THE ELEMENT EFFECT IN METHOXIDE ION SUBSTITUTION OF THE (*Z*) AND (*E*) ISOMERS OF *O*-METHYL-4-METHOXYBENZOHYDROXIMOYL HALIDES

A THESIS

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BY

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July 7, 1997
Date

To the Associate Vice President for Research and Dean of the Graduate School:

I am submitting herewith a thesis written by Debra D. Dolliver entitled "The Element Effect in Methoxide Ion Substitution of the (*Z*) and (*E*) Isomers of *O*-Methyl-4-methoxybenzohydroximoyl Halides." I have examined this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

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We have read this thesis
and recommend its acceptance:

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ABSTRACT

The (*Z*) and (*E*) isomers of *O*-methyl-4-methoxybenzohydroximoyl chloride [*p*-$OCH_3ArC(Cl)=NOCH_3$] and *O*-methyl-4-methoxybenzohydroximoyl bromide [*p*-$OCH_3ArC(Br)=NOCH_3$] were synthesized, and the rates of methoxide substitution were measured (90% dimethyl sulfoxide and 10% methanol at 44.6° C). Kinetic measurements demonstrated the reaction to be first order in methoxide and first order in the hydroximoyl halide. Two mechanisms were considered for this reaction: a multistep addition-elimination mechanism ($A_N + D_N$) and a concerted (S_N2-like) mechanism (A_ND_N). The element effect (k_{Br}/k_{Cl}) was investigated to determine if carbon-halogen bond cleavage occurs in the rate-determining step. A k_{Br}/k_{Cl} ratio ≥ 30 suggests that the bond is cleaved in the rate-determining step; a k_{Br}/k_{Cl} ratio approximately equal to 1 indicates that the bond is not broken in the rate-determining step. The (*Z*) isomers gave a k_{Br}/k_{Cl} ratio of 2.78, and the (*E*) isomers gave a k_{Br}/k_{Cl} ratio of 1.97. These findings support the addition-elimination type mechanism with nucleophilic attack being the rate-determining step.

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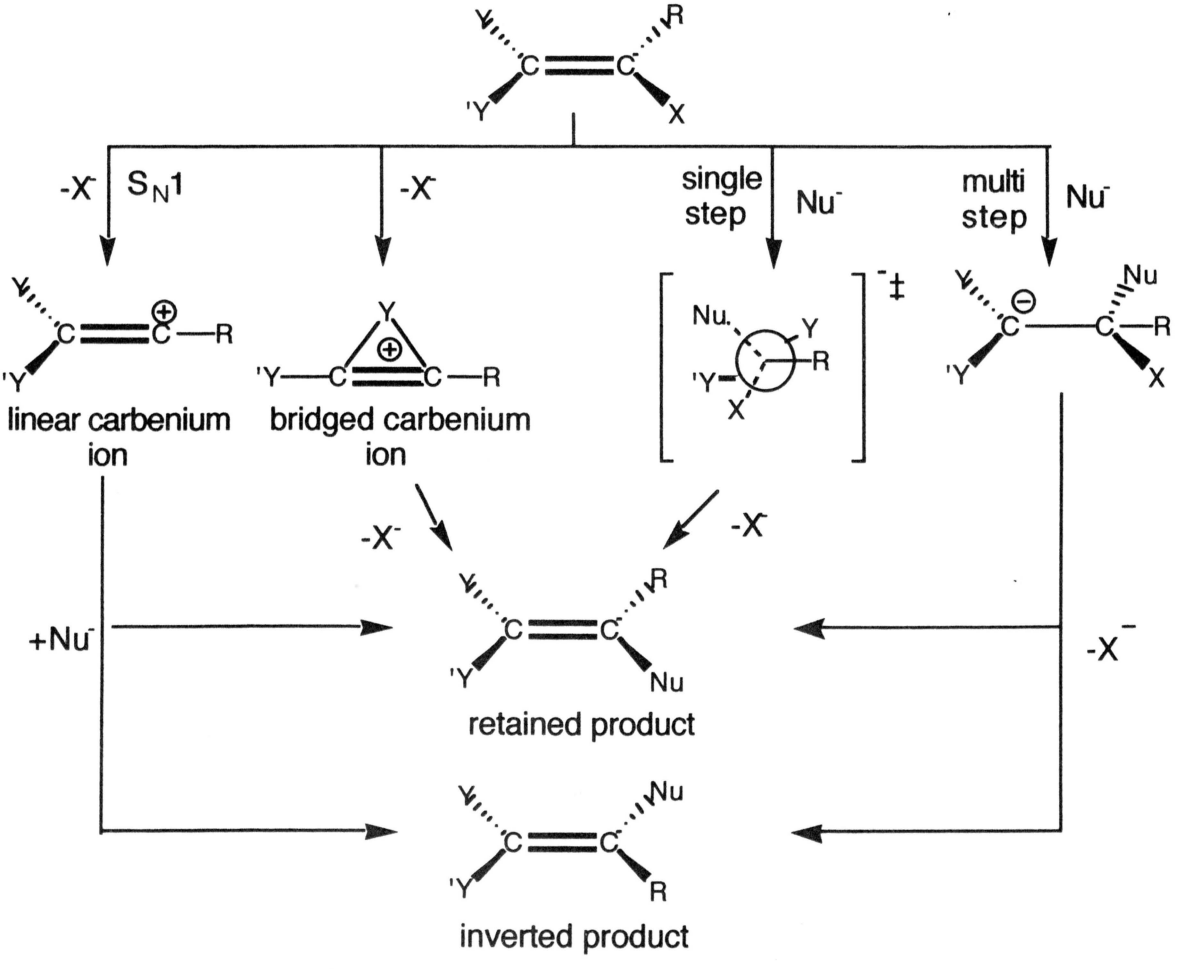
CHAPTER 1

INTRODUCTION

In 1981 Rappoport[1] proposed that nucleophilic substitution at an sp^2 hybridized carbon in a vinylic system might occur along a continuum of mechanistic possibilities ranging from limiting S_N1 (D_N+A_N) to multi-step addition-elimination depending upon the nucleophile, the solvent, the ß substituents, and the leaving group.



In this review article he emphasized that there was overwhelming evidence for multi-step substitution (addition-elimination) in systems with poor leaving groups or in systems with good leaving groups and strongly electron-withdrawing ß substituents. The S_N1 process had also been demonstrated earlier by Rappoport and Gal[2] in the solvolysis of ∝-chloro and ∝–bromo-4-methoxystyrene. However, despite little experimental evidence to support any concerted mechanisms, he maintained that adjustments in reaction parameters could shorten the lifetime of the tetrahedral intermediate so that it became effectively nonexistent.

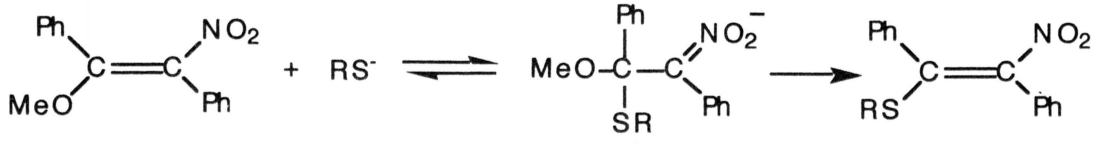
Rappoport's argument for the single step process was based in large part upon complete retention of configuration in the substitution reaction of certain systems. This could occur from π attack by the nucleophile as the nucleofuge is dissociating. An S_N1 process would be expected to result in partial or complete stereoconvergence. Also, one would expect partial to complete stereoconvergence in the addition-eliminiation mechanism if the rate of elimination is slower than the rate of rotation around the carbon-nitrogen single bond of the carbanionic intermediate.

In a later review article Rappoport[3] proposed that the concerted mechanism could only be seen in very unactivated vinylic systems with good nucleofuges. Although he repeated that evidence for an S_N2 type mechanism was scarce, he listed several systems which supported it: 1) substitution of ß-halostyrenes by a powerful nucleophile, Me_2CuLi, results in retention of configuration and gives a reactivity order of Br>Cl>F, 2) calculations reveal no distinguishable intermediate on the potential energy surface of the reaction of vinyl chloride with a hydride ion, and 3) *E*- and *Z*-1,2-dichloroethylene

substitution with thionucleophiles (MeS^-, *i*-PrS^-) results in 95% retention of configuration.

In a subsequent paper Rappoport[4], however, argued that almost all evidence appeared to favor the addition-elimination mechanism for nucleophilic substitution at the sp^2 hybridized carbon of vinylic systems. Based upon MO calculations he suggested that a significant hyperconjugative barrier exists for rotation of some carbanionic intermediates which results in retention of configuration in the product. In addition, intramolecular element effects in which vinylic systems were substituted with both Br and Cl demonstrated a small k_{Br}/k_{Cl} ratio, further supporting a rate-determining addition step followed by rapid loss of halogen.

An addition-elimination mechanism in vinylic systems is also substantiated by work of Bernasconi[5]. In reactions of alkylthiolate ions with (*E*)-ß-methoxy-∝-nitrostilbene (**1**) in 50% Me_2SO-50% water an absorption peak is observed spectrophotometrically which is distinctly different from either reactants or products and is believed to correspond to a carbanionic intermediate (**2**) produced in this reaction.

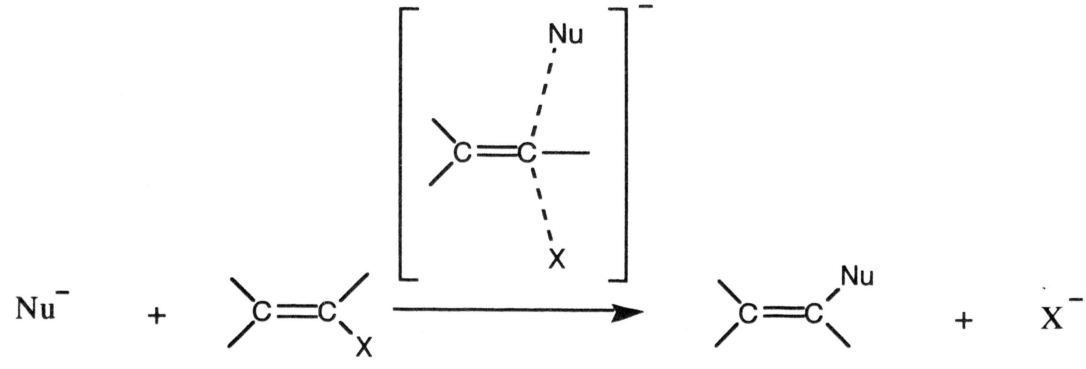


(1) (2)

This absorption peak appears immediately after mixing the reactants and then slowly converts to the absorption peak of the product . In this instance the rate determining step appears to be loss of the nucleofuge. However, in studies performed by Bernasconi[6] in which the same substituted stilbene is reacted with

different amines, no intermediate could be spectrophotometrically observed. This was attributed to the amines being poorer nucleophiles than the thiolate ion accounting for low rates of formation of the intermediate and to quick conversion of the intermediate to product because of a strong push from developing resonance in the product. Other attempts to identify the carbanionic intermediate in substitution of the ß-X-substituted ∝-nitrostilbene with hydroxide ion in water have also been unsuccessful[7].

In 1994 Glukhovtsev, Pross, and Radom[8] computationally investigated the feasibility of S_N2 substitutions on vinylic systems resulting from in-plane attack at the sp^2 center. This pathway had been previously viewed as a high energy one based on extended Hückel calculations. However, their *ab initio* calculations of Cl^- exchange on CH_2=CHCl revealed that in the gas phase the in-plane σ-type S_N2 mechanism resulting in inversion of configuration is actually energetically 42.4 kJ/mol lower than the out-of-plane π attack.



