JOC Article

Mechanism of Methoxide Ion Substitution in the *Z* and *E* Isomers of *O*-Methylbenzohydroximoyl Halides

James E. Johnson,*[,†] Debra D. Dolliver,*[,‡,§] Lonchun Yu,[†] Diana C. Canseco,[†] Michael A. McAllister,[‡,∥] and Jeffrey E. Rowe[⊥]

Department of Chemistry and Physics, Texas Woman's University, Denton, Texas 76204-5859, Department of Chemistry, University of North Texas, Denton, Texas 76203, and School of Chemistry, La Trobe University, Bundoora, Victoria 3086, Australia

jjohnson@twu.edu

Received October 6, 2003

Kinetics and stereochemical studies have been carried out on the reactions of the *Z* and *E* isomers of *O*-methylbenzohydroximoyl halides [**1Z** and **1E**, ArC(X)═NOCH$_3$] with sodium methoxide in 9:1 DMSO−methanol. The reactions of methoxide ion with hydroximoyl fluorides (X = F) are stereospecific. The reaction with **1Z** (X = F) gives only the *Z* substitution product (**1Z**, X ═OCH$_3$). The reaction of methoxide ion with **1E** (X = F) is less selective, giving ca. 85% *E* substitution product. The Hammett ρ-values for the *Z* and *E* isomers (X = F) are +2.94 and +3.30, respectively. The element effects for **1Z** (Ar = C_6H_5) are 2.21 (X = Br):1.00 (X = Cl):79.7 (X = F). The **1E** element effects are (Ar = C_6H_5) 1.00 (X = Cl):18.3 (X = F) and (Ar = 4-$CH_3OC_6H_4$) 1.97 (X = Br):1.00 (X = Cl):12.1 (X = F). The entropies of activation for these reactions are negative (for example, $\Delta S^{\ddagger}$ = −15 eu for **1Z** and $\Delta S^{\ddagger}$ = −14 eu for **1E**, Ar = 4-$CH_3OC_6H_4$, X = F). These experimental observations are consistent with a mechanism proceeding through a tetrahedral intermediate. Ab initio calculations were carried out to help explain the stereospecificity of these reactions. These calculations indicate that the tetrahedral intermediate from the *Z* isomer undergoes rapid elimination to the *Z* substitution product before stereomutation can take place. These calculations also show that the lowest barrier for rotation around the carbon−nitrogen single bond in the tetrahedral intermediate derived from **1E** leads to an intermediate that eliminates fluoride ion to give *E* product.

Introduction

The stereochemical outcome of a reaction can provide valuable information about the reaction's mechanism. In the study of nucleophilic substitution at the sp^2-hybridized carbons of alkenes (C═C), stereochemical outcomes can be monitored relative to other groups attached to the double bond. In nucleophilic substitution reactions on vinylic systems with good nucleophiles, a predominant retention of configuration in the product has been observed.[1,2] For some cases, it has been proposed that this stereochemical outcome arises from a single-step mechanism in which the leaving group departs on the same side as the attack of the incoming nucleophile.[3−5] Most, however, appear to react via a stepwise addition−elimination mechanism in which a significant hyperconjugative barrier prevents internal rotation of the resulting carbanionic intermediate (which could lead to partial or complete inversion of configuration).[1] Recent theoretical and experimental work has suggested that in unactivated alkenyl systems concerted nucleophilic substitution by relatively weak nucleophiles (Cl^- or Br^-) would preferentially occur by an in-plane, S_N2-like mechanism, resulting in complete inversion of configuration.[6−9] However, it is indicated that in these substitutions with stronger nucleophiles (OH^- or SH^-) an out-of-plane S_N2 mechanism with retention of configuration might be viable.[7]

A single-step S_N2-like mechanism has also been proposed for some nucleophilic substitution reactions at the sp^2-hybridized carbon of the acyl group (C═O).[10−18] While the stereochemical outcome of these reactions cannot be

* To whom correspondence should be addressed. Phone: 940-898-2567. Fax: 940-898-3198.
† Texas Woman's University.
‡ University of North Texas.
§ Current address: Southeastern Louisiana University, Department of Chemistry and Physics, Hammond, LA 70402.
∥ Current address: Agouron Pharmaceuticals, Alanex Division, San Diego, CA 92121-1194.
⊥ La Trobe University.

