Kinetics of the Reaction of Sodium Arylthiolates with Nitro-Carboxybenzyl Halide Derivatives

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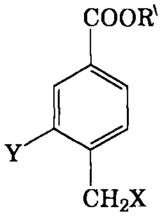
ABSTRACT

The rate constants for the reactions of 4-halomethyl-3-nitrobenzoic acids, the nonnitro derivatives, and their ethyl esters with arylthiolates were measured at different temperatures. It was found that the retardation in rate constants compared to benzyl halides is due to the electrostatic repulsion between the electronegative substituents (COO^- and/or NO_2) in the substrates and thiolate ions. Good correlations between log k_2 values of the acids and carbon basicities of thiolates were found while log k_2 values of the esters show good straight lines with Hammett σ constants, pk_a, and carbon basicities of arylthiolates. © 1996 John Wiley & Sons, Inc.

INTRODUCTION

The action of sodium hydroxide on 2-nitrobenzyl chloride in aqueous dioxane gave 2,2′-dinitrostilbene via carbene formed by an α-ElCB mechanism as well as a mixture of *cis* and *trans*-dinitrostilbene oxide [1]. While 2-nitrobenzyl bromide and iodide gave 2,2′-dinitrobenzylether, under the previous conditions, through an initial slow SN^2 hydrolysis step followed by a faster SN^2 etherification step [1]. The reaction of 4-halomethyl-3-nitrobenzoic acid (1) and the corresponding nonnitro derivative (2) with aqueous sodium hydroxide gave a mixture of the corresponding benzyl alcohol and/or dibenzyl ether derivative depending on the type of the halogen [2]. The treatment of (1), (2), and their corresponding ethyl esters (3) and (4) with sodium arylthiolates in ethanol yielded the corresponding thioethers [3–5].

This work reports the kinetic behavior of 4-halomethyl-3-nitrobenzoic acid (1), 4-halomethylbenzoic acid (2), ethyl 4-chloromethyl-3-nitrobenzoate (3), and ethyl 4-chloromethylbenzoate (4) towards sodium arylthiolates at different temperatures. It shows also interesting relationships between rate constants and Hammett σ constants, pk_a as well as log K (thermodynamic affinity of arylthiolates towards carbon).



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1, $X = Cl$, $Y = NO_2$, $R' = H$
2, $X = Cl$, $Y = H$, $R' = H$
3, $X = Cl$, $Y = NO_2$, $R' = C_2H_5$
4, $X = Cl$, $Y = H$, $R' = C_2H_5$
5, $X = I$, $Y = NO_2$, $R' = H$
6, $X = Br$, $Y = H$, $R' = H$
7, $X = I$, $Y = H$, $R' = H$

EXPERIMENTAL

The commercially available solvent was absolute ethanol. Sodium ethoxide solution was used to convert the thiol into thiolate and was prepared as needed from clean sodium and absolute ethanol.

Starting Materials

Arylthiols containing the following substituents were purified from commercial specimens as needed: 4-methyl, 4-methoxy, 4-bromo, 4-chloro, and 4-nitro.

Synthesis of 4-Chloromethylbenzoic Acid (2)

A mixture of *p*-toluic acid, (9 g, 0.066 mol), sulfuryl chloride (14 ml), and benzoyl peroxide (0.5 g) was refluxed for 2 h under ultraviolet irradiation. The reaction mixture, after cooling, was poured into ice-water. Solid 4-chloromethylbenzoic acid was obtained and crystallized from methanol as colorless needles, m.p. 201–3°C (lit. [6] 201°C).

Synthesis of 4-Chloromethyl-3-Nitrobenzoic Acid (1)

4-Chloromethylbenzoic acid was nitrated by a mixture of concentrated sulfuric acid and fuming nitric acid at temperature below −10°C. On pouring the reaction mixture on ice a yellow solid formed which crystallized from benzene as pale yellow needles, m.p. 138–140°C (lit. [6] 138°C).

