A RADICAL PATHWAY FOR REDUCTIVE DEHALOGENATION AND NUCLEOPHILIC SUBSTITUTION OF HETARYL HALIDES

By

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A DISSERTATION PRESENTED TO THE GRADUATE COUNCIL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA
1973

To My Wife,

Martha

ACKNOWLEDGEMENT

The author will always be indebted to Dr. John A. Zoltewicz, Chairman of his Supervisory Committee, for his perceptive guidance and patient support during the course of this research. Appreciation is also extended to the other members of his Committee: Dr. Merle A. Battiste, Dr. Richard D. Dresdner, Dr. Paul Tarrant, and Dr. Robert B. Bennett.

Special gratitude is due his wife, Martha, for her unfailing support and understanding during the disappointments and achievements of these years.

The friendship and assistance of other members of his research group will always be remembered.

Thanks are extended to his wife, Martha, and Mrs. Judi Nielsen for their help in preparing the manuscript.

Financial support from the Chemistry Department of the University of Florida and from the National Science Foundation is gratefully acknowledged.

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by

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March, 1973

Chairman: Dr. John A. Zoltewicz
Major Department: Chemistry

Evidence for a radical chain mechanism of reductive dehalogenation of 4-bromoisoquinoline by methanolic sodium methoxide was obtained from product and kinetic studies. Known radical and electron traps were employed to inhibit the reaction and to alter the product ratio. The reductive dehalogenation appears to be a general reaction for hetaryl halides which do not undergo rapid substitution by methoxide ion. It is concluded that methoxide ion is a better hydrogen atom donor to the proposed 4-isoquinolyl radical than is methanol.

Methoxide ion was also shown to promote nucleophilic substitution of 4-bromoisoquinoline by thiophenoxide ion. Known radical and electron traps provided evidence for a radical chain mechanism for nucleophilic substitution of the hetaryl halide by negatively charged sulfur nucleophiles.

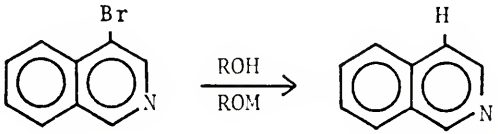
It was shown that the amide ion promoted substitution of 4-bromoisoquinoline by methylmercaptide ion in refluxing ammonia may not occur solely via a hetaryne mechanism; rather, a radical chain mechanism is suggested.

The existance and structure of some anionic sigma complexes of isoquinoline derivatives with amide ion in liquid ammonia was demonstrated, and the covalent amination products of some quaternized heteroaromatic salts in liquid ammonia were studied.

CHAPTER 1

INTRODUCTION

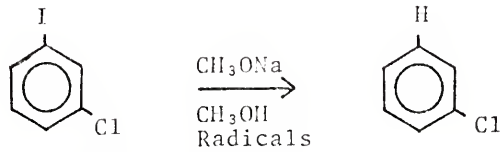
In 1940 Bergstrom and Rodda reported some very curious results.[1] In attempting to carry out what they expected to be a simple substitution reaction, they found that 4-bromoisoquinoline in the presence of methanol–sodium methoxide (7 hours at 235°) or t-butyl alcohol–potassium t-butoxide (200° and apparently the same time) gave isoquinoline instead of the expected 4-alkoxyisoquinoline, equation 1. The isoquinoline was isolated in 43-54% yields from several experiments. No explanation was offered for the unexpected result.



(1)

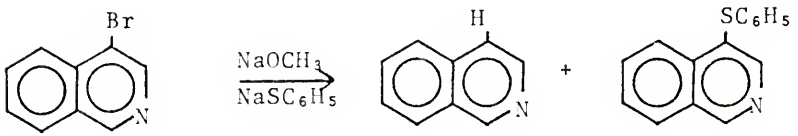
In 1967 Bunnett and Wamser reported the reductive deiodination of m-chloroiodobenzene in methanolic sodium methoxide in the presence of a source of radicals to initiate the reaction, equation 2.[2] They demonstrated that this new type of reaction proceeds by a radical chain mechanism. Their new results suggested to us the possibility that the reductive debromination of 4-bromoisoquinoline observed by

Bergstrom and Rodda proceeded by a similar radical chain mechanism. This prompted the investigation into the mechanism of the reductive debromination of 4-bromoisoquinoline. Results are presented in Chapter 2 and show that our expectations are met.



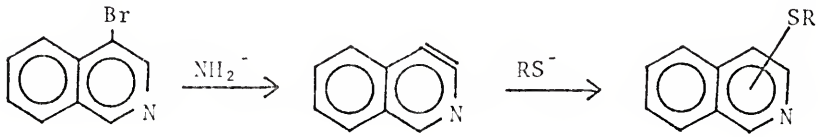
(2)

Once it became apparent that radical species were involved in the reductive debromination of 4-bromoisoquinoline, further studies were initiated in the form of trapping experiments with sulfur nucleophiles in hopes of shedding light upon the nature of the intermediate radicals and the details of the mechanism. The use of sodium thiophenoxide as a radical trap was very successful and led to the illucidation of a new mechanism for the substitution of hetaryl halides as the investigations in Chapter 3 will show. The reaction of 4-bromoisoquinoline with sodium methoxide and sodium thiophenoxide in methanol results in simultaneous reductive dehalogenation and substitution, equation 3.



(3)

Bergstrom and Rodda also reported that treatment of 4-bromoisoquinoline with potassium or sodium amide in refluxing ammonia yielded only tar.[1] Originally it appeared to us that the tar could have resulted from the reactions of the elusive, highly reactive 2,3-pyridyne type intermediate (in this case 3,4-isoquinolyne).[3-5] It was decided to attempt to trap this intermediate using negatively charged sulfur nucleophiles as had been successfully done for 3,4-pyridyne;[6] the proposed reaction scheme is illustrated by equation 4. As the results of our substitution studies on 4-bromoisoquinoline in methanol began to unfold, a second



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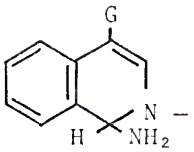
mechanism, a radical chain process, also appeared as a possibility. The results of these studies are presented in Chapter 4.

Finally, several experiments which were directed to the observation of possible intermediates in the reactions of 4-bromoisoquinoline in ammonia are reported in Chapter 5. The existance and structure (I) of sigma anionic complexes resulting from amide ion addition to an isoquinoline ring were established. These studies were extended so as to include the addition of ammonia to quaternized hetero-

aromatic compounds to give covalent amination products such as II.



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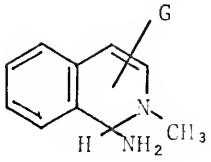


II

CHAPTER 2

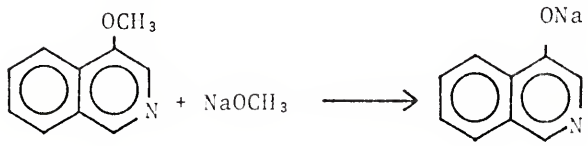
ALKOXIDE ION PROMOTED REDUCTIVE DEHALOGENATION OF HETARYL HALIDES

Results

Products and product ratios from the reaction of 4-bromoisoquinoline with sodium methoxide.-4-Bromoisoquinoline was reduced to isoquinoline by sodium methoxide at temperatures ranging from 143 to 165° in yields greater than 90 percent, Table 1. Reactions were generally carried out in sealed nmr tubes. The reaction mixtures were analyzed directly by nmr with t-butyl alcohol often serving as an internal area standard. The identity of isoquinoline was confirmed using tlc and glpc. At 165° in the presence of 0.79 M sodium methoxide, the reaction was complete after one hour. Reductive dehalogenation could also be made to take place on a larger scale. For example, 5.3 g of 4-bromoisoquinoline in the presence of excess sodium methoxide was reduced to isoquinoline in 97 percent yield (nmr analysis of the reaction mixture) after heating in a Monel bomb at 165° for 1000 minutes.

Two other isoquinoline products were detected in the reaction mixtures. Comparison (nmr spectra) with authentic materials revealed that they are 4-methoxyisoquinoline and 4-hydroxyisoquinoline. The latter compound is believed to arise from methoxide ion induced cleavage of 4-methoxyiso-

quinoline. Those reaction mixtures heated for long periods of time showed a decrease in the amount of 4-methoxyisoquinoline product while the amount of 4-hydroxyisoquinoline, present in its ionized form, increased. The conversion of 4-methoxyisoquinoline to 4-hydroxyisoquinoline was confirmed in separate experiments. Authentic 4-methoxyisoquinoline was converted to 4-hydroxyisoquinoline in methanol–sodium methoxide solution at 165°; this reaction has a rate constant of 9.7×10^{-5} mol^{-1} sec^{-1}. It is assumed that methyl ether is the other product of the cleavage reaction, equation 5.



(5)

In the absence of additives, the yields of substitution products were less than 10 percent. Hence the reduction to substitution ratio was always greater than 10, Table 1. Sodium formate is believed to be present as well. This identification rests on the observed chemical shift (τ 1.30) and reports that sodium formate forms when redox reactions are carried out in methanol–sodium methoxide solution.[7,8] From a reaction mixture which had been carried to completion, all solid was removed by filtration. This solid failed to melt below 274°, and therefore could not have contained a significant amount of sodium formate, mp 253°.[9] The solution (which must contain all the sodium formate formed) was

Table 1. Variation of the Product Ratio in the Reductive Dehalogenation of 4-Bromoisoquinoline.[a,b]

[$NaOCH_3$]	[Substrate]	T,°C	Additive	% Reduction / % Substitution
None	2.9	165	None	No reaction
0.79	0.30	165	None	>10
0.79	0.37	165	None	>10
1.0	0.40	165	None	>10
1.3	0.58	165	None	>10
1.3	0.51	165	None	>10
1.6	0.66	147	None	>10
2.5	0.44	143	None	>10
1.3	0.51	165	(Amber nmr tube)	>10
1.6	0.66	165	N_2 Saturated	>10
1.6	0.66	165	O_2 Saturated	>10
1.8	0.42	147	30% (V:V) Benzene	>10

Table 1. Continued.

[$NaOCH_3$]	[Substrate]	T,°C	Additive	% Reduction / % Substitution
1.6	0.66	147	0.3 M 2,2'-Dinitrobiphenyl	0.9
1.6	0.66	147	0.6 M 1,1-Diphenylethylene	5
2.5	0.44	143	0.05 M Nitrobenzene	4
2.5	0.44	143	0.5 M Azoxybenzene	5
3.3	0.5	143	0.6 M Azoxybenzene	1
0.87	0.38	165	0.95 M Hydrazine[c]	7
0.99	0.37	165	50% DMSO[d]	3
0.39	0.23	~23	90% DMSO[d]	>10
0.39	0.36	100	90% DMSO[d]	1
0.39	0.37	165	90% DMSO[d]	0.7
1.3	0.58	165	0.01 M $CuCl_2$	4
0.80	0.38	165	0.05 M $CuCl_2$	0.25
0.80	0.37	165	0.05 M CuCl	7

Table 1. Continued.

$[NaOCH_3]$	[Substrate]	T,C°	Additive	% Reduction / % Substitution
2.5	0.50	141	50% DMSO; $CuCl_2$	1
2.3	0.46	100	50% DMSO; $CuCl_2$	4

[a]Concentrations (mol/l) are corrected for thermal expansion of methanol except when DMSO is present.

[b]The product ratios were determined at or near completion of the reaction.

[c][NaOMe] is actually less than 0.87 M due to water in the 95+% hydrazine.

[d]Percent by volume of DMSO in methanol.

analyzed by nmr, and the isoquinoline to formate ion ratio was determined to be 2.0. The precipitate which failed to melt below 274° is believed to be sodium bromide.

Since sodium formate is only slightly soluble in methanol, some question exists as to whether the nmr analyses give a valid measure of the amount of sodium formate formed in the reaction. NMR analyses of a standard solution of 0.55 M isoquinoline and 0.26 M sodium formate in methanol gave an isoquinoline to sodium formate molar ratio of 2.04. The molar ratio was 2.12 by weight, and no precipitate was present in the prepared solution. Addition of excess sodium formate to this standard solution and subsequent analysis by nmr showed the saturated concentration of sodium formate to be 0.48 M in the absence of sodium methoxide. (In the presence of sodium methoxide, the solubility of sodium formate is reduced by the common ion effect.) Therefore the stoichiometric relationship between isoquinoline and sodium formate established by nmr analysis in the preceding experiment in which the isoquinoline concentration was near 0.5 M is valid.

An attempt to prepare a methanol solution of 2.0 M sodium methoxide and 1.5 M methyl formate resulted in the immediate formation of a large volume of white precipitate. This precipitate was presumed to be sodium formate, and analysis by nmr confirmed this presumption. It seems likely that the hydrolysis reaction involves residual water present in the solvent. In the presence of a relatively high concentration of sodium methoxide, the sodium formate was less

soluble than usual, and, with the addition of water, all remaining methyl formate was immediately converted to sodium formate, and a homogeneous solution was obtained.

A control run was conducted on a sodium methoxide solution (1.9 M) at 165°. After adding t-butyl alcohol for an internal area standard and flushing with nitrogen, the sealed tube was heated for 210 minutes. No methoxide ion was consumed, and no formate ion was formed. Therefore, it appears that formate ion formation is associated with the formation of isoquinoline.

Another control run showed that sodium methoxide is essential to the reductive dehalogenation process. When a solution of 4-bromoisoquinoline was heated in pure methanol at 165° for 1146 minutes, no reaction was detected by nmr.

So long as sodium methoxide was present in a greater than two-fold excess, the reductive dehalogenation reaction proceeded to completion. No rate retardation was detected when the reaction was carried out in an amber nmr tube, and therefore photocatalysis is not essential to the reaction. Saturation of the reaction solution at 0° with oxygen or nitrogen produced no dramatic rate change. After 10 minutes at 165° identical solutions, one saturated with nitrogen and one with oxygen, were analyzed by nmr, and the ratio of starting material to product was the same in both cases; the reaction was half complete at this point (0.4 M 4-bromoisoquinoline and 0.4 M isoquinoline). However, nmr analysis showed that the methoxide ion concentration was 0.16 M less

in the tube containing oxygen. The initial methoxide ion concentration was 2.0 M; this dropped to ~1.5 M after 10 minutes for the solution saturated with nitrogen and to ~1.3 M for the solution saturated with oxygen. A control experiment in which methanol was saturated with oxygen at -78° (dry ice–acetone) followed by addition of some sodium methoxide–methanol failed to show any methoxide ion consumption when the mixture was heated at 165°. If there were inhibition in the presence of oxygen, it was over quickly and could not be detected by only one analysis after 10 minutes at 165°. The reason for the apparent additional methoxide ion consumption in the presence of oxygen is unclear.

The relationship between methoxide ion consumption and isoquinoline formation is presented in Table 2. Results from three different reaction mixtures at two temperatures are given. They show that the molar ratio of methoxide ion consumed to isoquinoline formed is in the range of 1.5 to 2.1.

Several experiments were conducted to investigate the effects of potential radical inhibitors on the course of the reaction. Those organic compounds which had a noticeable effect on the reaction included 2, 2'-dinitrobiphenyl, 1,1-diphenylethylene, nitrobenzene, azoxybenzene, and hydrazine. The results are summarized in Table 1.

In the case of 2, 2'-dinitrobiphenyl (0.3 M), it was obvious from the slower rate of disappearance of 4-bromoisoquinoline that inhibition had occurred, but it was impossible to determine the reduction to substitution product ratio

Table 2. Stoichiometric Relationship Between Methoxide Ion and Isoquinoline in the Reductive Dehalogenation of 4-Bromoisoquinoline.

$[Substrate]_0$[a]	$[NaOCH_3]_0$	Minutes	Δ $[NaOCH_3]$	[Isoquinoline]	$\frac{\Delta\ [NaOCH_3]}{[Isoquinoline]}$
0.47[b]	1.0	2	0	0	—
		4	0.040	0.020	2.0
		6	0.11	0.062	1.8
		9	0.28	0.14	2.0
		12	0.45	0.22	2.0
		15	0.50	0.25	2.0
		18	0.57	0.28	2.0
		21	0.63	0.31	2.0
		24	0.67	0.34	2.0
		28	0.71	0.37	1.9
		32	0.73	0.42	1.8
		36	0.78	0.44	1.8
		108	0.90	0.45	2.0

Table 2. Continued.

$[Substrate]_0^a$	$[NaOCH_3]$	Minutes	$\Delta[NaOCH_3]$	[Isoquinolire]	$\frac{\Delta[NaOCH_3]}{[Isoquinoline]}$
0.38^b	0.99	4	0	0	–
		8	0.20	0.10	2.0
		12	0.32	0.19	1.7
		16	0.42	0.23	1.8
		20	0.47	0.22	2.1
		28	0.54	0.35	1.5
		36	0.57	0.38	1.5
		60	0.66	0.40	1.7
		120	0.70	0.41	1.7

Table 2. Continued.

$[Substrate]_0^a$	$[NaOCH_3]_0$	Minutes	$\Delta[NaOCH_3]$	[Isoquinoline]	$\frac{\Delta[NaOCH_3]}{[Isoquinoline]}$
0.80[c]	2.0	5	0.28	0.18	1.6
		10	0.62	0.38	1.6
		15	0.90	0.50	1.8
		20	1.06	0.57	1.9
		25	1.14	0.61	1.9
		30	1.16	0.63	1.8
		40	1.20	0.65	1.8
		50	1.28	0.69	1.9

[a]Concentrations (mol/l) are not corrected for thermal expansion of methanol. Initial concentrations of reactants are indicated.

[b]165°.

[c]147°.

directly by nmr because of overlap between the downfield singlet of 4-methoxyisoquinoline and the singlet from formate anion. However, the concentration of 4-methoxyisoquinoline may be estimated by assuming no new products or mass loss and by knowing the concentration of 4-bromoisoquinoline and isoquinoline. The product ratio calculated in this manner is 0.9 and differs from the product ratio in the absence of 2, 2'-dinitrobiphenyl by a factor of >10.

It was possible to determine the product ratio directly for the other four inhibitors used. In these cases overlap of the 4-methoxyisoquinoline and formate ion peaks did not preclude successful analysis by nmr. A concentration of much less than 0.6 M 1, 1-diphenylethylene reduced the ratio by at least factor of 2. The exact concentration of 1,-1-diphenylethylene is unknown because it is partially immiscible with methanol.

Nitrobenzene (0.05 M) and azoxybenzene (0.05 M) also reduced the product ratio by at least a factor of 2. In the case of nitrobenzene (and also 2, 2'-dinitrobiphenyl), the identity of the actual inhibitor(s) is uncertain. Nitrobenzene is known to react with methoxide ion at 69° to give azoxybenzene.[7] Nitrosobenzene and phenylhydroxylamine are postulated as intermediates in this reaction. A higher concentration (0.6 M) of azoxybenzene further reduces the product ratio to unity.

The product ratio was lowered by addition of (95%+) hydrazine. A known hydrogen atom donor,[10] hydrazine was the least effective of the additives and lowered the product

ratio by less than a factor of 2 despite being present at a nearly 1 M concentration. The mechanism effecting this change is not certain.

An attempt to trap intermediate radicals by the addition of 30 percent by volume of benzene to a methanolic solution of 4-bromoisoquinoline (0.42 M) and sodium methoxide (1.8 M) with t-butyl alcohol as an internal area standard failed. After 40 minutes at 147°, analysis by nmr indicated that isoquinoline was present in 94 percent yield. Although small amounts of 4-methoxyisoquinoline and 4-phenylisoquinoline may have been present, they could not be detected by nmr.

Use of DMSO as a cosolvent had a profound influence on the reaction rate and product ratio. The change in product ratio may arise from an enhancement of the direct substitution reaction by the excellent solvation properties of DMSO. The product ratio decreased by at least a factor of 3 in a 1:1 (V:V) DMSO and methanol solution, and the amount of material which normally precipitated from the reaction mixture was reduced. A more dramatic effect was observed when a 9:1 (V:V) DMSO–methanol solvent system was employed. In this solvent system 4-bromoisoquinoline was reduced to isoquinoline; no other products were present in sufficient quantity to be detected by nmr. This exclusive reduction occured at room temperature over a 2 1/2 day period. When the reaction was carried out at 165°, it was complete within 1 minute and gave a 0.7 product ratio. This represents a decrease in the product ratio by at least a factor of 10 relative to that at room temperature.

Copper salts had a dramatic effect on the reduction to substitution product ratio, Table 1. The effect of copper (II) chloride appears to be greater than that of copper (I) chloride. Solutions were heterogeneous, owing to the poor solubility of the copper salts; indicated concentrations do not reflect the actual amounts in solution. Instead, they indicate the amount of material which would have been present in solution if the salts were soluble. The substitution reaction increases in importance in the presence of these salts, and in one instance (0.05 M copper (II) chloride) the substitution product became the major product.

Closer examination of the effect of copper (II) chloride, Table 3, shows that the copper salt apparently simultaneously slowed the conversion of 4-bromoisoquinoline to isoquinoline and speeded up the substitution reaction by methoxide to give 4-methoxyisoquinoline. The net effect was a slower rate of disappearance of 4-bromoisoquinoline to give more substitution product. Note that the amount of substitution product does not increase after the initial observation. When the reaction was repeated on a preparative scale using one equivalent of the copper salt, a 47 percent yield of 4-methoxyisoquinoline was obtained. This suggests that copper (II) chloride may not be of great value as an inhibitor in kinetic studies involving radical chain reactions of hetaryl halides because of its effect on competing mechanisms such as direct substitution. The acceleration of the non-radical chain process masks the inhibition of the radical chain process

Table 3. Reaction of 0.58 M 4-Bromoisoquinoline at 165° with 1.3 M Sodium Methoxide in the Presence and Absence of ~0.01 M Copper (II) Chloride.[a]

Minutes	% 4-Bromoisoquinoline		% Reduction		% Substitution	
	No $CuCl_2$	With $CuCl_2$	No $CuCl_2$	With $CuCl_2$	No $CuCl_2$	With $CuCl_2$
5.9	41	57	59	20	trace	23
12.9	10	26	87	53	3	21
19.9	3	14	94	66	3	20

[a] In the absence of an internal standard, the percentages given are based upon the assumption that there is no mass loss and that starting material, isoquinoline, and 4-methoxyisoquinoline are all the compounds present.

by increasing the rate of disappearance of hetaryl halide. However, the preparative use of copper (II) chloride is apparent and was utilized.

A control run showed that when copper (II) chloride is allowed to react with a sodium methoxide solution at 165° in the absence of hetaryl halide, elemental copper is formed immediately.

Attempts to initiate the reduction of 4-bromoisoquinoline were made using ABIN (2,2'-azobis-isobutyronitrile). In two experiments ABIN was added to reaction mixtures which were heated at 100°. In one case a 0.32 M solution of 4-bromoisoquinoline in 0.30 M sodium methoxide and 0.63 M ABIN (assuming all dissolved) was heated for 90 minutes with no reaction. Then a 0.15 M solution of substrate was heated for 30 minutes in 0.30 M ABIN and 1.5 M sodium methoxide to give a 30 percent conversion to isoquinoline. These results indicate that high concentrations of methoxide ion are an essential requirement of the reaction. It is clear that ABIN does accelerate the reduction reaction because no reaction occurs under the same conditions over 3 hours in the absence of ABIN.

Kinetics of reduction of 4-bromoisoquinoline by sodium methoxide.-Data for the rate of disappearance of 4-bromoisoquinoline and methoxide ion, and for the rate of appearance of isoquinoline were obtained in the presence and absence of inhibitors using nmr. Figure 1 shows a typical plot for the rate of disappearance of sodium methoxide in a reaction

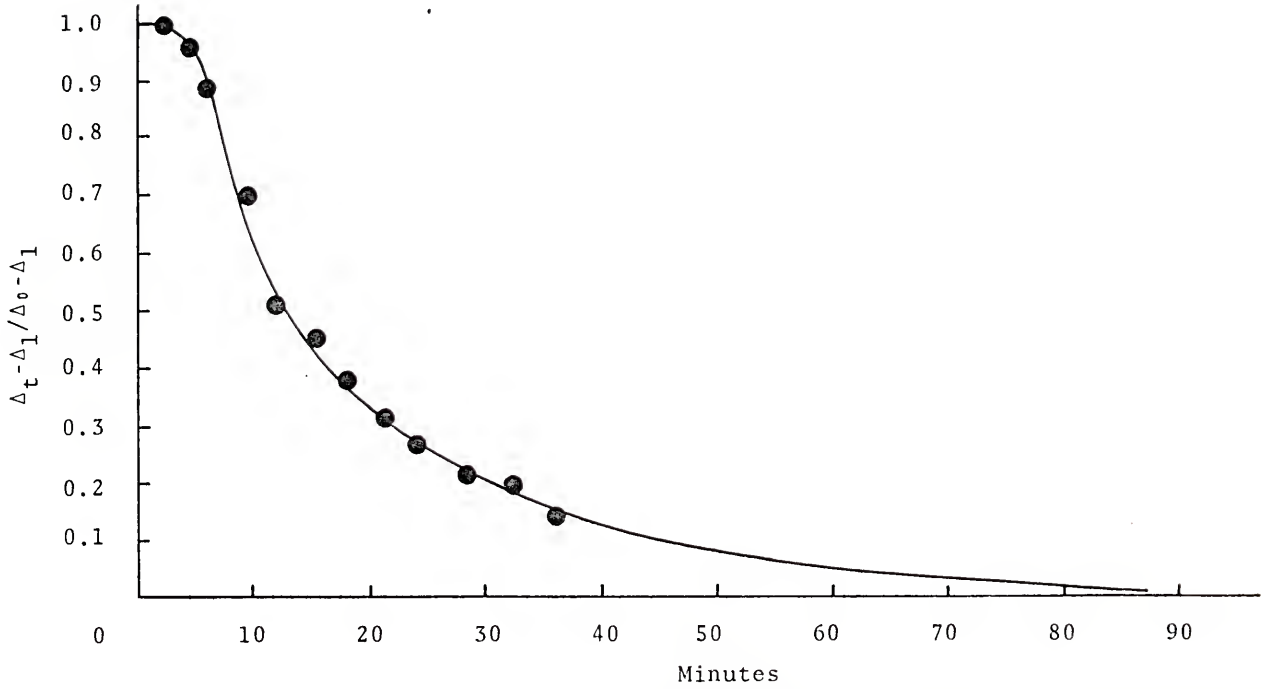


Figure 1. Rate of Consumption of Methoxide Ion in the Reductive Dehalogenation of 4-Bromoisoquinoline at 165°; $[NaOCH_3]_0$ = 0.79 M, [4-Bromoisoquinoline]$_0$ = 0.37 M. (The difference in chemical shift between the ^{13}CH and the hydroxyl proton peaks of methanol is used to determine the methoxide ion concentration. Subscripts $_0$, t, and 1 stand for time zero, intermediate time, and the last time, respectively.)

mixture containing 4-bromoisoquinoline and no added inhibitor. The shape of the concentration–time plot is similar to that (not shown) for the disappearance of the hetaryl halide. Note that the consumption of methoxide ion is slow in the very early stages of the reaction, suggesting the presence of an induction period. A mass balance calculated on the basis of starting material, and reduction and substitution products indicate that there is no build-up of intermediates at a level detectable by nmr analysis. Attempts to obtain second-order rate constants by considering the reaction to be first-order in 4-bromoisoquinoline and sodium methoxide are unsuccessful. Curvature results using experimentally determined sodium methoxide concentrations. These concentrations reflect the stoichiometry given in Table 2. This is not unexpected, considering the presence of an induction period.

