Measurement of the Relative Nucleophilicities of Thiolate Anions by the Base-Catalyzed Addition of Thiols to Maleic Anhydride[1]

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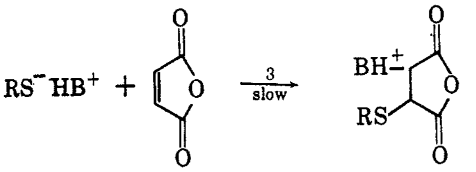
The base-catalyzed addition of thiols to maleic anhydride in nonpolar media provides a convenient method for determining the nucleophilicities of thiolate anions. Previous work suggested that the reaction proceeds by the reversible formation of an ion pair from thiol and base followed by the rate-limiting attack of the thiolate portion of the ion pair on maleic anhydride. Relative apparent pK_a values are presented for the dissociation step and third-order rate constants have been measured for the addition reaction in xylene at 27° using triethylenediamine catalyst. These data allow relative nucleophilicities to be determined for several aromatic and aliphatic thiolate anions. Reasonable correlations with the appropriate substituent constants are attained. Aromatic thiols, as expected, are more acidic than aliphatic thiols and electron-donating groups decrease the acidity. The most acidic thiol gives the highest rate of addition, indicating that the dissociation equilibrium between thiol and base dominates the over-all rate of addition. Correcting the third-order rate constants for the prior equilibria allows relative rate constants to be determined for the addition of thiolate anions to maleic anhydride. The anion of the most acidic thiol is the least nucleophilic. HMO calculations show good correlation with reactivity for aryl thiols.

The possibility of measuring the relative reactivities of species such as thiols, thiolate anions and thiyl radicals with unsaturated compounds (addition reaction) has been of interest for many years.[2a] Some quantitative work on relative reactivities of thiyl radicals in the addition reaction with olefins was accomplished several years ago.[2b] However, it has been difficult to obtain comparable quantitative data on thiolate anions in the addition reaction with olefins. The lack of these data[3] on reactivities of thiolate anions is explained[2a] by the great tendency of thiols to form the thiyl radical, a reactive free radical in many reactions, in the presence of light, oxygen, and trace amounts of metals. Thus, it has not been easy to find a system in which one could be certain that the ionic addition reaction was being studied without the complication of concurrent addition of thiyl free radicals to the double bond.

The base-catalyzed addition of thiols to maleic anhydride in nonpolar media[4] provides a uniquely convenient method for determining nucleophilicities of thiolate anions, since the reaction is essentially quantitative and the rates of reaction are in a convenient range.[5] Fortunately, the potentially competitive addition of the electrophilic thiyl radical to the electron-deficient double bond of maleic anhydride proceeds at a negligible rate under the conditions employed for the ionic reaction.

It has been suggested[6] that the addition proceeds by the reversible formation of an ion pair involving thiol and base followed by the rate-limiting attack of the thiolate portion of the ion pair on maleic anhydride. This sequence is illustrated by eq 1–3. The observed third-order rate constant, k_{obsd}, is equal

$$\mathrm{RSH} + \mathrm{B} \underset{2}{\overset{1}{\rightleftharpoons}} \mathrm{RS^-HB^+} \tag{1}$$



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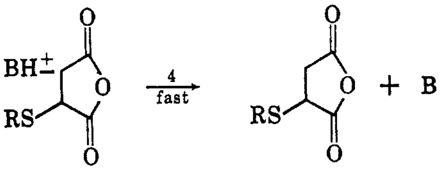

(3)

to $k_3K_a = k_1/k_2$. Using these relationships it is possible to obtain the thiolate nucleophilicities if relative measures of the prior equilibria can be determined. These data now have been obtained for alkyl and aryl thiolates. This report also is concerned with correlations of the experimental results with parameters of molecular orbital calculations carried out successfully, for the first time, on thiols.

Results

The thiols used in this study together with their apparent or nonthermodynamic pK_a values, third-order rate constants, and relative thiolate anion nucleophilicities collected are in Table I. Both acidity and rate measurements were made at 27°. The apparent pK_a listed is the pH at half-neutralization in 3:1 (v/v) acetone–water; this follows from the Henderson equation[7] and neglect of activity corrections. The

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(1) Presented at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964.

(2) (a) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. II, Chemical Publishing Co., Inc., New York, N. Y., 1960, p. 31. (b) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 83–84.

(3) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 21 (1962).