Synthesis of Ethyl Chloromethyl-3-Nitrobenzoate (3) and Ethyl Chloromethylbenzoate [5] (4)

A mixture of 4-chloromethyl-3-nitrobenzoic (1) or 4-chloromethylbenzoic acid (2) (0.1 mol) and few drops of concentrated sulfuric acid in absolute ethanol was refluxed for 10 h under dry conditions. The cooled reaction mixture was diluted with water and extracted with ether. Evaporation of the dried ether gave an oil which was purified by vacuum distillation. Ethyl 4-chloromethyl-3-nitrobenzoate, m.p. 40°C (lit. [5] 40°C). Ethyl 4-chloromethylbenzoate, b.p. 158°C/2 mmHg (lit. [5] 158°C/2 mmHg).

Synthesis of 4-Iodomethylbenzoic Acid (5)

The same method as previously reported was used [6]. On work up, a yellow solid is formed which crystallized from benzene as yellow crystals, m.p. 237–239°C (lit. [6] 235°C).

Synthesis of 4-Bromomethylbenzoic Acid (6)

The same procedure was followed as reported earlier [6]. After work up a yellow solid was obtained which crystallized from benzene as pale yellow solid, m.p. 228–230°C (lit. [6] 226°C).

Synthesis of 4-Iodomethyl-3-Nitrobenzoic Acid (7)

4-Chloromethyl-3-nitrobenzoic acid (1) was dissolved in a mixture of pure acetone and 1 N aqueous sodium iodide. The reaction mixture was left overnight with stirring at room temperature. When the reaction mixture was poured on ice a yellow solid was formed which crystallized from CH_2Cl_2 *n*-hexane mixture as yellow crystals, m.p. 160–162°C (lit. [6] 160°C).

Synthesis of 4-[Arylthiomethyl]-3-Nitrobenzoic Acids (8 a–f) [3] and the Corresponding Nonnitro Derivatives (9 a–f) [4]

4-Chloromethyl-3-nitrobenzoic acid (0.1 mol) or 4-chloromethylbenzoic acid (0.1 mol) in ethanol and sodium salt of arylthiol compound (0.1 mol) were refluxed for 1–2 h. Cooling, dilution, and acidification with aqueous hydrochloric acid gave a solid, which was purified by crystallization from aqueous ethanol. 4-[arylthio)methyl]-3-nitrobenzoic acids (8 a–f), (8 a), *p*-H 136°C; (8 b), *p*-OCH_3 121°C; (8 c), *p*-CH_3 147°C; (8 d), *p*-Br 176°C; (8 e), *p*-Cl 162°C; and (8 f), *p*-NO_2 179°C. 4-[arylthio)methyl] benzoic acid (9 a–f): (9 a), *p*-H 180°C; (9 b), *p*-OCH_3 155°C; (9 c), *p*-CH_3 217°C; (9 d), *p*-Br 160°C; (9 e), *p*-Cl 156°C; and (9 f), *p*-NO_2 182°C.

Synthesis of Ethyl 4-[Arylthiomethyl]-3-Nitrobenzoates (10 a–f) [5] and the Corresponding Nonnitro Derivatives (11 a–f) [5]

General Procedure

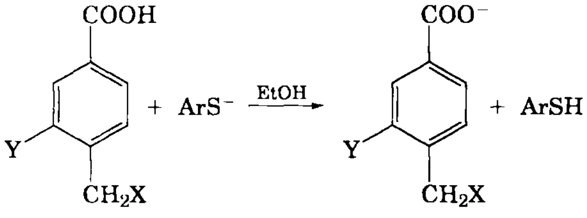
A mixture of the appropriate esters (3) or (4) (0.1 mol), arylthiol (0.15 mol), and a catalytic amount of sodium metal in ethanol was refluxed on a steam bath for 2 h. The reaction was cooled, diluted with 2% sodium hydroxide solution, and extracted with ether. Evaporation of ether layer gave a residue which was purified either by crystallization from ethanol or column chromatography (9:1 petroleum ether: ethyl acetate, respectively). Ethyl 4-[arylthiomethyl]-3-nitrobenzoate 10 a–f [5]: (10 a), *p*-H, n_D^{20} 1.550; (10 b), *p*-OCH$_3$, n_D^{20} > 1.70; (10 c), *p*-CH$_3$, n_D^{20} 1.574; (10 d), *p*-Br, 68°C; (10 e), *p*-Cl, 59°C; and (10 f), *p*-NO$_2$, 82°C. Ethyl 4-[arylthiomethyl]benzoate (11 a–f) [5]: (11 a), *p*-H, n_D^{20} 1.575; (11 b), *p*-OCH$_3$, n_D^{20} 1.585; (11 c), *p*-CH$_3$, n_D^{20} 1.574; (11 d), *p*-Br, 86°C; (11 e), *p*-Cl 64°C; and (11 f), *p*-NO$_2$, 105°C.