In addition, no two-step pathway involving a carbanionic intermediate was found in this system. These results appeared to also apply to Br^- exchange on CH_2=CHBr and I^- exchange on CH_2=CHI. The authors acknowledge that most substitution reactions on vinylic systems thought to proceed by concerted

mechanisms result in retention of configuration by experimental evidence. This is due, they claim, to the fact that most of these reactions have been performed on activated systems. However, they note that nucleophilic substitution has experimentally been seen to proceed by predominant inversion of configuration on simple vinyl triflates, complete inversion of configuration on 1,2 dibromo-1,2-difluoroethylene, and complete inversion of configuration on simple vinyliodinium salts. They state that these results have been either left unexplained or wrongly attributed to an ion-pair mechanism, and they suggest reanalyzing them in view of this new theoretical data supporting concerted in-plane nucleophilic substitution.

Other investigators have looked at the possibility of concerted substitution at the sp^2 hybridized carbon of a carbonyl group. In 1984 and 1985 Bentley, Carter, and Harris[9,10] proposed competing S_N2 and addition-elimination type mechanisms for the solvolysis of benzoyl chloride in aqueous media. In these studies rates of solvolysis of benzoyl chloride were plotted against Winstein-Grunwald Y_{Cl} values resulting in curved plots. This indicated that the mechanism of the reaction was changing with the ionization strength of the solvent. Reactions involving solvents of approximately the same ionizing power but differing nucleophilicities (CH_3OH/H_2O vs CF_3OH/H_2O) indicated that the rate of solvolysis of benzoyl chloride is dependent to some small degree on nucleophilic assistance from the solvent ($k_{40\%EtOH}/k_{97\%TFE} = 13$). Bentley argued that these results in highly ionizing solvent are consistent with an S_N2 type mechanism and that as the ionizing strength of the solvent is diminished the mechanism changes to an addition-elimination type.

Later studies by Bentley and Koo[11] supported this change from an addition-elimination mechanism to a concerted one with increases in ionization

strength of the solvent. Here they performed rate-rate profiles with *p*-methoxybenzoyl chloride as the model for an S_N1 reaction and *p*-nitrobenzoyl chloride as the model for the addition-elimination mechanism. It was noted that rates of solvolysis for the *p*-nitro compound decreased with increases in the water concentration of the solvent. In less aqueous media the rate of solvolysis of *p*-chlorobenzoyl chloride resembled those of the para-nitro compound; however, in solvents of high water concentration, the *p*-chlorobenzoyl chloride rate of reaction began to increase. This was interpreted as a change in mechanism occurring in the *p*-chloro compound from an addition-elimination type mechanism to a concerted mechanism as the aqueous nature of the solvent increased.

In addition, product selectivities, S, defined by equation 1, provided independent evidence for competing mechanisms.

$$(S) = [\text{ester}]_{prod}[\text{water}]_{solv}/[\text{acid}]_{prod}[\text{alcohol}]_{solv} \qquad (1)$$

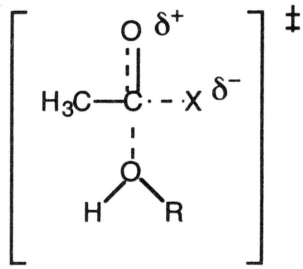
For the addition-elimination reaction channel (*p*-nitrobenzoyl chloride), the S value increased as the aqueous nature of the solvent increased. For the S_N1 reaction channel (*p*-methoxybenzoyl chloride) the S value remained approximately constant at around 0.7 for ethanol/water mixtures and 1:3 for methanol/water mixtures. For benzoyl chloride and other para-substituted benzoyl chlorides (*p*-Cl, *p*-Me) there were deviations from either trend indicative of a mechanism differing from either of the model mechanisms. The *p*-Cl compound followed the trend of the *p*-NO_2 compound until reaching the 40:60 EtOH:H_2O mixture where it began to deviate significantly with increasing concentrations of water. This supported the change from an addition

elimination mechanism with increasing ionization strength of the solvent. Rate-rate correlations, however, between *p*-chlorobenzoyl chloride and *p*-methoxybenzoyl chloride (the model for an S_N1 mechanism) were nonlinear which ruled out the possibility for a SN1 type mechanism for the *p*-Cl compound. The same nonlinearity was seen in rate-rate profiles of benzoyl chloride and *p*-methylbenzoyl chloride with *p*-methoxybenzoyl chloride. Therefore, the S_N1 and addition-elimination mechanisms were eliminated, and Bentley maintained that these reactions proceeded by a concerted mechanism.

This type of reaction has been termed by Song and Jencks[12] as a dissociative concerted displacement as they argue that simply distinguishing a mechanism as "concerted" is ambiguous and does not adequately represent the appearance of the transition state. They have looked at trying to characterize reaction conditions where the mechanism for solvolysis of substituted benzoyl fluorides and chlorides in water and benzoyl chloride in 90% trifluoroethanol changes from dissociative to associative. Correlation of rate constants of *p*-(dimethylamino)benzoyl fluoride with Y_{Cl} revealed a sharp change in slope at around 40% ethanol, indicating a mechanistic change, they argue, from an associative to a dissociative mechanism. This sharp break might also indicate a change, according to Bentley[13], from a concerted mechanism with approximately perpendicular nucleophilic attack by the solvent and the development of a partial negative charge on oxygen to a dissociative mechanism. Hammett correlations for hydrolysis rates in water revealed a change in slope at approximately $\sigma^+ = 0.5$ corresponding to the change between the *p*-anisoyl and *p*-dimethylamino compound. This indicated a mechanistic change with change of substituent. Song and Jencks proposed

that 1) the *p*-dimethylaminobenzoyl fluoride in highly aqueous solvent undergoes dissociation to form the free ion before reaction with the solvent and 2) the *p*-anisoylbenzoyl fluoride also reacts via a dissociative process but the solvent attacks the intermediate before the fluoride leaving group diffuses out of a solvent-separated ion pair.

In 1996 Bentley, Llewellyn and McAlister[13] proposed an S_N2 mechanism (involving in-plane attack and development of a positive charge on the carbonyl oxygen) for the alcoholysis, aminolysis and hydrolysis of acetyl chloride: a molecule which was believed previously to undergo solvolysis via an addition-elimination type mechanism. Unlike the findings for some benzoyl chlorides and fluorides, Grunwald-Winstein plots versus Y for the solvolysis of acetyl chloride resulted in a straight line, m = 0.9, indicating a single reaction process which is sensitive to the ionization strength of the solvent. Rate-rate profiles versus *p*-methoxybenzoyl chloride (the model for an S_N1 type reaction) were approximately linear. Selectivity values for acetyl chloride were approximately constant but did increase slightly in highly aqueous media. All the above were consistent with an S_N1 type mechanism; however, kinetic studies done in solvents of approximately equal ionizing strength but differing nucleophilicities (CH_3OH vs CF_3OH) indicated that the rate of reaction was dependent upon nucleophilic attack to some degree with $k_{40\%EtOH}/k_{97\%TFE}$ = 320. These results are consistent with the concerted mechanism with a loose transition state proposed by Bentley.

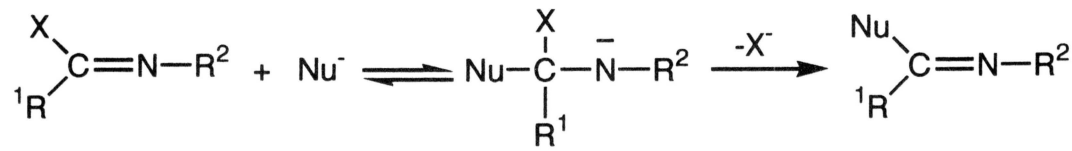


In addition, Kevill and Kim[14] have looked at the solvolysis of acetyl chloride with methanol in acetonitrile, and rate equations revealed both first order and second order terms for methanol indicating some nucleophilic participation by the solvent in the solvolysis of acid chlorides.

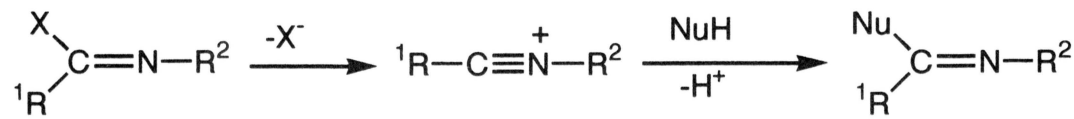
Investigations of concerted mechanisms at carbonyl carbons have not been limited to solvolytic studies of acid halides. Guthrie[15] has investigated the alcoholysis of esters through extended Marcus theory and predicted that phenols with 1<pKa>11 would undergo subsitution on aryl acetates via a concerted mechanism. Castro, Ibáñez, Salas and Santos[16] have studied the aminolysis of *O*-ethyl S-(2,4-dinitrophenyl) thiocarbonate, and a linear Brönsted-type plot was obtained with a slope ß = 0.56. This supported a concerted mechanism for this substitution at a thiocarbonate which was attributed to the instability of the putative tetrahedral intermediate caused by the oxygen of the EtO group.

As there appears to be evidence for concerted mechanisms at the sp^2 hybridized carbons of -C=O and -C=C-, one would suspect them also to exist in certain reactions of the carbon-nitrogen double bond. This would allow for three distinct mechanistic pathways for nucleophilic substitution in basic or neutral conditions at the carbon-nitrogen double bond.

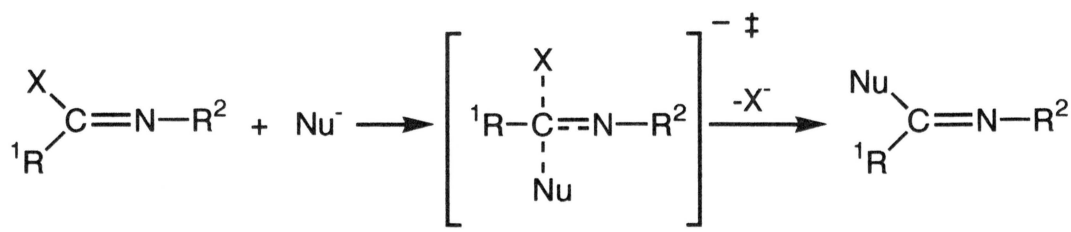
PATHWAY A ($A_N + D_N$; addition-elimination):



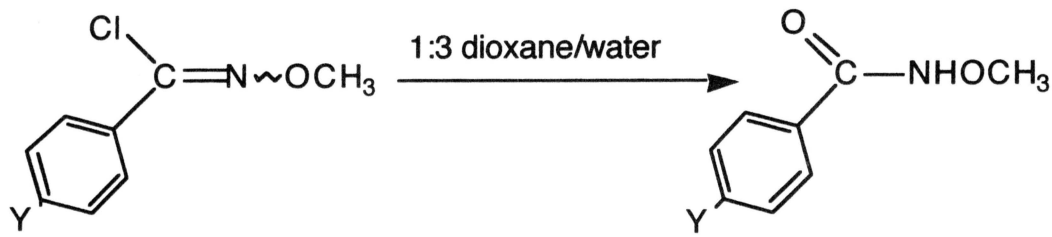
PATHWAY B ($D_N + A_N$; S_N1):



PATHWAY C (A_ND_N; S_N2):



Johnson, Riesgo and Jano[17] investigated the hydrolysis of (*Z*)- and (*E*)-*O*-methylbenzohydroximoyl chlorides (**3Z** and **3E**) in 1:3 dioxane:water and reported an S_N1 type mechanism for these reactions.