(4) F. B. Zienty, B. D. Vineyard, and A. A. Schleppnik, *J. Org. Chem.*, **27**, 3140 (1962).

(5) In the only closely related study, G. S. Krishnamurthy and S. I. Miller [*J. Am. Chem. Soc.*, **83**, 3961 (1961)] established the nucleophilicities of several aryl thiolates by measurement of the rates of addition of sodium thiolates to ethyl phenylpropiolates to form acrylates; these authors review the background work on nucleophilicities of thiols. S. I. Miller and G. S. Krishnamurthy [*J. Org. Chem.*, **27**, 645 (1962)] found that spectral data of thiols were not useful for measurement of nucleophilic reactivity. R. F. Hudson [*Chimia* (Aarau), **16**, 173 (1964)] and R. F. Hudson and G. Klopman [*J. Chem. Soc.*, 1062 (1962)] discussed the nucleophilic reactivity of thiols in S$_N$2 reactions. J. P. Daney and C. J. Noel [*J. Am. Chem. Soc.*, **82**, 2511 (1960)] measured the relative nucleophilic character of several mercaptans toward ethylene oxide.

(6) B. Dmuchovsky, B. D. Vineyard, and F. B. Zienty, *ibid.*, **86**, 2874 (1964).

(7) S. Glasstone, "Textbook of Physical Chemistry," 2nd ed, D. Van Nostrand Co., Inc., New York, N. Y., 1946, p 1003.

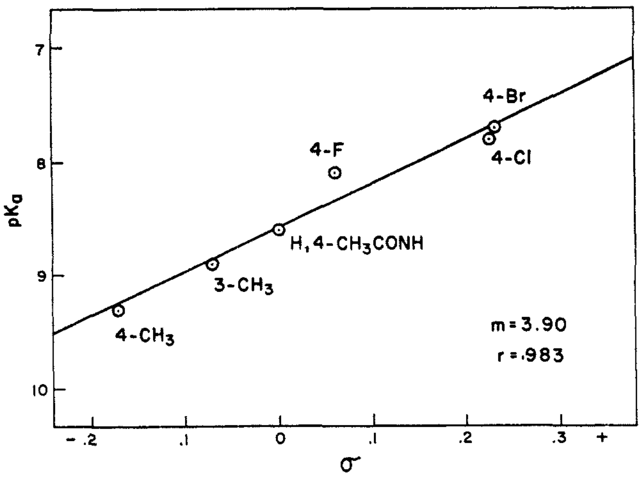

Figure 1.—Correlation between aromatic thiol acidity and the Hammett substituent constant.

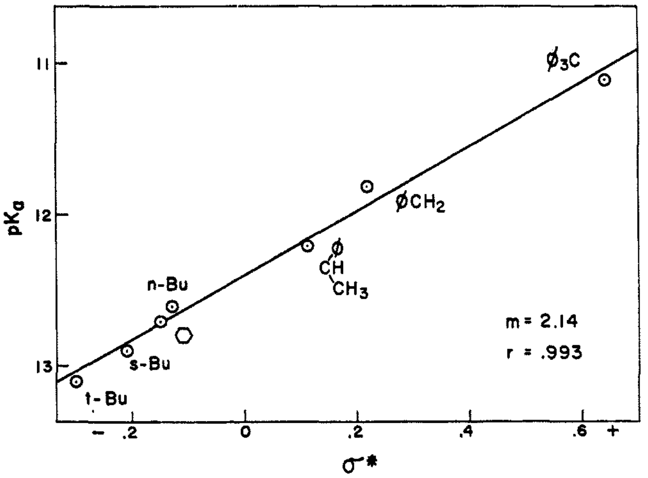

Figure 2.—Correlation between aliphatic thiol acidity and the Taft substituent constant.

rates of reaction were determined in homogeneous solution. Experiments with 4-acetamidobenzenethiol resulted in turbid solutions containing a white precipitate; as a result, rate data for this thiol are not included in Table I.

In each self-explanatory figure the slope of the line of least squares is denoted by *m* (usually equivalent to a *ρ* value) and the correlation coefficient[8] is designated as *r*. In all cases confidence is above the 95% level. The Hammett substituent constants, *σ*, were taken from the compilation of McDaniel and Brown.[9] The correlations between *σ* and apparent pK_a are shown in Figure 1. The Taft polar substituent constants, *σ**, were obtained from the literature[10] with two exceptions. A value of +0.64 was calculated for triphenylmethanethiol by assuming the additive nature of *σ** values[10a] and a lack of steric effects in the neutralization, which is confirmed by examination of molecular models. 2-Furanmethanethiol was assigned a value of +0.43 from the slope of Figure 2 and the observed acidity.

