manjini, and R. Passerini, *Gazz. chim. ital.*, **84**, 3 (1954). [d] See Experimental.

Only one other previously unreported compound, 3-methoxy-4-(methylthio)-N,N-dimethylaniline, was prepared for this investigation. The following scheme indicates its method of preparation.

Polarographic Oxidation Potentials and Charge Transfer Maxima. In Table II are reported the polarographic half-wave oxidation potentials of these methylthio-substituted compounds. The compounds were oxidized in acetonitrile solution at a rotating platinum electrode and, unless otherwise indicated, the polaro-

graphic wave was judged to be reversible on the basis of the diffusion current which was found to be of approximately the same value as the diffusion currents of known one-electron oxidations under the same conditions.[2] In several instances the generated cation was unstable as the diffusion current dropped to near zero immediately after the first oxidation wave. Most of the oxidation potentials were measured against a s.c.e. electrode; however, several were measured against a silver–0.1 M silver ion electrode, and a suitable correction was applied to the data reported.

Table II. Polarographic Oxidation Potentials and Charge-Transfer Maxima of Methylthio Aromatics

Compd.	$E_{1/2}$, (s.c.e.), v. (CH3CN)	$-\bar{\nu} \times 10^{-3}$ cm.$^{-1}$ p-chloranil	(CH2Cl2) TCNE
Thioanisole	+1.565	19.6	17.5
o-Bis(methylthio)-benzene	1.35	18.2[a]	15.6
m-Bis(methylthio)-benzene	1.45[f]	19.8	17.5
p-Bis(methylthio)-benzene	1.19	16.7	14.8
s-Tris(methylthio)-benzene	1.43	19.6	16.9[c]
1,2,4,5-Tetrakis-(methylthio)benzene	1.08	15.1[b]	13.0[d]
o-(Methylthio)anisole	1.35[f]	17.8	15.6[e]
m-(Methylthio)anisole	1.45[f]	19.2	17.1
p-(Methylthio)anisole	1.22[f]	17.4	15.4
o-(Methylthio)-N,N-dimethylaniline	0.91	18.2	21.3[g]
m-(Methylthio)-N,N-dimethylaniline	0.83[f]	15.4	14.2
p-(Methylthio)-N,N-dimethylaniline	0.635	13.3	11.8
3-Methoxy-4-methyl-N,N-dimethylaniline	0.58	. . .	. . .

[a] Band at 760 mμ. [b] Band at 765 mμ. [c] Band at 465 mμ. [d] Band at 525 mμ. [e] Band at 798 μ. [f] Increased by 0.30 v. from value obtained vs. Ag°–0.1 M Ag+ electrode. [g] Probably not the first charge-transfer band.

Also reported in Table II are the new absorption maxima which appeared on mixing these (methylthio)-benzenes with the π-electron acceptors p-chloranil and tetracyanoethylene (TCNE) in methylene chloride. These maxima may be due to transitions from the π-system of the (methylthio)benzenes to the π-acceptors. The possibilities also exist, however, that they are caused by n–π charge-transfer transitions, reaction products, or ion radicals (cf. Discussion).

Proton Magnetic Resonance Spectra. In Table III are reported the proton chemical shifts, in τ-units, of these (methylthio)benzenes. The measurements were

Table III. Proton Chemical Shifts in Some Methylthio Aromatics

Compd.	Chemical shift,[a,b] τ			
	Ring protons	SCH₃	N(CH₃)₂	OCH₃
Thioanisole	2.85	7.58	. . .	. . .
1,2-Bis(methylthio)benzene[e]	2.90	7.61	. . .	. . .
1,3-Bis(methylthio)benzene	2.9–3.1[c]	7.57	. . .	. . .
1,4-Bis(methylthio)benzene	2.89	7.60	. . .	. . .
1,3,5-Tris(methylthio)benzene	3.22	7.57	. . .	. . .
1,2,4,5-Tetrakis(methylthio)benzene	2.97	7.60	. . .	. . .
o-(Methylthio)anisole	2.9–3.4[c]	7.67	. . .	6.17
m-(Methylthio)anisole	3.24–3.52 (H$_{2,4,6}$), 2.91(H$_5$)	7.66	. . .	6.36
p-(Methylthio)anisole[e]	2.84 (H$_{2,6}$), 3.27 (H$_{3,5}$)	7.62	. . .	6.27
o-(Methylthio)-N,N-dimethylaniline	3.05[d]	7.67	7.31	. . .
m-(Methylthio)-N,N-dimethylaniline[e]	3.00 (H$_5$), 3.50 (H$_2$), ~3.60 (H$_{4,6}$)[d]	7.62	7.12	. . .
p-(Methylthio)-N,N-dimethylaniline[e]	2.86 (H$_{3,5}$), 3.45 (H$_{2,6}$)	7.67	7.12	. . .
3-Methoxy-4-(methylthio)-N,N-dimethylaniline	2.93 (H$_5$), 3.90 (H$_{2,6}$)[d]	7.78	7.12	6.20

[a] Five moles/liter in CCl₄. [b] Measured on A-60 instrument unless indicated. [c] A complex uninterpreted pattern. [d] Equivalent shifts for nonequivalent protons. [e] Measured on DP-60 instrument by method of audio side-band modulation.

made on 5 M solutions in carbon tetrachloride. The method of measurement was such (cf. Experimental) that the error in the assignment of the shifts, unless otherwise noted, is believed to be $\sim \pm 0.01$ p.p.m.

Discussion and Calculations

Charge-Transfer Maxima and Polargraphic Oxidation Potentials. Although relative polarographic oxidation potentials[18] and charge-transfer absorption maxima with a common acceptor[19,20] are indications of relative ionization potentials, the relationships in both instances are theoretically not expected to be precisely linear.[18,21] Experimentally a high degree of linearity is found between values obtained by both of these experimental methods and the energies of the highest filled molecular orbitals (HFMO's) of aromatics as calculated by the Hückel method.

Although the charge-transfer maxima of the methyl-thio-substituted aromatics with tetracyanoethylene and with p-chloranil are nicely related to each other in linear fashion, a considerably poorer relationship (Figure 1) exists between the charge-transfer maxima and the polarographic oxidation potentials of these
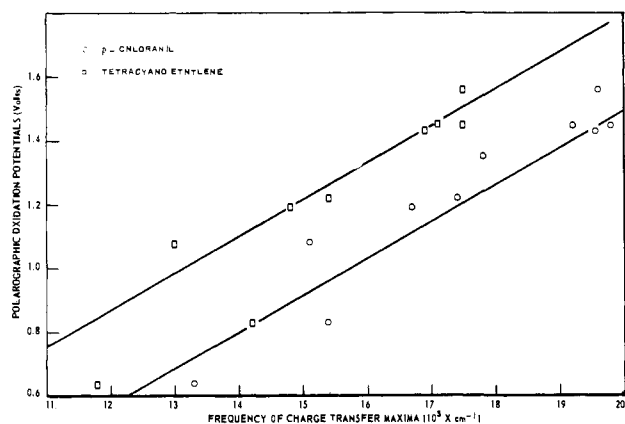

Figure 1. Plot of polaragraphic oxidation potentials of methyl-thio-substituted aromatics vs. their C–T maxima with p-chloranil and tetracyanoethylene.