Figure 2 shows the effect of 1, 1-diphenylethylene on the rate of disappearance of 4-bromoisoquinoline. A methanolic solution of substrate and sodium methoxide was divided between two nmr tubes, one of which contained some 1, 1-diphenylethylene. t-Butyl alcohol was added as an internal standard. The 1, 1-diphenylethylene was not completely miscible with the reaction mixture. However on heating, there was obvious inhibition of the reaction of 4-bromoisoquinoline, and the peaks representing 1, 1-diphenylethylene underwent change. Figure 3 gives superimposed plots for the rates of disappearance of substrate and methoxide ion in the presence of the inhibitor, 1, 1-diphenylethylene. The close fit of

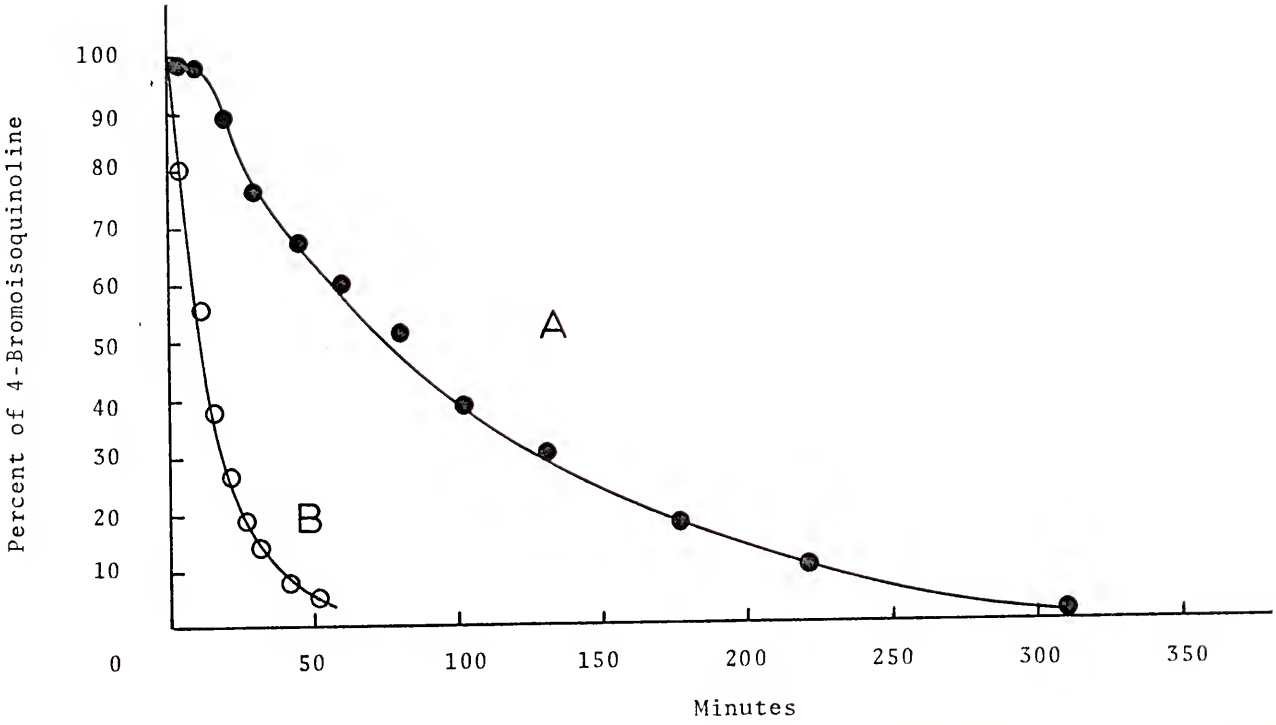


Figure 2. Rates of Disappearance of 0.66 M 4-Bromoisoquinoline in 1.6 M Sodium Methoxide with (A) and without (B) 0.6 M 1,1-Diphenylethylene at 147°.

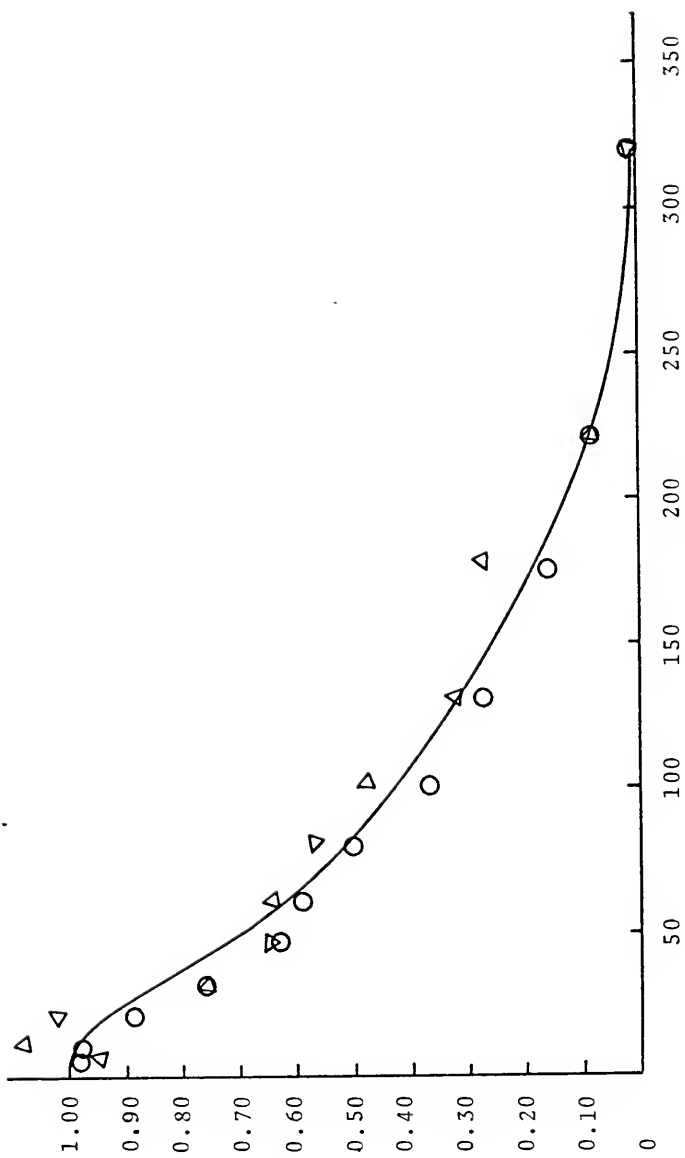


Figure 3. Superimposed Plots for Rates of Disappearance of 4-Bromoisoquinoline (O) and Sodium Methoxide (Δ) at 147° in the Presence of 0.6 M 1,1-Diphenylethylene. (Reactant concentration is [R]; subscripts are the same as those in Figure 1.)

the two curves indicates that in the presence of 0.6 M 1, 1-diphenylethylene the rate of the reaction as measured by the disappearance of methoxide ion is the same as that measured by the disappearance of 4-bromoisoquinoline. Therefore, methoxide ion is not being consumed by another route, e.g., reaction with the inhibitor.

The results of a similar experiment using 2, 2'-dinitrobiphenyl are given in Figure 4. Again inhibition of the reaction pathway for consumption of 4-bromoisoquinoline is obvious, and it appears to be more effective than that by 1, 1-diphenylethylene. Superimposed plots comparing the rates of disappearance of substrate and methoxide ion in the presence of 2,2'-dinitrobiphenyl are presented in Figure 5. In this case the line representing methoxide ion consumption lies below that for 4-bromoisoquinoline indicating that some methoxide was consumed by reaction with another substance, most likely to be the inhibitor, 2, 2'-dinitrobiphenyl.

Figure 6 shows the effectiveness of azoxybenzene and nitrobenzene in inhibiting the reduction of 4-bromoisoquinoline. Inhibition by nitrobenzene is particularly effective, and the plot shows complete inhibition and a classical induction period for 40 minutes. The extremely low concentrations of these inhibitors necessary to produce inhibition are also a good measure of their effectiveness.

Attempts were made to make the reduction and substitution reactions zero-order in sodium methoxide. This was done by decreasing the concentration of 4-bromoisoquinoline to

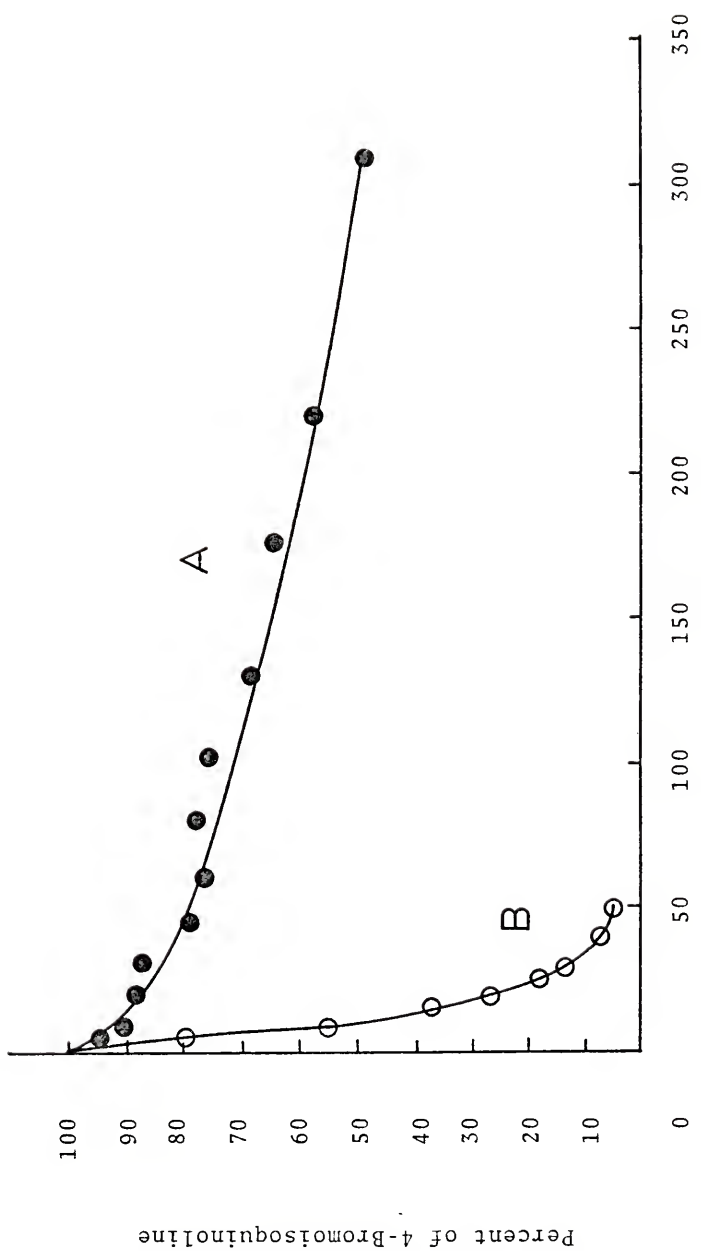


Figure 4. Rates of Disappearance of 0.60 M 4-Bromoisoquinoline in 1.6 M Sodium Methoxide with (A) and without (B) 0.3 M 2,2'-Dinitrobiphenyl at 147°.

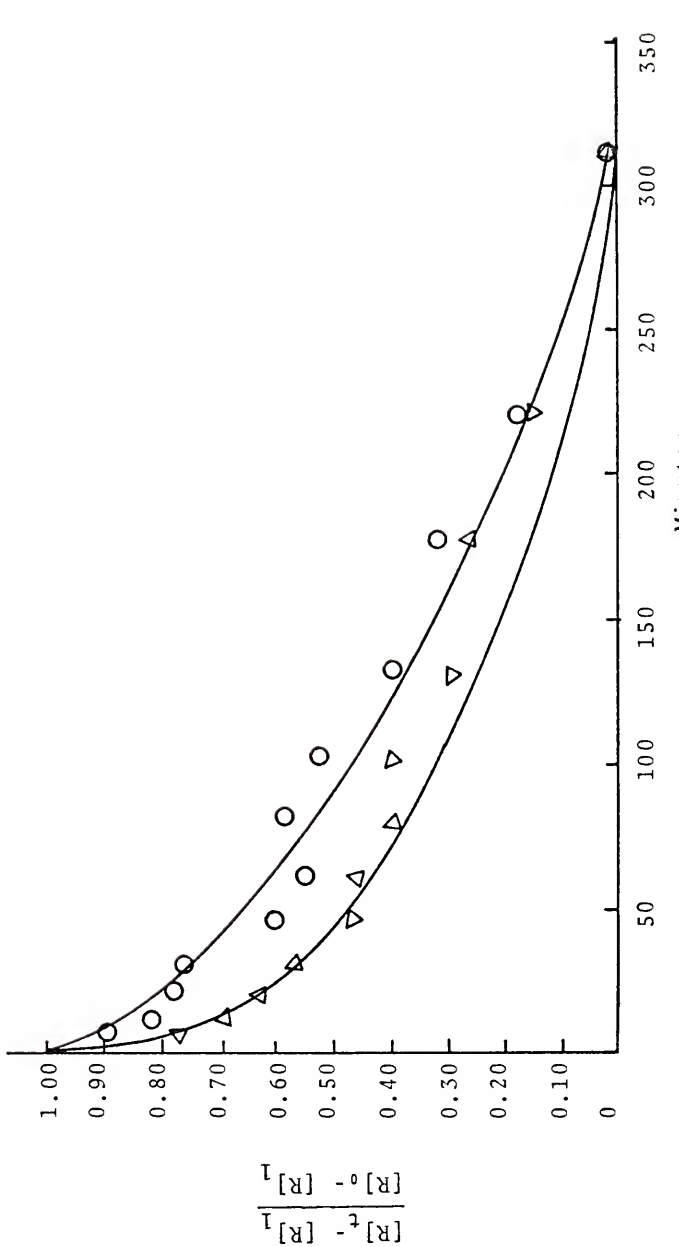


Figure 5. Superimposed Plots for Rates of Disappearance of 4-Bromoisoquinoline (O) and Sodium Methoxide (Δ) at 147° in the Presence of 0.3 M 2,2'-Dinitrobiphenyl. (Reactant subscripts are the same as those in Figure 1).

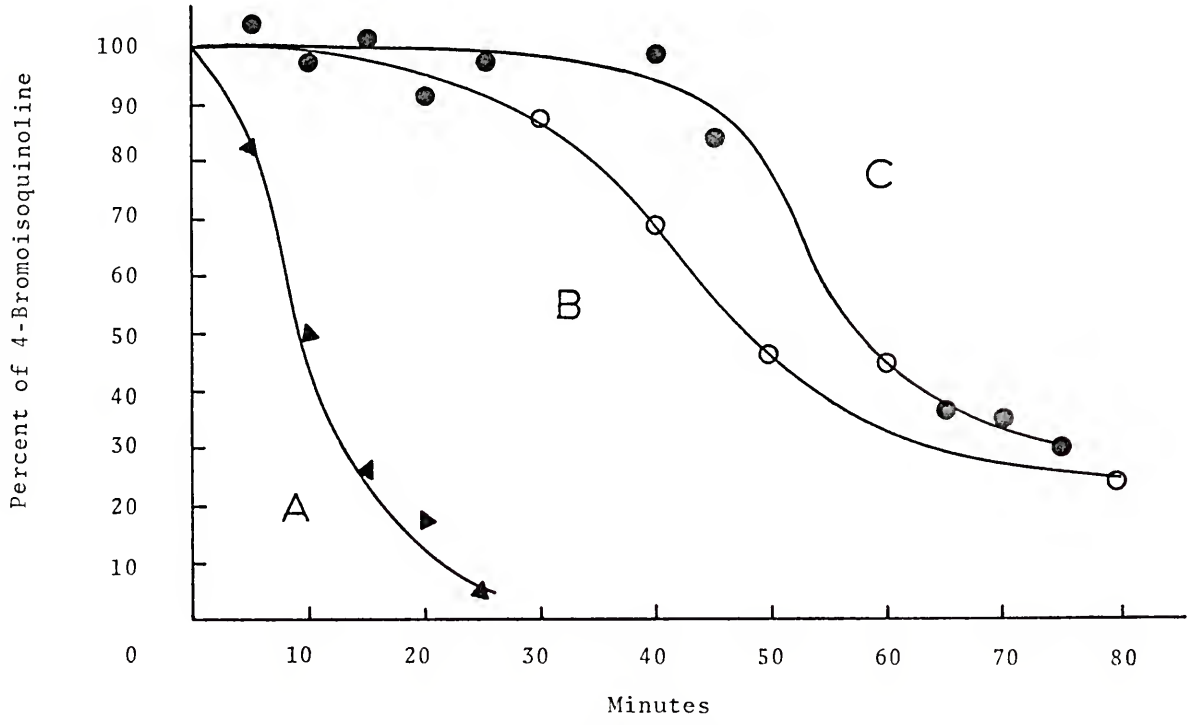


Figure 6. Rates of Disappearance of 0.44 M 4-Bromoisoquinoline in 2.5 M Sodium Methoxide (A) Showing the Effects of 0.05 M Azoxybenzene (B) and 0.05 M Nitrobenzene (C) at 143°.

approximately 0.02 M while maintaining the sodium methoxide concentrations near 1 M. This change required that analysis of the reaction mixtures be carried out by glpc. With the columns that were tried, the peaks for 4-bromo- and 4-methoxyisoquinoline could not be separated. Moreover, the method did not measure the amount of 4-isoquinolyl oxide formed from the cleavage of 4-methoxyisoquinoline.

The last two experiments in Table 4 were conducted to determine by isolation the amount of oxide formed in a reaction mixture initially about 0.02 M in substrate. The oxide was precipitated as 4-hydroxyisoquinoline by neutralizing a water–methanol solution with hydrochloric acid. The identity of the 4-hydroxyisoquinoline was confirmed by its melting point. A control run established that the rate constant for cleavage of 4-methoxyisoquinoline under conditions where the reaction is zero-order in sodium methoxide is 8.3×10^{-5} mol^{-1} sec^{-1}.

Table 4 presents the date obtained from several reaction mixtures analyzed by glpc. The mass balance was low in all runs and appeared to decrease with time in the one run for which analyses were conducted at various times. A control experiment was conducted to determine the stability of isoquinoline under the reaction conditions. A solution of 0.036 M isoquinoline and 0.99 M sodium methoxide was heated at 165° for 1210 minutes. Analysis by glpc indicated that over 75 percent of the isoquinoline was recovered unchanged. The reason for the poor mass balance is unclear, and so studies were discontinued.

Table 4. Reductive Dehalogenation of 4-Bromoisoquinoline by Sodium Methoxide Under Pseudo-first-order Conditions at 165°.[a]

$[NaOCH_3]$	[Substrate]	Minutes	Results
0.91	0.016	60	24% Isoquinoline; 103% mass balance
		310	35% Isoquinoline; 56% mass balance
		885	51% Isoquinoline; 51% mass balance
0.91	0.016	800	88% Isoquinoline
0.79	0.016	1090	34% Isoquinoline
0.75	0.015	950	7% 4-Hydroxyisoquinoline[b]
0.76	0.017	1063	20% 4-Hydroxyisoquinoline[b]

[a]Concentrations (mol/l) are corrected for thermal expansion of methanol.

[b]Isolated yields; no information is available concerning isoquinoline yields in these runs.

Reduction of other hetaryl halides by sodium methoxide.- Studies of the reduction of hetaryl halides other than 4-bromoisoquinoline were conducted on a limited basis. 4-Bromo-3-methylisoquinoline, 4-chloroisoquinoline, 3-bromoquinoline, and 3-iodopyridine underwent reductive dehalogenation. All reactions were studied by nmr. The formation of sodium formate accompanied each of these reductions. The product ratios resulting from competing direct substitution and reduction processes are given in Table 5. Almost exclusive reduction occurs in the brominated quinoline and isoquinoline substrates, whereas the 4-chloroisoquinoline and 3-iodopyridine undergo relatively more substitution. The reduction to substitution ratio for 3-iodopyridine was further reduced by the presence of azoxybenzene and copper (II) chloride. In the presence of copper (II) chloride, no reduction product could be detected by nmr in the case of 3-iodopyridine; only substitution product was detected.

Several potential inhibitors were used in attempts to inhibit the reduction of 4-bromo-3-methylisoquinoline. These included benzophenone, phenanthrene, phthalazine, pyridine N-oxide, 7,8-benzoquinoline, sodium formate, 2,2-diphenyl-1-picrylhydrazyl, and *meta*-dinitrobenzene. No inhibition was observed, but none of these potential inhibitors was shown to be effective in the case of 4-bromoisoquinoline. Methoxide ion consumption and decomposition occurred in the runs using 2,2-diphenyl-1-picrylhydrazyl and *meta*-dinitrobenzene.

Table 5. Reaction of Various Hetaryl Halides with Sodium Methoxide.[a]

Substrate (M)[b]	$[NaOCH_3]$[b]	T,°C	Additives (M)	%Reduction / % Substitution[c]
4-Bromo-3-methylisoquinoline (0.36)	1.5	165	–	>10
4-Chloroisoquinoline (0.33)[d]	1.2	165	–	6[e]
3-Bromoquinoline (0.36)	0.79	165	–	>10
3-Iodopyridine (0.42)	2.5	143	–	2.5[f]
3-Iodopyridine (0.42)	2.5	143	Azoxybenzene (0.05)	1[f]
3-Iodopyridine (0.95)	1.3	100 and 165[g]	$CuCl_2$[h]	<0.1

[a]Reactions were carried out and analyzed in sealed nmr tubes.

[b]Concentrations (mol/l) are corrected for thermal expansion.

[c]The product ratios were determined at or near completion of the reaction.

Table 5. Continued.

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[d]This kinetic run was conducted by Dr. A. A. Sale.

[e]This is the upper limit of the product ratio. The ratio is actually smaller due to cleavage of 4-methoxyisoquinoline to give the oxide which has the same chemical shift as isoquinoline H-3.

[f]There is considerable overlap of peaks, and product ratios are only approximate.

[g]Concentrations given are at 165°.

[h]The concentration of $CuCl_2$ was not determined, but it is about 0.05 M.

Copper (II) chloride not only drastically changed the product ratio as shown in Table 5, but it also had a marked influence on the rate of disappearance of 3-iodopyridine. A solution of 3-iodopyridine (0.95 M) and sodium methoxide (1.3 M) was divided between two nmr tubes, one containing copper (II) chloride. Neither solution showed evidence of reaction after 25 minutes at 100°, but the solution containing copper (II) chloride reacted completely in an additional 10 minutes at 165°. No reaction was detected in the absence of the copper salt under identical conditions.

The reason for the rate enhancement of direct substitution by copper (II) chloride is unclear. 3-Bromopyridine and 3-chloropyridine react much more slowly than 3-iodopyridine even in the presence of copper (II) chloride; 3-bromopyridine underwent very little reaction and 3-chloropyridine failed to react at all. In order to determine if the iodide ion freed in the reaction of 3-iodopyridine is essential to the rate enhancement process, a run was carried out using 3-chloropyridine and added potassium iodide. A solution of 3-chloropyridine (0.63 M), copper (II) chloride (0.03 M), potassium iodide (0.05 M), and sodium methoxide (1.6 M) was heated for 90 minutes at 165°. Only a trace of 3-methoxypyridine was produced. Therefore iodide ion does not play an essential role in the rate enhancement process.

The reaction of 4-chloroisoquinoline with sodium methoxide was also studied. The rate of disappearance of 4-chloroisoquinoline is approximately 3 times slower than that of

4-bromoisoquinoline under similar conditions. After correcting for the 14 percent of starting material which reacted with 2 moles of methoxide ion to give one mole of 4-isoquinolyl oxide ion, it was found that 1.2 moles of methoxide ion reacted with one mole of 4-chloroisoquinoline to give isoquinoline.

Reduction of hetaryl halides by alkoxides other than sodium methoxide.-Alcoholic solutions of lithium methoxide, sodium n-propoxide, and potassium t-butoxide reduced hetaryl halides when heated at 165°. These results are presented in Table 6. There are no gross differences in the rates of reduction of 4-bromo-3-methylisoquinoline by sodium n-propoxide or of 4-bromoisoquinoline by lithium methoxide from those with sodium methoxide. The reductive dehalogenation reaction appears to be a general reaction of alkalai metal alkoxides with the hetaryl halide.

Potassium t-butoxide reacted with 4-bromoisoquinoline at 140° and 165° in t-butyl alcohol to give what appeared by nmr analysis to be isoquinoline and a large amount of tars. The reaction mixture darkened immediately on heating and the resolution of nmr spectra deteriorated with continued heating. An external area standard (methanol) was employed, and the total mass balance decreased with continued heating. However both the degradation leading to tar formation and the formation of isoquinoline were retarded by small amounts of azoxybenzene (0.04 M) or 1,1-diphenylethylene (0.1 M).

Table 6. Reductive Dehalogenation of Hetaryl Halides by Metal Alkoxides.[a]

Substrate (M)	Alkoxide (M)	Additive (M)	T,°C	Results
4-Bromo-3-methyl-isoquinoline (0.7)	Sodium n-propoxide (∿1)	–	165	30% Reduction in 37 minutes
4-Bromo-3-methyl-isoquinoline (0.7)	Potassium t-butoxide (∿1)	–	165	Reduction and degradation
4-Bromo-isoquinoline (0.5)	Lithium methoxide (0.87)	–	165	50% Reduction in 30 minutes
4-Bromo-isoquinoline (0.5)	Potassium t-butoxide (∿1)	–	165	Reduction and degradation
4-Bromo-isoquinoline (0.65)[b]	Potassium t-butoxide (∿1)	–	140	Reduction and degradation
4-Bromo-isoquinoline (0.65)[b]	Potassium t-butoxide (∿1)	Azoxybenzene (0.04)	140	Inhibition of reduction and degradation
4-Bromo-isoquinoline (0.65)[b]	Potassium t-butoxide (∿1)	1,1-Diphenyl-ethylene (0.1)	140	Inhibition of reduction and degradation

[a]Reactions were carried out in sealed nmr tubes. Concentrations are not corrected for thermal expansion.

[b]Methanol was used as an external standard, and the concentration of potassium t-butoxide was identical in these three runs.

More specifically, after 30 minutes at 140° in the presence of ~1 M potassium t-butoxide and 0.1 M 1,1-diphenylethylene, 90 percent of the 4-bromoisoquinoline (originally 0.65 M) remained unreacted. The hydroxyl peak moved upfield by 10 cycles relative to the position before heating, suggesting the consumption of alkoxide ion. Under identical conditions in the absence of an inhibitor, only 40 percent of the 4-bromoisoquinoline remained unreacted and 25 percent isoquinoline was formed. The hydroxyl peak moved upfield by 50 cycles relative to the position before heating in this uninhibited run. Similar results were obtained using azoxybenzene as an inhibitor.

Discussion

A proposed mechanism for the sodium methoxide induced reductive dehalogenation of 4-bromoisoquinoline.-Several pieces of evidence support a radical chain process and eliminate a purely ionic process for the reduction of 4-bromoisoquinoline by sodium methoxide. These include (a) a change in the reduction to substitution product ratio in the presence of known radical and electron traps, (b) a decrease in the rate of disappearance of 4-bromoisoquinoline in the presence of known radical and electron traps, (c) an acceleration of the reduction reaction by a known radical initiator, and (d) the presence of induction periods in the absence of added inhibitor. These four pieces of evidence will be considered in turn in order to show that they are

consistent with a radical route leading to the formation of isoquinoline.

It is not clear how much, if any, 4-methoxyisoquinoline results from a radical substitution process. However, the fact that the amount of 4-methoxyisoquinoline increases in the presence of inhibitors does suggest that this product can form by a non-radical process at a rate comparable to that for the reduction reaction. This non-radical process is likely to involve the "classical" ionic aromatic nucleophilic substitution pathway. A change in the reduction to substitution product ratio in the presence of inhibitors indicates the operation of multiple mechanisms which are likely to be both radical and ionic.

In the absence of radical traps the reduction to substitution (by methoxide ion) ratio was always greater than 10, meaning that although 4-methoxyisoquinoline could be detected in the nmr spectrum, it was not present in sufficient quantity for meaningful integration, Table 1. The presence of low concentrations of nitrobenzene (0.05 M) and azoxybenzene (0.05 M) reduced this product ratio by a factor of about two. Nitrobenzenes are estabilished electron acceptors and inhibitors of radical chain processes.[11-16] Unfortunately, under the reaction conditions employed, nitrobenzenes react with methoxide ion to give azoxybenzenes.[7,8] However, azoxybenzenes, as well as the intermediates (nitrosobenzenes and phenylhydroxylamines)[7] in the reaction of nitrobenzene with methoxide ion, should also be electron acceptors and inhibitors

of radical chain processes. The presence of a high concentration of azoxybenzene has a profound effect upon the product ratio by effectively inhibiting the radical chain reaction leading to the formation of isoquinoline. 2,2'-Dinitrobiphenyl (0.3 M) also has a dramatic effect on the product ratio reducing it by a factor of greater than 10, and these results may be interpreted in the same manner as those for nitrobenzene.

1,1-Diphenylethylene (<0.6 M) reduced the product ratio by a factor of about two. This is a known radical trap which has been used in an ethanolic solution of sodium ethoxide for inhibition of a radical chain process for the decomposition of triarylsulfonium alkoxides.[17]

The retardation of the rate of disappearance of 4-bromoisoquinoline in the presence of radical inhibitors provides a strong argument for a radical chain process of reductive dehalogenation. This retardation by 1,1-diphenylethylene (<0.6 M), 2,2'-dinitrobiphenyl (0.3 M), azoxybenzene (0.05 M) and nitrobenzene (0.05 M) can be seen in Figures 2, 4, and 6. In view of this rate retardation by four different organic compounds, it would be very difficult to justify consideration of any ionic mechanism for the reductive dehalogenation of 4-bromoisoquinoline by sodium methoxide.

This retardation of the rate of disappearance of 4-bromoisoquinoline in the presence of inhibitors cannot be due entirely to side reactions which give the appearance of inhibition. The retardation must reflect the ability of the

inhibitor to interfere with a radical chain process. Since the reduction reaction is dependent on the concentration of sodium methoxide (kinetic order unknown), it is possible that the reduction reaction is retarded by side reactions between inhibitors and the base. These side reactions may decrease the concentration of the base and hence decrease the rate of reduction. While in some cases this may be true, it cannot be the entire explanation. These complications will be considered individually.