TABLE I

THIOL ACIDITIES AND THIRD-ORDER RATE CONSTANTS FOR TRIETHYLENEDIAMINE-CATALYZED ADDITION OF THIOLS TO MALEIC ANHYDRIDE IN XYLENE AT 27°

Compound	pK_a	Log k_{obsd}, M^{-2} sec^{-1}	k_n[a]
1-Butanethiol	12.6	2.11	1000
2-Butanethiol	12.9	1.38	380
2-Methyl-2-propanethiol	13.1	1.13	340
Cyclohexanethiol	12.7	1.47	300
Phenylmethanethiol	11.8	2.98	1200
1-Phenyl-1-ethanethiol	12.2	2.54	1100
2-Furanmethanethiol	11.3	3.55	1400
Triphenylmethanethiol	11.1	1.73	14
Benzenethiol	8.6	3.81	5
2-Methylbenzenethiol	9.2	3.34	7
3-Methylbenzenethiol	8.9	3.52	5
4-Methylbenzenethiol	9.3	3.66	18
4-Acetamidobenzenethiol	8.6	...	...
4-Fluorobenzenethiol	8.1	3.90	2
4-Chlorobenzenethiol	7.8	3.96	1
4-Bromobenzenethiol	7.7	4.04	1
2-Pyridinethiol	10.6	3.21	13

[a] Relative thiolate anion nucleophilicities.

Since 3-methylbenzenethiol was so far removed from the least-squares line in Figure 3 it was subjected to nmr analysis to 2-methylbenzenethiol, the presence of which would account for the depressed rate. The sample contained no *ortho* isomer under conditions where distinctions were readily apparent.

2-Pyridinethiol is not compared graphically with aromatic thiols because it is known to exist almost exclusively in the thione form.[11] One may thus be unjustifiably comparing an amine with thiols since the reaction products may be different.

A plot of the logarithm of k_3 against *σ** showed appreciable scatter for the aliphatic series; the results are now shown. Effects of changing solvent and dielectric constant on the rate of addition of benzenethiol to maleic anhydride and on the acidity of benzenethiol are shown in Table II.

TABLE II

BASE-CATALYZED ADDITION OF BENZENETHIOL TO MALEIC ANHYDRIDE. VARIATION IN ADDITION RATE AND ACIDITY OF BENZENETHIOL WITH CHANGING SOLVENT AT 27°

Solvent	*D*	Log k_{obsd}, M^{-2} sec^{-1}	pK_a
Xylene	2.3	3.81	
Chlorobenzene	5.6	4.44	
Acetone	20.7	4.75	
Nitrobenzene	34.8	5.28	
50% acetone–water	52		7.8
75% acetone–water	35		8.6

Discussion

The aromatic thiols and thiolate anions behave in an orderly manner consonant with the known electronic contributions of substituents.[12] The changes observed

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[8] H. S. Mickley, T. K. Sherwood, and C. E. Reed, "Applied Mathematics in Chemical Engineering," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1957, Chapter 2.

[9] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

[10] (a) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13. (b) M. M. Kreevoy, E. T. Harper, R. E. Duvall, H. S. Wilgus, III, and L. T. Ditsch [*J. Am. Chem. Soc.*, **82**, 4899 (1960)] correlated the acid dissociation constants of several mercaptans with the Taft *σ** parameters. (c) S. H. Marcus and S. I. Miller [*J. Phys. Chem.*, **68**, 331 (1964)] correlated the sulfhydryl pmr chemical shifts with Taft *σ** parameters.

[11] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 2384 (1959), and references cited therein.

[12] J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963. M. M. Kreevoy, E. T. Harper, R. E. Duvall, H. S. Wilgus, III, and L. T. Ditsch [*J. Am. Chem. Soc.*, **82**, 4899 (1960)] studied the relationship between inductive effects and acid dissociation constants of several mercaptans.

