Acid-catalyzed Hydrogen-Deuterium Exchange Reactions of Deuterated Anisole, Thioanisole and Benzene

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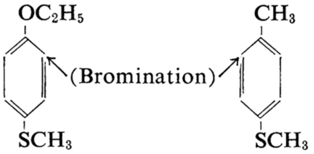
There have been many reports of the electron-pair releasing conjugative ability of divalent sulfides vs. that of the oxygen analogs. The dissociation constants of substituted benzoic acids[1], phenols[2] and anilines[2,3], the dipole moments of substituted benzenes[4], and the dimerization rates of *p*-substituted isopropenyl[5] benzene and a few other examples[6] have all pointed out that the electron-pair releasing conjugative effect of the sulfide function is smaller than that of the oxygen-analog. In both S_N1[7] and S_N2[8] reactions, chloromethyl alkyl ether has been shown to react substantially faster than the sulfur analog. The theoretical considerations, based on molecular orbital treatments, indicate that 3p-π-bonds are less stable than 2p-π-bonds[9].

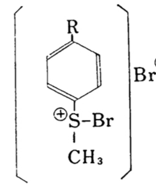
Baddeley[10] has also shown that the orders of the ratio of the packing radius vs. the single-bond radius are $F > Cl > Br > I$ and $O > S > Se > Te$.

In seeking better evidence of electrophilic aromatic substitution with which one can compare the relative activating and orienting effects of sulfide groups vs. those of oxygen analogs, we have come across only two examples in the literature; namely, the bromination has been shown to take place meta to the methylthio group in both *p*-ethoxyphenyl sulfide[11] and *p*-tolyl methyl sulfide[12].

Although, these data show that the methylthio group has much less activating ability than the methoxyl or even the methyl group, these examples are not very adequate, because the initial reaction of bromination should be the attack of bromine on the sulfur atom of the methylthio group, instead of on the benzene nucleus, leading to the formation of an intermediate complex I, which then further reacts to give the final product.



Neither the nitration[13] nor sulfonation[14] reaction is desirable, because the initial attack takes place on the sulfur atom, eventually oxidizing the sulfide group.



(I)

Mercuration is also not desirable for the same reason. The other possible electrophilic substitution reactions are the chloromethylation and hydrogen exchange reactions; we have chosen the latter. The acid-catalyzed hydrogen deuterium exchange reaction has been extensively studied by previous workers[15] and has thus been known to give a rate sequence of aromatic substituents identical with that of such well-studied reactions as nitration. Thus, we have studied the acid-catalyzed hydrogen-deuterium exchange reactions of *p*-deuterated anisole, thioanisole and mono-deuterated benzene as a reference compound, in acetic acid containing sulfuric acid as catalyst.

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Deuteration was accomplished by the Grignard reaction of the corresponding bromo-compounds, while *p*-bromothioanisole was made[16] by resting sodium methylmercaptide with diazotized *p*-bromoaniline.

The kinetic results, obtained through analyzing the compounds with a mass-spectrometer, are shown in Table I.

TABLE I. FIRST ORDER RATE CONSTANTS, k_1, AND ENTHALPIES AND ENTROPIES OF ACTIVATION OF THE HYDROGEN-DEUTERIUM EXCHANGE REACTIONS

Compound	Temp. °C	k_1, sec^{-1}	$H^{\neq}$, kcal./mol.	$S^{\neq}$ e. u.
Benzene-d$_1$	100.0	1.63×10^{-8}		
p-Deutero-anisole	60.8	3.61×10^{-6}	26.30	−4.44
	79.9	3.55×10^{-5}		
	96.6	1.89×10^{-4}		
p-Deuterothio-anisole	80.0	7.68×10^{-7}	27.60	−8.37
	99.3	6.35×10^{-6}		
	119.9	4.36×10^{-5}		

It has previously been established that the relative affinity for a proton is stronger for anisole than for thioanisole. This means that anisole is in a less favorable condition than thioanisole in using its lone electron pair for conjugation, while the electron-withdrawing inductive effect is also stronger for the methoxyl group than for the methylthio group. Yet one finds that the methoxyl group activates the benzene nucleus substantially more than the sulfur counterpart; i. e., anisole reacts thirty to forty times faster than the thioanisole, while both the enthalpy and entropy of the activation of the sulfur compound are larger than those of the oxygen analog by 1.5 kcal./mol. and 4 e. u. respectively.

