# Electronic Effects on the Formation of Two Adducts from the Reactions of N-Benzylisoquinolinium Halides with Hydroxide and Carbon Disulfide through the Isotope Dilution Method[1]

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Received March 19, 1971

N-Benzylisoquinolinium halides react with hydroxide and carbon disulfide in aqueous dioxane to form two kinds of adducts, mesoionic 3-phenylthiazolo[2,3-a]isoquinolinium-2-thione betaines and N-benzylisoquinolinium 4-dithiocarboxylates. Isotopic dilution experiments utilizing ^{35}S have led to accurate yield data for the two kinds of adducts derived from seven benzyl-substituted salts. The molar ratio of adducts determined by both isotopic dilution and quantitative product isolation techniques is correlated well by a Hammett plot: log [betaine/dithiocarboxylate] = 2.32σ − 0.12 (R = 0.971). The relevance of this quantitatively defined electronic effect to the mechanisms of the two competitive addition processes is considered.

From reaction mixtures derived from N-benzylisoquinolinium bromides (1), 11 N sodium hydroxide, and carbon disulfide in dioxane, Kröhnke and Steuernagel[3] were able to isolate mesoionic adducts identified[3-5] as 3-phenylthiazolo[2,3-a]isoquinolinium-2-thione betaines (2); in some cases, isoquinolones 3 were obtained as significant by-products.
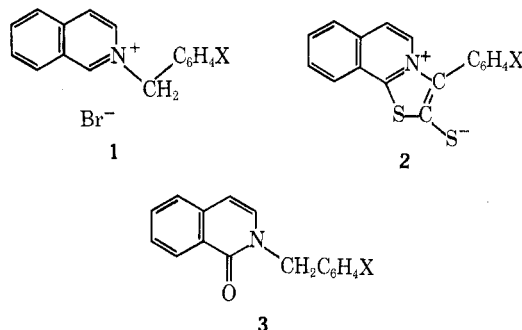
The yields of mesoionic adducts 2 were enhanced[3] by electron-withdrawing substituents (4′-X = CN, 40%; NO₂, 66%); for more electron-donating substituents (4′-X = Cl, CH=CH₂) the yields were only 20 and 34%, respectively.

Our concern with electronic effects on cycloreactions[6-8] prompted further study of this conversion. We soon uncovered a second class of adducts and eventually defined them as N-benzylisoquinolinium 4-dithiocarboxylates (4).[9,10] The present work reports a
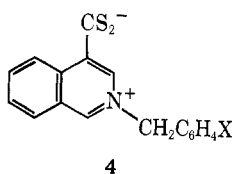
quantitative determination of yields of adducts 2 and 4 as a function of benzyl substituent X.

Isotope Dilution Method.—The conversion of 1 to a mixture of 2, 3, and 4 is ill suited to the more conventional techniques of quantitative scrutiny since the reaction mixture does not remain homogeneous. This circumstance, however, does not encumber the isotope dilution approach.

The reactions of 1 (X = 3-CH₃, H, 3-CH₃O, 4-Cl, 4-Br, 3-Cl, and 3-Br) with hydroxide and carbon disulfide-^{35}S of specific activity χ were run as usual in aqueous dioxane. The reaction mixture was then diluted with inactive samples of the corresponding mesoionic adduct 2 (a, mg) and dithiocarboxylate 4 (b, mg). Following isolation and purification of samples of the two types of adducts, they were counted (specific activities α and β). One may then calculate the absolute amount of radioactively enriched mesoionic adduct 2 (a*, mg) present in the reaction mixture before the dilution using the expression in eq 1;[11] an analogous calculation gives the absolute yield of 4 (b*).

$$a^* = a\left(\frac{\alpha}{\chi - \alpha}\right) \qquad (1)$$

Results

The activity of the CS₂* was determined by preparing ^{35}S-2 (4-Br) without dilution.