Since nitro-compounds are known to react with methoxide ion, it must be determined if retardation by nitrobenzene and 2,2'-dinitrobiphenyl is due to destruction of methoxide ion rather than to interception of radical intermediates. The stoichiometry of the reduction of nitrobenzene by methoxide ion to azoxybenzene requires that 3 moles of methoxide ion be consumed for every 4 moles of nitrobenzene.[18] Thus, the reaction of 0.05 M nitrobenzene would reduce the methoxide ion concentration by 0.04 M; this is an insignificant amount in light of the fact that the initial concentration of methoxide ion was 2.5 M. In the case involving 2,2'-dinitrobiphenyl the destruction of methoxide ion is likely to be more significant, and the effective methoxide ion concentration is expected to be reduced from 1.6 M to 1.2 M. This effect can be seen in Figure 5 where it is obvious that the rate of consumption of methoxide is greater than would be expected on the basis of reaction with 4-bromoisoquinoline alone. As a result the rate retardation in the presence of

2,2'-dinitrobiphenyl is probably due in small part to consumption of methoxide ion.

Azoxybenzene and 1,1-diphenylethylene are not expected to react with sodium methoxide under the reaction conditions.[7,17,18] Moreover, azoxybenzene was an effective inhibitor at 0.05 M concentration; it would be most unusual if azoxybenzene at this concentration level reacted to substantially effect a methoxide ion concentration initially 2.5 M. Figure 3 indicates that 1,1-diphenylethylene does not react with methoxide ion under the reaction conditions; that is, the rates of the reaction as measured by the disappearance of 4-bromoisoquinoline and by the disappearance of methoxide ion in the presence of 1,1-diphenylethylene are the same. If massive amounts of methoxide ion underwent reaction with 1,1-diphenylethylene, one would expect to see a separation of the two curves as in Figure 5 where methoxide ion did react with 2,2'-dinitrobiphenyl in addition to 4-bromoisoquinoline.

Interpretation of the results involving copper salts is complicated by a number of factors, including the presence of several oxidation states of copper and coordination of the heterocycle and oxidized copper. Copper (I) is known to form copper (I) methoxide which is unstable.[19,20] Copper (II) chloride undergoes reduction to elemental copper under the reaction conditions in the absence of heterocycle. Copper (II) ion forms a complex with 4-bromoisoquinoline at room temperature in methanol, and such complexes are expected to

enhance greatly the electrophilic reactivity of the heterocyclic ring. Copper (I) chloride, copper (II) chloride, and the copper (II) complex of 4-bromoisoquinoline are only slightly soluble under the reaction conditions.

However, copper salts are known to be electron acceptors and effective radical traps.[21,22] Copper (I) oxide is known to catalyze the reduction and nucleophilic substitution of aryl halides in alcoholic metal alkoxide mixtures, but the mechanisms have not been established.[23-26]

The presence of very low concentrations (<0.05 M) of copper (I) and copper (II) chlorides had a profound influence on the product ratio, Table 1. Moreover, comparison of the runs described in Table 3 after 5.9 minutes shows that the overall rate of disappearance of 4-bromoisoquinoline in the presence of ~0.01 M copper (II) chloride is slower than in the absence of the copper salt. This can only be due in small part to the destruction of methoxide ion by the reduction of copper (II) ion because the copper (II) ion to methoxide ion ratio is 130. But the rate of formation of substitution product, 4-methoxyisoquinoline, appears to be accelerated in the presence of copper (II) chloride. Therefore the rate of the reduction reaction has been retarded. After 5.9 minutes it appears that the reaction consuming copper (II) chloride is complete. There is no further formation of the substitution product and the reduction reaction appears to proceed at a normal rate. The reduction–substitution product ratio after the first 5.9 minutes of

the reaction is 0.87; after 7 additional minutes, the ratio has increased to 2.5. It appears that copper (II) ion is very effective in promoting substitution and inhibiting reduction, but that fast side reactions with methoxide ion giving elemental copper cause this effect to be short lived.

Strong evidence for a radical chain process is the initiation of the reduction reaction by a known free radical source. This evidence was obtained using ABIN[27] in the reaction mixture to accelerate the formation of isoquinoline. An initial short but real induction period, which is characteristic of radical chain processes, was also observed in all of the kinetic runs.

A radical chain mechanism of reduction of 4-bromoisoquinoline to isoquinoline is suggested in Scheme I. There is little in the experimental results to indicate the detailed steps of the reduction mechanism, and so Scheme I represents speculation. However much of this speculation has precedent.

Scheme I

Initiation:

$$\text{Donor}^- + \text{4BrIsoq} \rightleftarrows \text{Donor}\cdot + [\text{4BrIsoq}]^{\cdot -} \qquad (6)$$

Propagation:

$$[\text{4BrIsoq}]^{\cdot -} \rightarrow \text{Isoq}\cdot + \text{Br}^- \qquad (7)$$

$$\text{Isoq}\cdot + \text{CH}_3\text{O}^- \rightarrow [\text{IsoqH}]^{\cdot -} + \text{CH}_2\text{O} \qquad (8)$$

$$\text{Isoq}\cdot + \text{CH}_3\text{OH} \rightarrow \text{IsoqH} + \cdot\text{CH}_2\text{OH} \qquad (9)$$

$$\text{Isoq}\cdot + \text{CH}_3\text{O}^- \rightarrow \text{IsoqH} + \cdot\text{CH}_2\text{O}^- \qquad (10)$$

$$\cdot\text{CH}_2\text{OH} + \text{CH}_3\text{O}^- \rightleftarrows \text{CH}_3\text{OH} + \cdot\text{CH}_2\text{O}^- \qquad (11)$$

$$\cdot\text{CH}_2\text{O}^- + \text{4BrIsoq} \rightarrow \text{CH}_2\text{O} + [\text{4BrIsoq}]^{\cdot -} \qquad (12)$$

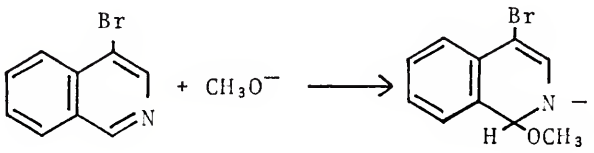
$$\cdot\text{CH}_2\text{O}^- + \text{4BrIsoq} \rightarrow \text{BrCH}_2\text{O}^- + \text{Isoq}\cdot \qquad (13)$$

The exact nature of the initiation step is not known. The electron donor, $Donor^-$ in equation 6, could be methoxide ion, which, on donation of an electron to 4-bromoisoquinoline. would give a methoxy radical which would most likely react to give the carbon radical, equation 15. The reaction in equation 15 has a rate constant of about 10^4 mol^{-1} sec^{-1}.[28] It has been suggested that the methoxide ion is a good reducing agent by virtue of observations that paraquat (1,1'-dimethyl-4,4'-bipyridylium ion) is reduced by methoxide ion.[29,30]

$$CH_3O^- + 4BrIsoq \rightleftarrows CH_3O\cdot + [4BrIsoq]^{\cdot} \qquad (14)$$

$$CH_3O\cdot + MeOH \rightarrow \cdot CH_2OH + MeOH \qquad (15)$$

Alternatively, the electron donor could be the anion resulting from the addition of methoxide ion to 4-bromoisoquinoline, equation 16. Electron donation by pi-delocalized



(16)

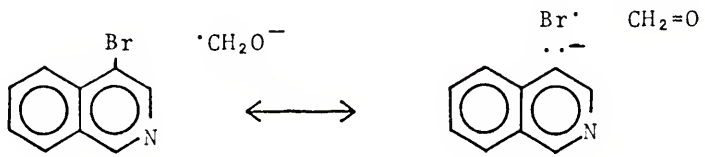
anions is well documented,[14] and the formation of radical anions under conditions giving anionic sigma complexes has also been reported.[13] The formation of the 1-methoxy anionic sigma complex of 4-bromoisoquinoline has not been directly observed; however the analogous formation of the 1-amino anionic sigma complex of 4-bromoisoquinoline and amide ion is reported elsewhere in this dissertation.

Several reports have appeared describing the results of electron transfer to halopyridines. Loss of halide ion follows the electron transfer, and the pyridyl radical is formed.[31-33] This process is analogous to the first propagation step in equation 7 showing loss of halide ion from the initially formed radical anion to give the 4-isoquinolyl radical. The exact structure of the 4-isoquinolyl radical is unknown, but since the 2-, 3-, and 4-pyridyl radicals are σ radicals,[31,32] it is reasonable to assume that the 4-isoquinolyl radical is also a σ radical. It has also been reported that halopyridines can be polarographically reduced to pyridine.[33]

Equations 9, 11, and 12 are analogous to those proposed by Bunnett and Wamser for the reduction of aryl iodides in alkaline methanol via a radical chain process.[2] An important difference between this work and the work being discussed here is that the deiodination of aryl iodides requires initiation by an external radical source while the reductive debromination of 4-bromoisoquinoline proceeds spontaneously on heating.

Radical abstraction of halogen by $\cdot CH_2OH$ to give an aryl radical was ruled out by Bunnett and Wamser[2] because this mechanism does not account for their observation that sodium methoxide is required. However, radical abstraction of halogen by the radical anion of formaldehyde, equation 13, seems to us to be a viable alternative route.

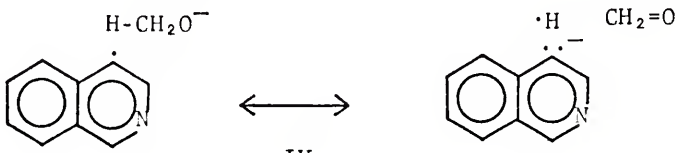
Bromine abstraction by $\cdot CH_2O^-$ in the case of 4-bromoisoquinoline is a possibility which must be considered seriously. Thus, substituent effect studies on free-radical abstraction of iodine from aromatic[34] and aliphatic iodides[35] show that the carbon atom from which the halogen is being removed has anionic character in the transition state. Consider now the polar transition state, III, for debromination of the isoquinoline. The likely sense of polarization is shown. This involves the generation of the 4-isoquinolyl anion. The 4-isoquinolyl anion is known to form when isoquinoline is deprotonated by base, and the annular nitrogen atom provides considerable inductive stabilization of the negative charge.[36] In the debromination reaction by $\cdot CH_2O^-$, the indicated polarization produces a formaldehyde-like structure. It seems likely with this polarization that $\cdot CH_2O^-$ will be more reactive than $\cdot CH_2OH$. The latter will give rise to a protonated formaldehyde-like structure in the transition state and is less favored energetically.



III

Either methanol or methoxide ion could serve as the hydrogen atom donor to the 4-isoquinolyl radical, equations 9 and 10. Methoxide ion is expected to be a better donor than methanol. (No comparison of these two donors appears to

have been published.) There are numerous reports that electron-donating substituents on the hydrogen atom donor facilitate this transfer.[37] In the present case this sense of polarization of the transition state, IV, for hydrogen atom transfer is particularly favorable. Again, a 4-isoquinolyl anion-like structure is produced and the oxide ion (from $\cdot CH_2O^-$) is expected to stabilize the transition state more than the hydroxy group (from $\cdot CH_2OH$). Oxide ion is a better electron donor than the hydroxy group.[38] The relative amount of hydrogen atom donation from the two donors cannot be gauged from the present study. The more reactive donor is present in lower concentration (typically about 1 M) relative to methanol (20 M[39] for the neat material at 165°). If methanol is a hydrogen atom donor, the hydrogen atom should come largely from the methyl group.[40]



IV

There is a possibility that isoquinoline forms by hydride transfer from methoxide ion to the 4-isoquinolyl radical, equation 8. A radical anion forms in this case. When this radical anion donates an electron to 4-bromoisoquinoline, product is formed and the chain is continued. Such a sequence seems to be unprecedented, however.

The termination steps in the proposed mechanism are obscure. However, since a good mass balance is observed for the reaction, it is likely that the radical chain is long and that the initiation and termination steps have little effect upon the stoichiometry of the reaction.

The formaldehyde formed in Scheme I most likely reacts under the reaction conditions to give methylformate. The methylformate subsequently reacts with hydroxide ion formed from methoxide ion and residual water to give the formate ion which was detected in the nmr spectra (equations 17 through 19).

$$2CH_2O \rightarrow HCO_2CH_3 \quad (17)$$

$$CH_3O^- + H_2O \rightarrow CH_3OH + OH^- \quad (18)$$

$$HCO_2CH_3 + OH^- \rightarrow HCO_2^- + CH_3OH \quad (19)$$

Furthermore the proposed mechanism requires that 0.5 mole of formate ion be produced per mole of isoquinoline. The experimental observation was exactly that. The formate ion to isoquinoline ratio was 0.5. No methylformate was observed in the reaction mixtures. It was shown that the nmr signals of methylformate overlap with the methanol and aromatic mass proton signals of the reaction mixtures. Moreover, methylformate reacts so quickly with hydroxide ion to give formate ion and methanol that a sufficient concentration for detection by nmr is never present.

The reductive dehalogenation reactions carried out with DMSO as a cosolvent may proceed by a different mechanism. This may involve the dimsyl anion. This mechanism is described

in equations 20 through 22 and has been reported for the reductive dehalogenation of aryl halides and bromothiophenes.[41-45] Briefly, this mechanism involves formation of the dimsyl anion by deprotonation of DMSO, nucleophilic displacement on halogen by the dimsyl anion forming a halomethyl sulfoxide and an aryl anion, and then proton abstraction from the alcohol solvent by the aryl anion. This mechanism does not involve formate ion formation as does the radical chain process.

$$CH_3O^- + CH_3SOCH_3 \rightarrow CH_3OH + CH_3SOCH_2^- \quad (20)$$

$$CH_3SOCH_2^- + ArX \rightarrow Ar^- + CH_3SOCH_2X \quad (21)$$

$$Ar^- + CH_3OH \rightarrow ArH + CH_3O^- \quad (22)$$

Extension of reductive dehalogenation to other bases and substrates.-Reductive dehalogenation appears to be a common reaction for hetaryl halides in which the halogen is *meta* to the annular nitrogen. (When the halogen is *ortho* or *para* to the annular nitrogen the nucleophilic substitution reaction is especially favored, and substitution occurs instead of reduction.) The reduction of 4-chloroisoquinoline in methanolic sodium methoxide shows that the reaction is not limited to a brominated isoquinoline and the reduction of 3-bromoquinoline and 3-iodopyridine shows that other halogenated heterocyclic ring systems undergo the reaction. A more highly substituted isoquinoline such as 4-bromo-3-methylisoquinoline is also reduced under these conditions. It seems likely that these reduction reactions proceed by the same kind of mechanism considered for 4-bromoisoquinoline.

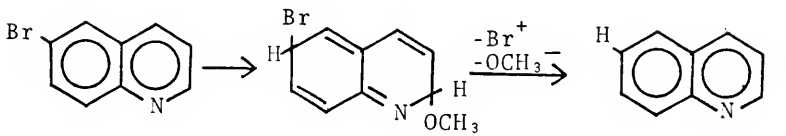
t-Butyl alcohol is a poor hydrogen atom donor because it has no alpha hydrogens. That t-butoxide was able to effect the reduction of 4-bromoisoquinoline via a radical chain process was a mild surprise. In fact, Bergstrom's observation that 4-bromoisoquinoline is reduced to isoquinoline by t-butoxide in about 50 percent yield (isolated as the picrate)[1] is confirmed by our analysis of reaction mixtures by nmr. Furthermore the rate of formation of isoquinoline in these mixtures is retarded by two different radical traps (azoxybenzene and 1,1-diphenylethylene), demonstrating that the reaction pathway involves a radical chain. An upfield shift of the hydroxyl peak also suggested that t-butoxide ion was consumed in the course of this reaction. It is not clear what serves as the hydrogen atom donor in this solvent. It should be noted that decomposition products are present in the reaction mixture as evidenced by the dark color. Perhaps the hydrogen atom comes from degraded material.

Related Investigations.-Although little has been reported to date on the mechanism of base catalyzed reductive dehalogenation of hetaryl halides, there have been several related reports on other systems. Some of these have already been mentioned when they were directly applicable; others deserve comment at this point.

The reductive debromination of hexabromobenzene in the presence of methoxide ion has been reported. A radical mechanism for the protodebromination of hexabromobenzene to give penta- and tetrabromobenzenes was quickly dismissed

because no biphenyls were detected when benzene was added to the reaction mixture, and the carbanion mechanism previously reported by Bunnett[46] was postulated. Hydrazine hydrate reacts with hexabromobenzene in ethanol to replace two adjacent bromine atoms with hydrogen via an unknown mechanism.[47]

6- and 8-Bromoquinolines were reported to undergo reductive dehalogenation with sodium methoxide at 125° in 48 and 71 percent isolated yields respectively. An ionic mechanism was suggested for these reactions in which methoxide ion addition to C-2 was followed by a proton adding at C-6 or C-8. Loss of positive bromine and methoxide ion then gave quinoline, equation 23. Little evidence was given to support this mechanism, and it is possible that the reactions proceed via a radical chain process.[48] By comparison, treatment of 7-bromoquinoline with sodium methoxide resulted in formation of 7-methoxyisoquinoline.[49] These observations follow the emerging pattern that substitution is favored when the negative charge of the initial anionic sigma complex can be delocalized onto the annular nitrogen, e.g. 7-bromoquinoline, but when this is not possible, reduction occurs instead.



(23)

CHAPTER 3

ALKOXIDE ION PROMOTED NUCLEOPHILIC SUBSTITUTION OF HETARYL HALIDES

Results

Products and product ratios from the reaction of 4-bromoisoquinoline with mixtures of sodium methoxide and sodium thiophenoxide.-4-Bromoisoquinoline underwent simultaneous reduction and substitution when heated in a methanolic solution of sodium methoxide and sodium thiophenoxide at 165°. Reactions were generally carried out in sealed nmr tubes, and the reaction mixtures were analyzed directly by nmr with t-butyl alcohol often serving as an internal standard. The identity of the products was confirmed by tlc and glpc. The time required for the reaction to proceed to completion was dependent upon the methoxide ion concentration. For example, a reaction mixture 0.36 M in 4-bromoisoquinoline, 0.62 M in sodium methoxide, and 0.75 M in sodium thiophenoxide required between 45 and 85 minutes at 165° to go to >95 percent completion. (The reaction mixture was not examined between these two times.) Another reaction mixture 0.40 M in 4-bromoisoquinoline, 1.9 M in sodium methoxide, and 0.79 M in sodium thiophenoxide required less than 10 minutes at 165° to go to >95 percent completion. The only substantial difference in these two reaction mixtures is the sodium methoxide concentra-

tion. There is little or no degradation of products under the reaction conditions, and the mass balance is high. A control run was conducted to verify the stability of 4-phenylthioisoquinoline under the reaction conditions. This compound is stable in 2 M sodium methoxide and methanol heated at 165° for 320 minutes. After 1441 minutes at 165°, a typical reaction mixture with sodium isobutyrate as an internal area standard was analyzed by nmr, and the analysis showed a combined product yield of 92 percent. Another reaction mixture heated at 147° for 90 minutes with t-butyl alcohol as an internal area standard was analyzed by nmr and the analysis showed a combined product yield of 105 percent. A small amount of degradation (<5 percent) may have occurred in the reaction mixture heated for 1441 minutes at 165°, but this is an unusually long reaction time for the experiments analyzed by nmr, and generally the nmr analyses are valid to ±5 percent.

The above results and others obtained at 165° are tabulated in Table 7 in order of decreasing sodium methoxide to sodium thiophenoxide ratio. In the presence of the more nucleophilic thiophenoxide ion and without added inhibitor, very little 4-methoxyisoquinoline was produced, and it could not generally be detected in the nmr spectrum. Therefore, Table 7 only lists the isoquinoline to 4-phenylthioisoquinoline product ratios. Considering the first five entries in Table 7, for which there is initially a sodium methoxide to 4-bromoisoquinoline molar ratio of greater than or nearly equal to 2, it is apparent that the isoquinoline to

Table 7. Product Ratios for the Reaction of 4-Bromoisoquinoline with Sodium Methoxide and Sodium Thiophenoxide.[a,b]

$[Substrate]_0$	$[NaOCH_3]_0$	$[NaSC_6H_5]_0$	$\frac{[NaOCH_3]_0}{[NaSC_6H_5]_0}$	$\frac{[NaOCH_3]_f}{[NaSC_6H_5]_f}$	T,°C	%Isoquinoline / % 4-Phenylthioisoquinoline
0.57	2.0	0.69	2.9	∿3.0	165	1.7
0.40	1.9	0.79	2.4	∿2.3	165	1.7
0.44	1.2	0.67	1.9	∿1.8	165	1.2
0.56	1.5	1.5	1.0	∿0.98	165	0.71
0.36	0.62	0.75	0.83	∿0.77	165	0.66
1.2	0.67	1.1	0.60	0	165	0.49
0.52	0.98	0.98	1.0	∿1.0	147	0.62
0.60	1.5	1.6	0.94	∿0.87	143	0.80

[a] Reactions were carried out in sealed nmr tubes. Concentrations are corrected for thermal expansion.

[b] Subscripts refer to initial and final concentrations; the final values are calculated values.

4-phenylthioisoquinoline ratio decreases as the initial concentration ratio of sodium methoxide to sodium thiophenoxide decreases. The former ranges from 1.7 to 0.66 as the latter ranges from 2.9 to 0.85. Those reactions in which there is less than a 1.5:1 molar ratio of sodium methoxide to 4-bromoisoquinoline could give an unusually low product ratio due to complete consumption of methoxide ion in the reduction process. In the experiment listed with less than a stoichiometric concentration of sodium methoxide, the product ratio is 0.49.

The final pair of reactions listed in Table 7 were conducted at temperatures lower than 165°. The effect of temperature on the product ratio is not certain, but it appears that lowering the reaction temperature lowers the reduction–substitution product ratio. Comparison of the last entry at 143° with an earlier entry of nearly the same concentrations shows that the product ratio dropped from 1.0 to 0.80 with the 22 degree temperature change.

As shown in Table 8, various additives had an effect upon the product ratio. Each of the radical inhibitors known to be effective in suppressing the reduction of 4-bromoisoquinoline decreased the product ratio so as to favor phenylthio substitution product. For the first three entries in Table 8, the product ratio from the control run in the absence of inhibitor is 1.0, and in each case the inhibited reaction gives a product ratio two-thirds or one-half that of the control run. At the lower temperatures

Table 8. Product Ratios for the Reaction of 4-Bromoisoquinoline with Sodium Methoxide and Sodium Thiophenoxide in the Presence of Inhibitors.[a]

$[Substrate]_0$	$[NaOCH_3]_0$	$[NaSC_6H_5]_0$	$\frac{[NaOCH_3]_0}{[NaSC_6H_5]_0}$	T,°C	% Isoquinoline[b]	% 4-Phenylthio-isoquinoline	Inhibitor
0.56	1.4	1.5	0.93	165	0.7	(1.0)	0.02 M 3-Carbamoyl-2,2,5,5,-tetramethyl 3-pyolin-1-yloxy radical
0.56	1.4	1.5	0.93	165	0.5	(1.0)	0.06 M[c] $CuCl_2$
0.56	1.4	1.5	0.93	165	0.5	(1.0)	0.2 M Nitrobenzene
0.52	0.98	0.98	1.0	147	0.44	(0.62)	0.2 M Azobenzene
0.60	1.5	1.6	0.94	143	0.2	(0.80)	0.4 M Azoxybenzene

[a]Reactions were carried out in sealed nmr tubes. Concentrations are corrected for thermal expansion.

[b]Product ratio in the absence of inhibitor is indicated in parentheses.

[c]This would be the concentration if all the $CuCl_2$ dissolved.

(147° and 143°), 0.2 M azobenzene reduces the product ratio by one-third, and 0.4 M azoxybenzene reduces the product ratio by three-fourths.

The product ratios which are listed in Tables 7 and 8 were taken near the end of the reactions. In the absence of inhibitors, these ratios adequately describe the course of the reaction and do not undergo gross variations with time. From Figures 8 and 9, the product ratios can be obtained at four different times during the reaction. Assuming a 2:1 stoichiometric relationship between methoxide ion consumed and isoquinoline formed and a 1:1 relationship between thiophenoxide ion and 4-phenylthioisoquinoline, Table 9 can be constructed. By the time a significant variation in the methoxide to thiophenoxide ion ratio occurs, the reaction is 90 percent complete, and there is no large effect on the product ratio. In fact, within an acceptable range the product ratio is a constant 61±6 percent throughout the reaction. This sort of analysis is generally true for all the reaction mixtures studied where the sodium methoxide and sodium thiophenoxide are initially present in excess over 4-bromoisoquinoline. Compare the initial and final ion ratio given in Table 7.

However the product ratios in the presence of inhibitors are not nearly as constant with time as those in the absence of inhibitors. As will be seen, this has a bearing on the significance of a small change in the final product ratio caused by the presence of the inhibitor. In Figures 8 and 9

Table 9. Product and Reactant Ratios at Various Times for the Reaction of 0.52 M 4-Bromoisoquinoline with 0.98 M Sodium Methoxide and 0.98 M Sodium Thiophenoxide at 147°.

Minutes	% 4-Bromoisoquinoline	$\frac{[NaOCH_3]}{[NaSC_6H_5]}$	$\frac{\%\ \text{Isoquinoline}}{\%\ \text{4-Phenylthioisoquinoline}}$
0	100	1.0	–
50	79	0.99	0.55
70	34	1.0	0.60
90	10	0.88	0.67
130	1	0.75	0.62

the same reaction as discussed in the previous paragraph is followed in the presence of 0.2 M azobenzene (Table 10). During the first 70 minutes, there is complete inhibition of isoquinoline formation (and presumably much of 4-phenylthioisoquinoline formation which occurs via a radical process), but the concentration of 4-phenylthioisoquinoline formed by direct aromatic nucleophilic substitution is increasing. When the inhibition period is largely over, there still remains 75 percent of unreacted 4-bromoisoquinoline. The final portion of the reaction proceeds normally, and the large effect of the inhibitor on the final product ratio is masked by the large contribution of the normal process to the final observed product ratio.

When a 9:1 (V:V) DMSO and methanol solution of 0.40 M 4-bromoisoquinoline, 0.38 M sodium methoxide, and 0.78 M sodium thiophenoxide was heated at 100°, the product ratio was 0.42. This is close to the value 0.49 obtained for a reaction mixture heated at 165° with a similar base to nucleophile ratio (Table 7). If the data in Table 7 are correct, then a 65° reduction in temperature should lead to a considerable enhancement in the amount of substitution product. Since this is not observed, it may be concluded tentatively that the DMSO facilitated the formation of reduction product.

Kinetics of the reaction of 4-bromoisoquinoline with sodium methoxide and sodium thiophenoxide.-Data for the rate of disappearance of 4-bromoisoquinoline, and for the

Table 10. Product Ratios at Various Times for the Reaction of 0.52 M 4-Bromoisoquinoline with 0.98 M Sodium Methoxide and 0.98 M Sodium Thiophenoxide in the Presence of 0.2 M Azobenzene at 147°.

Minutes	% Isoquinoline	% 4-Phenylthio-isoquinoline	% Isoquinoline / % 4-Phenylthio-isoquinoline
50	0	18	0
70	0	21	0
90	5	25	0.20
130	8	34	0.24
165	13	41	0.32
220	16	45	0.36
370	21	55	0.38

rate of appearance of isoquinoline and 4-phenylthioisoquinoline were obtained in the presence and absence of inhibitors using nmr. Figure 7 shows a typical plot for the rate of disappearance of 1.2 M 4-bromoisoquinoline at 165° in a methanolic solution of 0.67 M sodium methoxide and 1.1 M sodium thiophenoxide. Note the inflection point early in the reaction; this is indicative of initial inhibition of a radical process. Under these conditions the reaction is 93 percent complete within one hour and gives 58 percent 4-phenylthioisoquinoline, 30 percent isoquinoline, and ~5 percent 4-methoxyisoquinoline.

The effect of 0.02 M azobenzene on the course of the reaction is shown in Figures 8 and 9. The disappearance of 4-bromoisoquinoline and the appearance of isoquinoline are plotted in Figure 8 in the absence and presence of azobenzene at 147°. The concentrations of all other reactants are the same in both runs. (The results are not unlike those obtained in the reduction of 4-bromoisoquinoline by methoxide ion in the absence of sodium thiophenoxide.) In the absence of inhibitor, the 4-bromoisoquinoline is totally consumed in 120 minutes; whereas with 0.2 M azobenzene present 20 percent of the 4-bromoisoquinoline remains unreacted even after 370 minutes. The rate of formation of isoquinoline is also much slower in the presence of azobenzene.