(18) E. S. Pysh and N. C. Yang, *J. Am. Chem. Soc.*, **85**, 2124 (1963).
(19) M. J. S. Dewar and A. R. Lepley, *ibid.*, **83**, 4560 (1961).
(20) M. J. S. Dewar and H. Rogers, *ibid.*, **84**, 3577 (1962).
(21) R. S. Mulliken and W. B. Person, *Ann. Rev. Phys. Chem.*, **13**, 107 (1962).

compounds. This may be due in part to some systematic errors in assignment of some of the charge-transfer maxima. The latter are usually broad and frequently ill-defined, but in this series they were also sometimes asymmetric, suggesting the possibility of superposition of two or more independent band systems. Since the number of superimposed bands could not be determined, no attempt was made to decompose the spectra into their possible components.

Additional bands are likely to result from charge transfer from "lone pairs" of electrons on sulfur to the acceptor. Such charge transfer involving alkyl sulfides have been examined by several groups in recent years.[22–25] Van der Veen and Stevens[26] in a study of the 1:1 iodine complexes of some halo- and methyl-substituted thioanisoles concluded from the value of ΔH for the complexes that they were of the n–π type. A recent study of the thermodynamic and spectral properties of the thiophene–iodine complex,[27] however, suggests that thiophene acts as a π-donor in this instance.

Because of the possible uncertainty in the assignments of the charge-transfer maxima and because polarographic oxidation potentials of a series of polycyclic aromatic hydrocarbons could be measured more accurately and had shown a more closely linear relationship with ionization potentials, as calculated from Hückel HFMO's, than did the relative frequencies of charge-transfer maxima of a similar set of hydrocarbons,[18] we chose to examine the relationship of oxidation potentials and Hückel HFMO's for the methyl-thio-substituted compounds. Despite the poor theoretical value of the Hückel method, the uncertainties involved in parameter selection preclude effective employment of the more accurate SCF–MO methods at the present time.[28] Previously obtained oxygen and nitrogen parameters[2,3] were used in the Hückel calculations on the methylthio-substituted anisoles and N,N-dimethylanilines. It then becomes immediately clear

(22) H. Tsubomura and R. P. Lang, *J. Am. Chem. Soc.*, **83**, 2085 (1961).
(23) R. S. Drago, B. Wayland, and R. L. Carlson, *ibid.*, **85**, 3125 (1963).
(24) R. J. Niedzielski, R. S. Drago, and R. L. Middaugh, *ibid.*, **86**, 1694 (1964).
(25) M. Tameres and S. Searles, Jr., *J. Phys. Chem.*, **66**, 1099 (1962).
(26) J. Van der Veen and W. Stevens, *Rec. trav. chim.*, **82**, 287 (1963).
(27) R. P. Lang, *J. Am. Chem. Soc.*, **84**, 4438 (1962).
(28) Cf. Discussion by R. D. Brown in "Molecular Orbitals in Chemistry, Physics, and Biology," Academic Press Inc., New York, N. Y., 1964, p. 502.
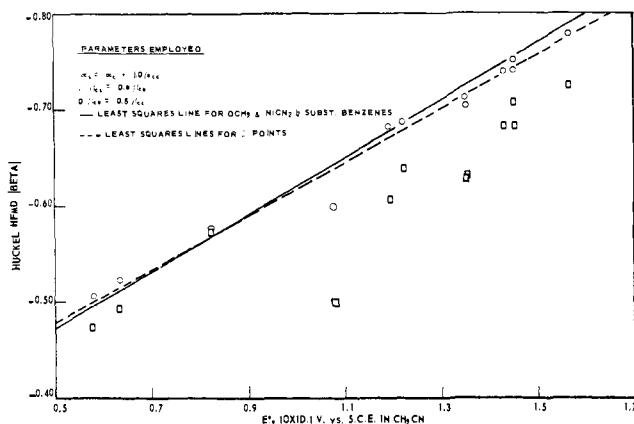
Figure 2. Plot of polarographic half-wave oxidation potentials of methylthio aromatics *vs.* Hückel HFMO's employing the p-orbital model.

Figure 3. Plot of polarographic half-wave oxidation potentials of methylthio aromatics *vs.* Hückel HFMO's employing the d-orbital model.

that the literature choice[12] of $\alpha_S = \alpha_C$ is inconsistent with the polarographic data. When $\alpha_S = \alpha_C$ is used in the Hückel calculations, with β_{CS} nominally chosen as $0.6\beta_{CC}$, the HFMO's of the mono-, *m*-di-, and *s*-trisubstituted compounds are all predicted to have identical energies, α, or nonbonding. As the polarographic oxidation potentials of these compounds cover a range of 0.73 v., it is apparent, even without a consideration of where α lies on the polarographic scale, that the parameter choice is unsatisfactory.

A plot of the HFMO's and polarographic oxidation potentials with $\beta_{CS} = 0.5\beta_{CC}$ and $\alpha_S = \alpha_C + 1.0\beta_{CC}$ shows fair semblance of linearity. All the points within one exception fall below the least-squares line which had been obtained for the 12 methoxybenzenes and N,N-dimethylanilines. The results suggested that $\beta_{CS} = 0.4\beta_{CC}$ be tried, and the very good fit represented by the circles in Figure 2 was then obtained. The least-squares equation, assuming the error is in the polarographic measurements, for the 12 compounds containing only the methoxy and dimethylamino substituents had been found[2] to be $E_{1/2}$(oxid.) $= -1.219 - 3.624X$ where $X = E - \alpha/\beta$, E is the HFMO energy and α and β are constants. The standard error using these parameters is 0.0597 v. The least-squares equation for the 12 methylthio-substituted compounds reported here is $E_{1/2}$(oxid.) $= -1.196 - 3.560X$ and the standard error is 0.0529 v., when $\alpha_S = \alpha_C + 1.0\beta_{CC}$ and $\beta_{CS} = 0.4\beta_{CC}$.