Application of the isotope dilution method gave values for the molar ratios of the two types of adducts [2]/[4] for seven substituted substrates 1. For the systems X = 4-CN, 3-NO₂, or 4-NO₂, no significant amounts of the dithiocarboxylate adducts could be isolated. In three other systems, so little of the minor product could be obtained that the isotope dilution approach became inconvenient; adequate amounts of cold adduct for dilution of a hot reaction mixture could not be readily secured. Instead, the yields were determined by isolating both adducts as quantitatively as possible, using extraction and chromatography. The three ratios so obtained (X = 4-CH₃O, 4-CH₃, and 3-CF₃) fell on the Hammett plot defined by the ratios measured through the isotope dilution experiments. The combined data are presented graphically as a Hammett plot with a slope of 2.32 (R = 0.971) in Figure 1, and in tabular form in the Experimental Section.

(1) Supported initially by Public Health Service Research Grants GM 14381 and GM 16576 and currently by National Science Foundation Grant GP 9259.

(2) National Institute of General Medical Sciences Predoctoral Fellow, 1969-1971.

(3) F. Kröhnke and H. H. Steuernagel, Angew. Chem., 73, 26 (1961); Chem. Ber., 97, 1118 (1964).

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(6) J. E. Baldwin and S. Y. Hong, Chem. Commun., 1136 (1967).

(7) S. Y. Hong and J. E. Baldwin, Tetrahedron, 24, 3787 (1968).

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(10) P. Coleman, J. A. Duncan, and B. W. Matthews, unpublished work.

(11) F. C. Henriques, Jr., and C. Margnetti, Ind. Eng. Chem., Anal. Ed., 18, 476 (1948).

Discussion

The slope in the Hammett plot of Figure 1 corresponds to a difference in ρ values for two reactions; one or both of the reactions may occur through multistep processes and have an overall ρ equal to the sum of ρ values for preequilibrium and the rate-determining steps.[12]

The reaction sequence leading to the *N*-benzylisoquinolinium 4-dithiocarboxylates **4** is believed[9] to involve preequilibrium formation of the pseudobase **5**; this 1,2-dihydroisoquinoline then behaves as an enamine which combines with carbon disulfide in the rate-determining step followed by a rapid 1,4 elimination of water.[13-15]

1 ⇌ [structure **5**]

5

[structure **6**] → **4**

6
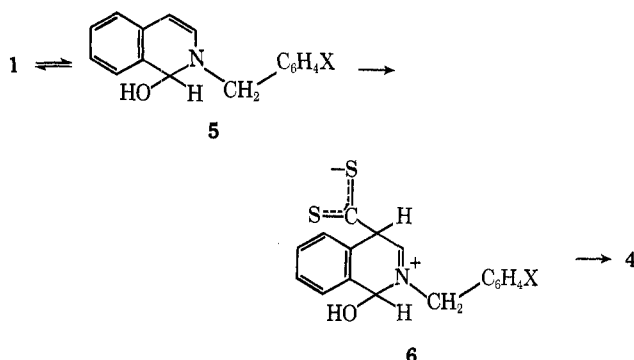
If this depiction is accurate, there should be only small changes in equilibrium constant or rate constant for the reaction of **5** with carbon disulfide with changes in the substituent X in the relative remote benzyl group, and the Hammett plot may be interpreted as providing an indication of overall ρ for the processes leading to adduct **2**.

A mechanistic proposal for generation of **2** must accommodate this estimate, $\rho \simeq 2.3$, and the results of deuterium labeling experiments[9]. Although the proton at C(1) of the isoquinolinium salt **1** exchanges under the strongly basic reaction conditions very rapidly, the benzylic methylene protons do not.[16,17]

Were the reaction sequence to involve an azomethine ylide 1,3-dipolar intermediate **7**, which through cycloaddition[18] and subsequent oxidation could produce the adduct **2**, the hydrogen abstraction step would be rate determining with $\rho \simeq 2.3$ and be irreversible, that is, be appreciably slower than the addition with carbon disulfide.

Figure 1.—Plot of log [betaine/dithiocarboxylate] against σ constants for the reactions of **1** giving adducts **2** and **4**. The open ovals are for data obtained through the isotope dilution technique the shaded ovals are for data from quantitative isolations of both products.

1 $\xrightarrow{\ ^-\text{OH}\ }$ [structure **7**] →

7

[structure **8**] ‑‑→ **2**

8

Any who find these two inferences hard to acknowledge as fully reasonable and sound will seek some alternative mechanistic formulation. The one now offered may serve as a useful spur to further experimentation and reflection.