Figure 9 shows the effect of the inhibitor on the rate of formation of 4-phenylthioisoquinoline in identical reaction mixtures but with and without 0.2 M azobenzene. During the

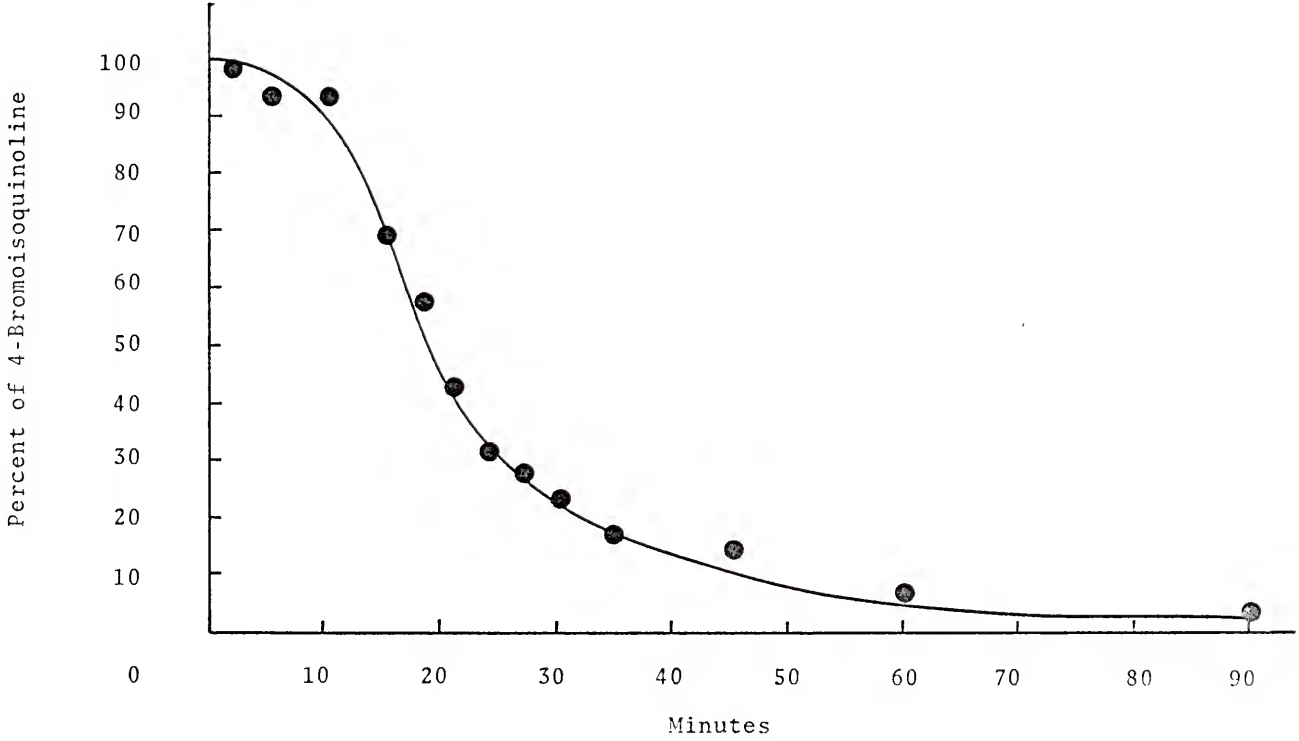


Figure 7. Disappearance of 1.2 M 4-Bromoisoquinoline in 0.67 M Sodium Methoxide and 1.1 M Sodium Thiophenoxide at 165°.

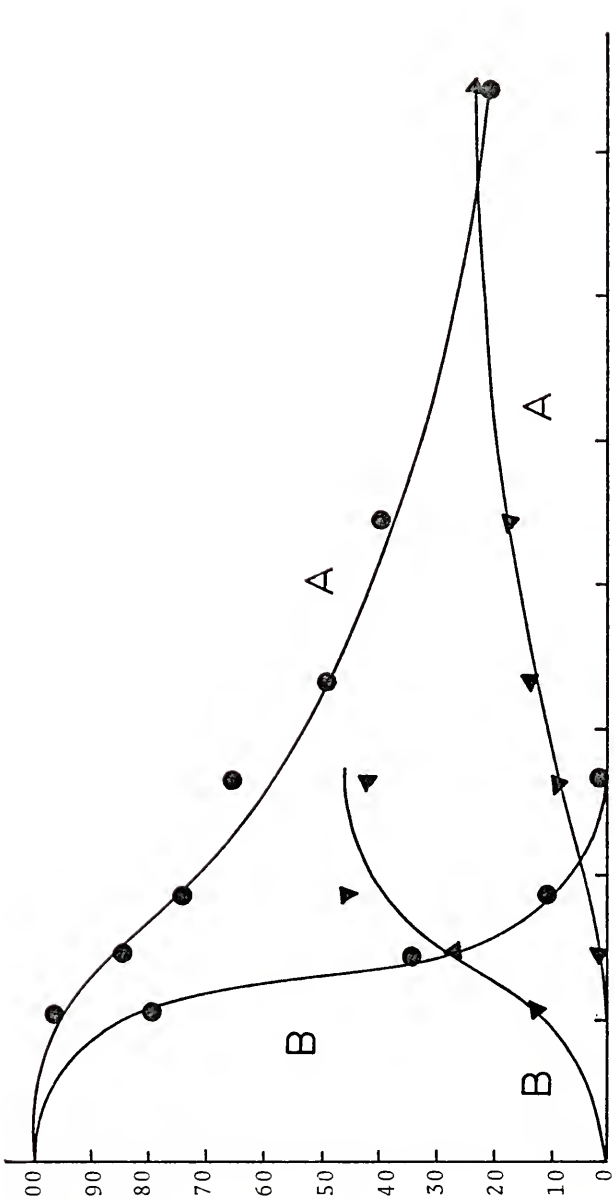


Figure 8. Rates of Disappearance of 0.52 M 4-Bromoisoquinoline (●) and Appearance of Isoquinoline (▲) in 0.98 M Sodium Methoxide and 0.98 Sodium Thiophenoxide at 147° with (A) and without (B) 0.2 M Azobenzene.

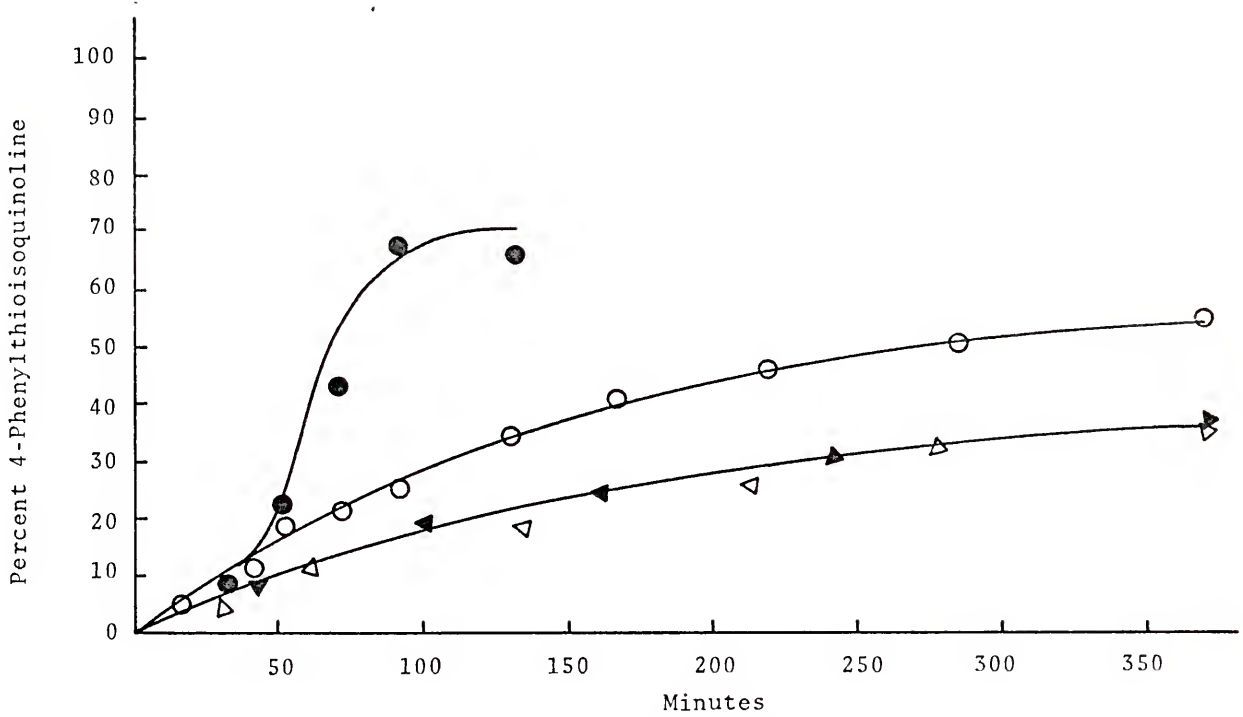


Figure 9. Rates of Appearance of 4-Phenylthioisoquinoline from 0.52 M 4-Bromoisoquinoline in 0.98 M Sodium Methoxide and 0.98 M Sodium Thiopenoxide at 147° in the Absence (●) and Presence (○) of ∿0.2 M Azobenzene and Rates of Appearance of 4-Phenylthioisoquinoline from 0.52 M 4-Bromoisoquinoline and 0.98 M Sodium Thiophenoxide at 147° in the Absence (△) and Presence (▲) of ∿0.3 M Azobenzene.

first 40 minutes of the reaction, 11 percent of the substitution product is formed in each of the reaction mixtures. Then the formation of 4-phenylthioisoquinoline rapidly increases in the reaction mixture containing no azobenzene and rises to 65 percent after 90 minutes. In the same time only 25 percent 4-phenylthioisoquinoline has been formed in the presence of 0.2 M azobenzene. In other words, about five times more substitution product is formed between 40 and 90 minutes in the mixture free of azobenzene. After 90 minutes the reaction mixture with no inhibitor is 90 percent complete, while the inhibited reaction is only 25 percent complete.

When an 0.2 M azobenzene and 0.72 M sodium methoxide methanolic solution was heated at 165° for 1 hour, there was no change in either the methoxide ion concentration or the azobenzene concentration. Analysis was done by nmr with t-butyl alcohol as the internal area standard. Furthermore, methanolic solutions of sodium thiophenoxide (0.84 M) and sodium methoxide (0.87 M) were heated for 1060 minutes in the presence and absence of azobenzene (~0.3 M). Again analysis by nmr showed no significant change in the concentration of any of the reagents. Azobenzene does not react with either sodium methoxide or sodium thiophenoxide under the reaction conditions.

The dependence of the rate of formation of the phenylthio substitution product on the concentration of sodium methoxide is shown in Figure 10. Two runs identical in 4-bromoisoquinoline (1.2 M) and sodium thiophenoxide (1.1 M) concen-

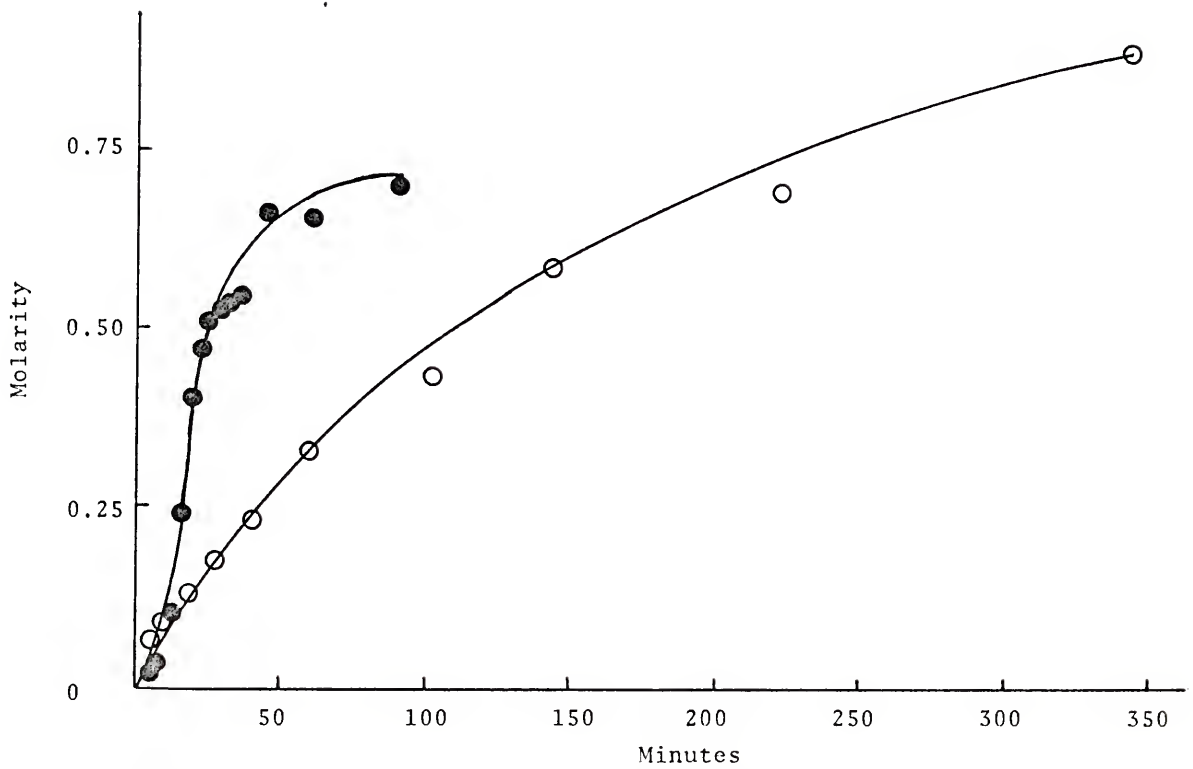


Figure 10. Rates of Appearance of 4-Phenylthioisoquinoline from 1.2 M 4-Bromoisoquinoline in 1.1 M Sodium Thiophenoxide at 165° in the Presence of 0.67 M Sodium Methoxide (●) and in the Absence of Sodium Methoxide (O).

trations, but one containing sodium methoxide (0.67 M) were heated at 165°. Rates for the first 10 minutes are about the same, but then the rate of formation of 4-phenylthioisoquinoline increases markedly in the methoxide ion promoted reaction. After about 80 minutes the maximum amount of 4-phenylthioisoquinoline (59 percent) has been formed in the run containing added sodium methoxide, but in the absence of sodium methoxide after 80 minutes only ~30 percent of the maximum has formed, and the maximum conversion to substitution product has not been reached even after 350 minutes.

Results similar to those obtained at 147° with azobenzene were obtained using much lower concentrations of azoxybenzene at 143°. These results are shown in Figure 11. When present in only 0.03 M concentration, azoxybenzene is an effective inhibitor of both the reduction and substitution reactions. In one hour in the absence of azoxybenzene, 4-bromoisoquinoline was converted completely to isoquinoline and 4-phenylthioisoquinoline; whereas the inhibited reaction mixture with identical initial reactant concentrations contained 75 percent 4-bromoisoquinoline after one hour, and even after 460 minutes 15 percent of the starting material remained. This is the most dramatic inhibition observed in any reaction mixture, with only a 0.03 M concentration of inhibitor extending the time required for complete reaction by more than 7-fold.

A solution of 0.60 M 4-bromoisoquinoline and 1.2 M sodium thiophenoxide was prepared and divided between two

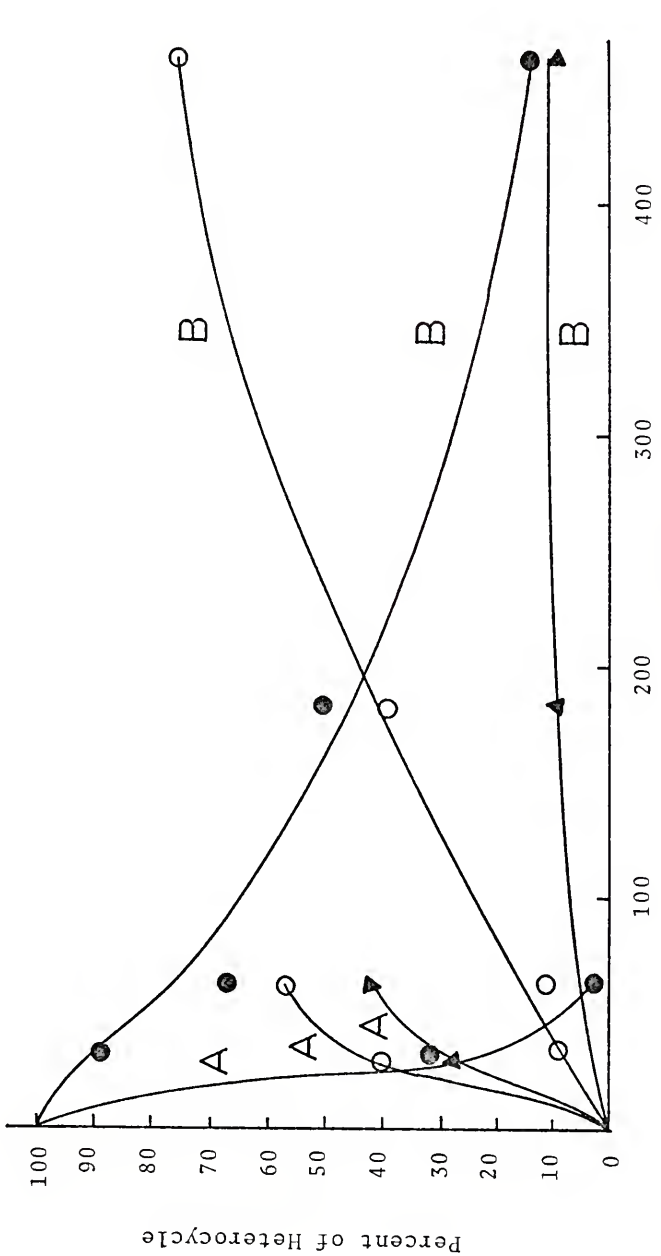


Figure 11. Relative Rates of Reaction of 0.60 M 4-Bromoisoquinoline in 1.5 M Sodium Methoxide and 1.6 M Sodium Thiophenoxide at 143° in the Presence (B) and Absence (A) of 0.03 M Azoxybenzene. (4-Bromoisoquinoline, ●; isoquinoline, ▲; 4-Phenylthioisoquinoline, ○).

nmr tubes, one containing azoxybenzene (~0.2 M). The reactions were followed at 175° rather than the usual 165° for convenience. Analyses at two different points in the reaction showed that less 4-phenylthioisoquinoline had been found in the tube containing azoxybenzene. The final analysis showed that after 120 minutes there was 53 percent product in the tube containing azoxybenzene compared to 72 percent product in the tube with no inhibitor. It appears that there may be slight inhibition of autocatalysis by sodium thiophenoxide. However, it is clear that this is not a gross effect, and if there is autocatalysis by sodium thiophenoxide it is insignificant compared to methoxide ion catalysis.

The concurrent reduction–substitution reaction of 4-bromoisoquinoline with methoxide and thiophenoxide ions was studied under pseudo-first-order conditions by glpc. The results of these studies are presented in Table 11, and they show the same general trend in product ratios as those studies conducted by nmr. Throughout any one of the four runs the reduction to substitution ratio remains constant to within ±20 percent of the mean value. However, redetermination of the product ratio 6 months later in one run gave a larger uncertainty, ±30 percent of the mean value. The total amount of isoquinoline and 4-phenylthioisoquinoline products found at completion varies from 38 to 72 percent. This is far below the expected 100 percent for reasons which are unclear. Perhaps this low mass balance is due to the formation of the anion of 4-hydroxyisoquinoline which is

Table 11. Kinetic Results for Concurrent Pseudo-first-order Reaction of 4-Bromoisoquinoline with Sodium Methoxide and Sodium Thiophenoxide at 165°.

Initial Concentrations	Minutes	% Substitution	% Reduction	% Reduction / % Substitution
$[Substrate]_0 = 0.014$	60			0.087
$[NaOCH_3]_0 = 0.39$	186	Not determined		0.083
$[NaSC_6H_5]_0 = 0.95$	300			0.076
$[Substrate]_0 = 0.015$	20	9.1	1.9	0.21
$[NaOCH_3]_0 = 0.8$	60	–	–	0.15
$[NaSC_6H_5]_0 = 0.8$	80	50	8.1	0.16
	100	51	7.7	0.15
	560	50	9.5	0.19

Table 11. Continued.

Initial Concentrations	Minutes	% Substitution		% Reduction		% Reduction / % Substitution	
		A[b]	B	A	B	A	B
$[Substrate]_0$ = 0.015	20	26	32	14	20	0.54	0.62
$[NaOCH_3]_0$ = 1.7	40	37	33	12	18	0.32	0.55
$[NaSC_6H_5]_0$ = 0.79	80	50	38	22	21	0.44	0.55
	120	44	39	25	26	0.56	0.67
$[Substrate]_0$ = 0.015	30	9.8		5.4		0.55	
$[NaOCH_3]_0$ = 0.90	60	20		10		0.50	
$[NaSC_6H_5]_0$ = 0.27	90	29		14		0.48	
	120	27		11		0.41	
	150	27		11		0.41	

[a]Reactions carried out using aliquots in sealed tubes. Analysis done by glpc. All concentrations are corrected for thermal expansion.

Table 11. Continued.

[b]A and B represent analyses carried out on two different glpc columns. A analyses were conducted some 6 months after the B analyses.

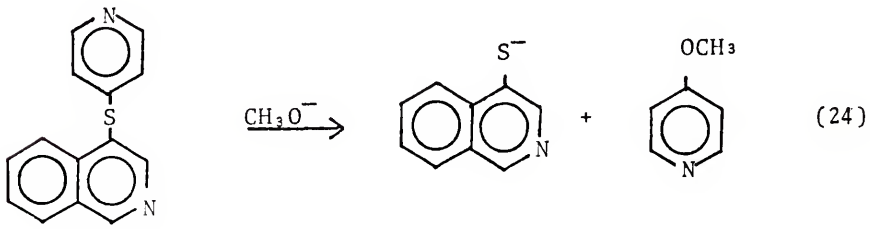
not measured by glpc. This anion arises from the cleavage of 4-methoxyisoquinoline. Hence the studies were discontinued.

An independent check on the product ratios from nmr analysis of reaction mixtures containing substrate in the 0.5 M concentration range was made using glpc. The glpc product ratios are in good agreement with those obtained by nmr on the same reaction mixtures. Also the glpc studies confirm the nmr product identifications.

Alkoxide ion promoted substitution of 4-bromoisoquinoline by negatively charged ions other than thiophenoxide ion.- Attempts were made to extend the alkoxide ion promoted substitution reaction of 4-bromoisoquinoline to include other negatively charged ions which would result in the formation of carbon–carbon, carbon–nitrogen, or carbon–oxygen bonds. The lithium and sodium salts of 2-nitropropane were generated *in situ* in a methoxide solution with excess 2-nitropropane. When 4-bromoisoquinoline was heated for two consecutive periods of 30 minutes each at 100° and 165° in these solutions, no reaction was observed. When the lithium salt of 2-nitropropane was isolated and then dissolved in DMSO or DMF, no reaction with 4-bromoisoquinoline (or 3-iodopyridine) could be detected when heated at temperatures of 100° or less for several hours. The presence of excess alkoxide ion in these reaction mixtures did not promote substitution at 100° and gave the usual isoquinoline and 4-methoxyisoquinoline products at 165°. Use of a mixed solvent system consisting of DMSO and methanol resulted in no substitution reaction

between 4-bromoisoquinoline and the lithium salt of 2-nitropropane in the presence of lithium methoxide. The mixture was heated at 100° for over an hour. No substitution reaction involving 4-bromoisoquinoline and either the sodium salt of acetonitrile or piperidine in excess methoxide ion and DMSO was observed at 100°; rather, reduction to isoquinoline occurred.

However 4-bromoisoquinoline did appear to undergo methoxide ion promoted substitution with negatively charged sulfur nucleophiles other than thiophenoxide ion. These included sodium methylmercaptide, sodium p-chlorothiophenoxide, and the sodium salt of 4-thiopyridone. The study of the reaction of 4-bromoisoquinoline with the sodium salt of 4-thiopyridone was impractical because of formation of large amounts of 4-methoxypyridine which presumably arose from nucleophilic substitution of the initially formed 4-(4-thiopyridyl)-isoquinoline by methoxide ion to give 4-methoxypyridine and 4-isoquinolylmercaptide ion, equation 24.



(24)

The reaction of 4-bromoisoquinoline with sodium methylmercaptide at 165° was complicated by the cleavage of the methyl-sulfur bond in the 4-methylthioisoquinoline product.

As a result the reaction could not be followed for long periods of time. No attempt was made to establish the mechanism of this cleavage reaction. The results obtained from those reactions observed for a short period of time are given in Table 12. Considering the first entry, in the presence of nearly equimolar amounts of sodium methoxide and sodium methylmercaptide, it can be seen that the reaction is complete within 5 minutes to give 65 percent substitution by methylmercaptide ion and 35 percent reduction. For the second entry where there is no sodium methoxide, the reaction is only 55 percent complete after 5 minutes and gives no reduction. It appears that sodium methoxide accelerates both the overall reaction and the formation of 4-methylthioisoquinoline, and that methoxide ion is essential to the reduction process. Finally, a reaction mixture containing no methoxide ion and the same concentration of sodium methylmercaptide as that for the second entry but with added 0.5 M azoxybenzene gives less substitution product in the same amount of time (36 percent compared to 55 percent). It appears that the inhibitor has slowed down the formation of product via autocatalysis by methylmercaptide ion. However, on the basis of only one observation, the relatively small difference is of questionable significance.

The problem of cleavage of 4-methylthioisoquinoline was partially overcome by lowering the reaction temperature to 127°. At this temperature less cleavage occurred, and correction could be made for the small amount which did occur.

Table 12. Reactions of ∿0.4 M 4-Bromoisoquinoline[a] with Sodium Methoxide and/or Sodium Methylmercaptide at 165°.

$[NaOCH_3]$[b]	$[NaSCH_3]$[b]	Minutes	Additive	Products
∿2.0	∿2.1	5	None	65% 4-Methylthioisoquinoline 35% Isoquinoline
—	∿2.0	5	None	55% 4-Methylthioisoquinoline 45% 4-Bromoisoquinoline
—	∿2.0	5	∿0.5 M Azoxybenzene	36% 4-Methylthioisoquinoline 64% 4-Bromoisoquinoline

[a]Reactions were carried out in sealed nmr tubes.

[b]Concentrations (mol/l) are corrected for thermal expansion. Concentrations are approximate due to the difficulty of introducing an accurately known weight of gaseous methylmercaptan.

The results of the usual control and inhibited runs are presented in Figure 12. A 0.47 M solution of 4-bromoisoquinoline in methanol with ~2.2 M sodium methylmercaptide and ~2.1 sodium methoxide was divided between two nmr tubes, one containing ~0.1 M azoxybenzene, and heated at 127°. The presence of inhibitor slows the formation of both isoquinoline and 4-methylthioisoquinoline. The inhibition is not as dramatic as in reactions involving thiophenoxide ion.

The reaction of 4-bromoisoquinoline (0.51 M) with sodium p-chlorothiophenoxide (0.98 M) and sodium methoxide (0.98 M) at 147° is followed in Figure 13. In this experiment no products were isolated, rather it was assumed that the usual substitution reaction took place, and the new peaks appearing in the nmr spectrum were from this product. A typical inhibition was observed in the presence of 0.4 M azoxybenzene. Thus, over 60 percent substitution product was formed in 100 minutes in the run without inhibitor, but in the presence of azoxybenzene only 15 percent product was formed in the same time.

An attempt was also made to observe substitution by a non-charged sulfur nucleophile, methyl disulfide, in the presence of sodium methoxide. This failed when the methoxide ion apparently reacted quickly with the methyl disulfide, and the 4-bromoisoquinoline remained unreacted.

Reaction of other heterocycles with sodium thiophenoxide and sodium methoxide mixtures.-Three compounds other than 4-bromoisoquinoline were studied briefly for alkoxide promoted

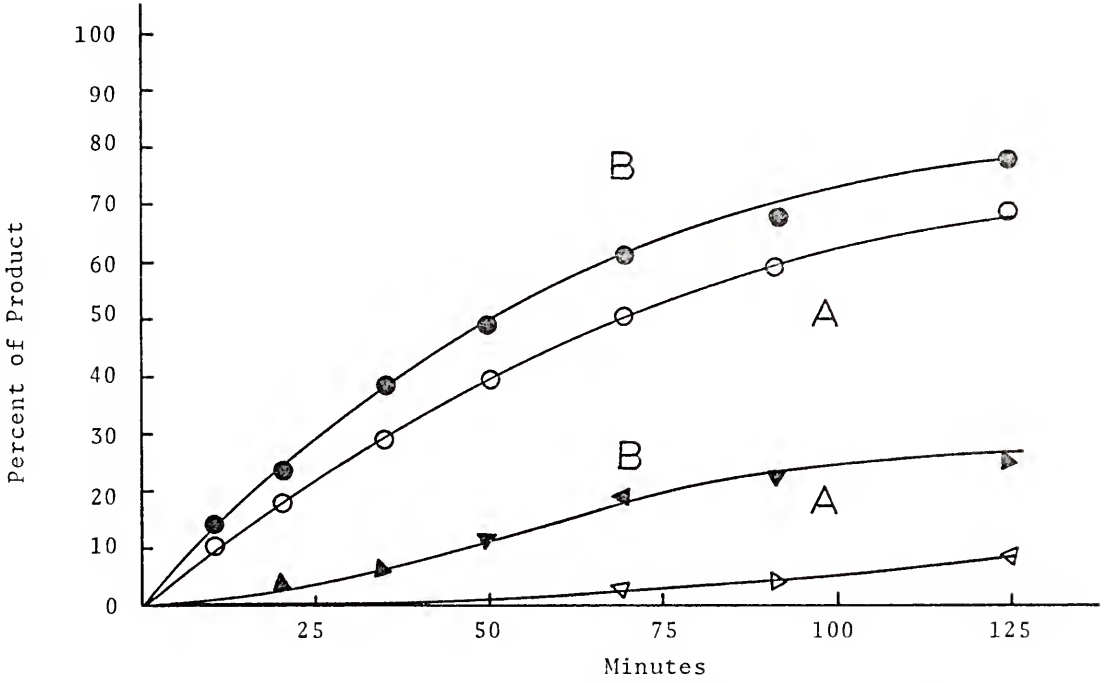


Figure 12. Appearance of 4-Methylthioisoquinoline (O,●) and Isoquinoline (Δ,▲) from 0.47 M 4-Bromoisoquinoline in ∿2.2 M Sodium Methoxide at 127° with (A) and without (B) ∿0.1 M Azoxybenzene.