If the above two sets are combined with the literature value for the oxidation potential ($+2.30$ v.) for benzene ($X = -1.000$), the least-squares correlation equation for the 25 compounds becomes $E_{1/2}$(oxid.) $= -1.170 - 3.526X$ with a standard error of 0.053 v. These sulfur parameters in this "p-orbital model" give as good an "internally consistent" correlation (actually slightly better) as the oxygen and nitrogen parameters alone. They are similar to those recently suggested by Kuboyama[29] who reported that the Hückel HFMO's of thianthrene, phenoxathiin, and diphenylene dioxide best correspond to the positions of their charge-transfer maxima with *p*-chloranil when $\beta_{CO} = 0.81\beta_{CC}$ and $\beta_{CS} = 0.42\beta_{CC}$, if $\alpha_O = \alpha_C + 2.0\beta_{CC}$, and $\alpha_S = \alpha_C + 1.0\beta_{CC}$ are assumed.

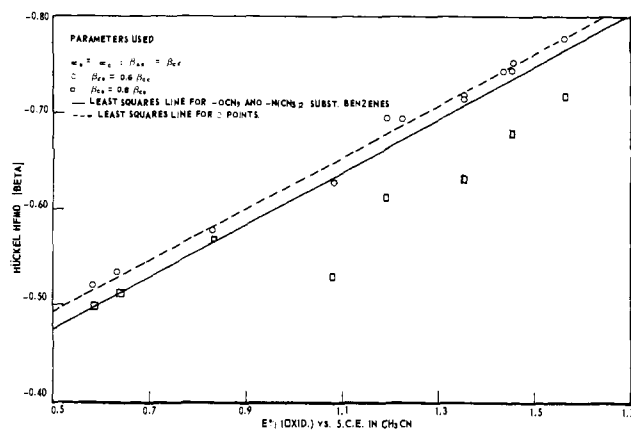(29) A. Kuboyama, *J. Am. Chem. Soc.*, **86**, 164 (1964).

The possibility of sulfur d-orbitals participation in the π-molecular orbitals may also be considered. Longuet-Higgins originally[17] proposed that two hybrid $3pd^2$-orbitals on sulfur could interact more readily with a conjugated 2p-system than could a pure 3p-orbital. For Hückel calculations, one does not need to know the detailed nature of the orbital hybridization; however, the question of one or two orbitals on sulfur interacting with the 2p-system might be answerable by such calculations. When Zahradnik and Koutecky[30] examined both the single- and double-core models for sulfur-containing heterocyclic, and compared the results of Hückel calculations to reactivity and spectroscopic data, they found both models fit about equally well. In Figure 3 we show the HFMO's of our methylthio aromatics calculated using the two sets of d-orbital parameters employed by Zahradnik and Koutecky, plotted against the polarographic oxidation potential data. A remarkably good fit is found with $\alpha_S = \alpha_C$, $\beta_{SS} = \beta_{CC}$, and $\beta_{CS} = 0.6\beta_{CC}$. The least-squares relationship for the 12 methylthio compounds (dotted line) is $E_{1/2}$(oxid.) $= 1.3455 - 3.7346X$ and the standard error is 0.03723 v. For all 25 compounds including benzene, the least-squares equation is $E_{1/2}$ (oxid.) $= -1.1896 - 3.5333X$ with a standard error of 0.0520 v.

The ~ 0.05-v. standard errors for both models with the indicated parameters are remarkable low since the range of potentials measured is *more* than 2 v. and the experimental error in the polarographic potential determinations is approximately 0.01–0.02 v. One cannot place significance in the difference in least-squares errors in the two models employed for sulfur. As far as the energies of the HFMO's are concerned, the models are effectively equivalent. Since the heteroatom parameters used are rounded to two places, both models may be refined to give still closer correlations.

Remaining Planar Substituted Aromatics. In Table IV are reported the energies of the highest filled molecular orbitals of the planar methoxy-, methylthio-, and dimethylamino-substituted benzenes which have not been experimentally investigated or previously re-

(30) R. Zahradnik and J. Koutecky, *Collection Czech. Chem. Commun.*, **28**, 1117 (1963).
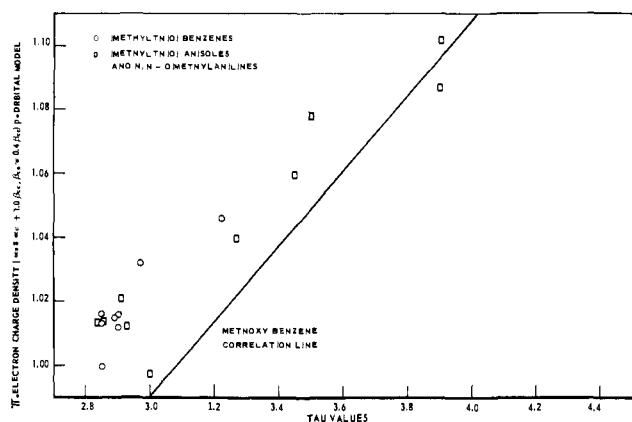
Figure 4. Plot of aromatic proton chemical shifts *vs.* calculated charge densities at attached ring positions in methylthio aromatics.

Table IV. Calculated HFMO's of Methylthio Aromatics Not Experimentally Investigated

Compd.	Calcd.[a] HFMO (βI)	Calcd.[b] oxidation potential
1,2,4-Tris(methylthio)-benzene	−0.6484	+1.12
4-(Methylthio)-1,3-di-methoxybenzene	−0.6434	1.10
2-(Methylthio)-1,4-di-methoxybenzene	−0.6410	1.09
4-(Methylthio)-1,2-di-methoxybenzene	−0.6420	1.09
5-(Methylthio)-1,3-di-methoxybenzene	−0.7468	1.46
5-(Methylthio)-1,2,4-tri-methoxybenzene	−0.5708	0.84
3,4-Bis(methylthio)-anisole	−0.6458	1.11
4,5-Bis(methylthio)-1,2-methoxybenzene	−0.5824	0.88[4]
2,4-Bis(methylthio)anisole	−0.6447	1.10
3,5-Bis(methylthio)anisole	−0.7392	1.44
4,6-Bis(methylthio)-1,3-dimethoxybenzene	−0.5829	0.88[5]
2,5-Bis(methylthio)-anisole	−0.6465	1.11
2,5-Bis(methylthio)-1,4-dimethoxybenzene	−0.5821	0.88[2]
2,4,5-Tris(methylthio)-anisole	−0.5921	0.92
5-(Methylthio)-N,N,N',-N'-tetramethyl-*m*-phenylenediamine	−0.5293	0.70
3,4-Bis(methylthio)-N,N-dimethylaniline	−0.5103	0.63
3,5-Bis(methylthio)-N,N-dimethylaniline	−0.5728	0.85
3-(Methylthio)-4-methoxy-N,N-dimethylaniline	−0.4900	0.56
3-(Methylthio)-5-methoxy-N,N-dimethylaniline	−0.5714	0.84