TABLE III

COMPARISON OF THIOL ACIDITIES

Compound	$(CH_3)_2CO-H_2O$[a]	$C_2H_5OH-H_2O$[b]	H_2O[c]	t-$C_4H_9OH-H_2O$[d]	$C_2H_5OH-H_2O$[e]
1-Butanethiol	12.6			11.5	12.4
2-Methyl-2-propanethiol	13.1		11.0		12.7
Benzenethiol	8.6	8.6	6.5	7.5	8.3
3-Methylbenzenethiol	8.9	8.9			
4-Chlorobenzenethiol	7.8	7.8			
4-Bromobenzenethiol	7.7	7.8			
Phenylmethanethiol	11.8				11.8

[a] Acetone-water (3:1 v/v), $D \sim 35$. [b] G. Schwarzenbach and E. Rudin, *Helv. Chim. Acta*, **22**, 360 (1939); data extrapolated to 3:1 (v/v) alcohol-water, $D \sim 35$. [c] M. M. Kreevoy, B. E. Eichinger, T. E. Stary, E. A. Katz, and J. H. Selstedt, *J. Org. Chem.*, **29**, 1641 (1964). [d] W. H. Fletcher, *J. Am. Chem. Soc.*, **68**, 2726 (1946); 23% aqueous *t*-butyl alcohol, $D \sim 70$. [e] J. Maurin and R. Paris, *Compt. Rend.*, **232**, 2428 (1951).

with structure are regular and are due solely to varying polar effects, since other factors remain constant in the series. The exception is a steric effect operating in 2-methylbenzenethiol which is responsible for the decrease in rate relative to the *para* isomer.

Greater acidity of the thiols is associated with electron-withdrawing groups. The rates of thiolate addition increase as thiol acidities increase. However, the thiolate anion derived from the strongest acid is the poorest nucleophile; the very factor which increases the acidity of the thiol, electron delocalization away from sulfur, causes the nucleophilicity of the anion to diminish. The order of thiolate anion nucleophilicities obtained by correcting the third-order rate constants for the prior equilibria compares well with that measured directly by Krishnamurthy and Miller[5] for the addition of thiols to triple bonds: $4\text{-}CH_3 > 3\text{-}CH_3 > H > 4\text{-}Cl$. This agreement serves to increase confidence in the results generated by this study and, at the same time, to confirm the mechanism proposed for the base-catalyzed addition of thiols to maleic anhydride.[6]

A comparison of thiol acidities is shown in Table III. Agreement is excellent for measurements in solvents of the same dielectric constant. The acidity differences are a function of the dielectric constant and these differences are constant between any two columns.[13] Changes in apparent pK_a with dielectric constant are in accord with the data of Table II and support the contention that the increase in rate of base-catalyzed thiol addition in solvents of increasing dielectric constant is due largely to the increase in acidity.

Because nitrogen is more electronegative than carbon, it might be expected that the apparent pK_a of 2-pyridinethiol should be lower than that of benzenethiol; however, the reverse is true indicating that the observed apparent pK_a for the nitrogen analog is a measure of the dissociation of an N-H bond in a thioketone as suggested by Albert and Barlin.[11]

In the aliphatic system steric effects, as well as polar effects, will vary with the alkyl moiety, but the data do not permit any separation of these effects nor do they allow any firm conclusions to be drawn. However, it appears satisfactory to consider that acidity is a function of the electron-donating ability of the alkyl group analogous to the relationship between acidity and substituents in aromatic thiols.

The absence of triphenylmethanethiol from Figure 4 demands comment. The point for the triarylthiol lies far off the line and is therefore not included. Its anomalous behavior can perhaps be explained by the suggestion of an unknown irregular steric factor in the rate-limiting step which reduces k_3.

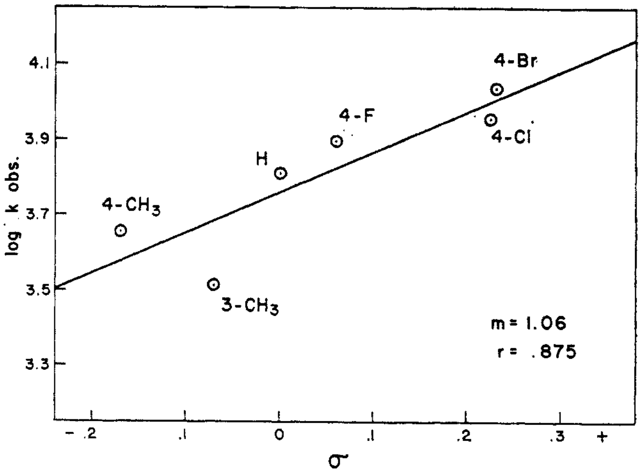

Figure 3.—Relationship between the Hammett substituent constant and the third-order rate constant for the base-catalyzed addition of aromatic thiols to maleic anhydride in xylene at 27°.