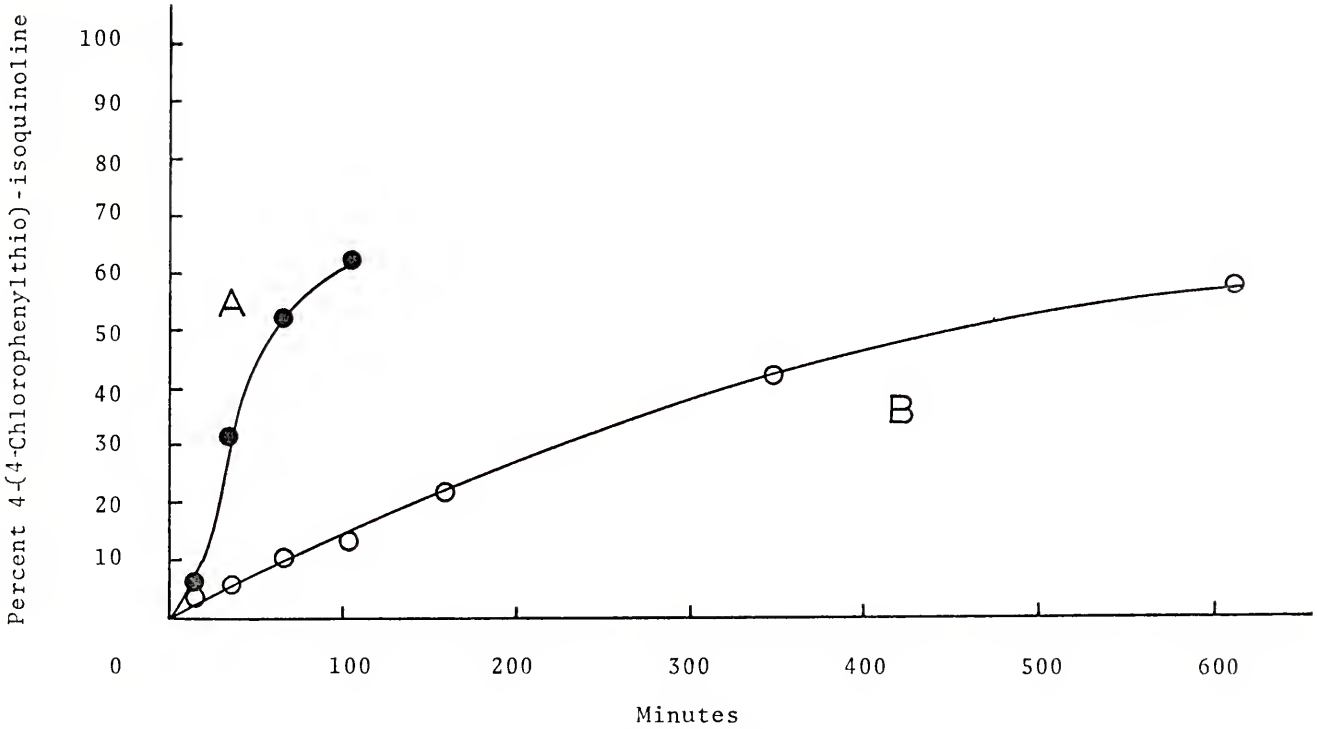


Figure 13. Rates of Appearance of 4-(4-Chlorophenylthio)-isoquinoline from 0.51 M 4-Bromoisoquinoline in 0.98 M Sodium 4-Chlorothiophenoxide and 0.98 M Sodium Methoxide at 147° with (B) and without (A) ∿0.4 M Azoxybenzene.

substitution by thiophenoxide ion. 3-Bromoquinoline (0.47 M) underwent reaction with sodium methoxide (1.7 M) and sodium thiophenoxide (0.87 M) at 165° in 30 minutes to give an nmr spectrum quite different from that of starting material. This was a complicated spectrum, presumably consisting of a mixture of 3-phenylthioquinoline and quinoline. 4-Bromo-3-methylisoquinoline (0.44 M) underwent reaction with sodium methoxide (1.4 M) and sodium thiophenoxide (0.63 M) at 165° in 1 hour to give a 3:1 mixture of 3-methylisoquinoline and another compound presumed to be the 4-phenylthio substitution product. 3-Iodopyridine (0.33 M) underwent partial reaction at 100° in 60 minutes with sodium thiophenoxide (0.71 M), sodium methoxide (1.2 M), and ABIN to give a product which is presumed to be the 3-phenylthio substitution product. Clearly, such reactions are worthy of future studies.

Discussion

A proposed mechanism for the reaction of 4-bromoisoquinoline with mixtures of sodium methoxide and sodium thiophenoxide.-There are several key observations from experiments involving the simultaneous reduction and substitution reactions of 4-bromoisoquinoline with mixtures of methoxide and thiophenoxide ions which must be accommodated by any proposed mechanism. These observations are: A short initial induction period is observed in the rate of appearance of 4-phenylthioisoquinoline; methoxide ion accelerates the rate of formation of 4-phenylthioisoquinoline; known radical inhibitors change the product ratio of isoquinoline to

4-phenylthioisoquinoline in favor of the substitution product; known radical inhibitors slow the rate of formation of 4-phenylthioisoquinoline; an increase in the initial methoxide ion to thiophenoxide ion ratio is reflected by an increase in the reduction to substitution product ratio.

In the absence of added sodium methoxide, 4-phenylthioisoquinoline is formed from 4-bromoisoquinoline and thiophenoxide ion in methanol. This reaction apparently proceeds by the "classical" ionic aromatic nucleophilic substitution mechanism, hereafter referred to as the ionic mechanism. Second-order rate plots for this reaction at 147° and 165° are linear through 80 percent conversion of 4-bromoisoquinoline; there is no evidence of an induction period, and azobenzene has no significant influence on the rate (147°). Note, however, that a question has been raised recently whether electron transfer may be involved in "classical" substitution reactions at an aromatic carbon.[50] In any case, the present study is concerned with the nature of the rate acceleration brought about by added methoxide ion. The present results should not be confused in any way with the rate acceleration brought about by added base in substitution reactions at an aromatic carbon involving amine nucleophiles.[51] The rate acceleration in these ionic reactions involves kinetic general base catalysis and is entirely different in mechanism from that considered here.

In the presence of sodium methoxide, 4-phenylthioisoquinoline is formed from 4-bromoisoquinoline and thiophenoxide

ion by a pathway which must involve radical intermediates. Evidence to support this is found in the induction period for the formation of the substitution product, Figures 9 and 10. As the results in these figures show, the initial rates of substitution in mixtures with and without methoxide ion are essentially the same, indicating the operation of the ionic substitution reaction as the major pathway to substitution product during the early portion of the reaction. But after this period, there is a considerable divergence in rates, that reaction mixture containing methoxide ion forming 4-phenylthioisoquinoline at a considerably faster rate.

A rough measure of the rate acceleration brought about by methoxide ion may be gained by estimating the rate of appearance of the substitution product by drawing a tangent to the illustrated concentration–time curves. A tangent should be selected early in the accelerated portion of the rate in order to minimize differences in concentrations between the runs with and without methoxide ion. About a 10-fold acceleration is produced by an initial 0.98 M concentration of sodium methoxide at 147° (Figure 9) and about a 6-fold acceleration is produced by 0.67 M sodium methoxide at 165° (Figure 10). The smaller acceleration probably largely reflects the lower concentration of methoxide ion. The temperature and initial concentration of 4-bromoisoquinoline are not the same. Clearly the effect of added methoxide ion is significantly large and must be associated with a second mechanism of substitution.

The effect of various added inhibitors on the isoquinoline to 4-phenylthioisoquinoline product ratio is given in Table 8, and in each case the effect of the added inhibitor is to lower the product ratio by increasing the amount of substitution product. This result is consistent with a mechanism in which isoquinoline arises by a radical chain process and 4-phenylthioisoquinoline is formed by direct nucleophilic substitution. It is also consistent with a mechanism in which isoquinoline arises by a radical chain process and the 4-phenylthioisoquinoline arises by multiple paths, one of which may be a radical chain reaction.

To distinguish between the two mechanisms of substitution suggested in the preceding paragraph, it is necessary to observe the rate of formation of 4-phenylthioisoquinoline in the presence and absence of inhibitors. Figure 9 shows that the rate of formation of 4-phenylthioisoquinoline in the presence of methoxide ion is decreased by the presence of ~0.2 M azobenzene. As shown earlier, the inhibitor also decreases the rate of formation of the reduction product. The inhibitor thus decreases the rates of formation of the reduction and substitution products, the reduction reaction being affected more. This is taken to mean that 4-phenylthioisoquinoline arises in part by a radical chain process which is influenced by the inhibitor and in part by a purely ionic pathway which is insensitive to the inhibitor.

The maximum amount of substitution product which arises by the ionic mechanism may be estimated as follows: At 90

minutes, Figure 9, the reaction containing methoxide ion is essentially complete and 65 percent of the 4-bromoisoquinoline is converted to 4-phenylthioisoquinoline, the remainder being largely isoquinoline. At the same time the reaction without methoxide ion has given rise to only 16 percent 4-phenylthioisoquinoline. Hence, no more than 16/65 or 25 percent of the substitution product in the methoxide ion promoted reaction arose by the ionic mechanism. This is a maximum value because it does not consider that the faster reaction with methoxide ion will have less 4-bromoisoquinoline available for the ionic pathway after the initial induction period, and so less substitution product will form by the ionic route. A similar consideration of the results in Figure 10 indicates a maximum of about 47 percent 4-phenylthioisoquinoline arose by the ionic route. This value is lower than the earlier value probably because the methoxide ion concentration is lower (0.67 *versus* 0.98 M).

The minimum amount of substitution product formed by the ionic mechanism may be estimated by considering the amount of substitution product present at the end of the induction period, assuming that substitution product essentially arises by the ionic route during the induction period. This amounts to about 15 percent in both cases. Note the shorter induction period in the reaction at the higher temperature.

Azobenzene (~0.2 M) was used to inhibit the methoxide ion promoted substitution reaction, Figure 9. Although the inhibition is effective, the rate of formation of 4-phenylthioisoquinoline in the presence of this inhibitor and methoxide ion still is faster than the rate of formation of the substitution product by the ionic mechanism. Azobenzene is known to accept electrons readily.[14,52-54] This retardation by azobenzene must represent true inhibition of the reaction. It cannot be due to some kind of reaction between thiophenoxide ion and azobenzene which lowers the concentration of thiophenoxide ion and thereby lowers the rate of substitution. A control run, Figure 9, involving 4-bromoisoquinoline and thiophenoxide ion shows that the rate of the ionic substitution reaction is not changed by the presence of 0.3 M azobenzene. Still another control shows that methoxide ion and azobenzene do not react under the conditions of the substitution reaction.

The fact that proven radical inhibitors affect the rate of formation of 4-phenylthioisoquinoline is strong evidence for a radical chain mechanism of substitution. Furthermore, it is certainly reasonable that this radical chain process be similar to that described for the reduction of 4-bromoisoquinoline by sodium methoxide. Such a mechanism with the 4-isoquinoyl radical as a common intermediate leading to both reduction and substitution is consistent with all the experimental data.

The additional propagation steps necessary for a radical chain process of substitution are given in equations 25 and 26. The key reaction in equation 25 has ample precedent. It has been shown that p-nitrophenyl radicals can be trapped by various anions,[55] and that thiophenoxide ion efficiently traps p-nitrocumyl radicals in DMF or DMSO.[56]

$$\text{Isoq}\cdot + C_6H_5S^- \rightarrow [\text{IsoqSC}_6H_5]^{\cdot} \quad (25)$$

$$[\text{IsoqSC}_6H_5]^{\cdot} + \text{IsoqBr} \rightarrow [\text{IsoqBr}]^{\cdot-} + \text{IsoqSC}_6H_5 \quad (26)$$

Examination of Table 7 shows that the sodium methoxide to sodium thiophenoxide ratio remains almost constant for all but one of the reaction mixtures studied, the exception being the mixture having excess substrate. There is a decrease in the ratio as the reaction proceeds. But assuming a stoichiometry such that 1.5 moles of methoxide ion is consumed for every mole of isoquinoline formed and that one mole of thiophenoxide ion is consumed for every mole of 4-phenylthioisoquinoline formed, the methoxide to thiophenoxide ion ratio never changes by more than 7 percent. Likewise, thiophenoxide ion is initially present in excess over 4-bromoisoquinoline and no more than 30 percent is consumed. All but one of the initial concentrations at 165° are within ±10 percent of 0.73 M. Based on the above considerations both the base to nucleophile ratio and the nucleophile concentration may be assumed to be constant for a semi-quantitative interpretation of the data.

On the basis of the data presented in this chapter and in Chapter 2, a radical chain process is the favored mechanism for both reduction and formation of a major portion of the phenylthio substitution product. In both processes the 4-isoquinolyl radical may be the key intermediate, and it is reasonable to assume that this species is the common intermediate in the simultaneous reduction and substitution reactions. Consequently, a kinetic scheme may be constructed to show how the product ratio depends on the concentration of methanol, methoxide and thiopenoxide ions, assuming they all compete for the 4-isoquinolyl radical. Assume that reduction occurs by hydrogen atom abstraction from methanol with rate constant k_2 and by hydrogen atom abstraction from methoxide ion with rate constant k_1; assume that radical substitution occurs by reaction with thiophenoxide ion with rate constant k_3. The product ratio is then given by equation 27. Certainly the methanol concentration is constant

$$\frac{\%IsoqH}{\%IsoqSC_6H_5} = \frac{k_1[CH_3O^-]}{k_3[C_6H_5S^-]} + \frac{k_2[CH_3OH]}{k_3[C_6H_5S^-]} \qquad (27)$$

throughout the reaction and is 20 M at 165°. Since the thiophenoxide ion concentration is also roughly constant for most of the runs, equation 26 assumes the form of a linear equation where the intercept is $k_2\ [CH_3OH]/k_3\ [C_6H_5S^-]$ and the slope k_1/k_3. The least squares line plotted from the first five entries (165°) in Table 7 is presented in Figure 14; the slope is 0.56±0.15, and the intercept is 0.18±0.30. The correlation coefficient is 0.978. The indicated uncertainty

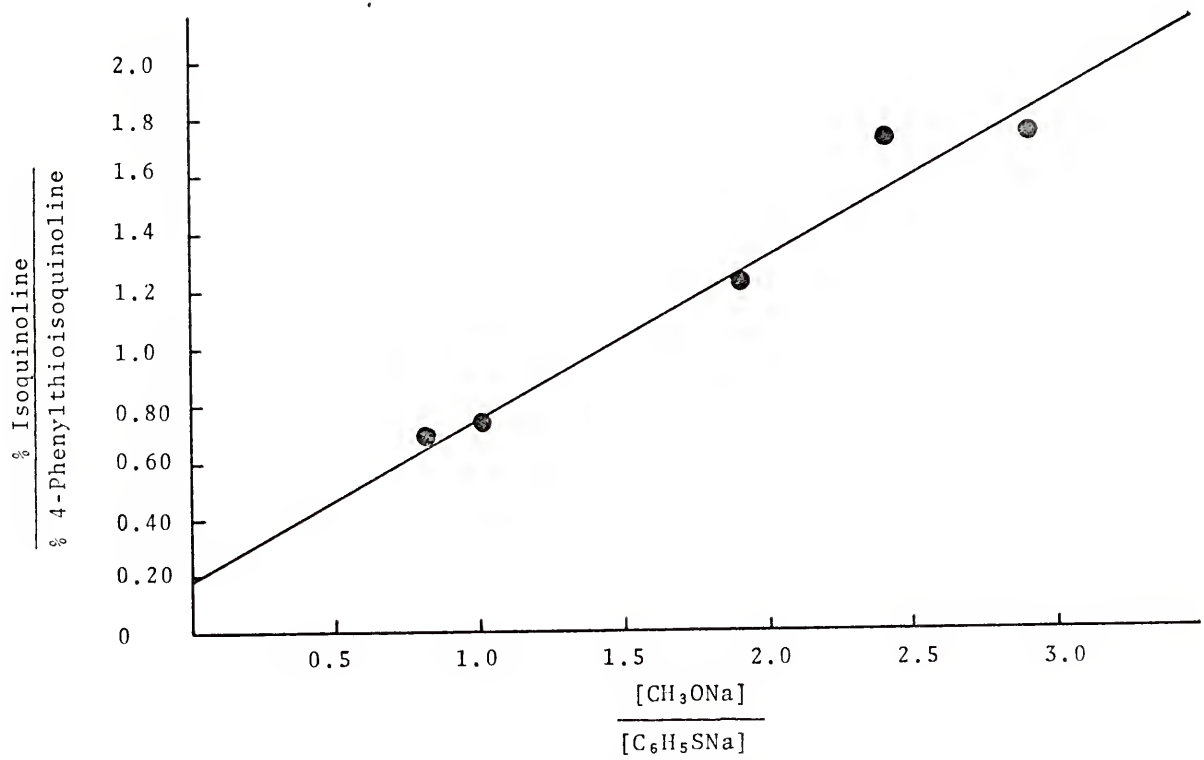


Figure 14. Product Ratios *Versus* Base Ratios in the Competition Reaction of 4-Bromoisoquinoline with Sodium Methoxide and Thiophenoxide at 165°.

is one standard deviation. The slope gives the rate constant ratio for the reaction of the 4-isoquinolyl radical with methoxide ion and thiophenoxide ion. The observed value means that methoxide ion donates a hydrogen atom to the radical less easily than thiophenoxide adds to the radical by factor of about six (corrected for 3 hydrogen atoms per methoxide ion).

Because the uncertainty in the intercept is so large, the value is not statistically meaningful. However, a comparison of the slope and intercept values which provide a measure of the ability of methoxide ion and methanol to donate a hydrogen atom to the 4-isoquinolyl radical is instructive. This comparison clearly shows that methoxide ion is the superior donor. If the 0.56 and 0.18 values are employed along with the concentrations of methanol and thiophenoxide ion a value of 90 is obtained for the rate constant ratio for methoxide ion compared to methanol. Due to the uncertainty in the intercept this must be a very approximate value.

Trapping of the 4-isoquinolyl radical by nucleophiles seems to be limited to negatively charged sulfur nucleophiles and includes methylmercaptide ion and p-chlorophenoxide ion. The ability of these negatively charged sulfur nucleophiles to trap efficiently the 4-isoquinolyl radical when other carbon, oxygen, and nitrogen nucleophiles (in addition to benzene) fail, underscores the potential usefulness of negatively charged sulfur nucleophiles for studying radical

reactions. It would seem to be worthwhile to extend this technique to those reactions giving reductive dehalogenation products with alkoxide ion.

Clearly there must be a mechanism other than "classical" aromatic nucleophilic substitution which results in substitution product formation. The only mechanism conceived to date which is consistent with all the experimental data is one involving a radical chain process. Bunnett and Kim have proposed that this type of mechanism be designated "$S_{RN}1$" standing for substitution, radical-nucleophilic, unimolecular.[57]

There are numerous reports in the recent literature of reactions which may involve radical nucleophilic substitutions of the type discussed here.[24,55,58,59] It is likely that further examples of radical nucleophilic substitution will be uncovered in the near future. Our approaches may prove useful in finding new examples.

CHAPTER 4

AMIDE ION PROMOTED NUCLEOPHILIC SUBSTITUTION OF 4-HALOISOQUINOLINES

Results

The reactions of 4-bromoisoquinoline, 4-bromo-3-methylisoquinoline, and 4-chloroisoquinoline with negatively charged sulfur nucleophiles are catalyzed by amide ion in liquid ammonia. The major product in these reactions is a 4-alkyl- or 4-arylthioisoquinoline isolated in yields up to 84 percent. Reactions were generally carried out in refluxing ammonia (about -33°) and were analyzed by nmr with cyclohexene or t-butyl alcohol as internal area standards. Product identities were confirmed using tlc and glpc and by comparison with authentic materials. The molar ratio of the haloisoquinoline:sulfur nucleophile:amide ion was generally 0.1:1.2:0.2, and the reaction time was 4 hours in most cases. Reactions are not homogeneous. Thin layer chromatography on silica gel indicated that all reaction mixtures contained several components; not all of these were identified. Some tars are present in all reaction mixtures.

Throughout this chapter molarity will be employed to express "concentrations", even though materials are not completely soluble. Since no attempt was made to determine true solubilities under reaction conditions, the "concentration"

term only indicates the amount of material available for reaction. Sodium amide clearly was not totally soluble under the most frequently employed reaction conditions (~0.2 M). Sodium methylmercaptide in the absence of other materials is soluble at the 1.2 M level. The solubility of 4-bromoisoquinoline at -33° in liquid ammonia is a few tenths molar. Under the reaction conditions it was impossible to tell if the 4-bromoisoquinoline was completely soluble.

When 0.1 M 4-bromoisoquinoline was exposed to 0.2 M sodium amide and 1.2 M sodium methylmercaptide in refluxing ammonia and a small volume of ethyl ether for 4 hours, 84 percent 4-methylthioisoquinoline was isolated. A duplicate run yielded 76 percent 4-methylthioisoquinoline as determined by nmr analysis. No 3- or 4-aminoisoquinolines or 3-methylthioisoquinoline could be detected by nmr or tlc in this reaction. However there were tars and as many as four minor products (tlc) which were never isolated or identified.

In the absence of sodium amide, 0.1 M 4-bromoisoquinoline was exposed to 1.2 M sodium methylmercaptide, ferric nitrate nonahydrate, and triphenylmethane for 8 hours (twice the time for the reaction in the presence of amide) in refluxing ammonia, and 94 percent of the unreacted 4-bromoisoquinoline was isolated. No methylthioisoquinoline was detected by nmr.

The reaction of 4-bromoisoquinoline and sodium thiophenoxide in the presence of amide ion was studied under conditions identical to those with sodium methylmercaptide.

4-Phenylthioisoquinoline was isolated in 20 percent yield with much difficulty and material loss. An nmr spectrum in carbon tetrachloride of that portion of the reaction mixture soluble in ether showed only 4-phenylthioisoquinoline was present. Since 4-bromoisoquinoline is soluble in both ether and carbon tetrachloride, it would seem that no starting material remained unreacted. The sample was not standardized and no quantitative data are available.

A 0.05 M solution of 4-bromoisoquinoline was kept at reflux with 0.05 M sodium anilide and 0.3 M sodium methylmercaptide in ammonia for 4 hours. Analysis of the reaction mixture by nmr showed a 5 percent yield of 4-methylthioisoquinoline and a 10 percent yield of isoquinoline, while 70 percent of the 4-bromoisoquinoline remained unreacted. In addition to the reactants mentioned, ethyl ether was present in 5 percent by volume along with aniline (0.05 M).

In an attempt to increase the amount of reduction occurring in the presence of a suitable hydrogen atom donor, a 0.1 M solution of 4-bromoisoquinoline and 0.2 M sodium amide was vigorously stirred in a 1:1 (V:V) solution of tetrahydrofuran and refluxing ammonia for 4 hours. The reaction was quenched with ammonium chloride, and the remaining THF solution was concentrated and analyzed by nmr with cyclohexene as an internal area standard. Isoquinoline was present in 15 percent yield, and 35 percent of the 4-bromoisoquinoline was unreacted. Numerous other poorly resolved peaks appeared in the nmr spectrum, and tlc

indicated at least four other products were formed. The brown product mixture most likely included decomposition products, and attempts to isolate and identify other products failed; tlc indicated that 3-aminoisoquinoline was not among the unidentified products. Unpublished work[60] involving the reaction of 4-bromoisoquinoline with potassium amide in liquid ammonia suggests that these unidentified products may include 1-amino-4-bromoisoquinoline, 4-aminoisoquinoline, 1-aminoisoquinoline, and 4,4'-biisoquinoline.

When 0.1 M 4-bromoisoquinoline was exposed to 1.2 M sodium methylmercaptide in refluxing ammonia initially containing no amide ion but containing 0.023 M dissolved sodium metal, 26 percent 4-methylthioisoquinoline and 8 percent isoquinoline were formed in 4 hours. No ether was present in the reaction mixture. Unreacted 4-bromoisoquinoline was present in 63 percent for a total mass balance of 97 percent. Addition of a crystal of triphenylmethane to the reaction mixture before the substrate was added verified that no amide ion was initially present. Sodium metal was added in small pieces of known weight, and the first piece dissolved to give the typical blue color to the reaction mixture. This blue color immediately bleached when 4-bromoisoquinoline was added, and the resulting golden mixture changed to olive when the second piece of sodium was added. The olive color persisted throughout the reaction but faded when the reaction was quenched with ammonium chloride. The combined product yield of 34 percent represents a 145 percent yield based on sodium metal.

4-Bromo-3-methylisoquinoline (0.1 M) was also inert to sodium methylmercaptide (1.2 M) in refluxing ammonia. It was necessary to add 23 percent by volume of ethyl ether to dissolve the substrate, but after 7.5 hours no reaction had occurred, and nmr analysis showed that 94 percent of the 4-bromo-3-methylisoquinoline was unreacted; 87 percent was isolated.

Amide ion also catalyzes the reaction of 4-bromo-3-methylisoquinoline with sodium methylmercaptide. When the usual concentrations of the reactants (0.1:1.2:0.2) were maintained for 4 hours in refluxing ammonia containing 17 percent ether by volume, 18 percent of 4-methlthio-3-methylisoquinoline was formed along with 11 percent of 3-methylisoquinoline. Unreacted starting material was present (41 percent). There were some tars formed in addition.

Similar results were obtained when 0.1 M 4-bromo-3-methylisoquinoline was heated at reflux in ammonia with 1.2 M sodium methylmercaptide, 0.2 M sodium anilide, and 0.2 M aniline with 9 percent by volume ether present. After 4 hours the deep purple reaction mixture gave 31 percent 4-methylthio-3-methylisoquinoline, 6 percent 3-methylisoquinoline and 45 percent unreacted starting material.

4-Chloroisoquinoline (0.1 M) reacted in the presence of sodium methylmercaptide (1.2 M) and amide ion (0.2 M) in refluxing ammonia to give 66 percent of 4-methylthioisoquinoline along with 23 percent unreacted 4-chloroisoquinoline.

On the other hand, 3-chloroisoquinoline is inert to sodium methylmercaptide in the presence or absence of amide ion. When 0.1 M 3-chloroisoquinoline was maintained at reflux in ammonia containing 1.2 M sodium methylmercaptide and 0.2 M sodium amide for 4 hours, a burgandy reaction mixture resulted, and the ether extracts contained no product. Instead a yellow precipitate insoluble in both water and ether with a melting point of 173-76° remained. This is 3-aminoisoquinoline.[61] It was the only detectable product, yield 52 percent. (No attempt was made to isolate 3-aminoisoquinoline in maximum yield from this reaction.) In the presence of only sodium amide (0.2 M), 3-chloroisoquinoline (0.1 M) was converted entirely to 3-aminoisoquinoline (100 percent crude yield, 63 percent after recrystallization from benzene) after 4 hours in refluxing ammonia. A control showed that 0.1 M 3-chloroisoquinoline was inert to 1.2 M sodium methylmercaptide in refluxing ammonia. After 4 hours, the starting material was unchanged. Ethyl ether was used as a cosolvent in the above reactions.

The presence of 0.2 M potassium bromide had little or no effect upon the reaction of 4-bromoisoquinoline with sodium methylmercaptide and sodium amide in the usual concentrations and reaction conditions. 4-Methylthioisoquinoline was produced in 68 percent yield and 8 percent of the starting material was unreacted after 4 hours.

Since 4-aminoisoquinoline is a likely product in the reaction of 4-bromoisoquinoline with amide ion in liquid ammonia, and none has been detected in significant quantity, 4-aminoisoquinoline (0.05 M) was kept at reflux with sodium

amide (0.09 M) in ammonia for 4 hours. Unreacted 4-aminoisoquinoline (75 percent) was recovered from this reaction mixture and tlc indicated that no other organic compounds were present in the reaction mixture. Thus, this compound is stable toward amide ion. Results presented in Chapter 5 on the anionic sigma complex of 4-methylthioisoquinoline in amide ion–liquid ammonia indicate that 4-methylthioisoquinoline is also stable to amide ion.

The results of the preceding reactions are summarized in Table 13.

Attempts were made to inhibit the amide ion catalyzed reaction of 4-bromoisoquinoline using inhibitors which had been tried in the reactions of 4-bromoisoquinoline with methoxide ion. 1,1-Diphenylethylene, oxygen, and azobenzene were employed as potential inhibitors.