Kinetic Measurements

The reaction solution was made up in 100 mL flask immersed in the thermostat with temperature constant to ±0.05°C. At measured times, 5 mL aliquot (8 or 9 per run) was withdrawn by a fast-delivery pipett and discharged into 20 mL of dilute 0.1 N sulfuric acid. The extent reaction in all samples was estimated by potentiometric titration of the chloride ion liberated, using a silver-silver chloride electrode vs. calomel electrode cell. Since arylthiol interferred with this cell, it was necessary to extract each sample with 10 mL ether (3 times) before titration.

In cell runs, the initial concentration of the benzyl halide was 0.01 M. In case of acid substrates (1) and (2), an exactly equivalent molarity (0.01 M) of a standard sodium ethoxide solution was added and the volume was made up to 25 mL by the ethanol. In another 100 mL flask a standard sodium thiolate solution (0.01 M standardized sodium ethoxide and 0.01 M thiol) was prepared. The two flasks were allowed to reach thermal equilibrium in a well stirred thermostat at the desired temperature ±0.5°C.

The function of first adding base in the case of substrates with carboxy groups is to neutralize the substrate. This is because the ionization of the acid sulfides will reduce the concentration of arylthiolate to very low values, eq. (1).



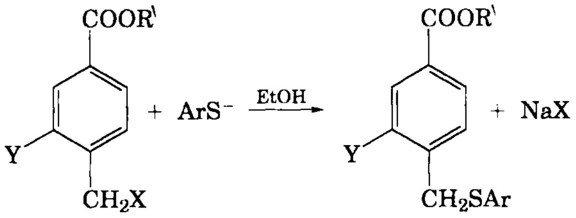
(1,2, 5–7)

(1)

The effect of excess sodium ethoxide under the same previous reaction condition is very small as observed from the low rate constant for the reaction of (1) with sodium ethoxide (100 times lower than the rate constant in presence of sodium benzenethiolate). Rate coefficients were calculated from the slope of the plot of 1/a–x vs. time, the slope being the second-order rate constant, k_2. The plots were linear without much scatter of points in the range 20%–70% reaction in most cases. Multiple runs were made for each reaction at each temperature.

RESULTS AND DISCUSSION

The reaction of arylthiolate ions with 4-halomethylbenzoic acid derivatives (1–7) in ethanol proceeded quantitatively according to the stoichiometric eq. (2).



(1–7)

(8–11)

(2)

The reaction of sodium arylthiolates with compounds (1–4) were followed potentiometrically by determining the liberated halogen under second-order conditions.

Tables I and II show that the second-order rate constants, enthalpy and entropy of activations ($\Delta H^{\#}$ and $\Delta S^{\#}$, respectively) depend upon the type of the halogen X, the substituent of sodium arylthiolate, the presence of carboethoxy group, as well as the nitro group in the substrate.

The rate constants for the reactions of the nitro compound (1) with thiolate anions are smaller than the corresponding ones for the nonnitro compound with the same nucleophiles, under the same kinetic conditions, a most unexpected result indicating an ortho effect phenomenon. Also, the smaller rate constants for the reaction of (1) are presumably due to the electrostatic repulsion of the negatively charged halogen atom, the negatively charged oxygen atoms of the nitro group and the carboxylate anion with arylthiolate anion [2]. This effect arises from the fact that, electron-attracting substituents of compound (1) (NO$_2$ and COO$^-$) may promote conjugation between the π-orbitals of the benzene ring and the π-orbitals

Table I Rate Constants (l mol^{-1} s^{-1}) and Activation Parameters for the Reactions of 4-Halomethyl-3-Nitrobenzoic Acid (1) and 4-Halomethylbenzoic Acid (2) with Aromatic Thiols R-C_6H_4SH