(1) Rappoport, Z. *Acc. Chem. Res.* **1992**, *25*, 474−479.
(2) Youssef, A. A.; Sharaf, S. M.; El-Sadany, S. K.; Hamed, E. A. *J. Org. Chem.* **1981**, *46*, 3813−3816.
(3) Rappoport, Z. *Rec. Trav. Chim.* **1985**, *104*, 309−349.
(4) Maffeo, C. B.; Marchese, G.; Naso, F.; Ronzini, L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 92−97.
(5) Dodd, D.; Johnson, M. D.; Meeks, B. S.; Titchmarsh, D. M.; Van Duong, K. N.; Gaudemer, A. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1261−1267.
(6) Glukhovtsev, M. N.; Pross, A.; Radom, L. *J. Am. Chem. Soc.* **1994**, *116*, 5961−5962.
(7) Kim, C. K.; Hyun, K. H.; Kim, C. K.; Lee, I. *J. Am. Chem. Soc.* **2000**, *122*, 2294−2299.
(8) Li, H. G.; Kim, C. K.; Lee, B.; Kim, C. K.; Rhee, S. K.; Lee, I. *J. Am. Chem. Soc.* **2001**, *123*, 2326−2333.
(9) Okuyama, T.; Takino, T.; Sato, K.; Ochiai, M. *J. Am. Chem. Soc.* **1998**, *120*, 2275−2282.
(10) Williams, A. *Acc. Chem. Res.* **1989**, *22*, 387−392.

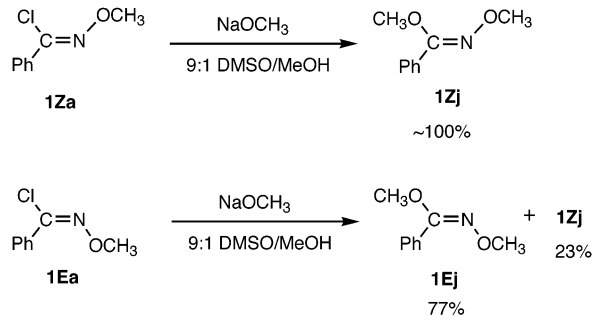
10.1021/jo030299e CCC: $27.50
Published on Web 03/17/2004

monitored, this type of mechanism has been proposed on the basis of Brønsted correlations,[11−14] correlation of the reaction with solvent ionizing power and nucleophilicity,[15,16] and isotope effects.[17,18] Calculations demonstrate that in a concerted gas-phase substitution of formyl chloride by chloride ion the barrier for in-plane attack ($S_N\sigma$) of the chloride ion is higher than for an out-of-plane attack ($S_N\pi$) in the mode thought to account for retained stereochemistry in the concerted substitution reactions of alkenes.[8,9]