[a] Parameter used $\alpha_S = \alpha_N = \alpha_C + 1.0\beta_{CC}$, $\alpha_O = \alpha_C + 2.0\beta_{CC}$, $\beta_{CO} = \beta_{CN} = 0.8\beta_{CC}$, $\beta_{CS} = 0.4\beta_{CC}$. [b] Calculated from $E_{1/2}$ (oxid.) *vs.* s.c.e. $= -1.170 - 3.526X$.

ported.[2,3] The parameters used to calculate these results were the best "standard" values employing the p-orbital model for sulfur. It is clear from this table that no planar combination or permutation of these three substituents can result in a molecule with an ionization potential nearly as low as that of N,N,N',N'-tetramethyl-*p*-phenylenediamine (0.20 v. *vs.* s.c.e.) All benzene derivatives having more than two dimethyl-amino substituents will be sterically hindered except the 1,3,5-trisubstituted compound which is calculated to be unsatisfactory. One must turn to heterocyclic, nonalternant, or condensed ring systems to achieve π-electron ionization potentials in neutral molecules lower than that of tetramethyl-*p*-phenylenediamine.

N.m.r. Spectra. In the methoxybenzene series[4] it was found that the ring proton chemical shifts ranged over more than one τ-unit, while the charge densities at the ring positions calculated by the Hückel method changed by more than 0.1 electron. A linear relationship was found with a proportionality constant, Q, of 10 p.p.m./e. The charge density at the benzene ring positions, normally unity, was greatly perturbed by the ethereal substituents because of the efficient resonance interaction of an oxygen electron pair with the ring. It is expected from Hückel theory that, in going to sulfur, the resonance interaction will become weaker and thus the ability of the substituent to alter the charge densities at the ring positions should diminish. However, an important difference now arises between the p- and d-orbital models for sulfur conjugation. While the p-orbital predicts a *diminished* perturbation on the ring charge densities, the d-orbital model, with $\alpha_S = \alpha_C$, predicts *no perturbation at all.*

Of course, the thioether substituents like any substituent may alter the ring proton chemical shifts in several other ways; however, these effects are relatively weak and unlike the resonance effect they should vary inversely with some power of the distance from the substituent.

In Figure 4 the proton chemical shifts are plotted against the contiguous ring position charge densities, using the parameter set in the p-orbital model which proved better in the oxidation potential studies. The chemical shifts of the methylthiobenzenes are differentiated in the figure from the methylthioanisoles and N,N-dimethylanilines. Both sets are seen to

parallel the methoxybenzene correlation line.[4] The variation in chemical shifts in the (methylthio)benzenes (almost τ 0.4) clearly follows the change in resonance influence on charge density predicted by the p-orbital model and thus does not agree with the d-orbital model. No other effect, such as magnetic anisotropy or the electric field effect,[31] can account, for example, for the τ 0.25 upfield ring proton chemical shift of 1,3,5-tris-(methylthio)benzene from 1,2,4,5-tetrakis(methylthio)-benzene.

We conclude from the n.m.r. data that the p-orbital model is the preferable way to describe the interaction of a methylthio group with an aromatic π-system within the Hückel framework.

Hindered Compound Results. The charge-transfer absorption maxima, polarographic oxidation potential, and proton magnetic shift data obtained for *o*-(methyl-thio)-N,N-dimethylaniline does not correlate with the Hückel calculations when the usual parameters are employed.

Decreasing the carbon–nitrogen resonance integral for this molecule improves the relationships with all the properties studied; however, besides heteroatom parameters, analytical corrections for solvation energy

(31) These effects and leading references are discussed in ref. 4.

Table V. Regression Study of Polarographic Oxidation Potentials and HFMO's

Parameter	Fixed β_0 and β_1	Minimization values — Unknown β_0 and β_1			90% confidence level
		Case 1	Case 2	Case 3	
β_0	−0.44	−1.17	−1.13	−1.52	0.44
β_1	−2.16	−3.17	−3.13	−3.52	0.45
h_O	1.72^5	1.78	1.76	1.86	1.34
h_N	0.55	0.88	0.87	0.93	0.45
h_S	1.02	1.12	1.13	1.14	0.10
k_{CO}	0.94	0.72	0.72	0.70	0.11
k_{CN}	1.01	0.79	0.80	0.73	0.21
k_{CS}	0.70	0.52	0.53	0.48	0.15
Standard deviation, v.	0.0451	0.0314	0.0316	0.0297	

terms such as those suggested by Chalvet, Daudel, and Peradejordi[32] are necessary for more quantitative correlations between properties of sterically hindered and unhindered substituted aromatics.

Nonlinear, Least-Squares Estimation Study. When molecular orbital calculations are compared with physical properties of heteroatomic compounds, the selection of parameters is of critical importance. The choice may be made purely from theoretical considerations or, as is the more common practice for both Hückel and SCF calculations, the parameters may be chosen to correspond to some physical result. Just how uniquely the chosen parameters correspond to the physical property is a question usually left unanswered. Vincow and Fraenkel[33] have studied the relationship of the electron unpaired densities and hyperfine splitting constants in aromatic semiquinones as a function of the choice of α_O and β_{CO}. Smith[34] examined Hückel and SCF parameter response surfaces corresponding to electronic transitions in indoaniline dyes using three coulomb parameters in a regression treatment. Other systematic parameter investigations employing graphical treatment of the data have also been reported.[35, 36]

As a good correlation of the polarographic oxidation potentials and Hückel HFMO's for 25 compounds, using only six parameters, had been obtained, it was of interest to learn just where in the six-dimensional parameter space does the minimum deviation from linearity lie. To answer this question, a Gaussian nonlinear, least-squares estimation procedure[37] was employed. Because of computer limitations and time considerations, only 16 of the molecules were examined in the regression study. The choice of these 16 was partially determined by symmetry considerations.[38] Only that portion of the factorizable matrices liable to contain the HFMO was included for each compound.

Two separate studies of parameter estimation were then made. In the first study, the linear equation parameters β_0 and β_1, for the equation

(32) O. Chalvet, R. Daudel, and F. Peradejordi, *J. chim. phys.*, **59**, 709 (1962).

(33) G. Vincow and G. K. Fraenkel, *J. Chem. Phys.*, **34**, 1333 (1961).

(34) W. F. Smith, Jr., *Tetrahedron*, **20**, 671 (1964).