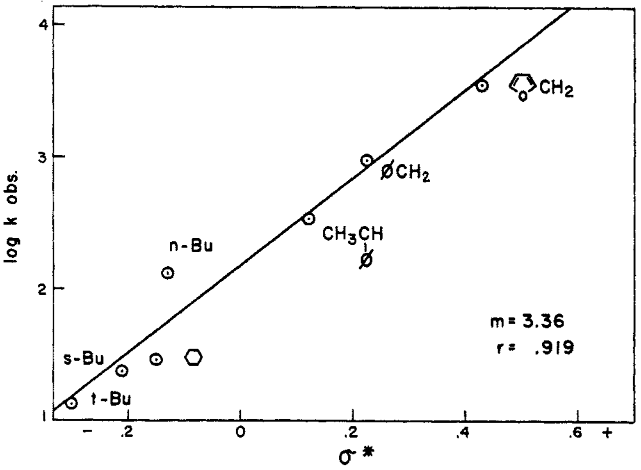

Figure 4.—Relationship between the Taft substituent constant and the third-order rate constant for the base-catalyzed addition of aliphatic thiols to maleic anhydride in xylene at 27°.

Relatively few molecular orbital calculations have been performed on sulfur compounds[14,15] and these have been chiefly on heterocyclic molecules such as thiophene,[16,17] 1-4-dithiadiene,[17] and isothianaphthene.[18]

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(13) See ref 10a, Chapters 2, 3, and 8.

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

(15) R. Zahradnik and J. Koutecky, *Tetrahedron Letters*, 632 (1961).

(16) H. C. Longuet-Higgins, *Trans. Faraday Soc.*, **45**, 173 (1949).

(17) M. M. Kreevoy, *J. Am. Chem. Soc.*, **80**, 5543 (1958).

(18) J. de Heer, *ibid.*, **76**, 4802 (1954).

TABLE IV

MOLECULAR ORBITAL CALCULATIONS ON SUBSTITUTED BENZENETHIOLS[a]

Molecule	Substituent parameters h_x	k_{cx}	δ	Self-atom polarizability $\pi_{r,r}$ for sulfur	π energy in units of β	L_R
Benzenethiol	...	...		0.241	9.598	1.598
2-Methylbenzenethiol[b]	2	0.7	−0.1	0.232	13.527	1.562
3-Methylbenzenethiol[b]	2	0.7	−0.1	0.238	13.563	1.598
4-Methylbenzenethiol[b]	2	0.7	−0.1	0.215	13.527	1.562
4-Fluorobenzenethiol	3	0.7	0.1	0.254	16.035	1.612
4-Chlorobenzenethiol	2	0.4	0.2	0.268	14.105	1.630
4-Bromobenzenethiol	1.5	0.3	0.2	0.261	12.970	1.622
Benzene	...	...			8.000	
Toluene	2	0.7	−0.1		11.965	
Fluorobenzene (X = F)	3	0.7	0.1		14.423	
Chlorobenzene (X = Cl)	2	0.4	0.2		12.475	
Bromobenzene (X = Br)	1.5	0.3	0.2		11.348	

[a] Sulfur parameters: $h_s = 0.5$, $k_{cs} = 1$, $\delta = 0.1$, used in all cases. [b] Heteroatom model for methyl used; a value of $-0.2\beta_0$ was applied to carbon attached to the methyl.[14]