		$k_2 \times 10^2$ l mol^{-1} s^{-1}						
Cpd	R	30°	40°	50°	55°	60°	$\Delta H^{\#}$ k Cal	$-\Delta S^{\#}$ cal mol^{-1} deg^{-1}
1	—H	1.11	1.91	2.46	2.99	3.52	6.74	45.65
	—OCH_3	1.06	1.75	2.31	2.63	3.05	6.22	47.43
	—CH_3	1.03	1.54	2.11	2.36	2.84	5.97	48.47
	—Br	1.35	1.89	2.30	2.68	3.00	4.58	52.38
	—Cl	1.39	1.94	2.60	2.94	3.55	5.46	49.58
	—NO_2	0.85	1.32	1.54	1.75	2.21	5.20	51.16
2	—H	1.28	2.29	3.55	4.41	6.20	9.49	36.79
	—OCH_3	1.21	2.13	3.09	3.89	4.98	8.52	39.94
	—CH_3	1.19	2.06	2.66	3.04	3.88	6.77	36.27
	—Br	1.41	2.22	3.22	4.03	5.14	7.38	43.36
	—Cl	1.41	2.25	3.47	4.19	5.48	7.96	41.57
	—NO_2	0.95	1.53	2.19	2.67	3.08	7.19	44.72
5	H		54.82					
6	H		35.44	67.96				
7	H		77.04					

of these substituents [7]. This increases the interaction energy with the nucleophile, and hence the bond-forming energy.

Presence of electron-donating substituents in a nucleophile increases its nucleophilicity leading to a higher reaction rate than for electron-withdrawing substituents. This is due to an increase in the electron density on the sulfur atom.

In contradiction to this fact, compound (1) showed a decrease in its k_2 values, Table I, confirming the existence of an electrostatic repulsion effect as previously mentioned. This was also observed in the reaction of benzyl bromide with benzenethiolate where its k_2 values (k_2 = 1.08 l-mol^{-1} s^{-1} at 20°C) [8] was shown to be greater than that of the reaction of compound (6) containing a carboxyl group with the same nucleophile. Also, data show that the effect of—COOH to retard reactions with thiolate anions is greater than that of the —NO_2 group. The electrostatic repulsion between the electronegative groups in compound (1) increases in the transition state of the SN^2 reactions due to the carbon–halogen bond stretching, a situation not found in the corresponding nonnitro analogues (2). The C—Cl bond length increases in the transition state from 1.76 to ca. 2Å and the dipole moment from 1.85 to ca. 4.0 D [9].

Table II Rate Constants (l mol^{-1} s^{-1}), Activation Parameters and ρ Values for the Reactions of Ethyl-4-Chloro Methyl-3-Nitrobenzoate 3 and Ethyl-4-Chloro Methylbenzoate with Aromatic Thiols R-C_6H_4SH

		$k_2 \times 10^2$ l mol^{-1} s^{-1}				
	R	10°	20°	30°	$\Delta H^{\#}$ k cal	$-\Delta S^{\#}$ cal mol^{-1} deg^{-1}
3	—H	8.28	12.39	17.54	6.73	39.81
	—OCH_3	15.41	22.47	30.38	5.82	41.71
	—CH_3	11.39	17.38	25.21	6.49	39.85
	—Br	5.29	8.11	11.52	7.06	39.53
	—Cl	5.88	8.58	12.11	6.96	39.78
	—NO_2	2.23	3.74	6.02	9.36	33.25
ρ		−0.81	−0.74	−0.64		
4	—H	4.48	7.49	12.53	9.48	31.37
	—OCH_3	8.75	15.29	22.94	8.79	32.34
	—CH_3	6.00	10.58	16.01	9.25	31.68
	—Br	2.60	4.71	7.54	10.62	28.57
	—Cl	2.99	5.37	8.82	10.96	27.40
	—NO_2	1.01	1.75	2.99	10.65	30.37
ρ		−0.93	−0.87	−0.83		

The activation parameters show small variations but no definite pattern. The spread in enthalpies is $\cong$ 2 K.cal; and the spread in the entropies of activation is $\cong$8 eu. The entropy of activation values are negative consisting with a bimolecular mechanism.

The plots of log k_2 values against the Hammett σ constants for different substituents in the arylthiolate ions gave a series of identical curves for compounds (1) and (2), respectively, Figures 1 and 2. The same pattern of curves was previously observed in the reactions of 4-substituted benzyl bromides with arylthiolates [8]. Our data show that both electron-donating and electron-withdrawing substituents in the arylthiolate ions decrease the nucleophilic attack which suggest a gradual change from bond making to bond breaking in the transition state [10].