(35) P. H. Rieger and G. K. Fraenkel, *J. Chem. Phys.*, **37**, 2795 (1962).

(36) R. W. Brandon and E. A. C. Lucken, *J. Chem. Soc.*, 4273 (1961).

(37) H. Margenau and G. M. Murphy, "The Mathematics of Physics and Chemistry, D. Van Nostrand Co., Inc., New York, N. Y., 1943.

(38) The compounds employed in the regression study were benzene, anisole, *p*-dimethoxybenzene, N,N-dimethylaniline, N,N,N',N'-tetramethyl-*m*- and -*p*-phenylenediamine, N,N-dimethyl-*m*- and -*p*-anisidine, thioanisole, *m*- and *p*-bis(methylthio)benzene, *s*-tris(methylthio)benzene, *m*- and *p*-(methylthio)anisole, and *m*- and *p*-(methylthio)-N,N-dimethylaniline.

$$E_{1/2}(\text{oxid.}) = \beta_0 + \beta_1 X \qquad (1)$$

were fixed by using the least-squares values obtained from the data reported for 21 alternant hydrocarbons by Pysh and Yang.[18] This procedure has the apparent advantage of fixing the heteroatom parameters to a line obtained for molecules without heteroatoms. The results are reported in the first column of data in Table V.

It was realized that molecular size varies considerably in the alternant hydrocarbon series, and as Pysh and Yang[18] pointed out, this may affect the solvation energy term in the determination of the oxidation potentials, although in a regular fashion so as to preserve a linear appearance. As the substituted benzenes are more similar to each other in size, a second study of the parameter minimization was made where β_0 and β_1 were treated as unknowns. The appreciably different results, with a significantly smaller standard deviation, are reported in the second data column of Table V.

To ensure that the Gaussian procedure had located the real minimum region[39] and had not merely found a local minimum in the parameter space, seven more minimization tests were made in the second study, with the seven starting points all equidistant from the original starting point and equidistant from each other in the six-dimensional parameter space. In data columns 3 and 4 of Table V are the two minimization results with the largest differences in values of β_0 and β_1. The differences are negligible and we can therefore confidently say that there exists a well-defined region in the heteroatom parameter space that gives better results than the standard parameters. The shape of this region is rather complicated (elongated in some directions, narrow in others). This must be kept in mind for a proper understanding of the confidence limits in the last column of Table V. The confidence limits are taken from the previous column which contained the smallest standard deviation (0.0297 v.) that we have found.

The parameters reported in data columns 3 and 4 of Table V were then employed to calculate the HFMO's of the nine methoxy-, dimethylamino-, and methylthio-substituted benzenes whose oxidation potentials had been measured but were not used in the regression study. The results are reported and compared with the best normal parameter data in Table VI. Only the two 1,2,4,5-tetrakis-substituted compounds faired

(39) Although it is unlikely, it must be admitted that another minimum region with possibly a smaller standard deviation lies outside the reasonable parameter range. Such a minimum could employ HFMO's not of the symmetry used in this investigation.

Table VI. Experimental and Calculated Polarographic Oxidation Potentials of Substituted Benzenes Not Employed in the Regression Study

| | | Oxidation potential, v. | | |
| | | Standard[b] | — Parameters of Table V — | |
Compd.	Experimental[a]	parameters	Data col. 3	Data col. 4
o-Dimethoxybenzene	+1.45	+1.45	+1.44	+1.45
1,2,4-Trimethoxybenzene	1.12	1.13	1.17	1.17
1,2,4,5-Tetramethoxybenzene	0.81	0.84	0.93	0.92
3,4-Dimethoxy-N,N-dimethylaniline	0.50	0.58	0.56	0.56
3,5-Dimethoxy-N,N-dimethylaniline	0.80	0.89	0.79	0.79
o-Bis(methylthio)benzene	1.35	1.10	1.26	1.27
1,2,4,5-Tetrakis(methylthio)benzene	1.08	0.64	0.84	0.83
o-(Methylthio)anisole	1.34	1.23	1.33	1.34
3-Methoxy-4-(methylthio)-N,N-dimethylaniline	0.58	0.54	0.56	0.56
$\sqrt{\text{Mean-square deviation}}$		0.18	0.10	0.10

[a] Vs. s.c.e. electrode in acetonitrile. [b] $h_O = 2.0, h_N = h_S = 1.0, k_{CO} = k_{CM} = 0.8, k_{CS} = 0.5, b_0 = -1.47, b_1 = -3.61$.

poorly when the regression parameters were employed. The results for the remaining compounds and the over-all results as judged by the square root of the mean-square deviation were very good. Although the cause of the poor showing of the tetrakis compounds is undoubtedly complex, their larger size and high symmetry may have resulted in an unusual solvation effect.

We conclude that the best parameters reported in the earlier sections are close enough to the regression study results to be generally useful for these substituents. However, further improvements, even within the approximate nature of the Hückel method, can be achieved by using the parameters suggested by the nonlinear least-squares estimation procedure.

Experimental[40]

Materials. Thioanisole. A commercial sample (Eastman Kodak Co.) was distilled prior to use. Its purity was estimated to be >99.9% by vapor phase chromatography.

o-Bis(methylthio)benzene. A 12.5-g. (0.090 mole) quantity of o-(methylthio)aniline (Aldrich Chemical Co.) was diazotized with 6.9 g. (0.10 mole) of sodium nitrite in 50 ml. of 10% HCl containing 5 g. of sodium acetate at 0°. After the addition was complete, the orange-red slurry was slowly added to a solution of 27.0 g. (0.169 mole) of potassium ethyl xanthate in 25 ml. of water with vigorous stirring and with the pot temperature kept at 70–80°. The mixture was stirred at 75° for 1 hr. further, then the aqueous layer was decanted from the dark oil. The oil was refluxed with 12.0 g. of potassium hydroxide and 12.0 g. of glucose in 200 ml. of ethanol for 3 hr. The ethanol was subsequently removed by distillation. The remaining oil was acidified with dilute sulfuric acid, 3.0 g. of zinc dust was added, and the resulting mixture was steam distilled. Extraction of the steam distillate with ether followed by drying the ether extract with sodium sulfate and concentration gave an oil. Distillation of this oil gave 1.90 g. collected from 85 to 105° (4 mm.).