This result is another support for the well-accepted concept that the electron-releasing conjugative effects decrease with the increasing atomic number of any periodic group.

It is interesting to note that thioanisole reacts fifty times faster than benzene. This means that the methylthio group, in spite of its small value ($\sigma=-0.047$)[17], actually activates the benzene ring in an electrophilic aromatic substitution. In fact, several previous workers have pointed out the strong electron-releasing conjugative effect of the methylthio group in electron-demanding reaction[1a,7,9,18].

Experimental

***p*-Deuteration.** — *p*-Deuteration was carried out by quenching with D_2O the Grignard reagents of *p*-bromoanisole, *p*-bromothioanisole and bromobenzene prepared in anhydrous ether. The boiling points of the deuterated compounds are as follows: anisole, 155.5°C/760 mmHg; thioanisole, 81∼81.5°C/18 mmHg; benzene, 81°C/760 mmHg.

Successful deuteration was confirmed by their infrared spectra, near 2200 cm^{-1} and 835 cm^{-1} for deuterated anisole and thioanisole and near 2200 cm^{-1} for benzene-d$_1$.

Kinetics. — In 10 ml. of acetic acid containing sulfuric acid (molar ratio, $CH_3COOH:H_2SO_4=50:1$) was dissolved 0.008 mol. of a deuterated compound, and aliquots (1 ml.) of this solution were reacted in ampoules at the desired temperature. At suitable time intervals the contents of the ampoule were poured into 10 ml. of an aqueous 4 N sodium hydroxide solution under cooling with an ice-salt mixture and were extracted with 5 ml. of ether except for benzene-d$_1$.

After being washed with 2 ml. of water, the ether layer was placed in a mass spectrometer-sample tube and the ether was removed by suction. Without further treatment, the residue was analyzed directly with a mass spectrometer (Atlas CH-3 type).

For benzene-d$_1$, quenched alkaline solutions were used directly for the analysis. The amount of *p*-deuteroanisole remaining in the reaction mixture (*p*-deuteroanisole plus anisole) was calculated by comparing the peak height of 109 plus 1/8 of that of 107 against that of 108 plus 7/8 of that of 107, assuming that both hydrogen and deuterium split off indiscriminately, giving the peak of 107. This assumption does not seem to be a terribly absurd one in view of the rather small difference in preference for the loss of hydrogen[19]. *p*-Deuterothioanisole gave its main mass peaks at 125,

TABLE II. SOME DATA OF DEUTERIUM ANALYSES

p-Deuteroanisole

$k_1=3.55\times10^{-5}$ sec^{-1}		Half-life 325 min.	Temp. 79.9°C.
Time, min.	$D/(D+H)$[a]	$\frac{D/(D+H)t}{D/(D+H)t_0}\times100$	$k_1(\times10^5)$, sec^{-1}
0	0.7570	100	—
20	0.7280	95.8	3.65
40	0.6992	91.5	3.74
70	0.6655	86.6	3.40
180	0.5467	69.3	3.41

p-Deuterothioanisole

$k_1=4.36\times10^{-5}$ sec^{-1}		Half-life 264 min.	Temp. 119.9°C.
Time, min.	$D/(D+H)$[a]	$\frac{D/(D+H)t}{D/(D+H)t_0}\times100$	$k_1(\times10^5)$, sec^{-1}
0	0.6820	100	—
55	0.5830	85.5	4.29
105	0.5169	75.8	4.38
180	0.4241	62.2	4.39
300	0.3105	45.5	4.37

a) *D* and *H* indicate deuterated and ordinary compounds respectively.

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124 and 123, wile deuterobenzene gave its at 79, 78 and 77. Similar treatments were carried out for both compounds for estimating the reaction rates.

The typical kinetic runs are shown in Table II, and the derived first-order kinetic constants are recorded in Table I.

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