[structure **9**]

9
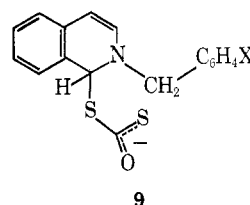
Under the strongly basic reaction conditions, the dithiocarbonate ion would surely be generated;[19] it would then add to the isoquinolinium ring system in competition with hydroxide to give the anion **9**.[20] (This system might react with carbon disulfide in addition to or in preference to the pseudobase **5** to lead to adduct **4**.) Such a 1,2-dihydroisoquinoline would not be expected to undergo facile proton abstraction at the benzylic methylene group and would retard formation of the isoquinolone side product **10**. In the absence of carbon disulfide, the isoquinolone **3** is formed extremely rapidly and in high yield.[9]

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(16) Compare J. A. Zoltewicz and L. S. Helmick, *J. Amer. Chem. Soc.*, **92**, 7547 (1970), and C. J. Cooksey and M. D. Johnson, *J. Chem. Soc. B.*, 1191 (1968).

(17) H. Quast and E. Schmidt, *Justus Liebigs Ann. Chem.*, **732**, 43, 64 (1970).

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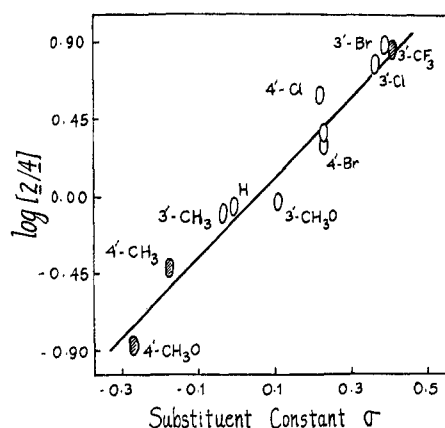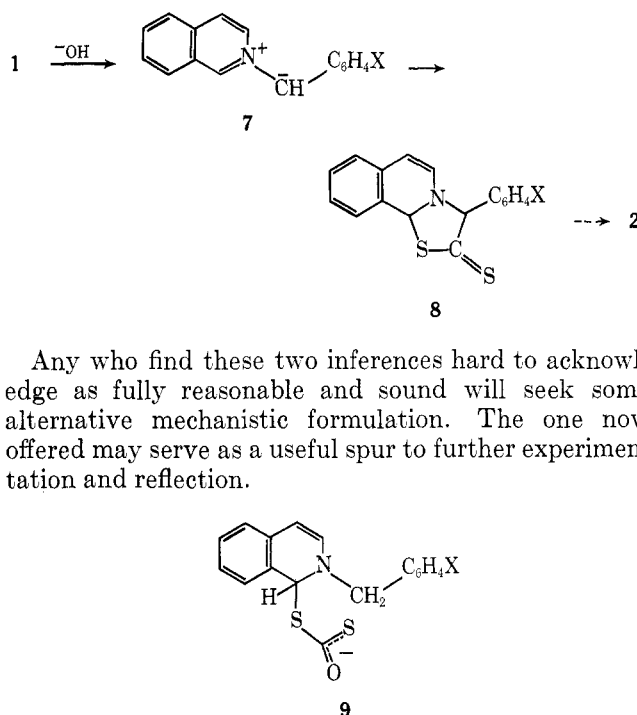
(19) M. Wronski, *Rocz. Chem.*, **32**, 849 (1958) [*Chem. Abstr.*, **53**, 4871*i* (1959)]; S. G. Hovenkamp, *J. Polym. Sci., Part C*, **2**, 341 (1963); B. Philipp and H. Dautzenberg, *Z. Phys. Chem. (Leipzig)*, **231**, 270 (1966); H. H. Schmiedeknecht and W. Claus, *ibid.*, **240**, 411, 415 (1969); H. Dautzenberg and B. Philipp, *Faserforsch. Textiltech.*, **20**, 213 (1969) [*Chem. Abstr.*, **71**, 64645n (1969)].