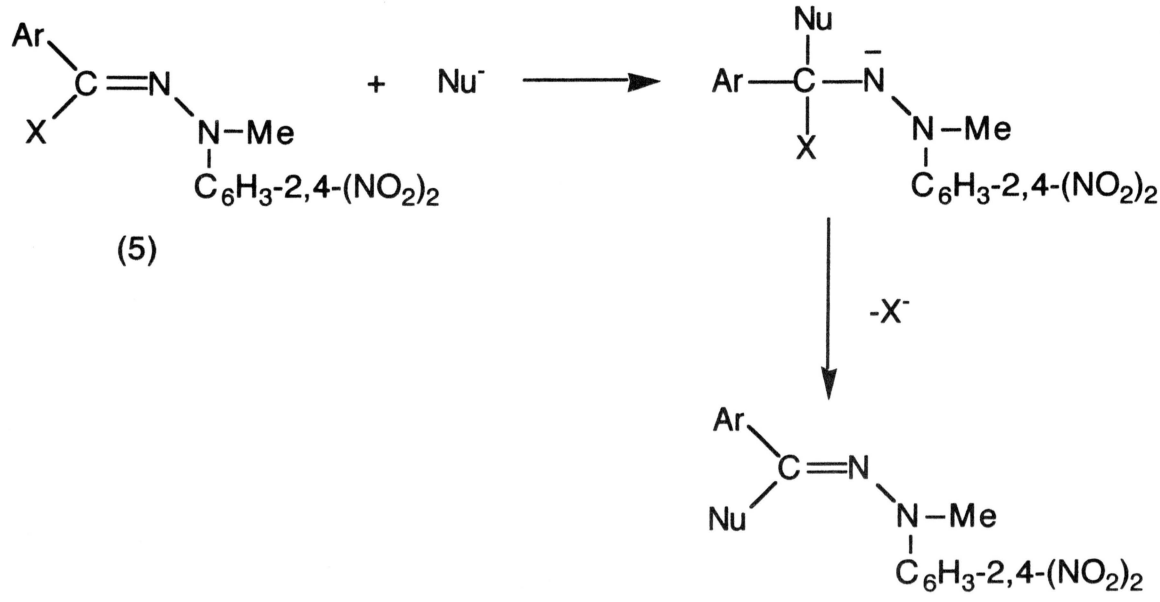
(3Z and 3E) (4)

3Za and 3Ea: Y = H
b: Y = OCH_3
c: Y = CH_3
d: Y = Ph

4a: Y = H
b: Y = OCH_3
c: Y = CH_3
d: Y = Ph

They found that these reactions followed first order kinetics and had a significant element effect in the *Z*-isomers when extrapolated to room temperature. Also, a Hammett plot for the *E*-hydroximoyl chloride versus σ^+ gave a ρ value of -1.4. Previous Hammett correlation of the *Z*-isomer with σ^+ had given a ρ value of -2.4[18]. All this data is consistent with rate determining elimination of the leaving group to form a nitrilium ion intermediate (pathway B).

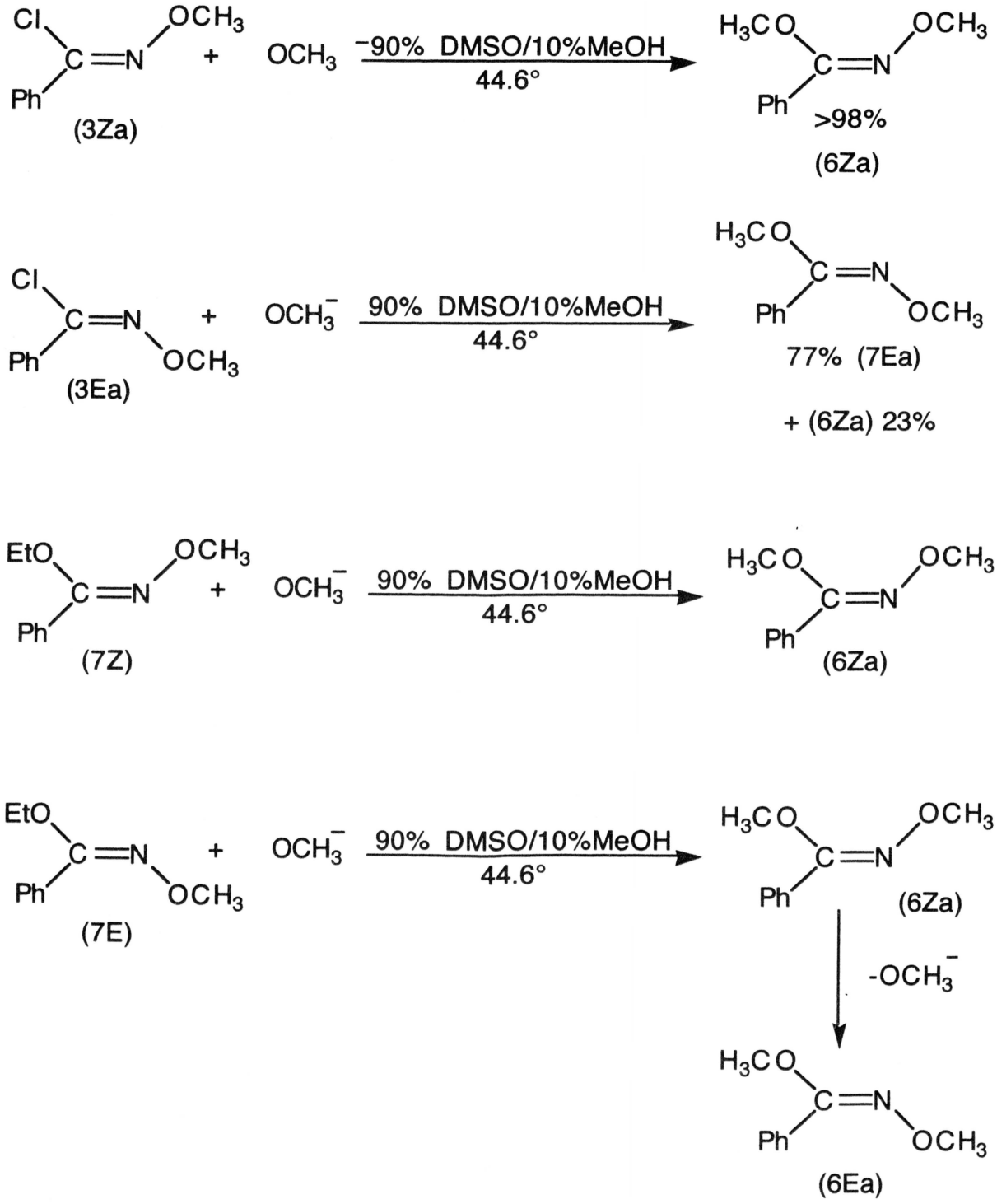
Several studies have confirmed stepwise addition-elimination type mechanisms (pathway A) with rate determining nucleophilic attack. Rowe and Papanelopoulos[19] have concluded that reactions of hydrazonyl halides (**5**) with good nucleophiles proceed by addition-elimination.



(5)

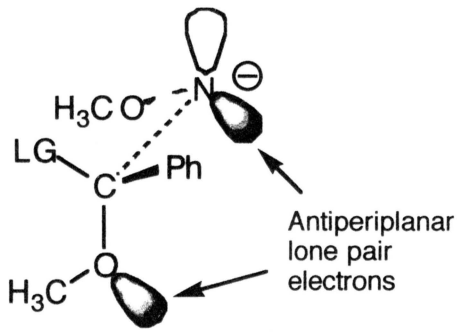
In reactions of hydrazonyl halides with methoxide ion, Hammet correlations give a ρ value of 1.58 for the fluoro compound, 1.95 for the chloro compound and 1.57 when 4-nitrobenzenethiolate ion is the leaving group. In addition, k_{MeOD}/k_{MeOH} ratios for these reactions are greater than 1, indicating the higher degree of solvation of the methoxide ion in MeOH and a subsquent lessening of its nucleophilicity relative to solvation in MeOD. Element effect studies demonstrate the following rate relationships: Cl:Br:F = 1.0:1.56:23.2. All the above findings are consistent with rate determining addition followed by rapid loss of the leaving group.

Johnson *et al*[20, 21, 22, 23] have investigated a number of different nucleophilic substitutions at the carbon-nitrogen double bond. They proposed that reactions of the *E* and *Z* isomers of *O*-methylbenzohydroximoyl chloride (**3Za and 3Ea**) and of ethyl *O*-methylbenzohydroximate (**7Z and 7E**) with methoxide ion undergo an addition-elimination type mechanism.


Cl
OCH3
C=N
Ph
(3Za)
+
OCH3
−90% DMSO/10%MeOH
44.6°
H3CO
OCH3
C=N
Ph
>98%
(6Za)
Cl
C=N
Ph
OCH3
(3Ea)
+
OCH3−
90% DMSO/10%MeOH
44.6°
H3CO
C=N
Ph
OCH3
77% (7Ea)
+ (6Za) 23%
EtO
OCH3
C=N
Ph
(7Z)
+
OCH3−
90% DMSO/10%MeOH
44.6°
H3CO
OCH3
C=N
Ph
(6Za)
EtO
C=N
Ph
OCH3
(7E)
+
OCH3−
90% DMSO/10%MeOH
44.6°
H3CO
OCH3
C=N
Ph
(6Za)
-OCH3−
H3CO
C=N
Ph
OCH3
(6Ea)

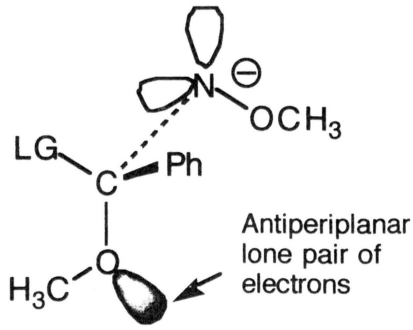
The reaction of the *Z* isomer of the hydroximoyl chloride yields almost exclusively *Z* product (**6Za**) (>98%), and the *E* isomer proceeds with predominant retention of configuration in the product (E:Z = 77:23). The *Z* isomer of the hydroximate also yields exclusively the *Z* isomer of the product (**6Za**), but the *E* isomer initially gvies the *Z* isomer of the product (**6Za**) which then slowly isomerizes to the *E* isomer of the product (**6Ea**). There is also a marked difference in the Z/E rate ratio of the two reactions (**3Za/3Ea** = 0.87; **7Z/7E** = 290).

These results were explained in terms of stereoelectronic control. In the *Z* isomers the carbanionic intermediate that results from methoxide attack (**8**) is a conformation with a lone pair of electrons on nitrogen and a lone pair of electrons on the methoxide oxygen antiperiplanar to the leaving group. These can adequately assist in pushing off the chloride or the ethoxide.