Strong electron supplying substituents e.g., —OCH_3 should increase the magnitude of the negative charge of the nucleophile, but should also increase the repulsion with the negatively charged —NO_2 and —COOH groups, thereby, delaying both C—X bond breaking and C—S bond making processes at the transition state. While electron-withdrawing substituents e.g., 4-Br and 4-Cl should increase the nucleophilicity of the thiolate ion by decreasing the negative charge on the sulfur atom favoring more enhancement of C—X bond breaking relative to C—S bond making process. However, the values of the element effect where $k_I/k_{Cl} = 28.7$ for the reaction of compounds (1) and (5), $k_{Br}/k_{Cl} = 15.4$ and $k_I/k_{Cl} = 33.64$ for the reactions of compounds (1), (6), and (7) with benzenethiolate ion, Table I, indicate that the C—X bond breaking is the slow step.

Tables I and II show that sodium 4-nitrobenzenethiolate is the least reactive nucleophile towards compounds (1) and (2). The nitro group should generally decrease the magnitude of the negative charge on the S atom by dispersion as well as conjugation. Although this will decrease the electrostatic repulsion with the electronegative substituents of compounds (1) and (2), the rate constant still remains the lowest. This is because the spreading of the negative charge of this ion will decrease the solvation energy leading to a decrease in the rate constant compared to the unsubstituted nucleophile.

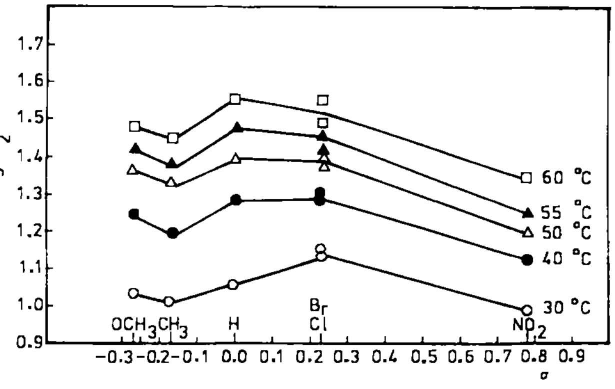


Figure 1 Plot of log k_2 against Hammett's σ-constants for the reaction of (1) with arylthiolates.

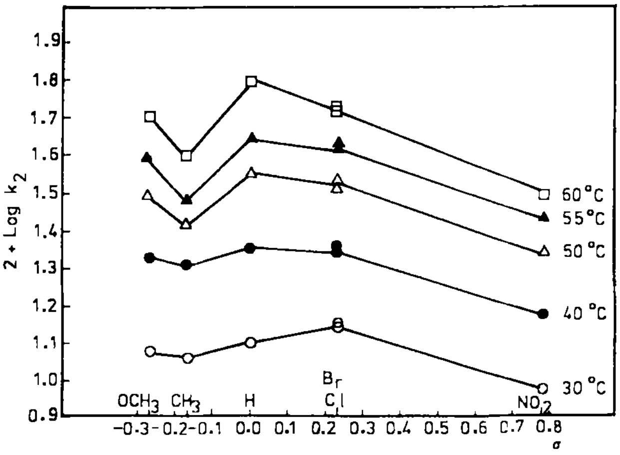
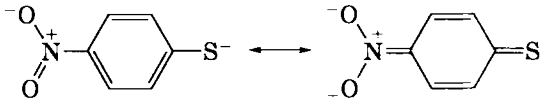


Figure 2 Plot of log k_2 against Hammett's σ-constants for the reaction of (2) with arylthiolates.



Second-order rate constants of the reactions of compounds (3) and (4) with arylthiolates as well as their activation parameters are given in Table II. There is no clear pattern of enthalpy $\Delta H^{\#}$ and entropy $\Delta S^{\#}$ of activations in the same series. However, these values are consistent with their bimolecular reactions.