The distillate was dissolved in 50 ml. of anhydrous methanol containing 5 ml. of dimethyl sulfate. With stirring, 5.0 g. of sodium hydroxide in 20 ml. of water was then added dropwise, keeping the temperature at 15–20° by means of external cooling. After the addition was complete, the methanolic solution was refluxed on a steam bath for 2 hr., cooled, and extracted

with three 50-ml. portions of ether. The ether extracts were combined, dried over sodium sulfate, and concentrated. The resulting oil was distilled at 1 mm. A total of 1.50 g. of distillate was collected at 70–80°. V.p.c. on a 10-ft. Apeizon L column at 180° showed that the distillate contained one major component (area % 76.2). By preparative v.p.c. a total of 0.83 g. (5.4% over-all) of this component, o-bis(methylthio)benzene[41] (>99% purity) was isolated from this distillate. The product was identified by analysis and its infrared and n.m.r. spectra.

Anal. Calcd. for $C_8H_{10}S_2$: C, 56.42; H, 5.92; S, 37.66. Found: C, 56.19; H, 5.94; S, 37.89, 37.81.

m-Bis(methylthio)benzene. Conversion of the disodium salt of m-benzenedisulfonic acid to m-benzenedisulfonyl chloride with chlorosulfonic acid was accomplished by the method of Spriskow and Aparyeva.[42] The m-benzenedisulfonyl chloride was then reduced to dithioresorcinol. After exploring several ways to effect the reduction, a method using zinc amalgam and H_2SO_4 similar to that described by Marvel and Caesar[43] was found to be reasonably satisfactory.

Into 300 ml. of 33% sulfuric acid was placed 10.0 g. of m-benzenedisulfonyl chloride (0.036[4] mole) and 50 g. of zinc amalgam.[43] With vigorous stirring, the mixture was heated to reflux and after several minutes steam distilled. Steam distillation was continued until the distillate was no longer milky (ca. 300 ml.). The distillate was saturated with sodium chloride and extracted with three 100-ml. portions of ether. The ether extracts were combined, dried over sodium sulfate, and concentrated to give usually ~2.5 g. (~48%) of crude dithioresorcinol as a pale yellow oil. By the same method as described in the preceding preparation, 8.67 g. (0.06 mole) of dithioresorcinol prepared by this method was treated with 18.9 g. (0.15 mole) of dimethyl sulfate and 21.1 g. (0.53 mole) of sodium hydroxide in 135 ml. of methanol to give 6.02 g. (58%) of distilled m-bis(methylthio)benzene, b.p. 90–94° (0.3 mm.). Purity as determined by v.p.c. was >99.9%.

p-Bis(methylthio)benzene. This compound was prepared from 54.7 g. (0.5 mole) of hydroquinone, 47.7 g.

(41) Prepared also by the methylation of o-benzenedithiol: J. Pollack, *Monatsh. Chem.*, **34**, 1681 (1913).

(42) A. A. Spriskow and N. V. Aparyeva, *J. Gen. Chem. USSR*, **19**, 1883 (1949).

(43) C. S. Marvel and P. D. Caesar, *J. Am. Chem. Soc.*, **73**, 1098 (1951).

(40) All melting points are uncorrected.

(1.0 mole) of methyl mercaptan, 20 g. of synthetic silica–alumina (13% alumina), and 20 g. of Aerocat® 2000 silica–alumina catalyst by heating to 175° under 15 atm. of N_2 in a glass-lined rocking pressure bomb. The product was extracted with a total of 1 l. of benzene and the benzene solution was washed with 300 ml. of 10% KOH, then with water. Concentration under *vacuo* followed by distillation (1 mm.) in a small Claisen column gave 0.5 g. of product collected at 85° (1% yield). Recrystallization from methanol gave lustrous plates, m.p. 85°, reported.[44]

s-Tris(*methylthio*)benzene. Using the same procedure as described for preparing *m*-bis(methylthio)benzene, 5.0 g. (0.0134 mole) of 1,3,5-trisulfonyl chloride (Eastman Kodak Co.) was reduced with zinc amalgam and steam distilled. The combined ether extracts from four such steam distillations were concentrated and methylated using dimethyl sulfate as described in the preparation of *o*-bis(methylthio)benzene. The product was purified by recrystallization from methanol followed by sublimation at 1 mm. and 80°. The yield was 0.16 g. (1.4%), m.p. 65–67° (lit.[45] 66–68°).

1,2,4,5-Tetrakis(methylthio)benzene. In a 500-ml. round-bottom flask cooled in a solid carbon dioxide–acetone bath was placed 100 g. (2.1 moles) of methanethiol (Eastman Kodak Co.). With stirring, 42.4 g. (0.22 mole) of cuprous chloride was added in small portions. The flask was fitted with a condenser and protected from moisture with a calcium chloride drying tube. The mixture was stirred in the cold for 4 hr., then was allowed to reach ambient temperature overnight. The remaining excess methanethiol was then removed by blowing dry nitrogen over the pasty solid product until little or no odor could be detected. A strong forced draft hood is essential for this operation!

To the pale yellow powder remaining in the reaction vessel was then added 100 ml. of quinoline and 40 ml. of pyridine.[46] After 15 min. of stirring, 20.0 g. (0.051 mole) of 1,2,4,5-tetrabromobenzene (Eastman Kodak Co.) was added and the mixture was heated to reflux. The reflux temperature rose from 140 to 170° over a 5-hr. period. The reaction mixture was cooled to 100°, then poured into 200 ml. of HCl in 1 kg. of ice with stirring. The product was extracted with three 300-ml. portions of diethyl ether. The combined ether extracts were washed with two 100-ml. portions of 10% HCl, 100 ml. of H_2O, three 100-ml. portions of concentrated NH_4OH, and finally with 100 ml. of water. The ether solution was dried over sodium sulfate and concentrated to give 15.4 g. of oil. After removing the more volatile components of this oil, 0.75 g. of orange solid was collected by sublimation at 100–145° at 0.2 mm. Recrystallization from ethanol gave 0.54 g. (4%) of pale yellow crystals, m.p. 125–126° (lit.[47] 123–127°).

Anal. Calcd. for $C_{10}H_{14}S_4$: C, 45.76; H, 5.38. Found: C, 45.42; H, 5.22.