Tetrahedral Intermediate
formed from Z isomer

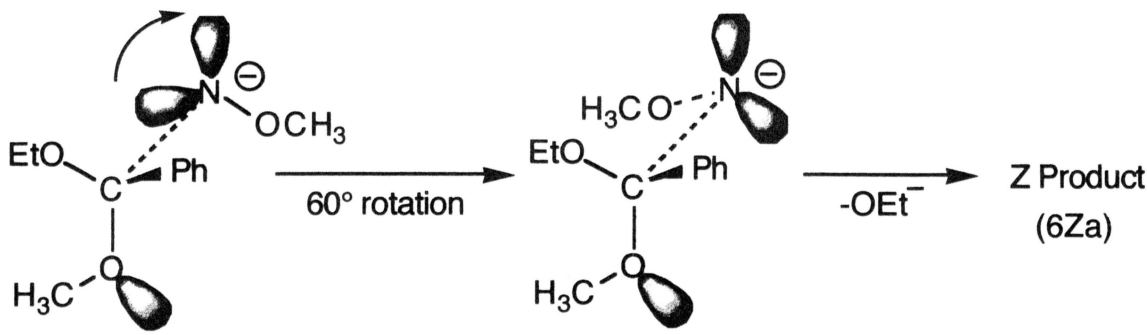
(8a: LG = Cl
  b: LG = Br)



Tetrahedral Intermediate
formed from E isomer

(9a: LG = Cl
  b: LG = Br)

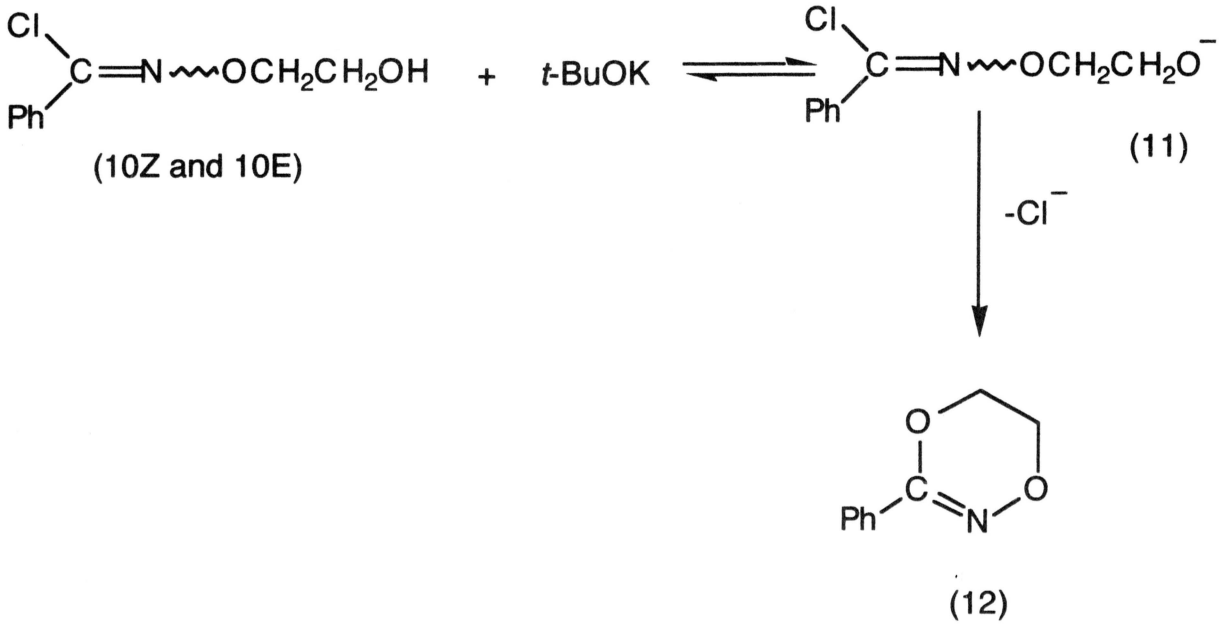
In the *E* isomer, however, the resulting tetrahedral intermediate (**9**) only has the lone pair of electrons on the methoxide oxygen located in an antiperiplanar orientation to the leaving group. As chloride is a good leaving group, a single pair of electrons antiperiplanar is adequate to assist in its elimination, but ethoxide, being a poorer leaving group, must have two pair of antiperiplanar electrons before it can be eliminated. Therefore, once the tetrahedral intermediate of the *E* isomer (**9**) is formed it must undergo a 60 degree rotation to align two pairs of electrons antiperiplanar to the ethoxide group before forming product.



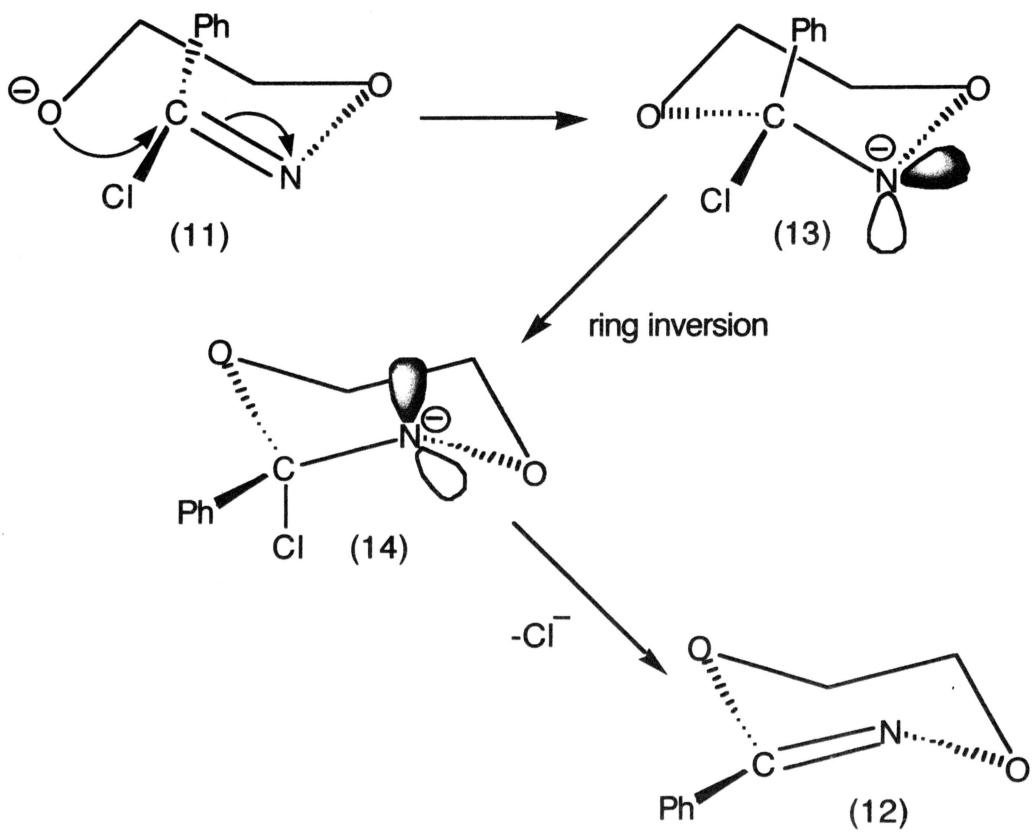
(9) (8)

This results in the *Z* isomer of the product (**6Za**) and explains the disparity in the rates between the *Z* and *E* isomers.

Recently Johnson and Li[24] have investigated intramolecular alkoxide substitution at the carbon-nitrogen double bond. The *Z* and *E* isomers of *O*-(2-hydroxyl)ethylbenzohydroximoyl chloride (**10Z and 10E**) were reacted with potassium *t*-butoxide in 60% DMSO and 40% *t*-butyl alcohol, and both yielded the same product (**11**) resulting from intramolecular alkoxide attack.



If the intramolecular substitution reaction proceeds by the same addition-elimination mechanism proposed for the intermolecular substitution one would expect the *E* isomer to react slower than the *Z* isomer. This would be a result of the tetrahedral intermediate formed from alkoxide attack of the *E* isomer of the starting material (**1 3**). Here there are no lone pair electrons antiperiplanar to the leaving group. Therefore, it would appear that the ring must undergo an inversion to position the chloride in an axial position with lone pair electrons antiperiplanar to it (**1 4**).



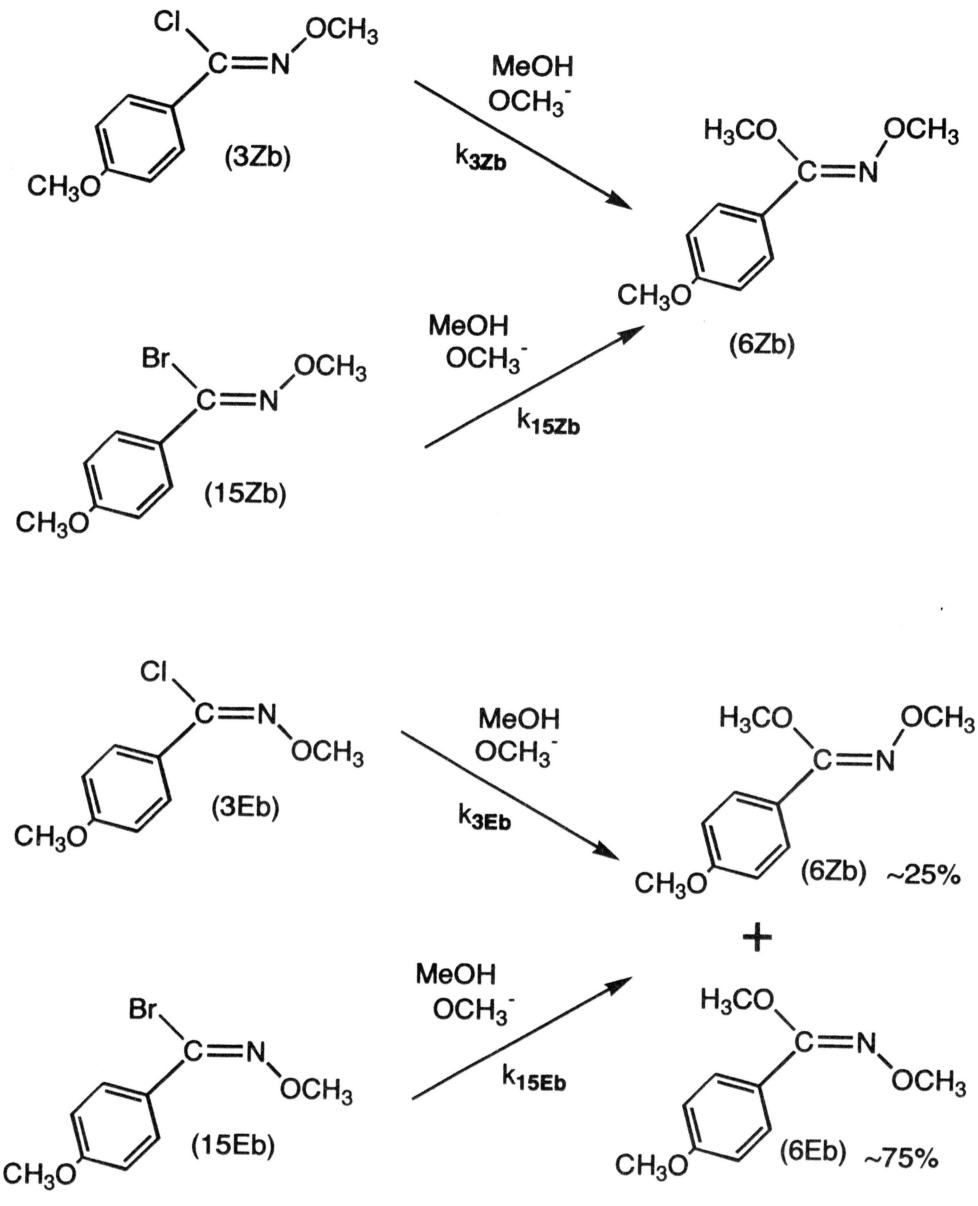
This ring inversion had been estimated to be greater than 10.9 ± 0.2 kcal/mol by comparison to similar systems. Surprisingly, when reaction rates were measured, it was found that the *E* isomer (**10E**) reacted approximately four times faster than the *Z* isomer (**10Z**) in this intramolecular alkoxide substitution. Possible explanations for this unexpected result included unassisted ionization of the chloride to form a planar zwitterionic intermediate or the involvement of a direct displacement mechanism in the alkoxide substitution of the (*E*)-*O*-(2-hydroxyl)ethylbenzohydroximoyl chloride (**10E**). It was proposed that an element effect study on this intramolecular substitution would provide evidence to support or rule out these alternative mechanisms.

With the possibility of a concerted reaction arising in the intramolecular alkoxide substitution of the *E* isomer of *O*-(2-hydroxyl)ethylbenzohydroximoyl chloride (**10E**) one must also consider a concerted process for the intermolecular substitution of hydroximoyl chlorides with methoxide ion. The mechanistic probes employed previously for these intermolecular reactions indicated nucleophilic attack occurring in the rate determining step, but provided no information about the position of the leaving group.[20, 21, 22, 23] Leaving group effects in which the rates of reaction are compared relative to their nucleofuges can be useful in determining any degree of bond breakage ocurring in the rate determining step. A common study done is the k_{Br}/k_{Cl} element effect.