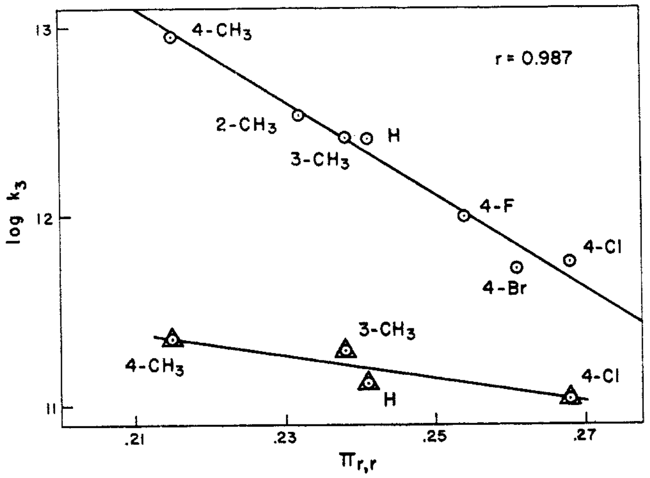

Figure 5.—Correlation between self-atom polarizability, $\pi_{r,r}$, and aromatic thiolate anion nucleophilicity as measured by the base-catalyzed addition of aromatic thiols to maleic anhydride in xylene at 27° is indicated by points ⊙. Correlation between $\pi_{r,r}$ and aromatic thiolate anion nucleophilicity as measured in ref 5 by the base-catalyzed addition of aromatic thiols to phenylpropiolates is indicated by points ⊙ enclosed in a triangle.

The thiol substituent, –SH, has been considered in two publications,[19,20] but no specific premise for further work resulted. This deficiency prompted us to undertake our own Hückel molecular orbital (HMO) calculations using the Streitwieser–Brauman program specifically adapted for the IBM 704 computer.

The method used has been described in recent publications.[14,21] As is customary, overlap and interaction of the $\sigma-\pi$ electrons, as well as participation of the sulfur d orbitals, were neglected. Changes in the mobile electron system occasioned by introducing a heteroatom X were made by the h_x and k_{cx} parameters in terms of the standard α_0 (Coulomb integral) and

$$\alpha_x = \alpha_0 + h_x\beta_0 \qquad (4)$$

$$\beta_{cx} = k_{cx}\beta_0 \qquad (5)$$

β_0 (resonance integral) referred to benzene and defined by eq 4 and 5. The model for sulfur in the benzenethiols involves a 3p orbital interacting with the ring and implies an appropriately altered Coulomb integral. It is equivalent to a modified benzylic carbanion. Values for the parameters h_x, k_{cx}, and the auxiliary inductive parameters, δ, suggested by Streitwieser[22] were used initially and only very minor adjustments were necessary for the best fit.

All calculations involving methyl substituents were performed with a correction of 0.2β applied to α for the ring carbon bearing the methyl group, as suggested by Streitwieser.[22] The final values are shown in Table IV.

The self-atom polarizability,[23] $\pi_{r,r}$, is one of the more important MO quantities in correlating reactivities and is defined in the Appendix. The values of $\pi_{r,r}$ for sulfur in each arylthiol studied are also shown in Table IV. In Figure 5 is shown the correlation between $\pi_{r,r}$ and log k_3 for the thiolate anion addition for 2-, 3- and 4-methylbenzenethiol, 4-fluorobenzenethiol, 4-bromobenzenethiol, 4-chlorobenzenethiol, and benzenethiol itself (data points indicated by circles). The correlation coefficient at 95% confidence limits for this line is 0.987. When acidities were used the plot was not so good. It is particularly interesting to note that 2-methylbenzenethiol behaved regularly. Apparently, the steric effect found experimentally is counterbalanced in the HMO treatment by an effect of equal but opposite magnitude. On the other hand, the localization energy (*vide infra*) for the *ortho* isomer did not correlate at all. Also exhibited in Figure 5 are the correlations between $\pi_{r,r}$ and kinetic data reported by Krishnamurthy and Miller[5] for the addition of aryl thiolates to phenylpropiolates; data for benzenethiol, 3- and 4-methylbenzenethiol, and 4-chlorobenzenethiol are represented by triangles.

An entirely different approach was tried using eigenvalue rather than eigenvector quantities. A localization energy, L_R, was calculated by the difference in total π energies of the benzenethiol and the molecule resulting from separating the sulfur atom from the π system. This is equivalent to viewing the thiolate anion as being bonded to maleic anhydride in the transition state and the calculation involves structures 1 and 2. The value obtained might be termed a neutral molecule localization energy. The β-energy differences between structures 1 and 2 for the various

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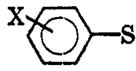
(19) A. Pullman, *Bull. Soc. Chim. France*, 641 (1958).

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

(21) J. D. Roberts, "Notes on Molecular Orbital Theory," W. A. Benjamin, Inc., New York, N. Y., 1961.

(22) See ref 14, Chapter 5.

(23) See ref 14, p 112.



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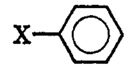

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benzenethiols are listed under L_R, in units of β in Table IV. The calculations for both thiol and thiolate anion were identical since the same h and k parameters were used for both. Good correlations were found between L_R and pK_a and log k_3 for all thiols except 2-methylbenzenethiol. Figure 6 displays a plot of the correlations between L_R and log k_3 as well as the similar correlations for the Krishnamurthy and Miller data for addition of thiols to phenylpropiolates.