(20) See W. R. Schleigh, *Tetrahedron Lett.*, 1405 (1969), and R. M. Wilson and F. DiNinno, Jr., *ibid.*, 289 (1970), for two interesting conversions dependent on such reactivity.

TABLE I
WEIGHTS OF UNLABELED ADDUCTS ADDED TO REACTION MIXTURES FROM *N*-BENZYLISOQUINOLINIUM BROMIDES AND CARBON DISULFIDE-^{35}S

Benzyl Substituent	Reaction time, hr	Mesoionic adduct, mg	Dithio-carboxylate adduct, mg
3-CH₃	8	146.06	296.16
H	8	104.71	355.20
3-CH₃O	8	107.11	361.37
4-Cl	8	349.16	191.89
4-Br	1	246.85	194.37
4-Br	4.5	222.95	195.12
3-Cl	8	102.49	174.95
3-Br	8	381.02	96.87

The experimental ρ value, +2.3, is of a magnitude more suggestive of a process in which proton abstraction occurs as a new bond is formed at carbon than one leading to a carbanionic intermediate. Rough analogies are available in the E2 eliminations of β-phenylethyl derivatives, where ρ values between 2 and 3 are typically found.[21] Either hydroxide attack on intermediate **9** with concomitant formation of a new C–C bond or perhaps intermolecular rearrangement of a hydrate of **9** such as the idealized structure **10** would lead in turn to **11** and **8** and finally the isolated adduct **2**.

10

11
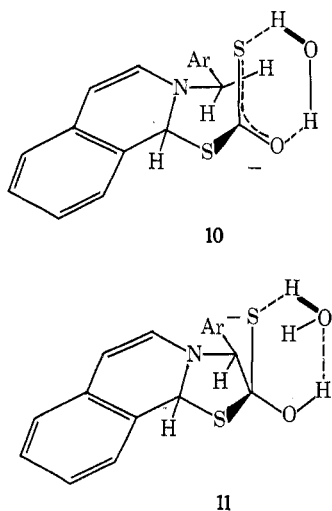
The accurate determination of electronic effects on the ratio of two adducts derived from *N*-benzylisoquinolinium salts in strongly basic aqueous dioxane–carbon disulfide through the isotope dilution method has thus lead to inferences based on the most familiar mechanistic rationale for the conversion **1 → 2** that are not convincingly logical, and an alternative interpretive scheme has been hypothesized. Further work will be required before one of these possibilities, or some third description, may be considered favored.

Experimental Section

A Mettler M5 microbalance and Kofler hot-stage were used. A Nuclear-Chicago 720 liquid scintillation spectrometer was made available by Professor A. R. Larrabee, to whom we express

(21) W. H. Saunders, Jr., and R. A. Williams, *J. Amer. Chem. Soc.*, 79, 3712 (1957); C. H. DePuy and C. A. Bishop, *ibid.*, 82, 2532, 2535 (1960); A. F. Cockerill, S. Rottschaefer, and W. H. Saunders, Jr., *ibid.*, 89, 901 (1967).

TABLE II
RECRYSTALLIZED ^{35}S-LABELED MESOIONIC ADDUCTS

Benzyl substituent	Weight, mg	Mp, °C	Specific activity,[a] cpm/μmol
3-CH₃	54	203–206	73.06
H	93	224–225	96.34
	41	223–225	93.71
3-CH₃O	85	170–172	98.44
	18	170–172	99.74
4-Cl	191	288–291	77.16
4-Br	126[b]	291–292	142.69
	152[c]	295–296	77.52
	111[d]	295–296	90.49
3-Cl	127	206–207	113.17, 115.76[e]
3-Br	227	229–230	78.64
	151	229–230	77.23

[a] Corrected for background, quenching, and decay. [b] Undiluted. [c] Reaction time, 1 hr. [d] Reaction time, 4.5 hr. [e] Independent determinations, made 55 days apart.

great appreciation. Unlabeled *N*-benzylisoquinolinium bromides 1, mesoionic adducts 2, and dithiocarboxylates 4 were available from an earlier study.[9]

Carbon Disulfide-^{35}S Solutions.—Radioactive carbon disulfide (1.9 mCi of ^{35}S in 16 mg; Amersham-Searle) was diluted with 5.0 ml of dry dioxane. Approximately 0.5 ml of this solution was combined with 110 ml of dry dioxane and 74 ml of unlabeled carbon disulfide to provide the stock solution used in reactions leading to labeled adducts. About 0.05 ml of the initial 5-ml solution was diluted with 82.5 ml of purified dioxane to provide a standard ^{35}S solution for liquid scintillation counting.