(44) T. Zincke and W. Frohneberg, *Ber. deut. chem. Ges.*, **42**, 2721 (1909); A. Buraway, J. P. Critchley, and A. B. Thompson, *Tetrahedron*, **4**, 403 (1958).
(45) J. Pollak and J. Carniol, *Chem. Ber.*, **42**, 3252 (1909).
(46) This procedure is similar to one described in *Org. Syn.*, **42**, 22 (1964).
(47) J. Pollack, *Monatsch. Chem.*, **35**, 1445 (1914).

o-(*Methylthio*)anisole. Into a 250-ml. flask was placed 10.0 g. (0.0715 mole) of *o*-(methylthio)phenol (Aldrich Chemical Co.), 18.0 g. (0.14 mole) of dimethyl sulfate, and 100 ml. of methanol. To the stirred solution, cooled in an ice–water bath, was added 15.0 g. of sodium hydroxide dissolved in 50 ml. of water. The temperature of the reaction mixture was not permitted to rise above 20° during the addition. After the addition was complete, the reaction mixture was heated on a steam bath for 1 hr., then poured into 300 ml. of water. The aqueous solution was extracted with three 100-ml. portions of ether. The ether extracts were combined, dried over sodium sulfate, and concentrated *in vacuo*. A clear, oily product weighing 4.35 g. (39%) distilled at 86–89° (1.0 mm.). The infrared spectrum of the product showed no SH and v.p.c. indicated a single product.

m-(*Methylthio*)anisole. Using the alkaline dimethyl sulfate methylation procedure described in the previous experiment, 7.34 g. of the *m*-(methylthio)phenol fraction, obtained by treatment of resorcinol with methanethiol over a silica–alumina catalyst in a pressure bomb, as described in the preparation of *p*-bis-(methylthio)benzene, was methylated with 13.65 g. (0.156 mole) of dimethyl sulfate and 22.09 g. (0.55 mole) of sodium hydroxide. Work-up and distillation yielded 2.78 g. (35%) distilling at 68–94° (0.35–0.70 mm.). A 99.9% pure sample was obtained by preparative v.p.c.

p-(*Methylthio*)anisole. This compound was prepared by methylation of 5.0 g. (0.036 mole) of 4-(methylthio)phenol (Aldrich Chemical Co.) with alkaline dimethyl sulfate according to the usual procedure. A 1.1-g. fraction, b.p. 68–70° at 0.75 mm. (lit.[48] 98–100° at 4 mm.), was estimated to be >99% pure by v.p.c.

o-(*Methylthio*)-*N*,*N*-dimethylaniline. To 12.2 g. (0.1 mole) of *o*-aminothiophenol, 50.4 g. (0.4 mole) of dimethyl sulfate, and 100 ml. of methyl alcohol was added, with stirring, a solution of 36.0 g. (0.4 mole) of sodium hydroxide in 100 ml. of water. The temperature was kept at 20° throughout the addition. The mixture was then refluxed for 1 hr. The product was extracted with ether. The ether extract was dried over sodium sulfate, concentrated, and distilled at reduced pressure. Distillation from a Vigreux column at 0.2–0.3 mm. gave 10.2 g. of product collected over a temperature range of 62–87°.

Gas phase chromatography, employing a polyethylene glycol adipate column at 200° and 10 p.s.i. of He, indicated three major and five minor components of this oil. The percentages and relative retention time of the three major components were 25% (1), 42% (1.32), and 28% (1.72). Infrared spectra of these components identified them as *o*-dimethylaminothioanisole, *o*-methylthioanisole, and *o*-aminothioanisole.

Repeated methylation of 11.63 g. of this mixture with 50.4 g. (0.4 mole) of dimethyl sulfate and 36.0 g. (0.9 mole) of sodium hydroxide, employing the same work-up conditions, gave 8.49 g. of oil distilling at 59–80° (0.15–0.25 mm.). Chromatography now showed that the desired first major component of the mixture, *o*-dimethylaminothioanisole, was present to

(48) F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 572 (1955).

the extent of 76% of the total. Preparative-scale gas chromatography was then used to obtain 1.7 g. of this fraction containing less than 0.5% impurity. The n.m.r. spectrum further identified this material as the desired o-(methylthio)-N,N-dimethylaniline.

m-(Methylthio)-N,N-dimethylaniline. Using the standard alkaline methylation procedure described in previous experiments, 25.0 g. (0.18 mole) of m-(methylthio)aniline (Aldrich Chemical Co.) was treated with 68.0 g. (0.54 mole) of dimethyl sulfate and 44.0 g. (1.1 moles) of sodium hydroxide in 570 ml. of methanol. A total of 3.58 g. of product distilled at 84–90° (0.3 mm.). V.p.c. indicated 95% purity. Preparative v.p.c. was used to obtain 0.5 g. of pure material.

p-(Methylthio)-N,N-dimethylaniline. Methylation of 25.0 g. (0.205 mole) of p-aminothiophenol with alkaline dimethyl sulfate was carried out in a manner exactly analogous to that described for the methylation of o-aminothiophenol. The distillate, collected at 81–85° (0.35 mm.), weighed 22.2 g. Gas phase chromatography of this distillate on a 2-m. polyethylene glycol adipate column at 200° using 25 p.s.i. of He indicated three major components. The percentages and relative retention times of these components in the order of their elution from the column were 45% (1), 34.2% (1.32), and 20.8% (1.40). A total of 2.4 g. of component 1 in >98% purity was separated on a preparative scale. N.m.r. and infrared spectroscopy identified this as p-(methylthio)-N,N-dimethylaniline. The other two components of the mixture were not further investigated.

2-Methyl-4-(methylthio)-N,N-dimethylaniline. The exothermic reaction between 25.0 g. (0.2 mole) of p-aminothiophenol (Aldrich Chemical Co.) and 42.0 g. (0.3 mole) of trimethyl phosphate after initial warming was extremely vigorous, almost explosive! After the exothermic reaction subsided, the reaction mixture was refluxed for 1 hr., then treated with 50 g. of sodium hydroxide in 500 ml. of water, and the mixture was refluxed further for 3 hr., then allowed to cool and stand overnight. The dark, oily layer was separated and the residue was washed with three 50-ml. portions of ether which was combined with the oil and dried over NaOH pellets.

Concentration and distillation in a semimicro Vigreux column at 0.8 mm. afforded fractions totaling 6.2 g. in the range 55–85°, whose infrared spectra indicated desulfurization of the aromatic nucleus. From 86 to 120° a fraction (8.66 g.) was collected, whose infrared spectrum showed considerable N–H (3400 cm.$^{-1}$) as well as dimethylamino and methylthio. This substance was refluxed with 8.0 g. of trimethyl phosphate and worked up as before to give a distillate which contained considerably less N–H as indicated by its infrared spectrum.

Gas phase chromatography on a 6-ft. Carbowax column at 200° using 23 p.s.i. of He showed that the distillate described above contained five major components with the following percentages and relative retention times: 2.0% (1), 12.7% (3.7), 5.5% (4.7), 68.4% (5.8), and 11.5% (9.5). On a preparative scale, 0.48 g. of the fourth component in 97.0% purity was isolated (2.4% of the third component and 0.7% of the second component). N.m.r. and ultraviolet spec-

troscopy established this substance as 3-methyl-4-dimethylaminothioanisole (*cf.* Discussion).