A k_{Br}/k_{Cl} ratio around unity indicates that there is no substrate-halogen bond breaking occurring in the rate determining step. In the case of the hydroximoyl halide intermolecular substitution with methoxide, this ratio would mean that the rate is solely dependent upon nucleophilic attack and that these reactions proceed by a true $A_{N\#}+D_N$ mechanism. A k_{Br}/k_{Cl} ratio significantly greater than one could indicate some substrate-halogen bond breakage occurring in the rate determining step, and one would expect this larger ratio if the substitution reaction of the hydroximoyl halide did occur by a concerted mechanism. Although Hoz, Basch, Wolk, Rappoport, and Goldberg[25] have recently cautioned that an element effect > 1 may represent a greater stabilization of the ground state of the chloride compound relative to that of the bromide compound, an element effect ≤ 1 is still considered a reliable indication that the substrate-halogen bond is not cleaved in the rate-determining step.

This research consists of an investigation of the element effect (k_{Br}/k_{Cl}) in methoxide substitution of the *Z* and *E* isomers of *O*-methyl-4-methoxybenzohydroximoyl halides (k_{3Zb}/k_{15Zb} and k_{3Eb}/k_{15Eb}) (Scheme I).

Scheme I


Cl
C=N
OCH3
CH3O
(3Zb)
MeOH
OCH3-
k3Zb
H3CO
OCH3
C=N
CH3O
(6Zb)
Br
C=N
OCH3
CH3O
(15Zb)
MeOH
OCH3-
k15Zb
Cl
C=N
OCH3
CH3O
(3Eb)
MeOH
OCH3-
k3Eb
H3CO
OCH3
C=N
CH3O
(6Zb) ~25%
+
Br
C=N
OCH3
CH3O
(15Eb)
MeOH
OCH3-
k15Eb
H3CO
C=N
OCH3
CH3O
(6Eb) ~75%

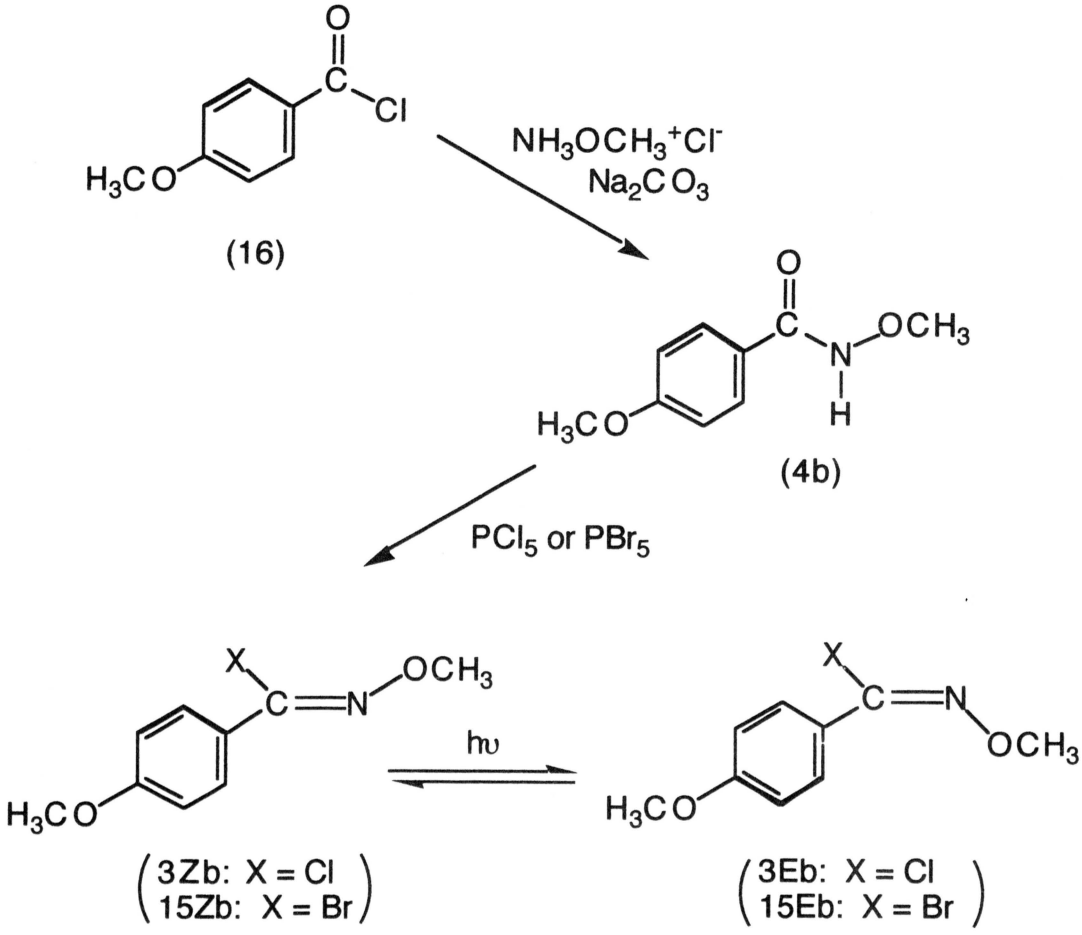
CHAPTER II

RESULTS AND DISCUSSION

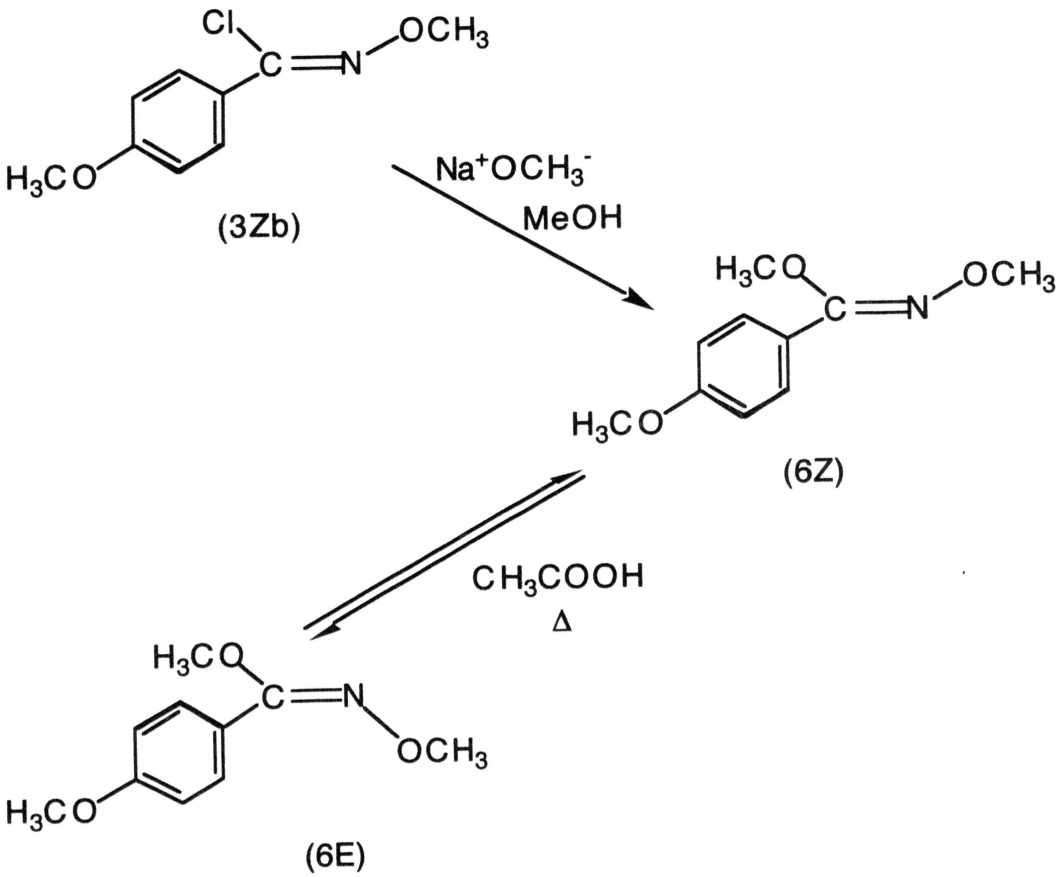
The *Z* and *E* isomers of *O*-methyl-4-methoxybenzohydroximoyl chloride (**3Zb** and **3Eb**) and bromide (**15Zb** and **15Eb**) were synthesized (Scheme II). Reaction of 4-methoxybenzoyl chloride (**16**) with methoxylamine hydrochloride in sodium carbonate solution gave the methyl 4-methoxybenzohydroxamate (**4b**). The methyl 4-methoxybenzohydroxamate was reacted with either phosphorous pentachloride or phosphorous pentabromide to form the (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl halide (**3Zb** or **15Zb**). The (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**3Zb**) in hexane was irradiated with ultraviolet light (low pressure lamp) to give a mixture of the *Z* and *E* isomers (**3Zb** and **3Eb**). The isomers were separated by column chromatography. (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl bromide (**15Zb**) was irradiated in hexane at 0°C using a medium pressure lamp according to the procedure recently reported by Sakamoto *et al*[26]. The mixture of the *Z* and *E* isomers (**15Zb** and **15Eb**) of the hydroximoyl bromide produced by this low temperature procedure were separated by column chromatography.

The *E* and *Z* isomers of *O*-methyl-4-methoxybenzohydroximate (**6E** and **6Z**) were synthesized (Scheme III). (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**3Zb**) was reacted with sodium methoxide in dimethyl sulfoxide to form methyl (*Z*)-*O*-methyl-4-methoxybenzohydroximate (**6Z**). This hydroximate was heated in glacial acetic acid resulting in a mixture of the *Z* and *E* isomers (**6Z** and **6E**). These isomers were separated by column chromatography.

Scheme II


O
C
Cl
H3CO
(16)
NH3OCH3+Cl-
Na2CO3
O
C
N
OCH3
H
H3CO
(4b)
PCl5 or PBr5
X
C
N
OCH3
H3CO
hυ
(3Zb: X = Cl
15Zb: X = Br)
X
C
N
OCH3
H3CO
(3Eb: X = Cl
15Eb: X = Br)

Scheme III


Cl
C
N
OCH3
H3CO
(3Zb)
Na+OCH3-
MeOH
H3CO
C
N
OCH3
H3CO
(6Z)
CH3COOH
Δ
H3CO
C
N
OCH3
H3CO
(6E)

Reaction rates for methoxide ion substitution in dimethyl sulfoxide:methanol 90:10 solution (v/v) at 44.6°C were studied under pseudo-first-order conditions at four different methoxide ion concentrations. Aliquots of the reaction were taken at intervals, brought to pH 4-7 with the addition of HCl solution, and analyzed by high performance liquid chromatography (HPLC).

Most of the kinetic runs were terminated when approximately half of the starting material had been consumed; however, a few reactions were monitored until >90% of the starting material had been consumed. Correction factors for the peak areas of the components of the reaction mixture were previously determined from standard mixtures consisting of the *O*-methyl benzohydroximoyl halide and the *Z* and *E* isomers of the methyl *O*-methylbenzohydroximate (**6Z** and **6E**). Samples of data for typical kinetic runs of all compounds are found in Tables 1-4.

All reactions were found to follow second order kinetics (first order in methoxide ion and first order in the *O*-methyl-4-methoxybenzohydroximoyl halide). Rate constants (k_{obs}) and errors were calculated using a statistical program (InStat). Plots of ln C_o/C versus time (s) yielded a straight line in all cases with a linear regression program (Cricket Graph) (Figure 1-4). The slope of the line divided by the methoxide concentration gave the second-order rate constant for the reaction (Table 5). Average reaction rate constants are found in Table 6. The average rate of reaction of (*Z*) *O*-methyl-4-methoxybenzohydroximoyl chloride (**3Zb**) measured in this study is 4.46×10^{-3} $M^{-1}s^{-1}$ which is very close to the rate determined previously by Johnson, Nalley, Weidig and Arfan[20] of 5.20×10^{-3} $M^{-1}s^{-1}$ which was measured directly under second order conditions.