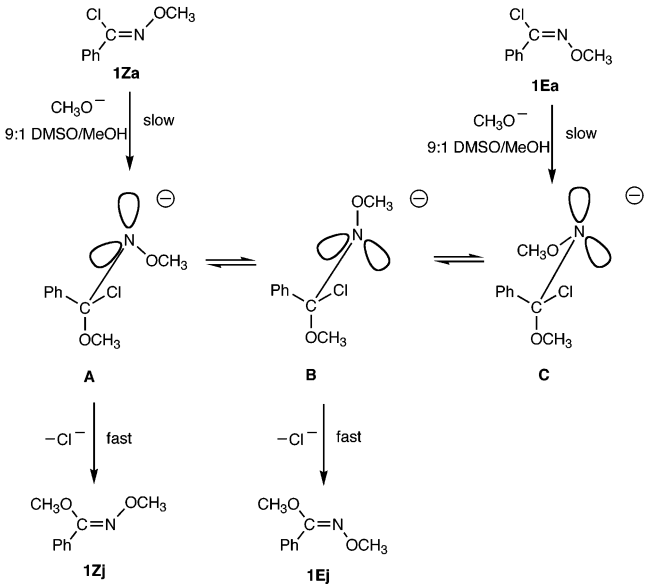
Nucleophilic substitution at the sp^2-hybridized carbon of an imine (C═N) has not received the same degree of attention as the C═C or C═O bonds, and to our knowledge, there has been no experimental evidence supporting a concerted type of mechanism of substitution with this moiety. It appears that only two mechanistic pathways for nucleophilic substitution at the carbon−nitrogen double bond have been experimentally identified: an ionization pathway ($D_N + A_N$)[19−21] and an addition−elimination pathway ($A_N + D_N$).[21−28] Recent theoretical work, however, demonstrates that concerted nucleophilic substitution at an imine carbon may either be mechanistically similar to that of the carbonyl ($S_N\pi$ resulting in retained stereochemistry) or that of an alkene ($S_N\sigma$ resulting in inverted stereochemistry).[9] It seems reasonable that the possibility of a concerted mechanism involving this bonding system should be considered, especially in cases where the stereochemical outcome is suggestive.

One such case is the nucleophilic substitution of methoxide ion on *O*-methylbenzohydroximoyl chlorides (**1Za** and **1Ea**) in 90:10 DMSO/MeOH (Scheme 1).[28] The reaction of the *Z* isomer (**1Za**) yields completely retained stereochemistry in the substitution product, while the *E* isomer (**1Ea**) yields preferential retention of stereochemistry (77% retention and 23% inversion). This unusual stereochemical outcome could not be readily explained

SCHEME 1



SCHEME 2



in view of the proposed stepwise addition−elimination mechanism in which the addition step was found to be rate determining ($A_N^{\ddagger} + D_N$) (Scheme 2).

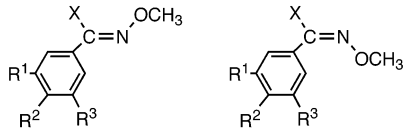
Results and Discussion

Our previous study[28] of the reaction of **1Z** included a Hammett correlation with σ (ρ = 1.90) and a rate comparison of the substitution of (*Z*)-*O*-methylbenzohydroximoyl bromide (**1Zc**) to (*Z*)-*O*-methylbenzohydroximoyl chloride (**1Za**) (Br/Cl = 2.2:1.0). This paper expands these findings by including kinetic data on selected (*Z*)- and (*E*)-hydroximoyl fluorides (**1Ze-i** and **1Ee-i**), bromides (**1Zd** and **1Ed**), and chlorides (**1Zb** and **1Eb**) (Chart 1) to provide full element effect data for this substitution reaction.

An investigation of the rate of (*Z*)- and (*E*)-hydroximoyl halides (**1Ze-i**, **1Ee-i**, **1Zd**, **1Ed**, **1Zb**, and **1Eb**) and sodium methoxide reactions showed each to be first-order in both hydroximoyl halide and methoxide ion (see Table 1S in the Supporting Information). With the hydroximoyl fluorides, the rate constant (Table 1) for substitution of the *Z* isomer (**1Ze-i**) in all cases was found to be larger than that for the *E* isomer (**1Ee-i**) (at 26.06 ± 0.04 °C; k_{1Ze}/k_{1Ee} = 4.78:1.00, k_{1Zf}/k_{1Ef} = 6.44:1.00, k_{1Zg}/k_{1Eg} = 2.69:1.00, k_{1Zh}/k_{1Eh} = 7.33:1.00, k_{1Zi}/k_{1Ei} = 1.87:1.00). Product distributions for the hydroximoyl fluorides were very similar to those seen for substitution reactions done on