Specific Activity of Carbon Disulfide-^{35}S Stock Solution.—Into a 100-ml three-necked flask fitted with a reflux condenser, overhead stirrer, and addition funnel was introduced 5.27 mmol (2.00 g) of dry *N*-(4-bromobenzyl)isoquinolinium bromide and 5.5 ml of water. Carbon disulfide-^{35}S stock solution (9.2 ml) was added carefully. The mixture was heated and, when the bath temperature reached 52°, 5.5 ml of 11 *N* sodium hydroxide was added quickly with stirring. The bath temperature was raised to 72° and maintained there for 8 hr, and then the heating bath was removed. Vigorous stirring was continued throughout the reaction and as the reaction mixture was cooled. After being stored without stirring at −20° for 2.5 days, the reaction mixture was filtered at room temperature through sintered glass. The crystallized mesoionic adduct was collected and washed with three 6-ml portions of warm water, air-dried, and recrystallized as detailed below.

Labeled Adducts from *N*-Benzylisoquinolinium Bromides and Carbon Disulfide-^{35}S.—Following the procedure described immediately above, 5.27 mmol of a dry *N*-benzylisoquinolinium bromide was allowed to react with carbon disulfide-^{35}S in aqueous alkaline dioxane. When the reaction mixture had been cooled to room temperature it was diluted with known amounts of the corresponding unlabeled mesoionic and dithiocarboxylate adducts (Table I) and stirred for 2 hr.

Storage of the diluted reaction mixture at −20° for 3 days, filtration, and washing with warm water gave a dark solid which was dried in the air. The sintered-glass funnel was washed clean with chloroform, and the combined filtrates were transferred to a separatory funnel. The aqueous layer was separated and extracted once with fresh chloroform. The combined chloroform solutions were washed with two 50-ml portions of 0.1 *N* hydrochloric acid and one 50-ml portion of water. The solution was dried over calcium chloride, filtered, and concentrated, leaving a thick black oil. Failure to evaporate all dioxane at this point rendered effective chromatography of the oil more difficult.

An 18 × 210 mm column of Woelm neutral activity grade II alumina was wet-packed with chloroform and covered with a small amount of sand. The oil obtained from extraction of the filtrate was diluted with a little chloroform and placed on the column, and the solid collected by filtration was added as a slurry in chloroform. The column was eluted slowly, and the orange to red fractions were evaporated to give a glass or a solid. Material from the top of the column was extracted with hot *N*,*N*-dimethylformamide; concentration of the extract gave a dark solid.

TABLE III

RECRYSTALLIZED ^{35}S-LABELED DITHIOCARBOXYLATE ADDUCTS

Benzyl substituent	Weight, mg	Mp, °C	Specific activity,[a] cpm/μmol
3-CH₃	232	195–199	55.66
	90	198–199	54.99
H	248	202–206	59.91
	141	209–210	58.31
3-CH₃O	302	215–218	60.77
4-Cl	30	208–209	50.97
4-Br	41[b]	206–207	54.18
	74[c]	206–207	73.58
3-Cl	121	210–213	47.24
3-Br	76	205–207	57.13
	32	207–208	55.23

[a] Corrected for background, quenching, and decay. [b] Reaction time, 1 hr. [c] Reaction time, 4.5 hr.