Table 1. Data from a typical run of methoxide substitution of (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**3Zb**) in 90:10 DMSO:MeOH at 44.6°C.

time (s)	% (**3Zb**)	ln C_o/C
622	88.1	0.1267
1202	77.9	0.2497
1791	68.4	0.3798
2415	59.9	0.5125
2986	52.8	0.6387
3585	46.3	0.7700
4212	40.5	0.9039
4777	35.2	1.0441

Figure 1. Typical first order plot of the reaction of (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**3Zb**) with methoxide ion; [**3Zb**] = 2.37 X 10^{-4} M, [OCH_3^-] = 4.67 X 10^{-2} M.

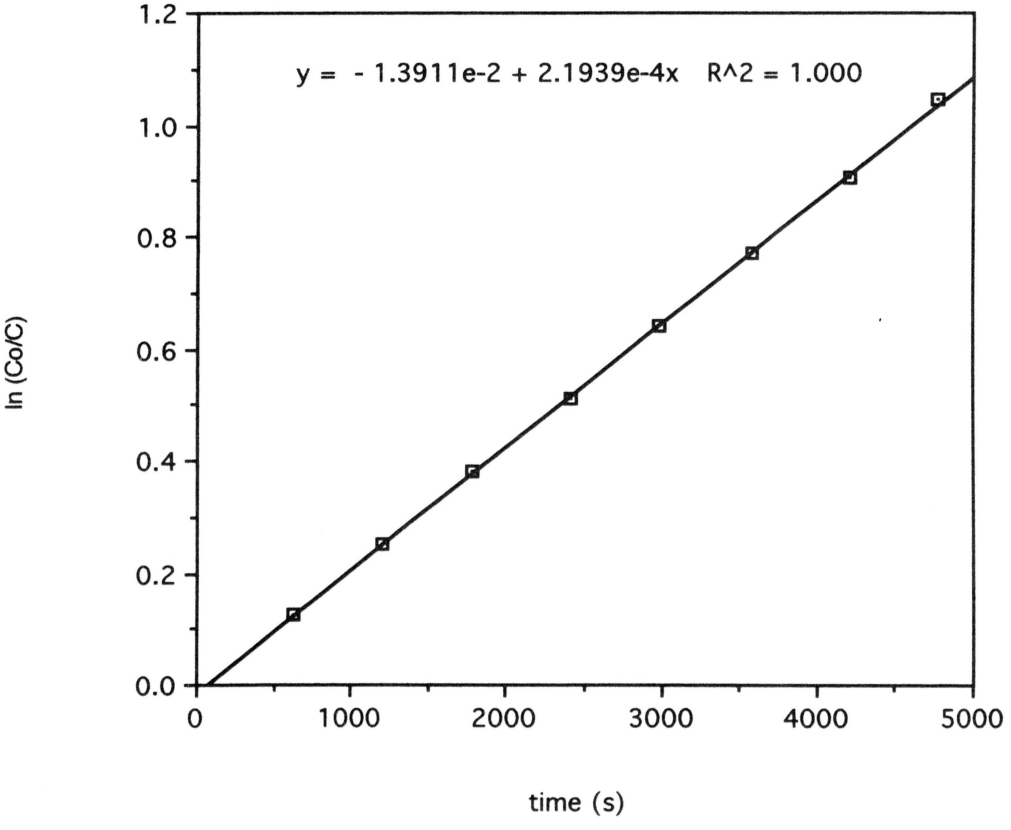


Table 2. Data from a typical run of methoxide substitution of (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl bromide (**15Zb**) in 90:10 DMSO:MeOH at 44.6°C.

time (s)	% (**15Zb**)	ln C_o/C
564	65.0	.431
1139	41.9	.870
1708	25.5	1.366
2267	15.6	1.858
2907	8.44	2.472
3404	5.81	2.846
3993	3.38	3.387
4695	2.15	3.840

Figure 2. Typical first order plot of the reaction of (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl bromide (**15Zb**) with methoxide ion; [**15Zb**] = 1.29 X 10^{-4} M, [OCH_3^-] = 6.13 X 10^{-2} M.

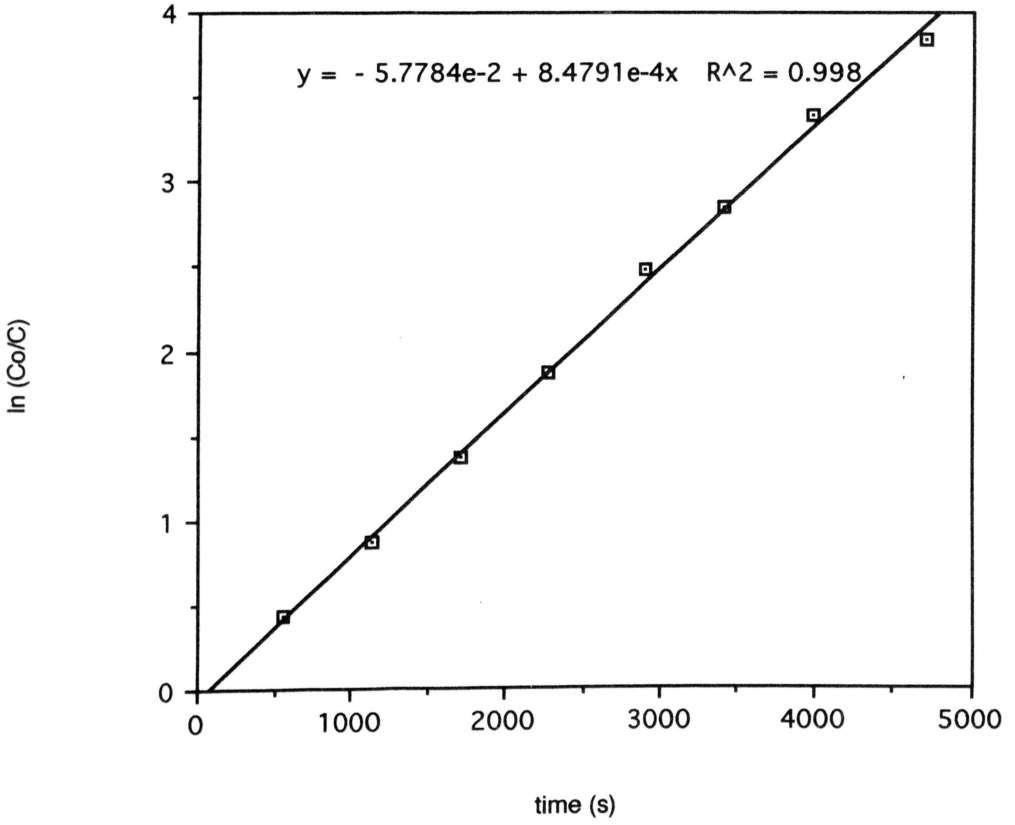


Table 3. Data from a typical run of methoxide substitution of (*E*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**3Eb**) in 90:10 DMSO:MeOH at 44.6°C.

time (s)	% (**3Eb**)	ln C_o/C
448	92.1	0.08230
856	85.6	0.1555
1283	79.6	0.2282
1680	73.7	0.3052
2111	67.6	0.3916
2563	63.0	0.4620
2962	58.1	0.5430
3458	53.9	0.6180

Figure 3. Typical first order plot of the reaction of (*E*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**3Eb**) with methoxide ion; [**3Eb**] = 2.14 X 10^{-4} M, [OCH_3^-] = 4.50 X 10^{-2} M.

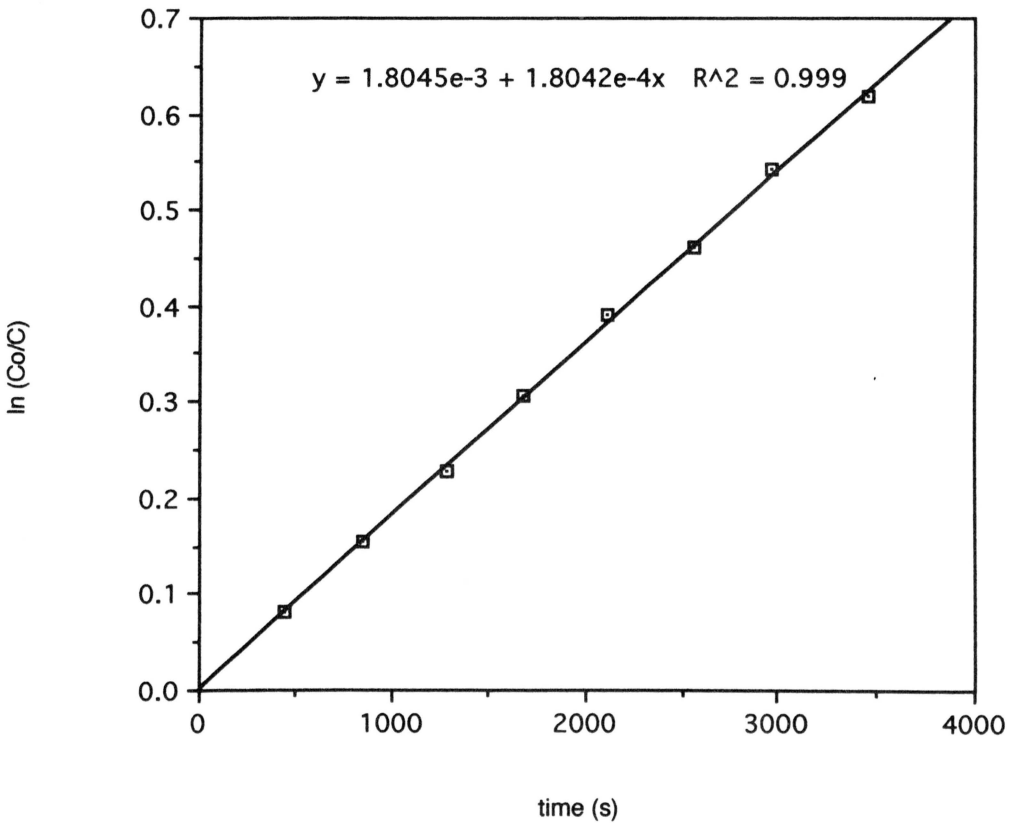


Table 4. Data from a typical run of methoxide substitution of (*E*)-*O*-methyl-4-methoxybenzohydroximoyl bromide (**15Eb**) in 90:10 DMSO:MeOH at 44.6°C.

time (s)	% (**15Eb**)	ln C_o/C
267	87.4	0.1347
453	79.2	0.2332
705	69.3	0.3667
938	61.9	0.4797
1169	56.3	0.5745
1422	48.5	0.7236
1623	42.6	0.8533
1888	37.7	0.9755

Figure 4. Typical first order plot of the reaction of (*E*)-*O*-methyl-4-methoxybenzohydroximoyl bromide (**15Eb**) with methoxide ion; [**15Eb**] = 2.95 X 10^{-4} M, [OCH_3^-] = 6.13 X 10^{-2} M.