(11) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1998**, *63*, 6820−6823.
(12) Castro, E. A.; Pavez, P.; Santos, J. G. *J. Org. Chem.* **1999**, *64*, 2310−2313.
(13) Stefanidis, D.; Cho, S.; Dhe-Paganon, S.; Jencks, W. P. *J. Am. Chem. Soc.* **1993**, *115*, 1650−1656.
(14) Ba-Saif, S. A.; Colthurst, M.; Waring, M. A.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1901−1908.
(15) Kevill, D. N.; Oldfield, A. J.; D'Souza, M. J. *J. Chem. Res., Synop.* **1996**, 122−123.
(16) Bentley, T. W.; Llewellyn, G.; McAlister, J. A. *J. Org. Chem.* **1996**, *61*, 7927−7932.
(17) Hengge, A. C.; Hess, R. A. *J. Am. Chem. Soc.* **1994**, *116*, 11256−11263.
(18) Hengge, A. *J. Am. Chem. Soc.* **1992**, *114*, 6575−6576.
(19) (a) Johnson, J. E.; Riesgo, E. C.; Jano, I. *J. Org. Chem.* **1996**, *61*, 45−50. (b) Johnson, J. E.; Cornell, S. C. *J. Org. Chem.* **1980**, *45*, 4144−4148.
(20) Hegarty, A. F.; Cronin, J. D.; Scott, F. L. *J. Chem. Soc., Perkin Trans. 2* **1975**, 429.
(21) Salvelova, V. A.; Popov, A. F. *Russ. J. Org. Chem.* **1999**, *35*, 797−828.
(22) Johnson, J. E.; Jano, I.; McAllister, M. A. *J. Phys. Org. Chem.* **1999**, *12*, 240−246.
(23) Rowe, J. E.; Lee, K. *Aust. J. Chem.* **1997**, *50*, 849−852.
(24) Rowe, J. E.; Papanelopoulos, D. A. *Aust. J. Chem.* **1995**, *48*, 2041−2046.
(25) Johnson, J. E.; Todd, S. L.; Gardner, J. L.; Gardner, T. M.; Buck, P.; Ghafouripour, A.; Zimmerman, W. *J. Phys. Org. Chem.* **1994**, *7*, 352−358.
(26) Johnson, J. E.; Todd, S. L.; Dutson, S. M.; Ghafouripour, A.; Alderman, R. M.; Hotema, M. R. *J. Org. Chem.* **1992**, *57*, 4648−4653.
(27) Rowe, J. E.; Hegarty, A. F. *J. Org. Chem.* **1984**, *49*, 3083−3087.
(28) Johnson, J. E.; Nalley, E. A.; Weidig, C.; Arfan, M. *J. Org. Chem.* **1981**, *46*, 3623−3629.

CHART 1



1Z **1E**

1Za and 1Ea: X = Cl; $R^1 = R^2 = R^3 = H$
b: X = Cl; $R^2 = OCH_3$; $R^1 = R^3 = H$
c: X = Br; $R^1 = R^2 = R^3 = H$
d: X = Br; $R^2 = OCH_3$; $R^1 = R^3 = H$
e: X = F; $R^1 = R^2 = R^3 = H$
f: X = F; R^2 = Cl; $R^1 = R^3 = H$
g: X = F; $R^2 = CH_3$; $R^1 = R^3 = H$
h: X = F; $R^2 = OCH_3$; $R^1 = R^3 = H$
i: X = F; $R^1 = R^3 = CF_3$; $R^2 = H$
j: X = OCH_3; $R^1 = R^2 = R^3 = H$
k: X = OCH_3; R^2 = Cl; $R^1 = R^3 = H$
l: X = OCH_3; $R^2 = CH_3$; $R^1 = R^3 = H$
m: $X = R^2 = OCH_3$; $R^1 = R^3 = H$
n: X = OCH_3; $R^1 = R^3 = CF_3$; $R^2 = H$
o: X = Cl; $R^1 = R^3 = CF_3$; $R^2 = H$
p: X = Br; $R^1 = R^3 = CF_3$; $R^2 = H$