The conclusion with respect to the HMO calculation is that straightforward application of the basic theory can produce satisfactory correlations with the reactivities of benzenethiols bearing a variety of substituents. The fact that two basically different MO parameters, the self-atom polarizability and the localization energy, gave correlations was unexpected and lends encouragement to future use of the theory in this area.

Experimental Section

The thiols used are all commercially available and were distilled or crystallized and stored under nitrogen prior to use. The physical constants are in accord with those reported in Beilstein's Handbook.

The apparent or nonthermodynamic pK_a values at 27° were found by determining the pH at the half-neutralization point using 0.01 mole of thiol in 50 ml of 3:1 (v/v) acetone–water solvent. A glass electrode and a saturated calomel electrode were used in conjunction with a Leeds and Northrup potentiometer. Reproducibility was within 0.1 pH units.

Except where noted, all the rate measurements were conducted at 27.0 ± 0.1° using xylene solutions that were 4.0×10^{-3} M in thiol and maleic anhydride and 4.0×10^{-4} M in triethylenediamine. A reaction vessel similar to that described by Krishnamurthy and Miller[5] was employed. Reproducibility among runs (at least two per thiol) was about 8% using analytical methods described previously.[6]

Acknowledgments.—Mr. Hector Yepez aided in the performance of the kinetic experiments. Sincere thanks are due Professor Andrew Streitwieser, Jr., for the molecular orbital program, written in collaboration with J. I. Brauman. The assistance of R. F. Brooks in adapting the program to the IBM 704 is gratefully recorded.

Appendix

The Streitwieser and Brauman program sets up the customary HMO matrix, allows for variation of the α and β input, and prints out the orbital energies, total π energy, coefficients, and derived quantities such as the atom–atom polarizabilities in easily readable form. For description of the method, see ref 14 and 21.

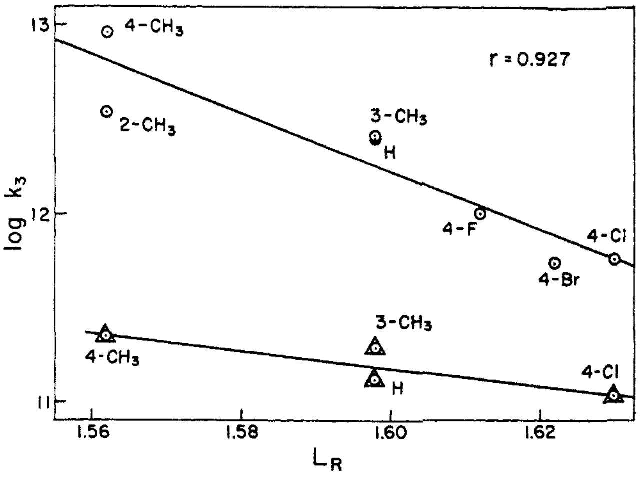

Figure 6.—Correlation between localization energy, L_R, and aromatic thiolate anion nucleophilicity as measured by the base-catalyzed addition of aromatic thiols to maleic anhydride in xylene at 27° is indicated by points ⊙. Correlation between L_R and aromatic thiolate anion nucleophilicity as measured in ref 5 by the base-catalyzed addition of aromatic thiols to phenylpropiolates is indicated by points ⊙ enclosed in a triangle.

The polarizability of any two atoms r and s is given by the following equation. Here c is a coefficient of the wave equation, e is an orbital energy, and the summations are carried out over the occupied (m) and the unoccupied (n) orbitals. The atom–atom polarizability for the case of r = s is termed the *mutual atom* or *self-atom* polarizability.

$$\pi_{r,s} = 4\sum_{j=1}^{m}\ \sum_{k=m+1}^{n} \frac{c_{jr}c_{kr}c_{js}c_{ks}}{e_j - e_k} \tag{6}$$

For calculating the localization energy with respect to structures **1** and **2**, the negative charge is said to be localized on the sulfur atom, effectively removing two electrons from the π system. Of the total energy which in the Hückel approximation is given in terms of α and β, only the β part is used.

$$L_R = M_1 - M_2\beta \tag{7}$$

The symbol M is the coefficient of β in the expression for the total π energy in each case.