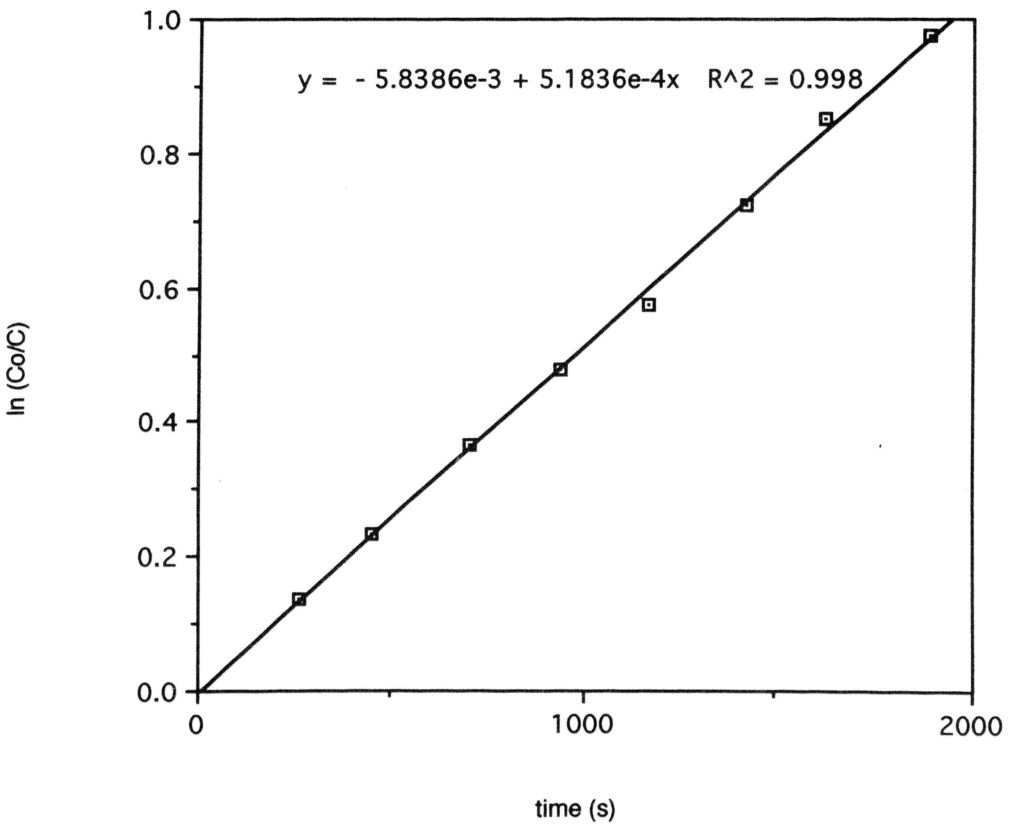


Table 5. Second Order Rate Constants for Methoxide Substitution of *O*-Methyl-4-methoxybenzohydroximoyl Halides

compound	10^{-4}[compd], M	10^{-2}[MeO^-], M	$10^{-3}k$, M^{-1} s^{-1}
15Zb	1.25	2.93	11.1 ± 0.1
15Zb	1.00	2.93	11.4 ± 0.1
15Zb	1.62	4.50	11.9 ± 0.1
15Zb	1.74	4.50	11.8 ± 0.1
15Zb	1.35	4.67	12.9 ± 0.1
15Zb	1.02	4.67	13.8 ± 0.1
15Zb	1.16	6.13	12.2 ± 0.1
15Zb	1.29	6.13	13.8 ± 0.1
3Zb	1.35	2.93	4.12 ± 0.19
3Zb	2.26	2.93	3.92 ± 0.12
3Zb	2.36	4.50	3.88 ± 0.10
3Zb	1.50	4.67	4.65 ± 0.38
3Zb	2.37	4.67	4.70 ± 0.07
3Zb	4.31	6.13	4.65 ± 0.18
3Zb	1.54	6.13	4.78 ± 0.13
3Zb	4.17	6.13	4.95 ± 0.19
15Eb	2.38	2.93	8.23 ± 0.59
15Eb	2.00	2.93	8.39 ± 0.32
15Eb	2.73	4.50	8.30 ± 0.34
15Eb	3.81	4.50	8.78 ± 0.26
15Eb	1.64	4.67	9.36 ± 0.31
15Eb	3.11	6.13	8.54 ± 0.43
15Eb	2.95	6.13	8.46 ± 0.36
3Eb	4.68	2.93	4.29 ± 0.10
3Eb	1.41	2.93	4.16 ± 0.15
3Eb	3.36	4.50	4.06 ± 0.09
3Eb	2.14	4.50	4.01 ± 0.09
3Eb	1.48	4.67	4.67 ± 0.05
3Eb	1.35	4.67	4.76 ± 0.14
3Eb	2.80	6.13	4.52 ± 0.09
3Eb	1.34	6.13	4.44 ± 0.35

Table 6. Average Rate Constants for Methoxide Substitution of *O*-Methyl-4-methoxybenzohydroximoyl Halides

compound	average reaction rate constants
15Zb	12.4 X 10^{-3} $M^{-1}s^{-1}$
3Zb	4.46 X 10^{-3} $M^{-1}s^{-1}$
15Eb	8.58 X 10^{-3} $M^{-1}s^{-1}$
3Eb	4.36 X 10^{-3} $M^{-1}s^{-1}$

Product distributions for the *E* isomers were similar to those found previously[20] with (*E*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**3Eb**) giving a *Z*:*E* product ratio of 33.5:66.5, and (*E*)-*O*-methyl-4-methoxybenzohydroximoyl bromide (**15Eb**) giving a *Z*:*E* product ratio of 29.4:70.6. The *Z* isomer of both hydroximoyl halides (**3Zb** and **15Zb**), however, appeared to yield almost exclusively the *Z* isomer of the product (**6Z**) in this study whereas in the previous work[20] the product contained approximately 2% of the E isomer of the hydroximate (**6E**). If any of the *E* isomer of the product was produced in these reactions, it was below the detection limit of the UV detector of the HPLC. The detection limit of the UV detector of the HPLC for this E isomer was experimentally determined to be at a concentration of 9.30 X 10^{-7} M . Therefore, in the reaction of the *Z*-hydroximoyl halide which yielded the highest concentration of *Z*-hydroximate (**6Zb**) (2.68 X 10^{-4} M) the minimum detectable concentration of *E*-hydroximate (**6Eb**), if present, would only account for 0.35% of the product. Since the concentration of the *E* isomer of the product (**6Eb**) is below this limit when reacting the *Z*

isomer of the hydroximoyl halides (**3Zb** and **15Zb**) it can be said that the (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl halides (**3Zb** and **15Zb**) undergo methoxide substitution with > 99.6% retention of configuration.

This difference from the previous study could be due to better separation of the stereoisomers of the starting material in the present study. The purities of the compounds were assessed by integration of the gas chromatogram generated from the GC/MS spectrometer and are given in Table 7.

Table 7. Purity of the Compounds Used for Kinetic Runs

Compound	% *Z* isomer	% *E* isomer	% Other
3Zb	99.59	0.00	0.41
15Zb	99.69	0.00	0.31
3Eb	0.09	99.15	0.76
15Eb	0.17	99.27	0.57

In all cases there was less than 0.2% of the other stereoisomer in the compounds used for the kinetic studies.

The second-order rate constants (Table 5) were calculated by dividing the observed first-order rate constants by methoxide concentration. The second-order rate constants change only slightly with an increase in the methoxide ion concentration. It is concluded that the rates of the reactions are first-order in both hydroximoyl halide and methoxide ion. This finding could support either an addition-elimination ($A_N + D_N$) or a concerted mechanism

(A_ND_N) but rules out more complicated mechanistic possibilities involving another methoxide ion in the rate-determining step.

The *Z* and *E* isomers of *O*-methyl-4-methoxybenzohydroximoyl chloride (**3Zb** and **3Eb**) appear to react at the same rate with the ratio of the average rates $k_{3Zb}/k_{3Eb} = 1.02$. In addition, the average reaction rates for the *Z* and *E* isomer of *O*-methyl-4-methoxybenzohydroximoyl bromide (**15Zb** and **15Eb**) also appear to be approximately the same with a ratio $k_{15Zb}/k_{15Eb} = 1.45$. This could support both isomers of the hydroximoyl chloride and bromide reacting by the same mechanism.

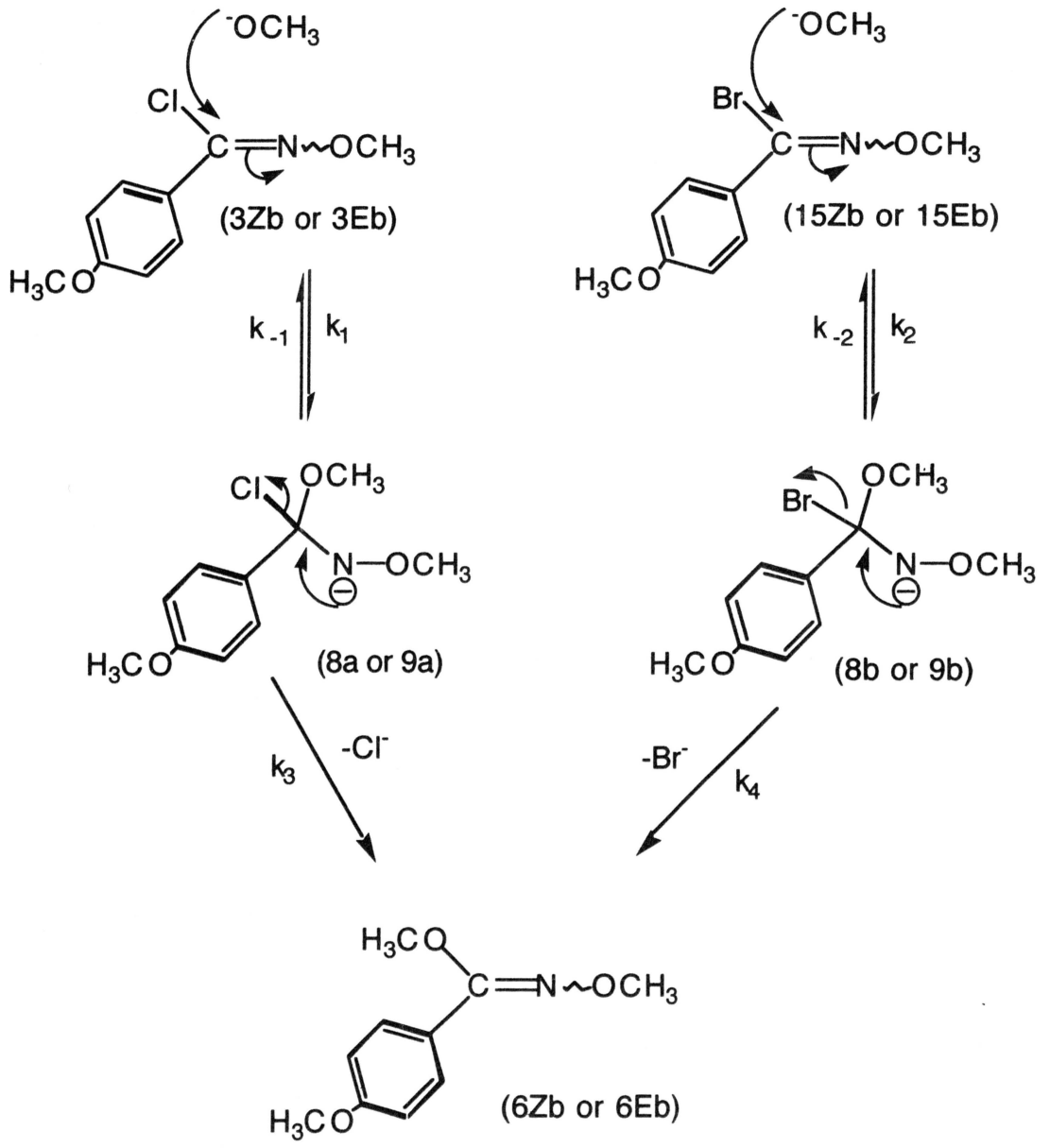
These kinetic studies, however, were mainly undertaken to determine whether the methoxide substitution mechanism is truly stepwise addition-elimination or concerted. To distinguish between these two possibilities, the degree of substrate-nucleofuge bond breakage in the rate determining step must be ascertained. If there is no noticeable dissociation of the nucleofuge but there is association of the nucleophile to the substrate in the rate determining step, the mechanism is considered truly stepwise $A_N + D_N$.