It is observed that k_2 values of the reactions of compounds (3) and (4) are higher than those of compounds (1) and (2), respectively, with the same nucleophile. This could be attributed to the change of —COOH group to —COOEt group which inhibits the electrostatic repulsion between the substrate and the thiolate ion. Furthermore, Table II shows the k_2 values of the reaction of compound (3) which contains a nitro group are higher than those of the nonnitro compound (4) with the same nucleophile and $\Delta S^{\#}$ values of the former reaction are less negative than those with the latter one. This could be explained by the concept that the nitro group in compound (3) increases the electrophilicity of the benzyl carbon by induction and overcomes its ortho effect. This also reflects more interaction with the thiolate ion leading to a more ordered transition state.

Table II reveals that k_2 values of compounds (3) and (4) are increased by the presence of electron donating substituents and decreased by the presence of electron-withdrawing substituents in the arylthiolate ions. This is consistent with the nucleophilicity of thiolate derivatives [11].

In polar displacement reactions both the breaking of an existing bond and the making of a new bond takes place. One of these steps proceeds further than the other in the transition state. The magnitude of the change in charge depends upon whether the bond breaking or the bond making is more complete in the transition state which in turn reflects upon the magnitude of the charge at the electrophilic center. This is determined quantitatively by measuring the ρ constant of the reaction.

Plots of log k_2 for reactions of arylthiolate ions with (3) and (4) vs. Hammett σ constants gave good straight lines where negative ρ values ranged between 0.64–0.81 and 0.83–0.93, respectively, depending upon the temperature obtained, Figures 3 and 4. These values indicate that a bimolecular reaction takes place and the C—X bond breaking was not completed in the transition state.

Plots of log k_2 for the reactions of compounds (1) and (2) with thiolate ions against pK_a values [11] of the corresponding thiols at 30°C show deviations from the Bronsted relationship. These deviations, show that the energy factors which contribute to the activation energy [12] are not correlated to the corresponding changes for the combination of the nucleophile with a proton.

A distinction has been drawn [13,14] for nucleophiles between basicity, which relates to equilibria, and nucleophilic reactivity, which relates to rate phenomenon. The carbon basicity of a series of arylthiolate ions were compared by measuring their thermodynamic affinity for carbon using eq. (3) in which stable Meisenheimer complexes are formed. Attempts are made to correlate the reactivities of arylthiolates towards (1–4) with the corresponding carbon basicities (log K) [11].

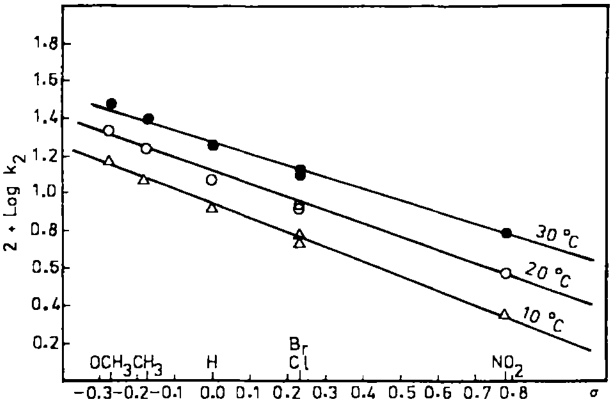


Figure 3 Plot of log k_2 vs. Hammett's σ-constants for the reaction of (3) with arylthiolates.

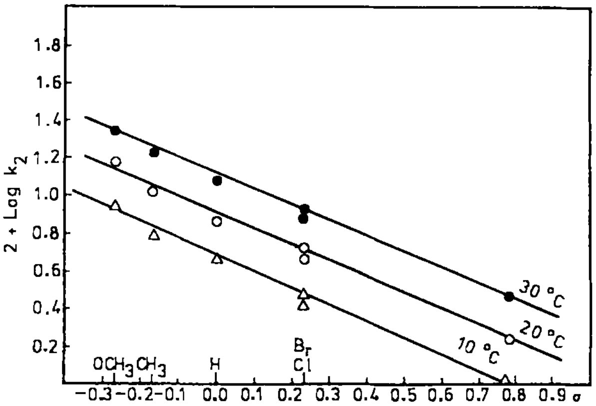
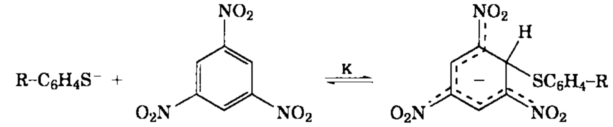


Figure 4 Plot of log k_2 vs. Hammett's σ-constants for the reaction of (4) with arylthiolates.