TABLE IV

YIELDS OF MESOIONIC AND DITHIOCARBOXYLATE ADDUCTS FROM N-BENZYLISOQUINOLINIUM BROMIDES AND CARBON DISULFIDE-^{35}S BY THE ISOTOPIC DILUTION TECHNIQUE

Benzyl substituent	Mesoionic adduct, mg	Dithiocarboxylate adduct, mg	Total yield, %	Molar ratio, [2]/[4]	Substituent constant, σ
3-CH₃	153	188	21.0	0.814	−0.069
H	209	251	29.7	0.833	0.000
3-CH₃O	243	268	29.9	0.907	+0.115
4-Cl	411	107	29.9	3.84	+0.226
4-Br	294[a]	119	21.0	2.47	+0.232
	386[b]	208	30.2	1.77	
3-Cl	416	86.5	29.0	4.81	+0.373
3-Br	458	60.9	27.4	7.71	+0.391

[a] Reaction time, 1 hr. [b] Reaction time, 4.5 hr.

TABLE V

YIELDS OF MESOIONIC AND DITHIOCARBOXYLATE ADDUCTS FROM N-BENZYLISOQUINOLINIUM HALIDES AND CARBON DISULFIDE[a]

Benzyl substituent	Halide	Mesoionic adduct, g	Dithiocarboxylate adduct, g	Total yield, %	Molar ratio, [2]/[4]	Substituent constant, σ
4-CH₃O	Br	0.201	1.56	18.6	0.130	−0.268
4-CH₃	Br	0.392	1.04	16.0	0.379	−0.170
3-CF₃	Cl	2.15	0.30	23.4	7.21	+0.415

[a] Run with 29 mmol of each N-benzylisoquinolinium salt for 8 (CH₃O, CH₃) or 16 hr (CF₃) at 72° under standardized conditions.

With the 4-bromobenzyl and 4-chlorobenzyl salts, extraction of the initial filtrate with chloroform was unnecessary; almost all of the mesoionic adducts were obtained with the crystallized material.

Recrystallization of Labeled Adducts.—The dithiocarboxylate adducts were recrystallized from *N,N*-dimethylformamide-acetonitrile; the crystals were allowed to form slowly at 25°. The mesoionic adducts were either recrystallized from chloroform or dissolved in excess pyridine, followed by filtration, concentration under reduced pressure, and seeding. The dithiocarboxylate adducts were washed with acetonitrile, the mesoionic with ethyl acetate. All were dried at 1 mm over phosphorus pentoxide at 60–100°.

Scintillation Solution.[22]—A solution of 250 ml of scintillation grade dioxane, 250 ml of analytical reagent xylenes, and 150 ml of absolute ethanol was prepared. Naphthalene (50.0 g), 3.25 g of 2,5-diphenyloxazole (PPO), and 0.0325 g of *p*-bis[2-(5-phenyloxazolyl)]benzene (POPOP) were dissolved with stirring in 400 ml of the solvent; the solution was finally diluted to 650 ml with more solvent.

Liquid Scintillation Counting.—Between 2 and 5 mg each of the samples were weighed into small aluminum boats. The samples and boats were placed into 20-ml glass scintillation counting vials. The dithiocarboxylate adducts were dissolved by adding 0.25 ml of *N,N*-dimethylformamide and heating the capped vials on a steam bath. To each vial was added 20 ml of the scintillation solution. Each sample was subjected to sun or fluorescent light until it was colorless or, for the dithiocarboxylate adducts, nearly colorless. The radioactivities of the adducts in counts per minute (cpm) were recorded after the bleaching process was complete, as judged by constant cpm values. Each sample

(22) F. E. Rinard, *Rev. Sci. Instrum.*, **28**, 293 (1957).

was counted three to five times for 10⁴ counts, and the cpm determined were averaged. The cpm values ranged from 250 to 1100. The background cpm reading was determined daily. To each sample after counting was added 50 μl of the standard ^{35}S solution, using a Yanker disposable Micropet; the radioactively augmented samples were then counted three times for 10⁴ counts and the values were averaged to provide the necessary data for a quenching correction. The radioactivities of the various samples determined after corrections for background and quenching as described above are listed in Tables II and III. The absolute yields and molar ratios calculated from the data in Tables I, II, and III are summarized in Table IV.

Product ratios from 1 (X = 4-CH₃O, 4-CH₃, and 3-CF₃) were obtained through isolation of adducts 2 and 4, as quantitatively as possible. The reactions were run and worked up as in preparative runs;[9] repeated column chromatography with careful monitoring led to the results gathered in Table V.