Leaving group effects can help to identify any dissociation of the nucleofuge in the rate determining step. Isotopic leaving group effects [$k(^{35}Cl)/k(^{37}Cl)$ or $k(^{79}Br/^{81}Br)$] are perhaps the most reliable indicators of bond breakage but experimental measurement is extremely difficult. Therefore, element effects comparing reaction rates of two systems differing only in their nucleofuge serve as a more practical indicator for bond breakage. Several studies have been performed comparing reaction rates with Cl^- and Br^- leaving groups [17,27,28,29,30]. The substrate-halogen bond is usually considered to be dissociating in the rate determining step if the k_{Br}/k_{Cl} ratio ≥ 30[17], but recent

calculations suggest that cautious interpretation of ratios around 30 would be warranted[25]. If $1 \leq k_{Br}/k_{Cl} \geq 30$, substrate-halogen cleavage is thought to be a quick process which does not affect the overall rate of the reation.

In this study the element effect appears to be negligible for both the *Z* and *E* isomers. For the Z isomers (**3Zb** and **15Zb**) the average rate ratio k_{Br}/k_{Cl} = 2.78. For the E isomers (**3Eb** and **15Eb**) the average rate ratio k_{Br}/k_{Cl} = 1.97. These ratios would indicate that the carbon-halogen bond is not cleaved in the rate-determining step. This appears to rule out the possibility that methoxide substitution in *O*-methyl-4-methoxybenzohydroximoyl halide is a concerted process in either the *Z* or the *E* isomer. It, however, supports the addition-elimination ($A_N + D_N$) mechanism previously proposed by Johnson *et al* [18,20,21,22, 23] in which the rate determining step involves nucleophilic attack to form the tetrahedral intermediate (**8a**, **8b**, **9a**, or **9c**) followed by rapid loss of the halogen (Scheme III). These findings do not explain the relatively fast intramolecular alkoxide substitution reaction of (*E*)-*O*-(2-hydroxyl)ethylbenzohydroximoyl chloride (**10**). The element effect (k_{Br}/k_{Cl}) for this compound is needed to support or rule out a concerted process for the *E* isomer of this compound.

Scheme III. Proposed Mechanism for Methoxide Substitution of *O*-Methyl-4-methoxybenzohydroximoyl Chloride (**3Zb** and **3Eb**) and of *O*-Methyl-4-methoxybenzohydroximoyly Bromide (**15Zb** and **15Eb**).



$k_3 >>> k_1$ $k_4 >>> k_2$

CHAPTER III

EXPERIMENTAL

A. General Procedures

All chemicals used in this research are reagent grade except as noted. (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl bromide (**15Zb**) and (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**3Zb**) were synthesized by procedures described by Johnson *et al*[17]. Isomerization of the bromide and separation of the isomers were performed by procedures described by Sakamoto *et al* [26]. Isomerization of the chloride was performed as outlined by Johnson *et al* [17] substituting hexane for the solvent. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR Spectra were determined from Nujol mulls between sodium chloride plates. NMR spectra were obtained at 200 MHz. Low resolution mass spectra were determined on a Varian Saturn 3 ion-trap GC/MS spectrometer. Ultraviolet spectra were performed with a Shimadzu UV-2101PC scanning spectrophometer. Elemental analyses of the new compounds were performed by Atlanta Microlab, Inc., Atlanta, GA.

1. The Column Chromatography Procedure

Silica gel (MN-Kieselgel 60, 0.1-0.2 mm/70-130 mesh) was packed into the column (22 X 400 mm). A ratio of 80:1 (silica:sample) was used. The eluent for separation of the hydroximates was a mixture of hexane and chloroform in a 1:1 ratio (v/v). The eluent for separation of the hydroximoyl chlorides was a mixture of hexane and benzene in a 4:1 ratio (v/v). In each case the sample was dissolved in the eluent and then introduced onto the column.

2. The GC/MS Procedure

The degree of separation of the E and Z isomers was assessed by GC/MS spectrometry. The GC/MS used in this research was a Saturn 3 (ion trap) from Varian Associates. The capillary column in the GC was a J & W DM-5MS (I.D. of 0.25 mm and a length of 30 m, coated with 0.25 μm film of 5% phenylmethylpolysiloxane).

3. The HPLC Procedure

The HPLC equipment consisted of a Spectra Physics IsoChrom LC pump, a Rheodyn injector, and a Spectra Physics 8450 variable wavelength UV/VIS detector with a 10 mm pathlength cell. It was connected to a Burdick & Jackson OD5 octadecyl column. A Hewlett Packard HP 3396A integrator was used to record and integrate the chromatograms. The mobile phase used to monitor the kinetics of the Z-hydroximoyl halides consisted of 55:45

acetonitrile:water (v/v). The mobile phase for the E-hydroximoyl halides was 66:33 acetonitrile:water (v/v). Retention times and normalization factors for peak areas were determined by analysis of samples containing known amounts of reactants and products.

4. The Kinetic Method

One 50 mL and two 25 mL volumetric flasks were dried in a 100° C oven. The 50 mL flask was removed from the oven, filled with dry nitrogen, quickly capped, and brought to room temperature in a dessicator. The hydroximoyl halide (1.2-3.0 mg) was weighed into this 50 mL flask on an analytical balance. The previously prepared DMSO (38 mL) was added to this 50 mL flask by blowing nitrogen into the closed dropping funnel of the DMSO storage flask for five minutes, opening the stopcock, removing the drying tube cap and the outer septum and inserting class A pipettes through the inner septum. After removing the DMSO, the outer septum was replaced, the stopcock on the dropping funnel was closed, and the drying tube was recapped.

The two 25 mL volumetric flasks were removed from the oven, filled with dried nitrogen, and quickly capped. Standardized sodium methoxide solution (7 mL) was placed in one of the flasks, and dry DMSO (10 mL) was placed in the other by the procedure outlined above for transfer of solvents from storage flasks.

All three volumetric flasks were thermally equilibrated in a 44.60 $\pm$ 0.01° C water bath (temperature checked with a quartz thermometer). The sodium methoxide solution (5 mL) was pipetted into the 50 mL volumetric flask

containing the hydroximoyl halide which was then shaken and quickly filled to the mark with the thermostatted DMSO. Timing was begun upon addition of the last drop of sodium methoxide to the 50 mL flask.

Aliquots (2 mL), taken at regular intervals, were quenched in HCl solution (2 mL) of the same molarity as the sodium methoxide in the 50 mL flask. The pH of the aliquots was measured with a pH meter and was adjusted with additional drops of the HCl solution. The pH was between 4 and 7.

20 μl of each aliquot was injected into a Burdick & Jackson OD5 octadecyl column (55:45 acetonitrile:water mobile phase for the Z-hydroximoyl halides, 66:33 acetonitrile:water mobile phase for the E-hydroximoyl halides) attached to a Spectra-Physics UV-Vis detector. Normalization factors for peak areas were determined by analysis of samples containing known amounts of reactants and products. Rate constants and errors were determined by a statistics program (InStat).

5. Preparation and Titration of Solvents used for Kinetics

Dimethyl sulfoxide (Sigma-Aldrich HPLC grade and Burdick & Jackson) was stored over NaOH pellets for greater than 24 hours and then distilled under vacuum into a three-neck round-bottomed flask fitted with a CaCl drying tube, a double septum, and a ground-glass-jointed dropping funnel. Once the distillation was complete, the stopcock on the dropping funnel was closed, and the drying tube was capped.

To prepare the sodium methoxide solution, methanol was distilled from magnesium turnings into a three neck round-bottomed flask fitted with a

Ca_2SO_4 drying tube, a double septum, and a ground-glass-jointed dropping funnel. The distillation was performed with a constant stream of dry nitrogen purging the distillation apparatus. After distillation, with nitrogen still purging the three-neck receiving/storage flask, the double septum was removed, sodium was added to the flask, and the double septum was quickly replaced. When the reaction was complete the stopcock was closed, and the drying tube was capped.

For standardization of the HCl solution used to titrate the sodium methoxide solution, primary standard sodium carbonate (99.89%) was dried in a 200°C oven for 1 1/2 hours and then cooled to room temperature in a dessicator. This dried sodium carbonate was weighed into a 125 mL Erlenmeyer flask, and 50 mL of distilled water was added. Using methyl red indicator, the solution was titrated quickly with HCl until the solution turned reddish in color. The solution was then boiled for one minute, and the color returned to yellow. This solution was cooled to room temperature and then carefully titrated with HCl solution to a pink end point.

The sodium methoxide solution was titrated by transferring 5 mL of the sodium methoxide solution from the storage flask into a 125 mL Erlenmeyer containing 50 mL of water. This transfer was done by flushing the closed dropping funnel on the storage flask with dry nitrogen for 5 minutes and then opening the stopcock and uncapping the drying tube, allowing nitrogen to slowly purge the three-neck flask. The outer septum was removed, and a 5 mL class A pipette was inserted through the inner septum to remove the sodium methoxide solution. After the transfer, the outer septum on the three-neck flask

was replaced, the stopcock on the dropping funnel was closed, and the drying tube was recapped.

The sodium methoxide solution in the 125 mL Erlenmeyer flask was then titrated with the standardized HCl solution using methyl red indicator.

B. Synthesis of methyl (*Z*)*O*-methyl-4-methoxybenzohydroximate (**6Zb**)

Sodium metal (0.97 g, 0.0422 mol) was dissolved in methanol (26 mL) in a 250 mL round-bottomed flask fitted with a condenser, a dropping funnel and a J-KEM 9900 temperature probe. A solution of*O*-methyl 4-methoxybenzohydroximoyl chloride (2.45 g, 0.0123 mol) in dimethyl sulfoxide (230 mL) was added through the dropping funnel with stirring. The mixture was heated at 51°C for 22 h. The flask was allowed to cool to room temperature, and the contents were poured into ice-cold water (225 mL). The mixture was extracted with ether (4 x 50 mL), and the combined ether extracts were dried over anhydrous magnesium sulfate. The ether was removed by rotary evaporation under aspirator pressure, and the residual yellow oil was microdistilled (0.1 mmHg at 84°C) to yield white crystals (1.70 g, 0.0087 mol, 71%): mp 31.7-32.5, R_f 0.05 (1:1 chloroform:hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ3.8001 (s, 3H, OCH_3), 3.8008 (s, 3H, OCH_3), 3.8118 (s, 3H, OCH_3), 6.894, 7.773 (AA'BB', J = 8.6, 4 H, aromatic H); ^{13}C NMR (200 MHz, $CDCl_3$) δ54.4679, 55.2201, 62.0784, 113.211, 121.947, 130.613, 160.800; IR (Nujol) 1615 cm^{-1}. ; Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.64; H, 6.76; N, 7.07.

C. Synthesis of methyl (*E*)-*O*-methyl-4-methoxybenzohydroximate (**6Eb**)

A glacial acetic acid (15 mL) solution of Z-hydroximate (0.54 g) was heated at 80°C for 4 h. The reaction mixture was quenched by mixing it with an excess of 6M sodium hydroxide (100 mL) solution. The resulting solution was extracted with ether (3 X 75 mL). The ether extracts were dried with magnesium sulfate, and the ether was evaporated under aspirator pressure giving a yellow oil. GC-MS analysis of the oil showed two peaks due to the Z-hydroximate and the E-hydroximate in a ratio of 27:73. The E-hydroximate was separated by column chromatography which yielded white crystals. mp 37.9-38.8, R_f 0.24 (1:1 chloroform:hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ3.8136 (s, 3H, OCH_3), 3.8038 (s, 3H, OCH_3), 6.889, 7.583 (AA'BB', J = 8.9, 4 H, aromatic H); ^{13}C NMR (200 MHz, $CDCl_3$) δ55.342, 59.319, 62.310, 113.864, 128.871; IR (Nujol) 1609 cm^{-1}. ; UV (methanol) 254 nm (ε 10730); Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.42; H, 6.76; N, 7.07.

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