(3)

Plots of log k_2 vs log K at 30°C gave good straight lines for reactions of compounds (1) and (2) with thiolate ions, Figure 5. An interesting behavior is observed in these plots where negative slopes −0.066 ± 0.025 ($r = 0.93$) and −0.045 ± 0.017 ($r = 0.93$) were obtained, respectively. One interpretation of reactivity-carbon basicity plots would be that in the transition state the repulsion between the nucleophile and the electronegative substituents of these substrates retards the reactivity with respect to the unsubstituted nucleophile. Therefore, there is markedly better correlation of the nucleophile reactivities of thiolates with their carbon basicities rather than with their pK_a and Hammett σ constants.

Plots of log k_2 for reactions of compounds (3) and (4) with thiolate ions vs. log K at 30°C gave excellent straight lines with slopes 0.24 and 0.25, respectively, Figure 5. Similar plots of log k_2 vs. pK_a values of the corresponding thiols showed considerably more scattering, Figure 6.

It has been pointed out that great caution must exercised in the interpretation of Bronsted β and ρ values [15,16]. However, it is of great interest to find out that the nucleophilic reactivities of thiolates towards compound (3) and (4) gave good correlations

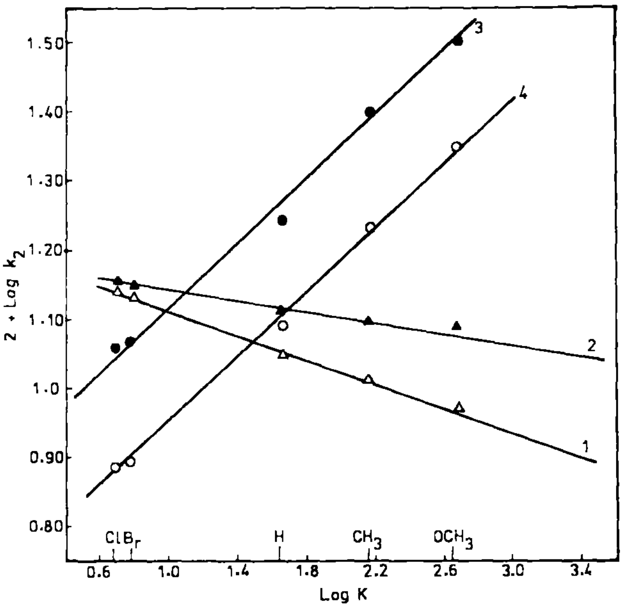


Figure 5 Correlations of nucleophilic reactivities (for compounds 1, 2, 3, and 4 at 30°C) and carbon basicities (log K) for arylthiolates.

with Hammett σ constants, pk_a, and carbon basicity of thiolates.

More generally it is of interest to see how well the nucleophilic reactivities of arylthiolate ions in other types of reactions correlate with their carbon basicities. We find that the rate constants for reaction of arylthiolate ions with benzyl bromides [8] and with ethyl aryl propiolates [17] correlate well with carbon basicities, although naturally different slopes are obtained. The similarity in behavior between the reactions of these thiolates towards the above compounds and towards compounds (1–4) reflects the fact that these reactions involve the formation of a sulfur-carbon bond [18].

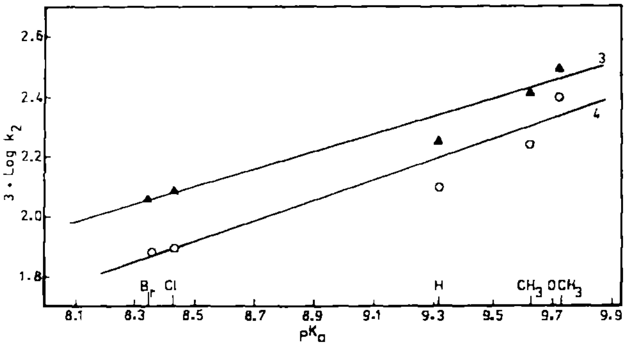


Figure 6 Plots of log k_2 for the reaction of (3) and (4) with arylthiolates against the corresponding pk_a values of thiols.

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