A mixture of 0.6 M potassium methylmercaptide, 0.1 M potassium amide, and 0.01 M 1,1-diphenylethylene in refluxing ammonia was prepared and cooled to -78°. Enough 4-bromoisoquinoline was added for a 0.02 M solution, and the reaction was kept for one hour at ~-65°. Analysis by nmr indicated that 4-methylthioisoquinoline was produced in 87 percent yield and 9 percent of the starting material was unreacted. An identical reaction mixture in the absence of 1,1-diphenylethylene gave 68 percent substitution product in 10 minutes at ~-65°, while 29 percent of the 4-bromoisoquinoline was unreacted. Apparently there was little or no inhibition by 1,1-diphenylethylene.

Table 13. Summary of the Reactions of Substituted

Substituted Isoquinoline	Base	Nucleophile	Additive
4-Bromo-	$NaNH_2$	$NaSCH_3$	–
4-Bromo-	$NaNH_2$	$NaSCH_3$	–
4-Bromo-[b]	–	$NaSCH_3$	–
4-Bromo-	$NaNH_2$	$NaSC_6H_5$	–
4-Bromo-[d]	$NaNHC_6H_5$	$NaSCH_3$	Ether
4-Bromo-	$NaNH_2$	–	THF (50% by volume)
4-Bromo-	–	$NaSCH_3$	Sodium
4-Bromo-	$NaNH_2$	$NaSCH_3$	KBr
4-Bromo-3-methyl-[e]	–	$NaSCH_3$	Ether
4-Bromo-3-methyl-	$NaNH_2$	$NaSCH_3$	Ether
4-Bromo-3-methyl-	$NaNHC_6H_5$[f]	$NaSCH_3$	Ether
4-Chloro-	$NaNH_2$	$NaSCH_3$	–
3-Chloro-	–	$NaSCH_3$	–
3-Chloro-	$NaNH_2$	$NaSCH_3$	–
3-Chloro-	$NaNH_2$	–	–
4-Amino-[h]	$NaNH_2$	–	–

Isoquinolines with Various Bases in Refluxing Ammonia.[a]

% Isoquinoline	% Substituted Isoquinoline	% Starting Material
–	84	–
–	76	–
–	–	94
–	>20[c]	–
10	5	70
15	–	35
8	26	63
–	68	8
–	–	94
11	18	41
6	31	45
–	66	23
–	–	99
–	52[g]	–
–	63[g]	–
–	–	75

Table 13. Continued

---

[a]Unless noted otherwise, the concentrations of the substrate, base, and nucleophile are 0.1 M, 0.2 M, and 1.2 M, respectively, and the reaction was quenched with excess ammonium chloride after 4 hours.

[b]Reaction time was 480 minutes.

[c]Difficulty was experienced during isolation, and this represents a minimum yield.

[d]4-Bromoisoquinoline (0.05 M), sodium anilide (0.05 M), sodium methylmercaptide (0.3 M), and excess aniline (0.05 M) were present.

[e]Reaction time was 450 minutes.

[f]Excess aniline (0.2 M) was present.

[g]3-Aminoisoquinoline.

[h]4-Aminoisoquinoline (0.05 M) and sodium amide (0.09 M) were present.

Another reaction mixture identical to the previous one was prepared and oxygen was bubbled through the mixture before the addition of 4-bromoisoquinoline and during the reaction. After one hour, 87 percent of the 4-bromoisoquinoline was recovered unreacted. This appears to be very effective inhibition, but it may only be the end result of amide ion destruction by oxygen.

A refluxing ammonia solution of 0.1 4-bromoisoquinoline, 0.4 M potassium amide, 0.8 M potassium methylmercaptide, and 1.0 M azobenzene was sampled at various times, using mesitylene as an internal area standard. However, samples at times 5 and 150 minutes showed no meaningful difference in starting material to product ratio. Both reactions were about 80 percent complete with 4-methylthio- to 4-bromoisoquinoline ratios of 2.9 and 3.4 respectively. During the course of the reaction the mixture was deep purple instead of the usual brown color. The deep purple color faded when the reaction was quenched with ammonium chloride. Despite this colorful indication, no gross inhibition was observed.

Several experiments were conducted in the absence of inhibitors in which the reaction mixture was sampled at various intermediate times. Both potassium and sodium metals were used to generate the alkali metal methylmercaptide and amide salts, and the reactant concentrations were the usual 0.1 M substrate:0.2 M amide ion:~1.2 M methylmercaptide ion. When sodium amide and methylmercaptide were used, the reaction was 80 percent complete at -33° within 12 minutes;

and when potassium amide and methylmercaptide were used this reaction was >95 percent complete at -33° in 5 minutes. These experiments were later discontinued because samples examined after 80 percent of the 4-bromoisoquinoline had reacted gave random results. However, large amounts of 4-bromoisoquinoline were never observed after the first few minutes of reaction in the presence of both amide and methylmercaptide ions, and from this it is apparent that the reaction is much faster than had been originally supposed. It was also learned late in this study that the reaction of 0.8 M 4-bromoisoquinoline with 1.6 M potassium amide and 0.8 M potassium methylmercaptide is complete to yield 90 percent 4-methylthioisoquinoline in less than 15 minutes.

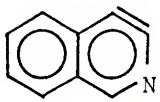
Attempts were made to sample reaction mixtures containing 4-bromoisoquinoline in low concentration (~0.2 M) and to analyze these samples by glpc. Potassium salts were used to maximize the amount of reactants in solution. However analysis of the samples confirmed the non-homogeneity of the reaction mixtures and the technique was discontinued. The composition of samples varied in a random manner. However, the identity of 4-methylthioisoquinoline was confirmed by glpc, and there were no peaks in the gas chromatogram of the ether extract except those representing isoquinoline, 4-bromoisoquinoline, and 4-methylthioisoquinoline.

However, when 0.6 M 4-bromoisoquinoline is mixed in an nmr tube with 3.0 M potassium amide and 1.0 M potassium methylmercaptide in liquid ammonia at -78° and brought to room

temperature before analysis, a new spectrum is observed which represents the major product. The material in the presence of amide ions shows the following spectrum: A 1 proton broad absorption at τ1.5-2.3, a 4 proton multiplet at τ2.3-3.1, and a 1 proton doublet at τ4.10. This is believed to be ionized material. After addition of ammonium chloride, the spectrum of the sample in ammonia becomes a 1 proton multiplet at τ1.3-1.6, a doublet (H-3, $J_{3,4}$=6 Hz) τ2.09, a 3 proton multiplet at τ2.2-2.8, and a doublet (H-4, $J_{3,4}$=6 Hz) τ3.02. Addition of the tube contents to 10 ml of water and recrystallization yielded 20 mg (20 percent) of white crystals mp 117-119°. On this basis the product was identified as 1-aminoisoquinoline, mp 122-23°.[61] This assignment was confirmed by comparing the nmr spectrum of the product with those of 3- and 4-aminoisoquinolines. They were distinctly different. Furthermore a nmr spectrum of 1-hydroxyisoquinoline in base closely resembled the spectrum of the ionized 1-aminoisoquinoline. An attempt to repeat this reaction on a larger scale in the absence of methylmercaptide ion and to isolate in high yield what appeared by nmr to be the only product was unsuccessful. A metal bomb was charged with 1 M 4-bromoisoquinoline and 3 M potassium amide and quickly brought to room temperature. After 1.5 hours the reaction was quenched; only 0.32 g (22 percent) of 1-aminoisoquinoline could be recovered. No 4-methylthioisoquinoline was detected when methylmercaptide ion was present. It is not apparent why the new conditions give rise to a new major product.

Discussion

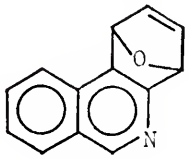
Possibility of a hetaryne mechanism.-Any mechanism suggested to account for the formation of 4-methylthioisoquinoline from 4-bromo- or 4-chloroisoquinoline in ammonia must account for the following key observations: (1) Amide ion is required. No substitution product results in its absence. (2) In the presence of amide ion the reaction is fast; it appears to take place in a matter of a few minutes or less. An early working hypothesis for the amide ion-promoted reaction of 4-bromoisoquinoline with sodium methylmercaptide in refluxing ammonia involved the 3,4-isoquinolyne intermediate. It has been well established that aryne intermediates are easily trapped by sulfur nucleophiles,[62-63] and sodium methylmercaptide has been successfully employed to trap 3,4-pyridyne generated under very similar conditions to those used in the present study.[6] In the case of 4-bromoisoquinoline, dehydrohalogenation can occur between the 3- and 4-positions to give the heretofore uninvestigated hetaryne, V. This is expected to react with methylmercaptide ion to give a mixture of 3- and 4-methylthioisoquinolines.



V

As the investigation proceeded, more and more evidence accumulated which not only was difficult to explain by a hetaryne mechanism, but which effectively excluded considera-

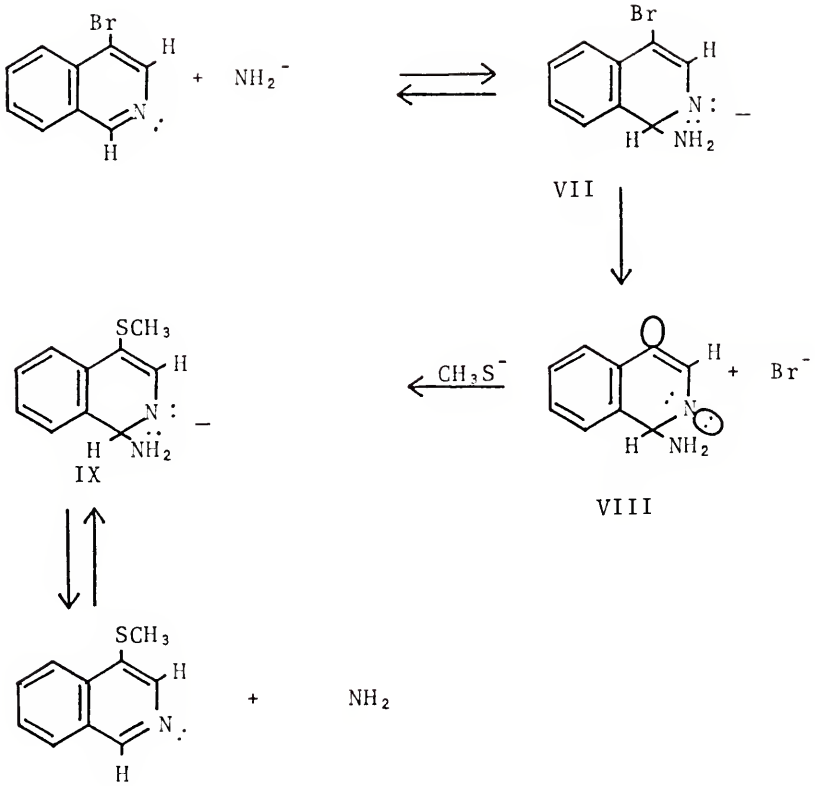
tion of this mechanism. Only 4-methylthioisoquinoline was isolated from the reaction mixture. The 3-isomer could not be detected by nmr, tlc, or glpc. When the 3-position was blocked from deprotonation by substituting a methyl group for the hydrogen, the reaction of 4-bromo-3-methylisoquinoline with sodium methylmercaptide in the presence of amide ion proceeded unimpaired. This reaction cannot be explained by a hetaryne mechanism. Attempts to trap the hypothesized intermediate with tetrahydrofuran failed to give any VI,[3] and instead resulted in an increased amount of isoquinoline. In the face of these results the possibility of the reaction proceeding via 3,4-isoquinoline is indeed remote.



VI

An alternative but unprecedented mechanism is outlined in Scheme II[64] and involves a species (VIII) with two sp^2 orbitals occupied by one pair of electrons, thus resembling a *meta*-benzyne. This is formed by elimination of bromide ion from the amide ion anionic sigma complex of 4-bromoisoquinoline (VII). Addition of methylmercaptide ion to VIII yields the anionic sigma complex of the product 4-methylthioisoquinoline which on loss of amide ion gives product. Species VII and IX have been observed by nmr and these results are reported in Chapter 5. However, the detection by nmr at ~30° of a

Scheme II


Br
H
+ NH2-
N
H
Br
H
N:
H NH2
VII
SCH3
H
N:
H NH2
IX
CH3S-
O
H
+ Br-
N
H NH2
VIII
SCH3
H
+ NH2
N
H

species believed to be VII argues against Scheme II as a possibility. The lifetime of this key intermediate is much too long to account for the very rapid formation of 4-methylthioisoquinoline.

A suggested mechanism for amide ion promoted substitution in liquid ammonia.-The results and discussion for the previous chapters dealing with substitution in methanol certainly suggest another mechanism for the reaction in ammonia. This is a radical chain mechanism.

In ammonia as in methanol the identity of the electron donor which starts the radical chain is not known; a likely candidate is the anionic sigma complex resulting from addition of amide ion to 4-bromoisoquinoline, VII.[14] That such anionic sigma complexes may transfer electrons is shown for isoquinoline. Note, however, the presence of crown ether. In the absence of this ether no electron transfer was detectable by relaxation of the nmr spectrum. It is possible that the same process may occur for 4-bromoisoquinoline and its complex, although this has not been observed directly. The rate of electron transfer between a compound and its anionic sigma complex is fastest when the compound initially present is half-converted to its complex. That is, if the rate is given by k [compound] [complex], the maximum value is achieved at half-conversion to complex.

That the reaction involves electron transfer from a donor to 4-bromoisoquinoline is consistent with the result in which the blue color of solvated electron from sodium

metal in a refluxing ammonia solution of sodium methylmercaptide is immediately bleached on addition of 4-bromoisoquinoline. A 145 percent combined yield of reduction and substitution product based on the amount of sodium metal added is consistent with a radical chain process.

The presence of small yields of isoquinoline in the reaction product mixtures is also consistent with a radical process. Increased yields of isoquinoline in the presence of a known good hydrogen atom donor such as THF argues for a radical mechanism of reduction and, by inference, substitution.

A radical chain mechanism, such as that proposed in Scheme I for the reductive dehalogenation of 4-bromoisoquinoline and later for the substitution in methanol, is consistent with the production of a single isomer of the substitution product, the observed reaction with substrate having a methyl group at position 3, and with reductive dehalogenation of the haloisoquinoline.

Unfortunately the inhibition experiments which were so successful for the methoxide ion–methanol experiments were not very helpful in the amide ion–ammonia experiments. This may be due to greater reactivity of the amide ion–ammonia system. Even at -33° the reactions in this system appeared to be over in a few minutes. With a fast reaction an inhibition period could go undetected.

A radical chain mechanism for reactions in amide ion–liquid ammonia systems is not without precedent. Bunnett and Kim[57] have proposed an analogous mechanism for the amination of pseudocumyl iodides by amide ion in refluxing ammonia. It now appears that this $S_{RN}1$ mechanism has been extended to hetaryl halides as well.

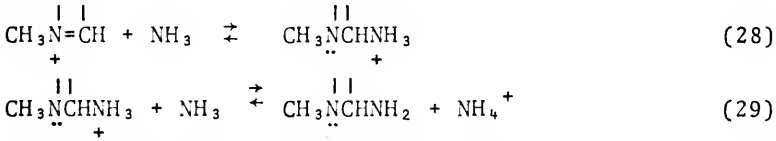
The formation of 3-aminoisoquinoline, instead of the anticipated 4-methylthioisoquinoline, from 3-chloroisoquinoline in the presence of amide ion most likely does not occur via a radical chain process. Rather it has been suggested[65] that following amide ion addition to the heterocyclic ring, the ring opens and recloses with the newly incorporated nitrogen atom from the amide ion becoming the annular nitrogen.

CHAPTER 5

COVALENT AMINATION AND ANIONIC SIGMA COMPLEXES OF ISOQUINOLINE DERIVATIVES

Results

Reactions of quaternized heteroaromatic compounds in liquid ammonia.-Quaternized isoquinoline derivatives and some other heteroaromatic salts were dissolved in liquid ammonia in sealed nmr tubes at 0° or below. The ammonia quickly and completely adds to these compounds to give covalent amination products as shown in equations 28 and 29.



(28)

(29)

Chemical shifts and coupling constants of amino compounds formed in ammonia are summarized in Table 14. Product proton signals from the heterocyclic ring appear at higher fields than those of starting material, by from 2 to 4.4 ppm in the case of 2-methylisoquinolinium ion. Both the iodide and perchlorate salts of 2-methylisoquinolinium, 1-methylquinolinium, and 1,2-dimethylquinolinium ions were studied, and identical spectra were obtained (representing decomposition in the case of 1,2-dimethylquinolinium ion), eliminating the possibility that iodide ion rather than ammonia served as the nucleophile.

Table 14. Chemical Shifts and Coupling Constants for Aminodihydro Compounds from the Addition of Ammonia to Various Heteroaromatic Ions.[a]

Ion	Carbocyclic H	H-1	H-2	H-3	H-4	CH_3	Coupling Constant, Hz
2-Methyl-isoquinolinium	2.7-3.0	4.85	–	3.63	4.55	NCH_3,6.90	$J_{3,4}$=7.0
2,3-Dimethyl-isoquinolinium[b]	2.7-3.0	4.97	–	–	4.67	CCH_3,8.06 NCH_3,7.02	–
1-Methyl-quinolinium	2.6-3.4	–	5.21[c]	4.14	–[d]	NCH_3,6.97	$J_{3,4}$=9.8 $J_{2,3}$=5.5
2-Methyl-phthalazinium	2.4-2.7	4.87	–	–	2.45	NCH_3,6.78	–
2-Methyl-4-bromo-isoquinolinium	2.6-2.9	4.81	–	3.35	–	NCH_3,6.93	–
1-Methyl-quinoxalinium	3.41	–	6.04[e]	5.93	–	NCH_3,7.10	$J_{2,3}$=2.5

[a]Benzene, τ 2.60 or trimethylamine, τ 7.87, standards. Substrate, 0.5-1 M.

[b]Undergoes demethylation at room temperature to give 3-methylisoquinoline and methylamine.

[c]Assignment based on spectrum of 1-methyl-2-deuteroquinolinium ion in liquid ammonia recorded by Dr. Larry S. Helmick.

Table 14. Continued.

[d]H-4 is included in carbocyclic mass.

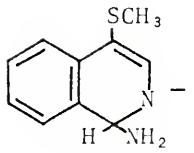
[e]Assignment of H-2 and H-3 is arbitrary; both are on tetrahedral carbons in this di-adduct.

That ammonia and not amide ion formed from the dissociation of ammonia must be the nucleophile was demonstrated by adding 2-methylisoquinolinium ion to a solution of 1 M ammonium iodide in liquid ammonia. Based on the pKa of ammonia, 1 M ammonium iodide should lower the amide ion concentration by a factor of $10^{13.8}$. Yet amino addition product formation is complete by the time (about 30 minutes) observed in liquid ammonia for phthalazine N-oxide, quinoxaline di-N-oxide, or 1,4,5-triazanaphthalene. s-Triazine reacted with ammonia to give degradation products.

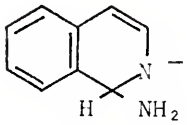
Anionic sigma complexes of isoquinoline derivatives in liquid ammonia.-Isoquinoline derivatives react completely with excess amide ion to give anionic sigma complexes. If substrate is present in excess, spectra for both complexed and free heterocycle are observed, and there is no evidence for signal averaging and no evidence for electron transfer in the form of relaxed spectra. A significant change occurs in the pattern of the signal for the proton on the tetrahedral carbon of the complex when the amide ion concentration is varied. At high concentrations of amide ion this signal is a singlet; at lower concentrations, it becomes a triplet. This is interpreted to mean that amide ion catalyzes proton transfer between the amino group of the adduct and the solvent, thereby leading to spin decoupling between the amino protons and CH proton at the tetrahedral center. This change serves as a useful method of assigning the signal for the tetrahedral center in the nmr spectrum.

The spectrum of the complex between isoquinoline and amide ion at -10° shows a broad multiplet at τ2.7-3.65, a triplet (J_{CHNH}=7.0 Hz) at τ4.66 which collapses to a singlet when amide ion is present in excess and a doublet ($J_{3,4}$=5.5 Hz) at τ5.13. The triplet–singlet change identifies this signal as that of the tetrahedral center of the adduct, and the lack of further splitting of this signal indicates that the adduct is formed by the addition of amide ion to C-1. If the amide ion had added to any other ring carbon, a more complex multiplet would have resulted. The doublet at τ5.13 could be associated with either H-3 or H-4 of the complex.

The assignment of the doublet just mentioned is clarified by the spectrum of a substituted isoquinoline complex, that of 4-methylthioisoquinoline. When exposed to potassium amide, this isoquinoline derivative, which has a proton at C-3 and none at C-4 gives a spectrum with a broad multiplet at τ2.83-3.65, a triplet (J_{CHNH}=7.2 Hz) at τ4.93 (H-1), and a singlet methylthio signal at τ8.11. No other signal near τ5 was observed. These nmr shifts allow an unambiguous assignment (H-4) of the doublet at τ5.13 in the unsubstituted isoquinoline complex. The H-3 signal must lie in the broad multiplet associated with the protons of the carbocyclic ring in the case of X.



IX

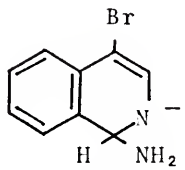


X

When isoquinoline forms amide complex X, the signals of H-1 and H-4 shift upfield by 4.1 and ~3 ppm, respectively. In the case of 4-methylthioisoquinoline complex IX, the H-1 and methylthio shifts are 4.0 and 0.65 ppm, respectively. Other signals due to ring protons shift smaller amounts. These shifts provide further strong evidence for the existance of sigma complexes of isoquinoline derivatives in amide ion–ammonia mixtures.

When a mixture of isoquinoline, the anionic sigma amide complex of isoquinoline, and excess dicyclohexyl-18-crown-6-ether is allowed to remain in ammonia at room temperature for a few days, the nmr signals attributed to isoquinoline and the amide complex disappear and are replaced by new signals. A doublet at τ1.46 (J=6 Hz) and an apparent triplet at τ2.27 of approximately equal area make up the new spectrum. The spectrum is very similar to those obtained for isoquinoline and sodium metal in liquid ammonia, and for isoquinoline and potassium metal in hexamethylphosphoramide.[66] These spectra presumably result from isoquinoline which is extensively relaxed by rapid electron transfer involving a low concentration of electrons.

4-Bromoisoquinoline appears to form an anionic sigma complex VII with sodium amide in liquid ammonia. Due to solubility difficulties this complex did not give a well resolved nmr spectrum at low temperatures, but at probe temperature, a better spectrum having a multiplet at τ2.8-3.6 and a singlet at τ4.9 was obtained. This spectrum is very similar to those for the other amide ion complexes involving isoquinolines, Table 15. If the singlet at τ4.9 is assigned to H-1, an upfield shift of 4.2 ppm is observed for the H-1 of the complex from H-1 of 4-bromoisoquinoline. Again this is almost identical to that observed for 4-methylthioisoquinoline. The aromatic multiplet of the 4-bromoisoquinoline complex is shifted upfield by about 1 ppm, and H-3 of the complex is most likely contained in this aromatic multiplet.



VII

A broad multiplet and singlet also appeared at approximately the same chemical shifts indicated above when 0.7 M 4-bromoisoquinoline was exposed to 1.4 M sodium amide and 1.4 M sodium methylmercaptide in liquid ammonia. The solution was very viscous and dark brown. Spectra taken at -40° and 0° were both poorly resolved.

Table 15. Chemical Shifts of Anionic Sigma Complexes Formed by the Addition of Amide Ion to Isoquinolines.[a]

Starting Material	H-1	H-4	Other Protons
Isoquinoline	4.66	5.13	2.7-3.65
4-Methylthioisoquinoline	4.93	–	2.83-3.65
4-Bromoisoquinoline	4.9	–	2.8-3.6

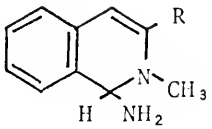
[a] τ values are indicated.

Discussion

Covalent amination of quaternized heteroaromatic compounds in ammonia.-Structural assignments for covalent amination products are based on the nmr data listed in Table 14 and on the well-established principle that the nucleophile will add to a carbon center so as to neutralize the charge on the quaternized nitrogen atom. This center generally will be located *alpha* or *gamma* to the nitrogen atom. The large shielding factors noticed in the nmr spectra are similar to those known to result when nucleophiles add to aromatic rings.[67] Chemical shifts and coupling constants are consistent with those of known dihydro structures.[68-70] No spin coupling between the amino group and the proton of the newly formed tetrahedral carbon is found and none is expected. The ammonium ion liberated by the reaction is expected to catalyze proton exchange between solvent and the amino group, leading to spin decoupling.[71] In agreement with this the solvent peak is a singlet.

It is most likely that 2-methyl- and 2,3-dimethylisoquinolinium ions react with ammonia at C-1 to give aminodihydro compounds XI and XII. Of all the ring proton signals, that for H-1, easily recognized by the absence of large spin-coupling, is found at the highest field, Table 14. This is consistent with the formation of a tetrahedral center at C-1 by an addition reaction. Addition to C-3 or to a carbon atom of the carbocyclic ring can be ruled out if it is assumed that the proton at the tetrahedral center will resonate

at high field. Such a proton is not expected to show a single, small (1.2 Hz) coupling as is found in the present case. This coupling is likely to involve H-1 and H-3 of XI. The coupling constant for protons at the vinyl center directly bonded to the annular nitrogen is 7 Hz. In the case of XII a new spectrum is obtained at room temperature, corresponding to methylamine and 3-methylisoquinoline (demethylation products).



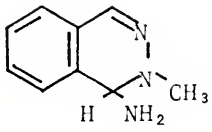
XI, R=H

XII, R=CH_3

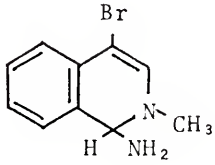
Although ammonia could add to the C-2 and C-4 positions of 1-methylquinolinium ion to give mixed mono-addition products, varying the temperature from -50° to 25° had no influence on the nature of the spectrum. Hence only a single structure is evident. That ammonia added to C-2 and not C-4 follows from the spectrum of the adduct having deuterium at C-2.[72] The large coupling constant (9.8 Hz) found for the vinyl protons in the non-aromatic ring is also consistent with the proposed structure (VIII).

VIII

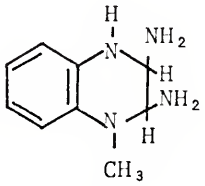
1-Amino-2-methyl-1,2-dihydrophthalazine (XIV) results from the amination of 2-methylphthalazinium ion. The chemical shift of the proton at the tetrahedral center (C-1) is nearly the same as those for H-1 of the analogous isoquinoline compounds XI and XII, Table 14.



XIV



XV



XVI

Of particular interest to this investigation, 1-amino-2-methyl-1,2-dihydro-4-bromoisoquinoline (XV) is formed from 2-methyl-4-bromoisoquinolinium ion. The chemical shifts of H-1 and H-3 of the product are in good agreement with those of other aminohydro compounds, Table 14. Furthermore, ammonia addition at C-1 is analogous to the proposed addition of amide ion at C-1 of the parent molecule to form the anionic sigma complex.

An especially interesting result is obtained with 1-methylquinoxalinium ion. Diaddition product XVI is observed over the temperature range -30° to 30°. Evidence for this unusual structure is found in the high field chemical shifts (τ5.93 and 6.04) of the two protons bonded to the heterocyclic ring. A mono-adduct should show one of these protons

at considerably lower field. Diaddition to the 1-methylquinoxalinium ion is not unprecedented. Most recently, di- as well as mono-adduct formation in water and methanol were observed.[68]

The discovery that heteroaromatic molecules may be transformed into covalent primary amines in liquid ammonia is of great importance. In the amination process an ammonia molecule serving as a nucleophile adds to a ring carbon atom to give an amino derivative. This brings about major changes in the physical and chemical properties of the original substance[73-74] and must be taken into consideration when dealing with the chemistry of heteroaromatic compounds in ammonia.

Anionic sigma complexes of isoquinoline derivatives in liquid ammonia.-The large upfield chemical shifts which are observed for the heterocyclic protons when isoquinoline derivitives are exposed to amide ion in liquid ammonia leaves little doubt that anionic sigma complexes are being formed.

4-Bromoisoquinoline, 4-methylthioisoquinoline, and isoquinoline are rapidly converted to their anionic sigma amide complexes (VII, IX, and X) in liquid ammonia containing amide ion. This means that in the reactions described in Chapter 4 these compounds are not present in solution solely as the uncharged parent molecule. In the presence of excess amide ion, 4-bromoisoquinoline is immediately converted to its anionic sigma complex, and very little 4-bromoisoquinoline remains in solution as such. Likewise, the products

from the reactions in Chapter 4, isoquinoline and 4-methyl-isoquinoline, are most likely present in solution as the amide sigma complexes.

CHAPTER 6

EXPERIMENTAL

Instrumentation

Proton nmr spectra were recorded on a Varian A-60A spectrometer equipped with a V-6040 variable-temperature controller. Melting points were determined in a Thomas-Hoover Unimelt melting point apparatus, and they are uncorrected. Potentionmetric titrations were carried out using a Radiometer Titrator TTTlc with a Sargent-Welch (S-30070-10) miniature combination electrode. A Lauda constant temperature oil bath was employed to maintain a constant temperature for kinetic runs which were not done in a vapor bath. Mineralight UVS11 and Blak Ray UVL21 lamps made by Ultra-Violet Products, Inc. were used for examination of tlc plates. Gas chromatographic analyses were accomplished with an Aerograph HY-FI Model 600D gas chromatograph equipped with a Model 328 temperature programmer. The gas chromatogram was recorded by a Sargent Model SR recorder which included a Disc Instruments Model 204 disc chart integrator. Analytical weighings were accomplished on a Sartorius-Werke A6 analytical balance. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Chemicals

All common laboratory chemicals were obtained from various suppliers, and, unless noted to the contrary, were used without further purification.