Anal. Calcd. for $C_{10}H_{15}NS$: C, 66.24; H, 8.34; N, 7.73; S, 17.69. Found: C, 66.43; H, 8.19; N, 7.64; S, 16.66.

3-Methoxy-4-(methylthio)-N,N-dimethylaniline. p-Acetamino-o-methoxythiophenol acetate (3.0 g., 0.013 mole), prepared according to a literature procedure,[49] was refluxed with 1.5 g. of sodium hydroxide in 15 ml. of water and 10 ml. of methyl alcohol for 90 min. The mixture was cooled to 25° and 2.0 ml. of dimethyl sulfate in 10 ml. of methyl alcohol was added dropwise. The mixture was refluxed for 1 hr., then poured into 200 ml. of water and extracted with three 50-ml. portions of ether. Combining and drying the ether layers gave *ca.* 0.6 g. of semisolid. The infrared spectrum indicated disulfide and amide as well as SCH_3 and OCH_3. This material was subsequently dissolved in 10 ml. of ethanol, and 5 ml. of concentrated hydrochloric acid in 10 ml. of water was added. The mixture was refluxed for 10 min., cooled, and then neutralized with sodium bicarbonate, and extracted with three 50-ml. portions of ether. Concentration of the product gave an oil which on methylation with alkaline dimethyl sulfate again showed considerable amide. Refluxing this oil with 5 ml. of hydrochloric acid in 10 ml. of water for 3 hr. further followed by work-up and methylation as before gave an oil whose infrared spectrum corresponded essentially with that expected for 3-methoxy-4-(methylthio)-N,N-dimethylaniline. Molecular distillation at 60° (0.1 mm.) gave 0.01 g. of colorless oil. The n.m.r. spectrum of this material showed N-methyl, O-methyl, and S-methyl and an ABX pattern of aromatic ring protons with the correct integrated intensities. Several small impurity peaks were also observed. Further purification was prevented by the sensitivity of the compound to oxygen and heat.

Measurements. Charge-Transfer Maxima. These were obtained by mixing concentrated methylene chloride (spectral grade) solutions of the methylthio-substituted aromatics and the acceptors in equimolar proportions, then diluting, if necessary. All spectral measurements were made on a Cary 14 spectrophotometer at 22°. Since only charge-transfer maxima were relevant to this investigation, no attempt was made to measure equilibria and extinction coefficients for the complexes. Quantitative ultraviolet spectra were also obtained on the Cary 14 instrument.

Polarographic Oxidation Potentials. This data was obtained at room temperature on a Leeds and Northrup electrochemograph, Type E, instrument. Oxidations were carried out at a rotating platinum electrode with 0.1 *M* tetra-n-propylammonium perchlorate as supporting electrolyte. The electrochemical cell used to carry out controlled potential electrolyses in the e.s.r. cavity was essentially the same as that described in the literature.[50,51]

N.m.r. Spectra. The proton magnetic resonance

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spectra were measured at a concentration of 5 moles/l. in carbon tetrachloride containing a small amount of tetramethylsilane as an internal standard. The spectra were obtained either on a Varian Model DP60 spectrophotometer at 56.4 Mc./sec and calibrated by the method of audio side-band modulation, as previously described,[4] or were measured directly on a Varian A-60 spectrophotometer. The chemical shifts measured either way are believed to be accurate to better than 0.01 p.p.m. The aromatic coupling patterns, where reported, were evaluated by standard treatment. The assignments were made on the basis of the known values of *ortho*, *meta*, and *para* proton coupling constants in aromatic molecules.[52]

Molecular Orbital Calculations. These were made on a Burroughs Model 205 computer using programs especially written for this machine.

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The Exchange Labeling of Keto Steroids with Tritium by Adsorption Chromatography on Basic Alumina[1]

Peter D. Klein and John C. Knight

Contribution from the Division of Biological and Medical Research, Argonne National Laboratory, Argonne, Illinois. Received January 29, 1965

Keto steroids may be labeled with tritium by chromatography on basic alumina treated with tritiated water. The tritium is not removed by recrystallization in hydroxylic solvents but 95% can be back-exchanged under strongly basic conditions. Reduction of the keto steroids with lithium aluminum hydride occurs without loss of label and provides the corresponding alcohols in which the tritium is no longer exchangeable. The method provides pure, highly labeled products with remarkable economy of tracer.

A number of investigators have reported the use of gas chromatographic systems to carry out isotopic exchange reactions of the type

$$AX + BX^* \longrightarrow AX^* + BX$$
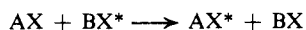
where BX* is a labeled support or stationary phase in the column and AX is the sample containing the exchangeable atom X, which may be halogen or hydrogen.[2-7] Elias[6] has pointed out that the use of a chromatographic system to carry out such exchanges has the inherent advantages of speed, economy, efficiency, and a high purity of the labeled compound which is obtained. To date, however, the catalog of such exchange reactions which have been carried out with organic compounds includes only simple alcohols, alkyl halides, and other compounds which are volatile and stable at the temperature of the gas chromatographic column. Furthermore, the introduction of radio-

activity has been limited to those easily exchangeable atoms which, unfortunately, back-exchange readily in unlabeled media and thus have limited utility in tracer or metabolic studies.

This investigation was undertaken with two objectives in mind, to establish the applicability of liquid-solid chromatographic systems to such exchange reactions and to investigate means for the replacement of less labile hydrogens in a molecule. Because of obvious applications to the study of intermediates in sterol metabolism, the replacement of enolic hydrogens in keto steroids during passage through a basic alumina column was selected for these prototypical experiments. The results indicate that it is possible to prepare labeled steroids with tritium contents of 5-10 mc./mmole, whose radioactivity is stable under all conditions short of strong alkali, by this simple procedure.

Experimental

Melting points were observed on a Fisher-Johns heating block and are uncorrected. Optical rotations were measured in chloroform using a Schmidt and Haensch Lippich manual polarimeter. Ultraviolet spectra were run on a Cary Model 11 MS recording ultraviolet spectrophotometer. All compounds reported were purified until they gave a single spot on thin layer chromatography with silica gel HF_{254} (Brinkmann Instruments, Inc.). Chromatoplates were developed in hexane containing various amounts of ethyl acetate and, after drying, were sprayed with ceric sulfate solution (2% in 2 N sulfuric acid) and heated in an oven to produce charring.

Column Preparation and Operation. Basic alumina (33 g., Merck, suitable for chromatography) was mixed with 1 ml. of HTO containing 1 c./ml. The deactivated adsorbent was thoroughly stirred and allowed to equili-

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