Internal standards used for nmr analyses included t-butyl alcohol, isobutyric acid, cyclohexene, and mesitylene. These were sufficiently pure as received for nmr use. For glpc analyses, 7,8-benzoquinoline was used as an internal standard. This compound was obtained from Aldrich and recrystallized from hexane prior to use: mp 49-51° (lit.[61] 52°).

Solvents most often used included methanol, t-butyl alcohol, and dimethyl sulfoxide. Methanol was dried by distillation from magnesium methoxide, t-butyl alcohol from potassium t-butoxide. Dimethyl sulfoxide was dried over Linde 4A molecular sieves.

Quaternized heterocyclic salts for which a preparation is not described were available from previous studies. They were prepared by the same general procedures as described.

Dicyclo-18-crown-6-ether was obtained from Aldrich, dried over sodium metal, and stored under vacuum prior to use.

4-Bromoisoquinoline, 3-iodopyridine, 3-bromoquinoline, and 3-methylisoquinoline were obtained from Aldrich; they were used as received for preparation of other compounds and for kinetic runs monitored by nmr. For those kinetic runs monitored by glpc, 4-bromoisoquinoline was recrystallized from ethyl ether (using a dry ice and acetone bath to induce crystallization) or hexane to remove traces of isoquinoline.

Isoquinoline was obtained commercially from Pfaltz and Bauer. It was further purified by vaccum distillation from zinc dust. Even after distillation, it remained contaminated with a trace of quinoline (less than 5 percent). No attempt was made to purify this compound further.

Preparations

4-Bromo-3-methylisoquinoline.-This compound was prepared by bromination of 3-methylisoquinoline. A mixture of 72 g (0.50 mol) of 3-methylisoquinoline and 70 ml of 40 percent hydrobromic acid was evaporated to near dryness in a fume hood; 80 g (0.50 mole) of bromine was then added to this semisolid mixture, and the resulting solution was refluxed for 6.5 hours. Sufficient aqueous sodium hydroxide was then added to obtain a basic solution. The organic phase was separated and vacuum distilled; 46 g (0.21 mol) of a distillate was obtained at 120°/3.0 torr for a yield of 42 percent. A second vacuum distillation at 92°/0.40 torr gave a quantitative yield of a white solid mp 30-33°. Anal. Calcd for $C_{10}H_8BrN$: C, 54.08; H, 3.63; N, 6.31. Found: C, 54.04; H, 3.79; N, 6.20. NMR (CCl_4) τ7.25 (s, 3), 1.95-2.97 (m, 4), 1.18 (s, 1).

4-Chloroisoquinoline.-This compound was prepared by a modification of a procedure used to prepare 4-bromoisoquinoline.[75] To a solution of 40 g (0.45 mol) of sodium bicarbonate in 700 ml of water was added 48 g (0.45 mol) of cyanogen bromide followed by 58 g (0.45 mol) of freshly distilled isoquinoline. The resulting precipitate was

filtered and dried under vacuum to give 69 g (0.40 mol) of crude 2-cyano-1,2-dihydro-1-hydroxyisoquinoline for a 90 percent yield. A solution of 100 ml water, 200 ml tetrahydrofuran, and 15.8 g (0.092 mol) of the isoquinoline derivitive was prepared. This solution was cooled in an ice bath and 13 g (0.37 mol) of chlorine gas was added through a dispersion tube while maintaining the reaction mixture below 30°. The mixture was then diluted with 1 liter of water and extracted with ether. The ether was removed, and 250 ml of 2 M hydrochloric acid was added to the residue. This solution was heated on a steam bath for 1.5 hours, diluted with 1 liter of water, extracted with 200 ml of chloroform, made basic with sodium hydroxide, and extracted with 300 ml of ether. The ether and chloroform extracts were combined, and the solvents removed on a rotary evaporator. This residue was distilled at 77°/10.3 torr to yield 2.0 g of product (13 percent yield). Further purification was accomplished by column chromatography on a silica gel column using 20 percent ether in pentane (V:V), mp 27-29° (lit.[76] 28.5-29.5°).

4-Methylthioisoquinoline.-This compound was prepared by adding 1.4 g (0.019 mol) of sodium methylmercaptide and 1.0 g (0.0048 mol) of 4-bromoisoquinoline to 10 ml of dimethylformamide. The solution was maintained at 100° for 2 hours with stirring. The reaction mixture was diluted with 100 ml of water, and the resulting precipitate was removed by filtration; 0.40 g (0.0022 mol) of crude product was recovered,

mp 50-53°, for a yield of 48 percent. Recrystallization from hexane yielded 0.20 g (0.0011 mol) of light yellow needles, mp 65-66° (24 percent yield). Anal. Calcd for $C_{10}H_9NS$: C, 68.51; H, 5.17; N, 7.99. Found: C, 68.88; H, 5.14; N, 7.89. NMR (CCl_4) τ7.46 (s, 3), 1.77-2.67 (m, 4), 1.63 (s, 1), 1.07 (s, 1).

No attempt was made to maximize the yield of 4-methylthioisoquinoline in the above preparation. The primary value of the preparation is that it provides an unambiguous source of isomerically pure material which can be easily isolated.

4-Phenylthioisoquinoline.-This compound was prepared by two two methods. A. In order to insure isomeric purity, the compound was first prepared by adding 2.6 g (0.02 mol) of sodium thiophenoxide and 2.0 g (0.0096 mol) of 4-bromoisoquinoline to 10 ml of dimethylformamide. The solution was maintained at 100° for 3 hours with stirring. The reaction mixture was diluted with 50 ml of water, and the resultant oil was separated and vacuum distilled at 97°/0.65 torr. The residue (not the distillate, which was primarily unreacted starting material) was recrystallized from hexane to give 0.35 g (15 percent yield) of crude 4-phenylthioisoquinoline. Two more recrystallizations from hexane gave 0.05 g (2 percent yield) of yellow crystals, mp 60-61°. The purity of this compound was confirmed by tlc using a 1:1 (V:V) benzene and ether eluent. The nmr of the crude product showed adsorptions

at all positions reported for 4-phenylthioisoquinoline isolated in the following preparation.

B. 4-Phenylthioisoquinoline was also prepared by amide ion promoted substitution in liquid ammonia. A three-necked round bottom flask was equipped with a dry ice condenser and Truebore Hershberg stirrer. The apparatus was flushed with nitrogen, flamed, and fitted with a calcium chloride drying tube. The flask was chilled in a dry ice–acetone bath, and 13 g (1.2 mol) of benzenthiol was frozen in the bottom of the flask. Sodium thiophenoxide was then generated *in situ* by the condensation of 100 ml of ammonia and subsequent addition of an equivalent of sodium metal. When the blue color of the solvated electrons persisted in the solution, it was assumed that an equivalent of sodium metal had been added. The above procedure must be followed in the generation of sodium thiophenoxide because when one attempts to introduce liquid benzenethiol into liquid ammonia, the immediate formation of a hard white solid through the system obscures the contents of the flask and clogs the syringe or pipette used to add the benzenethiol. This hard white solid is most likely ammonium thiophenoxide.

After the sodium thiophenoxide was generated, a small crystal of ferric nitrate nonahydrate and a few crystals of triphenylmethane were added. The former was used to catalyze amide ion formation, and the latter to indicate amide ion formation by the pink color of the weaker base, triphenylmethide ion. Small pieces of sodium metal were added until

amide ion formation was evident from the pink coloration of the ammonia solution, and then 0.50 g (0.022 mol) of additional sodium metal was added. When amide ion generation was complete, 2.1 g (0.01 mol) of 4-bromoisoquinoline in 10 ml of ethyl ether was added and the resulting mixture was allowed to reflux for 4 hours. Excess ammonium chloride was then added to destroy any remaining amide ion, and the ammonia was allowed to evaporate. The remaining solids were dissolved in water and the resulting mixture was extracted three times with ether. The combined ether extracts were concentrated under vacuum. This concentrate was allowed to sit overnight, and large yellow crystals appeared in the brown oil, mp 60-61°. Attempts to isolate in substantial percentage of the crystalline material from the brown oil were only marginally successful. After several manipulations, 0.37 g (0.0016 mol) of 4-phenylthioisoquinoline was finally recovered from a mixed solvent system of cyclohexane–benzene (9:1 by volume) for a 16 percent crude yield. Two more recrystallizations from hexane produced 0.10 g (0.00048 mol) of material, mp 60-61°. This 5 percent yield of 4-phenylthioisoquinoline is far below what was expected from an nmr analysis of the initial reaction mixture which showed that 4-phenylthioisoquinoline was the major material present in the original ether extract. This low yield can be attributed to the difficulties in purification. Anal. Calcd for $C_{15}H_{11}NS$: C, 75.91; H, 4.68; N, 5.90. Found: C, 76.05; H, 4.59; N, 5.78. NMR (CCl_4) τ2.89 (s, 5), 1.70-2.70 (m, 4), 1.39 (s, 1), 0.88 (s, 1).

4-Methoxyisoquinoline.-A solution of 3.5 g (0.026 mol) of anhydrous copper (II) chloride in 50 ml of absolute methanol was added to a solution of 5.0 g (0.024 mol) of 4-bromoisoquinoline in 15 ml of absolute methanol. The resulting light green precipitate was removed by filtration and placed in a Monel bomb with 23 ml of 4.30 M sodium methoxide in methanol. The bomb was sealed and heated at 165° for 30 minutes. After cooling to room temperature, the bomb was opened, and the reaction mixture was filtered to remove solid by-products. The supernatent was diluted with 20 ml of water and extracted three times with 20 ml portions of ether. The ether layer, dried over calcium chloride, was concentrated on a rotary evaporator. The concentrate was recrystallized from anhydrous ether using a dry ice–acetone bath to induce crystallization; 1.8 g (0.011 mol) of white crystals were obtained, mp 71-75°, for a yield of 47 percent. Anal. Calcd for $C_{10}H_9NO$: C, 75.42; H, 5.70; N, 8.81. Found: C, 75.56; H, 5.75; N, 8.74. NMR (CCl_4) τ5.99 (s, 3), 1.80-2.60 (m, 5), 0.70-1.78 (s (broad), 1).

The absorption between 0.70 and 1.78 ppm becomes a singlet in methanol and other solvents. The absence of any resolution in carbon tetrachloride is most likely the result of a relaxation phenomenon.

4-Hydroxyisoquinoline.-The copper (II) complex of 4-bromoisoquinoline was prepared by mixing a solution of 4.0 g (0.019 mol) of 4-bromoisoquinoline in 15 ml of absolute methanol with a solution of 2.6 g (0.019 mol) of copper (II)

chloride in 15 ml of absolute methanol. The resulting light green precipitate was removed by filtration and added to a Monel bomb containing 20 ml of 4.30 M sodium methoxide in methanol (0.086 mol). The bomb was sealed and heated at 165° for 793 minutes. After cooling, the bomb was opened, and 75 ml of water was added to the reaction mixture. This mixture was filtered to remove solid by-products, and the supernatent liquid was extracted three times with 25 ml portions of ether to remove any isoquinoline formed. The remaining water solution was then neutralized to pH 7 with hydrochloric acid. Near pH 7 a pale green precipitate formed and was removed by filtration. Subsequent vacuum sublimations yielded 0.19 g (0.0013 mol) of 4-hydroxyisoquinoline, mp 220-25° (lit.[61] 223-24°) for a 7 percent yield.

3-Chloroisoquinoline.-This compound was prepared from homophthalic acid via a known three-step synthesis.[77-79] Homophthalimide was prepared from homophthalic acid and ammonium hydroxide in 71 percent yield; mp 233-37° (lit.[77] 230-33°). 1,3-Dichloroisoquinoline was prepared from homophthalimide and phosphorus oxychloride in 41 percent yield; mp 120-21° (lit.[78] 122-23). Finally 3-chloroisoquinoline was prepared in 57 percent yield partially reducing 1,3-dichloroisoquinoline in red phosphorus, hydriodic acid and acetic acid; mp 41-45° (lit.[79] 46.5-47.5°). The overall yield was 17 percent.

4-Aminoisoquinoline.-According to a known synthesis, 4-bromoisoquinoline, 5.0 g (0.024 mol), was heated in a Monel

bomb with 20 ml of liquid ammonia, 0.05 g of copper (II) nitrate, and some copper shavings for 20 hours at 100°. The bomb was cooled and the ammonia allowed to evaporate. The residue was recrystallized from benzene following treatment with Norite to give 1.6 g (0.011 mol) of 4-amino-isoquinoline, mp 107-08° (lit.[1] 108°) for 46 percent yield.

3-Methyl-4-methylthioisoquinoline.-This compound was prepared by adding 4.0 g (0.018 mol) of 4-bromo-3-methyl-isoquinoline and 5.0 g (0.71 mol) of sodium methylmercaptide to 30 ml of DMSO and heating at ~100° for 30 minutes. After the solution cooled, 120 ml of water was added, and the resulting mixture was extracted three times with 20 ml portions of ether. The ether was removed on a rotary evaporator and the residue was vacuum distilled to yield 2.4 g (0.013 mol) of a colorless liquid at 103°/0.6 torr for a 72 percent yield. Anal. Calcd for $C_{11}H_{11}NS$: C, 69.79; H, 5.87; N, 7.40. Found: C, 70.00; H, 5.96; N, 7.23. NMR (CCl_4) τ7.72 (s, 3), 7.12 (s, 3), 2.10-2.76 (m, 3), 1.57 (d, 1, J=9 Hz), 1.02 (s, 1).

1-Methylquinolinium iodide.- Quinoline, 5.0 g (0.039 mol) was heated at reflux with 11 g (0.077 mol) of methyl iodide in 10 ml of methanol for 8.5 hours. The iodide was precipitated from the reaction mixture by the addition of ethyl ether, and was recrystallized from methanol for a yield of 9.9 g (0.037 mol), 95 percent, mp 130-33° (lit.[61] 133°).

1-Methylquinolinium perchlorate.-1-Methylquinolinium iodide, dissolved in a minimum amount of absolute ethanol, was added to a solution of absolute ethanol, 70 percent perchloric acid, and ethyl acetate (17:11:80 by volume). The 1-methylquinolinium perchlorate separated on standing; mp 103-106°. A mixed melting point of the perchlorate and iodide salts of 1-methylquinolinium ion was 60-80°.

4-Bromo-2-methylisoquinolinium iodide.-This salt was prepared by refluxing 3.0 g (0.014 mol) of 4-bromoisoquinoline and 14 g (0.10 mol) of methyl iodide in 10 ml of methanol for 3 hours. As the reaction proceeded the iodide precipitated as yellow crystals. These crystals were removed by filtration and dried under vacuum; 3.9 g (0.011 mol) of the isoquinolinium salt, mp 237-40° (lit.[61] 233°) was obtained for a 79 percent yield.

Sodium methylmercaptide.-This salt was prepared by reacting ammonium methylmercaptide with sodium metal dissolved in liquid ammonia. Methylmercaptan gas was introduced into a flask of refluxing liquid ammonia, and flaky white crystals of ammonium methylmercaptide formed immediately. Sodium metal and more methylmercaptan were then alternately added. When an equivalent amount of both reactants had been added, a colorless solution resulted. The ammonia was allowed to evaporate under a stream of nitrogen, and the remaining solid sodium methylmercaptide was collected under dry nitrogen, d~300° (gas evolution). The yield was quantitative with respect to sodium metal.

Sodium Thiophenoxide.-This salt was prepared by the same procedure as sodium methylmercaptide. Benzenethiol was added to a flask of refluxing ammonia along with an equivalent of sodium metal. The resulting solution of sodium thiophenoxide was colorless. The ammonia was allowed to evaporate under a stream of nitrogen, and the sodium thiophenoxide was collected and stored under nitrogen, mp >300°.

Thin Layer Chromatography Plates

Thin layer chromatography was carried out utilizing glass plates 5 by 20 cm coated with a 0.025 mm layer of silica gel GF_{254} obtained from E Merck Ag., Darmstadt, Germany. The plates were prepared from a water slurry of the silica gel using a Desaga apparatus. After the silica gel slurry congealed, the plates were dried at 110° and stored in a dry box until use. Development of the plates was accomplished with various solvent systems by vertical solvent ascension in a closed solvent tank. Observation of the chromatogram was accomplished by irradiation with an ultraviolet light.

Gas–Liquid Phase Chromatography Columns

Columns of two different lengths (40 and 200 cm) were used. Both were prepared using Chromosorb W HMDS 60/80 for support with 10 percent sodium carbonate and 20 percent Versamid 900. A 1:1 (V:V) solution of n-butanol and chloroform was used to dissolve the Versamid prior to coating the support. After preparation the packing was dried under

vacuum, sifted with a 60 mesh sieve, packed in 1/8 inch o.d. copper tubing, and cured at 250° for 18 hours in a stream of helium.

Stock Solutions

Sodium methoxide stock solutions were prepared by dissolving freshly cut sodium metal in dry methanol under a nitrogen atmosphere. These solutions were standardized by potentiometric titration. Aliquots of the sodium methoxide solution were acidified with excess standard hydrochloric acid, and the resulting acidic solution was potentiometrically titrated with standard sodium hydroxide. Fisher Primary Standard grade potassium hydrogen phthalate dried at 110° for 2 hours was used to prepare a standard acid solution against which the sodium hydroxide solution was potentiometrically titrated.

Other alkali metal alkoxide solutions used included potassium t-butoxide, sodium n-propoxide, and lithium methoxide. The first two solutions were prepared by dissolving the alkali metal in the appropriate alcohol under a nitrogen atmosphere, and the last solution was obtained commercially from Foote Mineral Company. The potassium t-butoxide and sodium n-propoxide solutions were not standardized, but the concentrations were approximated from the amount of alkali metal used in preparing the solutions and the volume of the final solution.

Solutions for Kinetic Runs

NMR method.-Volumes of one to five ml of solution were prepared for each run. The solutions were between 0.2 and 1.2 M in substrate, and they were usually prepared by the addition of substrate to a tared flask followed by a known volume of stock metal alkoxide solution delivered with a Hamilton microliter syringe. The contents of the flask were then diluted to mark with dry solvent.

Solutions containing a nucleophile in addition to the alkoxide base were sometimes prepared by addition of the salt of the nucleophile (sodium thiophenoxide, the lithium salt of 2-nitropropane) to the tared flask along with the substrate. More often the nucleophilic salt was generated *in situ* by the addition of a sufficient excess of stock metal alkoxide solution to a mixture of substrate and the conjugate acid of the nucleophilic base (benzenethiol, 2-nitropropane). The metal alkoxide was assumed to react completely with the conjugate acid of the weaker base, and the individual concentrations could then be calculated.

Inhibitors were generally added to an nmr tube prior to transfer of an aliquot of the prepared solution to the tube. The amount of inhibitor in these cases was so small that any volume change in the solution was neglected. (The maximum volume change resulting from the addition of inhibitor to any kinetic run was calculated to be 5 percent.)

Internal standards used included t-butyl alcohol and sodium isobutyrate (generated *in situ* from the reaction of isobutyric acid with alkoxide ion).

After preparation, aliquots of the solutions (between 0.5 and 1.5 ml) were transferred to nmr tubes which were immediately sealed with a torch.

GLPC method.-The solutions used in this method were about ten times more dilute in substrate than those studied by nmr. They were approximately 0.02 M and were prepared by transferring stock sodium methoxide solution to 25 ml volumetric flasks containing substrate and benzenethiol. (Benzenethiol was present for the competition experiments only.) The solutions were diluted to mark with dry methanol, and 4 ml aliquots were pipetted into preconstricted test tubes which were immediately sealed with a torch.

Methods of Kinetic Runs

NMR method.-Kinetics were obtained by heating the sample solutions in sealed nmr tubes. For kinetic runs at 164.7±0.5°, two techniques were used to maintain constant temperature. The nmr tube was either immersed in a refluxing vapor bath of mesitylene or a constant temperature oil bath. Runs for which the temperature was maintained at 100° were carried out in a steam cone. For all temperatures other than 100° and 165°, the oil bath was used for maintaining constant temperature. The temperature of the oil bath was initially set and occasionally checked using a National Bureau of Standards thermometer.

Periodically the nmr tube was removed from the bath, quenched in water at room temperature, and the proton nmr

spectrum of the solution was recorded. Peak areas were determined by repeated integrations in both directions, and the average value was calculated. Reactions were followed by measuring the change in the integrated areas of the protons of interest with respect to the combined areas of the protons of the internal standard. The entire spectrum (500 Hz sweep) was recorded each time so that the chemical shift difference between the hydroxyl proton and the ^{13}CH satellite peak of methanol could be determined. This shift difference was used to determine the methoxide ion concentration.

As can be seen in Table 16, the chemical shifts of protons of 4-bromoisoquinoline and those of its reduction and substitution products are similar. For instance, the peak for H-1 of 4-bromoisoquinoline is separated from the peak for H-1 of isoquinoline in a mixture of the two by only 3-4 Hz. This separation was insufficient for accurate determination of individual peak areas; therefore the area of the peaks for the H-3 doublet of isoquinoline was used.

In the study involving reductive dehalogenation of 4-chloroisoquinoline by sodium methoxide, a further complication arose. The downfield leg of the H-3 doublet of isoquinoline was partially overlapped by the H-3 peak of the 4-chloroisoquinoline. In this case the relative areas of the H-3 signals of starting material and product were determined by addition and subtraction of appropriate areas. The

Table 16. Chemical Shifts for Low Field Protons of Reactant and Products in the Reaction of 4-Bromoisoquinoline with Metal Alkoxides and Sulfur Nucleophiles in Methanol.

Compound	τ[a] H-1	H-3	Other Peaks, τ
4-Bromo-isoquinoline	0.92	1.47	
Isoquinoline	0.85	1.62 (d, J=6 Hz)	
4-Phenylthio-isoquinoline	0.86	1.53	
4-Methylthio-isoquinoline	1.05	1.77	
4-Methoxy-isoquinoline	1.22[b]		
Sodium 4-isoquinolyloxide			2.08 (s,1); 1.66 (s,1); 1.55 (m,1, J=6 Hz, J=3 Hz)
Sodium formate			1.30

[a] t-Butyl alcohol (τ 8.72) was used as internal standard for isoquinoline; all other shifts are relative to H-3 of isoquinoline.

[b] Almost completely relaxed in CCl_4; H-3 is in carbocyclic mass.

ratio of the downfield peak of the H-3 doublet of isoquinoline to the upfield peak was determined to be 0.77 from the spectrum of pure isoquinoline. This ratio and the integrated area of the upfield peak of the doublet was used to determine the amount of 4-chloroisoquinoline from the relative peak areas of the overlapped peaks.

In studies involving thiophenoxide ion and 4-bromoisoquinoline in sodium methoxide solution, overlap of the H-3 signals of isoquinoline and 4-phenylthioisoquinoline again created problems for analysis by nmr. A reliable means was developed for determining the relative contributions from H-3 of 4-phenylthioisoquinoline and the downfield peak of the H-3 doublet of isoquinoline. A correction factor was calculated from a mixture of the two compounds in known concentrations. Such a standard mixture was prepared in methanol containing sodium thiophenoxide and sodium methoxide in concentrations similar to those employed in the competition studies. From the integrated spectrum of this mixture, the correction factor was calculated by equation 30.

$$R = \frac{A_2 - fA_1}{A_1 + fA_1} \quad \text{or} \quad f = \frac{A_2 - RA_1}{A_1 + RA_1} \tag{30}$$

R=concentration ratio of 4-phenylthioisoquinoline to isoquinoline

f=correction factor

A_1=area of upfield peak due to H-3 doublet of isoquinoline

A_2=area of combined peak due to H-3 of 4-phenylthioisoquinoline and downfield signal from H-3 doublet of isoquinoline

A value of 0.71 was obtained for the correction factor. This is a measure of the ratio of the areas of the low and high field peaks of H-3 of isoquinoline. This value is slightly less than that (0.77) obtained for pure isoquinoline, but both values are the same within the typical uncertainty (5 percent) of the nmr method.

The concentration of methoxide ion was followed by observing the change in the chemical shift of the hydroxyl proton of methanol.[80,81] In Figure 15, the differences between the chemical shifts of the hydroxyl proton of methanol and the low field ^{13}CH satellite signals are plotted *versus* methoxide ion concentration. The resulting straight line has a reciprocal slope of 50 Hertz per mole, and it is linear from zero methoxide ion concentration to almost 4 molar.

A series of control experiments were conducted to determine if any of the reactants or products in the reduction reaction of 4-bromoisoquinoline had an effect on the chemical shift of the hydroxyl proton of methanol in a methanolic solution of sodium methoxide. The chemical shift difference in sodium methoxide solutions saturated with sodium bromide or sodium formate were unchanged from the difference in the absence of these salts. The addition of 4-bromoisoquinoline or isoquinoline in approximately 0.5 M concentration to a sodium methoxide solution increased by separation by 10 Hertz. This was not a serious problem since the total amount of heterocycle remains constant in a reaction mixture, and consequently the increased separation remains constant.

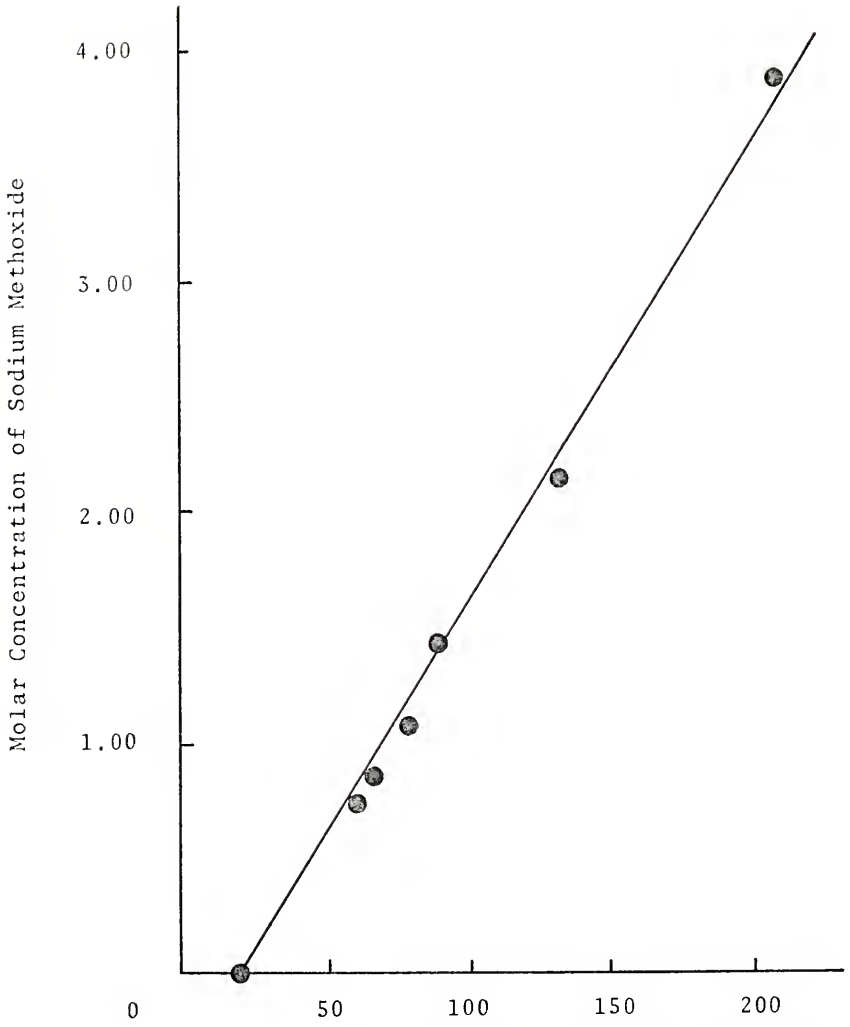


Figure 15. Calibration Curve Used to Determine the Concentration of Sodium Methoxide in Methanol by NMR.

As a result in any given run, the difference between the shift difference at time zero and that at time infinity was taken as a measure of the total methoxide ion consumed. At any intermediate time the percentage of total methoxide ion consumed was easily obtained from the separation of the hydroxyl and ^{13}CH peaks.

GLPC method.-Kinetics were obtained by heating sample solutions in sealed test tubes at 164.7°±0.5° in an oil bath. Periodically a tube was removed from the constant temperature bath and quenched in water at room temperature. The temperature of the oil bath was initially set and occasionally checked using a National Bureau of Standards thermometer.

After a tube had cooled, it was broken open, and the contents were quantitatively transferred to a separatory funnel containing 20 ml of an aqueous solution of sodium chloride (5.1 M) and sodium hydroxide (0.2 M). The contents of the funnel were extracted 3 times with 4 ml portions of ether. The combined extracts were transferred to a small flask containing a known amount of 7,8-benzoquinoline. This solution was concentrated by allowing some of the ether to evaporate under a stream of nitrogen, and the concentrate was analyzed by glpc.

The quantitative nature of the foregoing procedure was verified by control experiments. There was no gross discrepancy between analyses of reaction mixtures extracted and those analyzed directly. (Occasionally reaction

mixtures were analyzed directly without extraction. This insured no material loss in workup, but precluded use of the disc integrator because of bad tailing of the methanol solvent peak under the peak representing isoquinoline. Extraction of the reaction mixture with ether reduces the amount of methanol present.) There was no loss of material during concentration of the ether extracts. Analyses of some reactions conducted by nmr were verified by glpc analyses.

The molar response factors used in these glpc analyses were determined from solutions of known concentrations by the use of equation 31.

$$f_x = \frac{A_r}{A_x} \cdot \frac{M_x}{M_r} \cdot f_r \qquad (31)$$

The reference compound, 7,8-benzoquinoline, indicated by a subscript r, was arbitrarily assigned a response factor, f_r, of 1.0. The symbols A_r and M_r represent the peak area and molarity of the reference compound. A_x, M_x, and f_x represent comparable quantities of the compound for which the molar response factor was being determined. These response factors were subsequently used for analyses carried out under conditions similar to those under which the response factors were determined.

The following response factors were determined using the 200 cm long column (helium flow rate: 27 cc/min; column: 180°; injection port: 210°):

7,8 Benzoquinoline- 1.00;

Isoquinoline- 1.33±3%;

4-Bromoisoquinoline- 1.32±2%;

4-Phenylthioisoquinoline- 1.11±3%.

Molar response factors were also determined using a second column of the same construction as the first but only 40 cm long. All analyses on this column were conducted under identical conditions. The helium flow rate was 24 cc/min; the hydrogen flow rate was 23 cc/min; the oxygen flow rate was ~300 cc/min; the injection port temperature was 240°; the initial column temperature was 130° and was raised to 230° beginning 3 minutes after the injection at the rate shown in Figure 16. Under these conditions the following response factors and retention times were obtained:

7,8 Benzoquinoline- 1.00; 8 minutes;

Isoquinoline- 1.51±5%; 3 minutes;

4-Bromoisoquinoline- 1.39±3%; 6 minutes;

4-Phenylthioisoquinoline- 1.19±5%; 12 minutes;

4-Methoxyisoquinoline- 1.51±1%; 6 minutes.

As may be seen from comparison of the retention times 4-bromoisoquinoline and 4-methoxyisoquinoline overlap in this analytical technique. The response factors were determined for each in the absence of the other.

The glpc analyses were actually conducted by injection of from 1 to 10 ml of sample solution into an injection port maintained at 250°. Column temperature was varied between

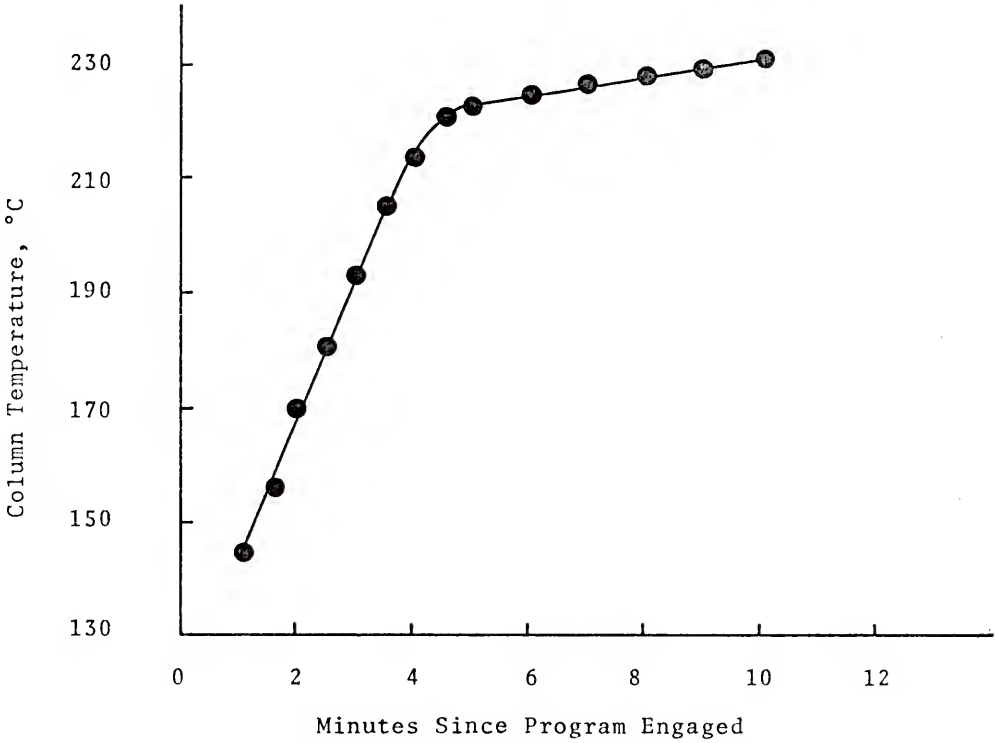


Figure 16. Rate of Column Temperature Rise with Program Set at Maximum Power as Used in All GPC Analyses Requiring Temperature Changes.

130° and 240° during the analyses with a ballistic temperature programmer adjusted to raise the temperature as shown in Figure 16. The programmer was engaged to raise the column temperature only after isoquinoline had reached the detector.

The number of moles of a compound present in the sample was calculated from equation 32 ($f_r = 1.0$).

$$\text{Moles}_x = f_x \cdot \frac{A_x}{A_r} \cdot \text{moles r} \qquad (32)$$

Reactions in Liquid Ammonia

General procedure.-A three-necked round bottom flask equipped with a dry ice condenser and a Truebore Hershberg stirrer was flushed with nitrogen, flamed, and fitted with a calcium chloride drying tube. Ammonia was then distilled into the flask, followed by gaseous methylmercaptan. An immediate reaction occurred resulting in the copious precipitation of slightly soluble white ammonium methylmercaptide. Freshly cut sodium or potassium metal was then added in small pieces. The resulting blue color was quickly dissipated by a reaction with the ammonium methylmercaptide to give soluble sodium methylmercaptide and hydrogen gas. Neither the white precipitate nor the blue color of solvated electrons were present when equimolar amounts of the reactants had been added. The two reagents were added alternately until the desired concentration of alkali metal methylmercaptide was present. The alkali metal methylmercaptide concentration was calculated from the amount of alkali metal

added. A small crystal of ferric nitrate nonahydrate and a small amount of triphenylmethane were added, the latter serving as an indicator of the presence of amide ion. (Triphenylmethide ion is pink in ammonia solution.) Small pieces of alkali metal were added until amide ion formation began as evidenced by the formation of a pink color. Then a calculated amount of alkali was added. The formation of amide ion in the presence of ~1.2 M sodium methylmercaptide took from a few hours to a few days for unknown reasons. Generally the amide ion formation was complete within 4 hours if sufficient ferric nitrate nonahydrate had been added. At this point the reaction mixture was generally a cloudy light pink, presumably because the amide was not completely soluble or a small amount of methylmercaptide was coming out of solution. The substrate was added (sometimes dissolved in a small amount of ether to aid solubility), and a deep color immediately appeared. The reaction was allowed to reflux and ammonium chloride (a two-fold excess over amide ion) was then added to quench the reaction. The deep color faded immediately. Around 50 ml of ether was then added, and the liquid ammonia was allowed to evaporate. The resulting moist solid was dissolved in water to give a two phase mixture which was extracted three times with portions of ether (carbon tetrachloride was also used); the ether extracts were combined, dried (sodium sulfate), and concentrated under vacuum. An internal standard was added to the ether solution (cyclohexene or t-butyl alcohol) and

the mixture was analyzed by nmr; alternatively the product was isolated from the ether solution. Yields based on nmr analysis were calculated using the following equation:

$$\% = \frac{\text{Area of H-3 peak of product} \cdot \text{Moles } C_4H_9OH \cdot 100}{\text{Area } C_4H_9OH/9 \cdot \text{Moles Haloheterocycle}} \qquad (33)$$

If sodium thiophenoxide is used, thiophenol must be frozen in the bottom of the flask prior to the introduction of gaseous ammonia to prevent formation of a hard solid presumed to be ammonium thiophenoxide.

Sodium anilide was formed by the addition of a two-fold excess of aniline after the reaction mixture with sodium amide had been prepared by the general procedure.

Sometimes two flasks were employed. The alkalai metal mercaptide was made in one flask, and the alkalai metal amide in the second. When both reactions were complete, the contents of the two flasks were mixed. The resulting solution was then used for reaction with the hetaryl halide.

Kinetic studies were attempted using a modified 50 ml three-necked flask. A ground glass stopcock was attached near the bottom of the flask so that samples could be withdrawn at various times. An internal area standard (mesitylene) was added to the reaction mixture, and portions were withdrawn into 3 X 30 cm test tubes containing ammonium chloride and cooled in a Dewar flask with dry ice and acetone. The aliquots were immediately stirred until the deep color

dissipated. Some ethyl ether was added to the tube and the liquid ammonia was allowed to evaporate at room temperature. The samples were then analyzed by nmr. (A control experiment similar in all respects to that above except that amide ion was not present showed that mesitylene is a suitable standard. The ratio of mesitylene to 4-bromoisoquinoline determined by nmr agreed with that by weight to within ±10%.)

For studies involving examination of liquid ammonia reaction mixtures by nmr, amide ion was formed by the above procedure except that methylmercaptan was not added. Amide ion formation was usually complete in a few hours when potassium was used and took a little longer when sodium was used. Care was taken not to add too much ferric nitrate nonahydrate since the paramagnetic ion may cause broadening of the nmr spectrum. The stopcock on the round bottom flask was fitted with a capillary tube by a short length of Tygon tubing, and stirring was carried out with a glass encased magnetic stirring bar. After amide ion formation was complete, two different procedures were followed: a) Substrate was added directly to the flask and the resulting mixture was transferred to an nmr tube; b) substrate was added to an nmr tube and amide ion solution was then transferred to the nmr tube. In both cases the nmr tube was cooled in a dry ice–acetone bath and was sealed with a torch shortly after the transfer. Trimethylamine and benzene were used as chemical shift internal standards. The first of the two methods permits a more accurate determination of reactant

concentrations and provides for a more thorough mixing of reactants. The second method permits several studies from one amide ion solution and maintains the reactants at or near -78° until the temperature is raised higher in the nmr probe.

If the study of a reaction mixture containing methylmercaptide ion was to be conducted, procedure b) was employed. Substrate and solid sodium methylmercaptide were placed in an nmr tube prior to the addition of the amide solution. Reaction mixtures prepared by method a) proved to be too viscous to transfer when sodium methylmercaptide was present.

In covalent animation studies, liquid ammonia and trimethylamine were distilled directly into the nmr tube containing the heteroaromatic salt. Again the nmr tube was kept in a Dewar flask with dry ice and acetone during the distillation and immediately thereafter sealed with a torch.

Control Experiments

Rate of conversion of 4-methoxyisoquinoline to 4-hydroxyisoquinoline by sodium methoxide.-Method A. The rate at which 4-methoxyisoquinoline undergoes cleavage of the ether linkage in the presence of sodium methoxide to give methyl ether and the conjugate base of 4-hydroxyisoquinoline was determined by nmr. A solution of 4-methoxyisoquinoline (0.71 M) and sodium methoxide (1.1 M) containing a drop of t-butyl alcohol as an internal area standard was sealed in an nmr tube. This sample was heated at 165° in a

constant temperature bath, removed periodically and immediately quenched to room temperature, and analyzed by nmr. The results are plotted in Figure 17. For this plot the concentration of 4-methoxyisoquinoline was determined directly by comparison to the internal standard and the concentration of sodium methoxide at any time was indirectly determined by substracting the number of moles of 4-methoxyisoquinoline reacted from the number of moles of sodium methoxide initially present. This is based upon an assumed stoichiometry of 1 to 1 and gives a second order rate constant of 9.7×10^{-5} mol^{-1} $sec.^{-1}$.

There were no apparent problems in the nmr analysis of reaction mixtures containing only 4-methoxyisoquinoline as a starting material. The H-1 peak of 4-methoxyisoquinoline and peaks representing the cleavage product are nicely separated. However in reaction mixtures including isoquinoline, the H-3 peak of isoquinoline overlaps with the peaks from the 4-isoquinolyl oxide ion. This is a potential problem in the analyses of reaction mixtures of 4-bromoisoquinoline and sodium methoxide where isoquinoline and sodium 4-isoquinolyl oxide are products. The problem is minimal when reaction times are short and the concentration of 4-methoxyisoquinoline is low.

Method B. The rate at which the cleavage of 4-methoxyisoquinoline occurs under conditions which are zero-order in sodium methoxide was determined by glpc analysis. Aliquots (4 ml) of a 0.020 M 4-methoxyisoquinoline, 0.017 M

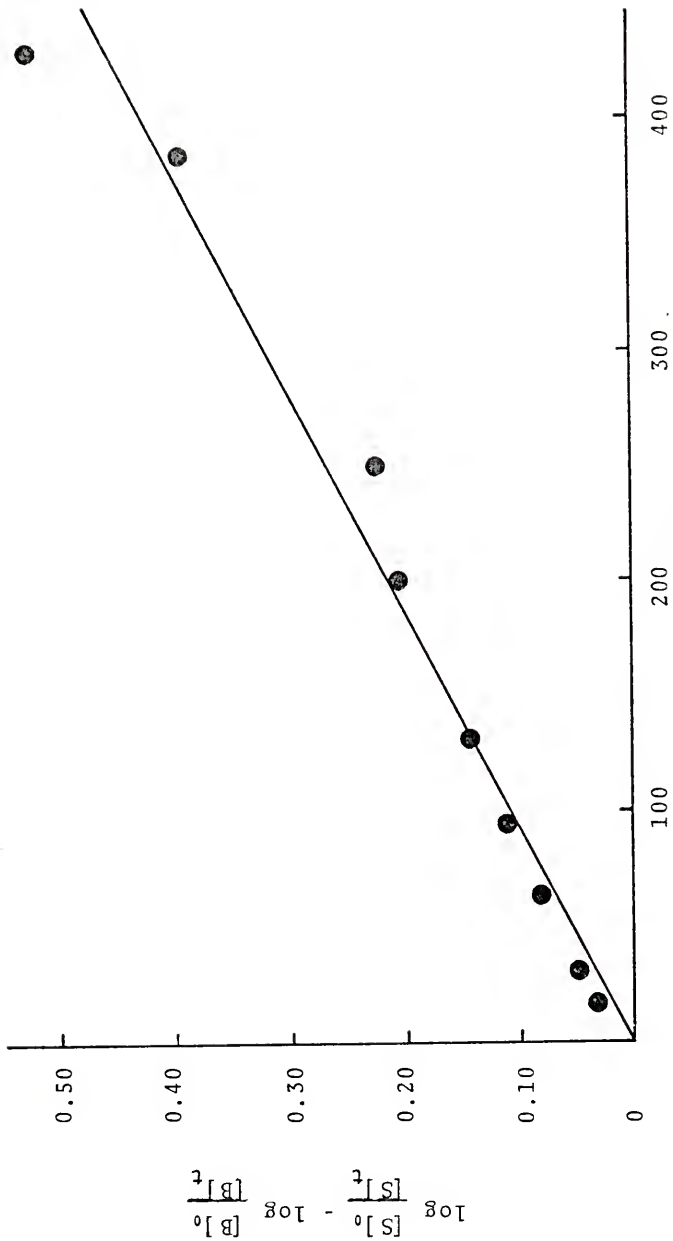


Figure 17. Second-order Plot for the Rate of Cleavage of 0.71 M 4-Methoxyisoquinoline by 1.1 M Sodium Methoxide in Methanol at 165°. (S stands for substrate, and B stands for base; subscripts o and t stand for time zero and intermediate time, respectively.)

7,8-benzoquinoline (internal area standard), and 0.91 M sodium methoxide solution were sealed in tubes and heated at 165°. The tubes were periodically removed, quenched, opened, and analyzed by glpc without further work-up. The results plotted in Figure 18 give a second-order rate constant of 9.4×10^{-5} mol^{-1} sec^{-1}.

Rate of aromatic nucleophilic substitution of 4-bromoisoquinoline by sodium thiophenoxide in methanol.-The rate of direct attack by thiophenoxide ion on 4-bromoisoquinoline in methanol at 165° was obtained by heating a sealed nmr tube containing a methanolic solution of 4-bromoisoquinoline (1.17 M) and sodium thiophenoxide (1.13 M) with t-butyl alcohol as an internal area standard. The nmr signals for H-1 and H-3 of the starting material and product turned out to be too close for reliable integration, and the relative peak heights were used to provide data for Figure 19. The t-butyl alcohol internal area standard insured that the combined peak areas represented the total mass area. A second-order rate constant of 6.3×10^{-5} mol^{-1} sec^{-1} was obtained.

Likewise the rate of the substitution reaction of 0.52 M 4-bromoisoquinoline with 0.98 M sodium thiophenoxide in methanol at 147° was determined. Using a slower sweep time than before, it was possible to obtain reliable integrals. A rate constant of 2.7×10^{-5} mol^{-1} sec^{-1} was obtained (Figure 20).

From the two rate constants just obtained, an energy of activation was determined from equation 34. A value of

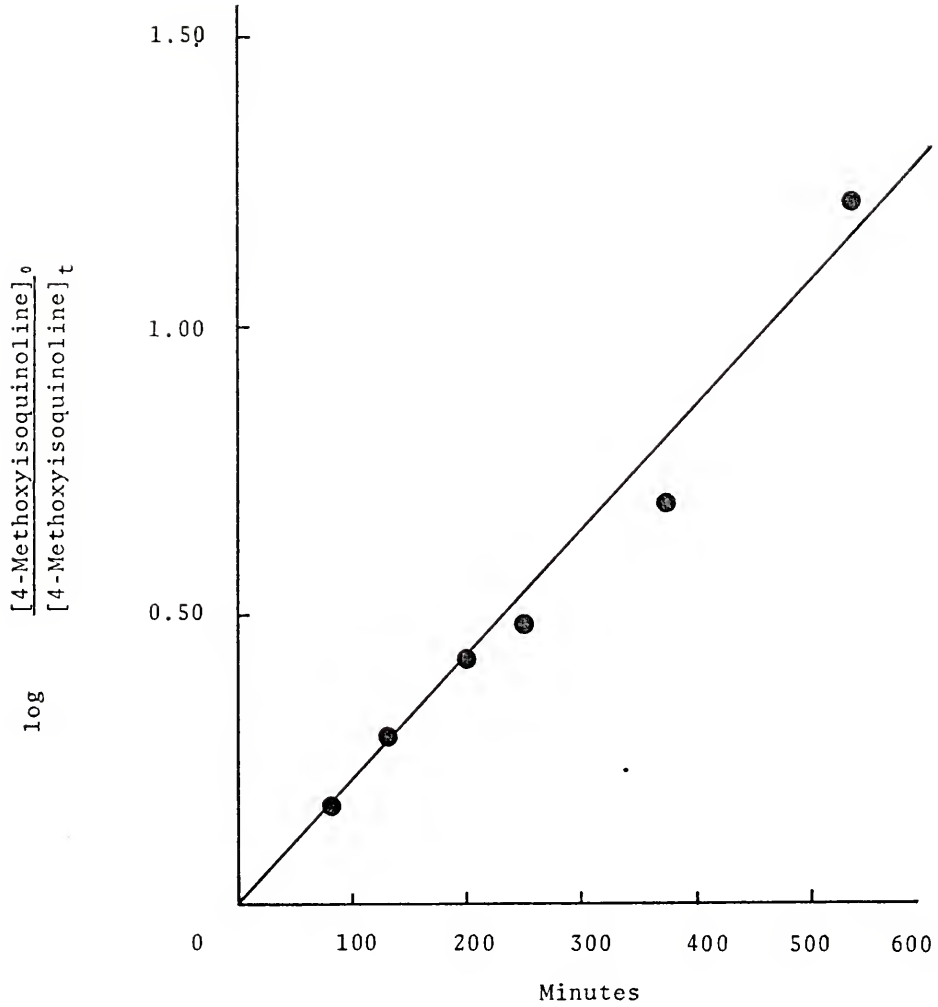


Figure 18. Pseudo-first-order Plot for the Rate of Cleavage of 0.020 M 4-Methoxyisoquinoline by 0.91 M Sodium Methoxide in Methanol at 165°.

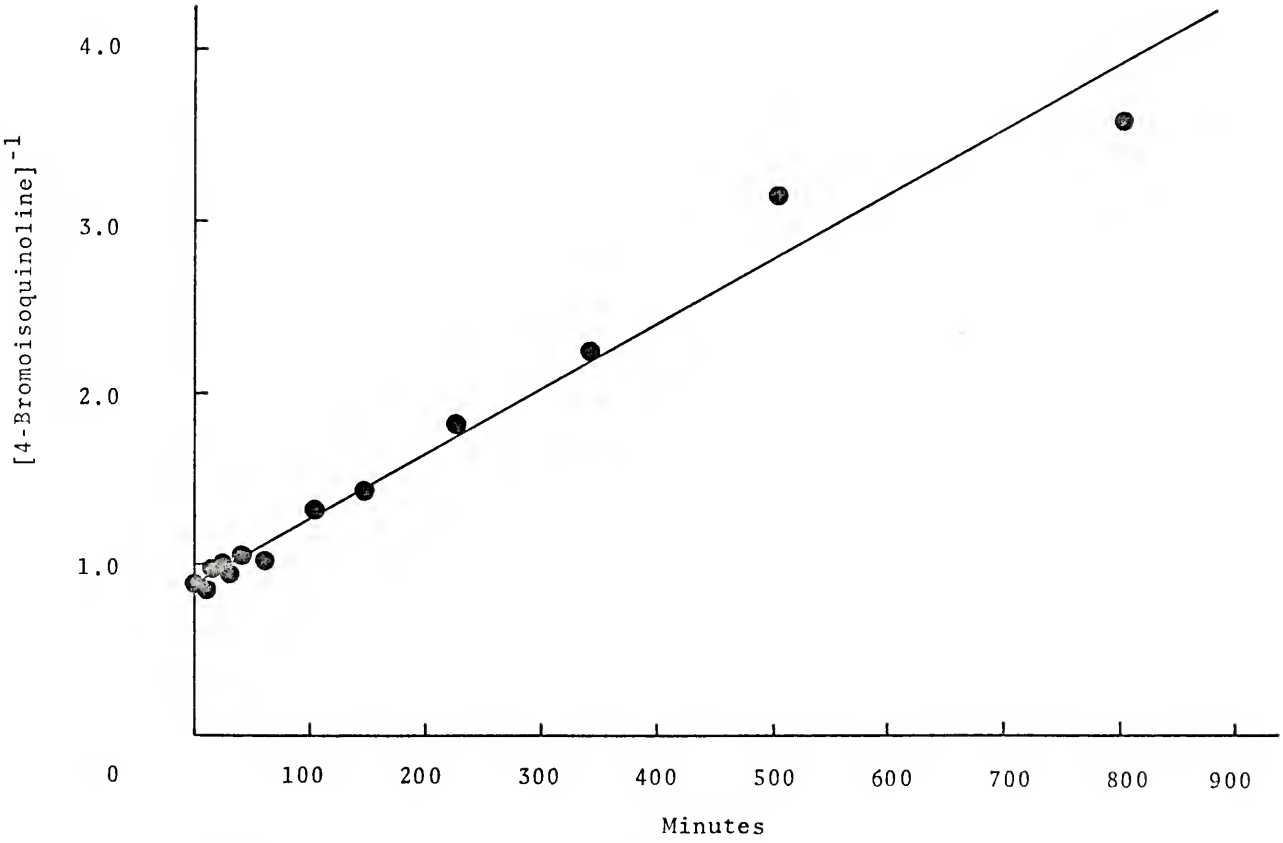


Figure 19. Second-order Rate Plot for the Reaction of 1.17 M 4-Bromoisoquinoline with 1.13 M Sodium Thiophenoxide in Methanol at 165°.

1.73×10^4 cal was calculated.

$$\log k_2 - \log k_1 = (E/4.576)\ ((T_2-T_1)/T_2T_1) \qquad (34)$$

The entropy of activation at 147° was calculated from equation 35 to be -41.6 e.u. This is very negative and may be incorrect, since it was determined from data at only two different temperatures.

$$\frac{\Delta S^{\pm}}{4.576} = \log k - 10.753 - \log T + E/4.576\ T \qquad (35)$$

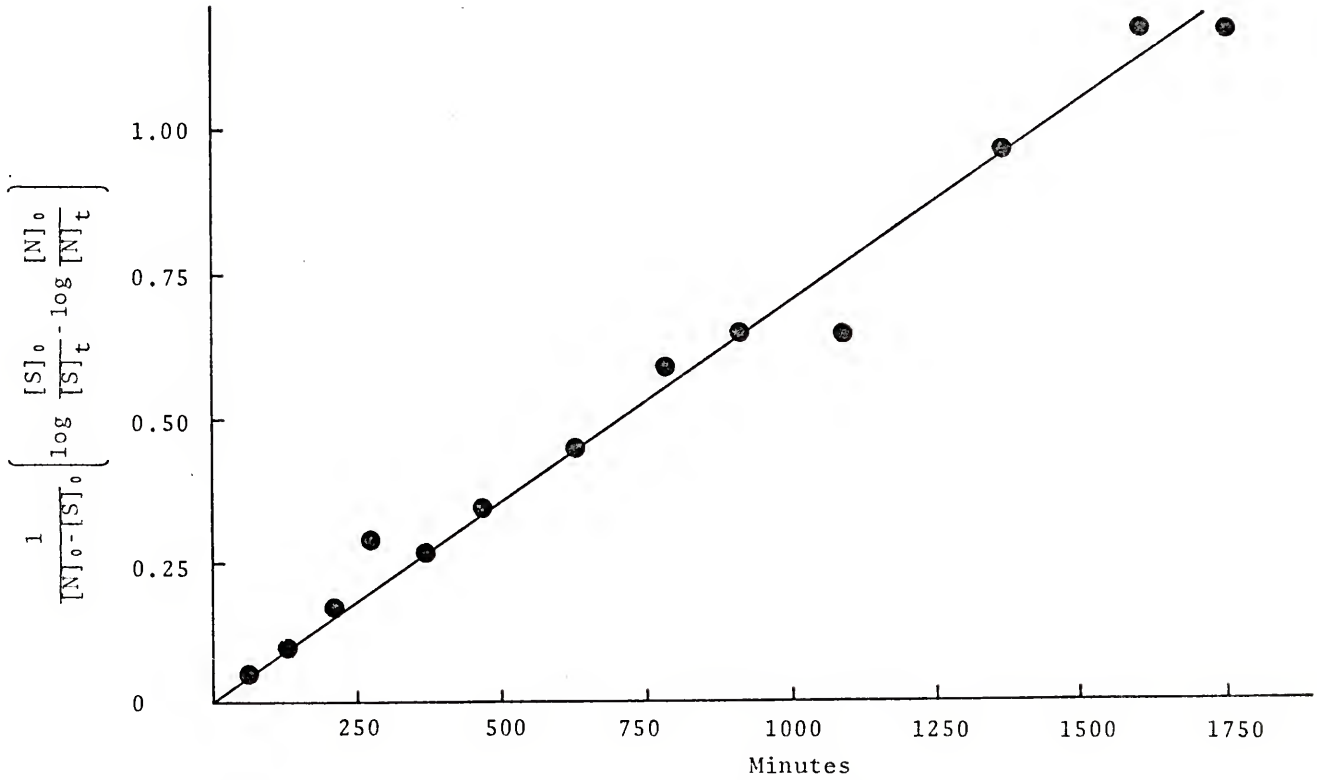


Figure 20. Second-order Rate Plot for the Reaction of 0.52 M 4-Bromoisoquinoline with 0.98 M Sodium Thiopenoxide at 147°. (S stands for substrate and N stands for nucleophile; subscripts are the same as Figure 17.)

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BIOGRAPHICAL SKETCH

Terence Miller Oestreich was born on August 28, 1942, in Fulton, Missouri. He attended Fulton High School, and in May, 1960, graduated from East Richland High School, Olney, Illinois, where he was selected the outstanding science student in the graduating class. After attending Hendrix College and the University of Missouri, he received the degree of Bachelor of Arts, cum laude, from Westminster College, Fulton, Missouri, in January, 1964. He attended Naval Officer Candidate School in Newport, Rhode Island, and was commissioned an officer in the United States Naval Reserve in August, 1964. After three years of active duty aboard the destroyers U.S.S. Bauer and Hank, he returned to civilian life and enrolled in the Graduate School of the University of Florida in 1967. He was a Graduate Teaching Assistant from 1967-1971 and a Graduate Research Assistant from 1971-1973 while pursuing his work toward the degree of Doctor of Philosophy.

Terence Miller Oestreich is married to the former Martha Bell Gordon. He is a member of the American Chemical Society.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

John A. Zoltewicz, Chairman
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Richard D. Dresdner
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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This dissertation was submitted to the Department of Chemistry in the College of Arts and Sciences and to the Graduate Council, and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Dean, Graduate School

March, 1973