the hydroximoyl chlorides and bromides. The *Z*-hydroximoyl fluorides (**1Ze-i)** gave only the *Z*-hydroximate (**1Zj-n)** and the *E*-hydroximoyl fluorides (**1Ee-i**) gave mixtures of the *E*- and *Z*-hydroximates with the *E*-hydroximate predominating (ca. 85% *E*, Table 2).

Activation parameters for the hydroximoyl fluorides (**1Ze**, **1Ee**, **1Zh**, and **1Eh**), hydroximoyl chlorides (**1Zb** and **1Eb**), and hydroximoyl bromides (**1Zd** and **1Ed**) were measured and are compared to the previously acquired values for (*Z*)- and (*E*)-*O*-methylbenzohydroximoyl chlorides (**1Za**, **1Zb**, and **1Ea**)[28] (Table 3). All entropies of activation ($\Delta S^{\ddagger}$) are negative, consistent with an associative process occurring in the rate-determining step in all the reactions.

The effect of substituents attached to the phenyl ring of the (*Z*)- and (*E*)-hydroximoyl fluorides was also investigated for this reaction. Reasonably good Hammett correlations were obtained with σ for the *Z* isomer with a ρ value of 2.94 ($r = 0.995$) and for the *E* isomer with a ρ value of 3.30 ($r = 0.993$) (Figure 1).

With the measurement of the rates of methoxide substitution on the *O*-methylbenzohydroximoyl fluorides, a full element effect rate comparison could be made for this reaction. Rates for substitution of the hydroximoyl chlorides and bromides had been measured previously[28] at 44.60 °C. At this temperature, the substitution of the hydroximoyl fluorides occurred too quickly to be accurately measured by the technique utilized in this study. Therefore, the rate constants for substitution of the hydroximoyl fluorides were extrapolated to 44.60 °C using the slope from a plot of ln *k* vs 1/*T*. The element effects at 44.6 °C for **1Z** are 2.21 (X = Br, **1Zc**[28]):1.00 (X = Cl, **1Za**[28]):79.7 (X = F, **1Ze**). The **1E** element effects at 44.6 °C are 1.00 (X = Cl, **1Ea**):18.3 (X = F, **1Ee**) and 1.97 (X= Br, **1Ed**):1.00 (X = Cl, **1Eb**):12.1 (X = F, **1Eh**).

In all situations, the hydroximoyl fluoride reacts significantly faster than either the hydroximoyl chloride or hydroximoyl bromide. This would be expected if the reaction proceeded by an addition−elimination mechanism in which the addition step was rate limiting ($A_N^{\ddagger} + D_N$).[28−34] There appears to be a much stronger rate enhancement due to the halogen in the *Z* isomer of these compounds than in the *E* isomer.

TABLE 1. Second-Order Rate Constants for the Reaction of Methyl Benzohydroximoyl Halides with Sodium Methoxide in 9:1 DMSO−Methanol Solution[a,b]

hydroximoyl halide	*T*, °C	10^2k, M^{-1} s^{-1}
1Ze	20.25	11.4 ± 0.6
1Ze	26.06	23.4 ± 1.0
1Ze	30.08	32.4 ± 1.8
1Ze	35.55	47.0 ± 2.2
1Ze	39.22	61.1 ± 2.3
1Ee	20.25	2.63 ± 0.38
1Ee	26.06	4.90 ± 0.32
1Ee	30.08	8.45 ± 0.60
1Ee	37.30	12.6 ± 1.3
1Ee	40.67	18.4 ± 2.0
1Zf	26.06	121 ± 14
1Ef	26.06	18.8 ± 2.2
1Zg	26.06	6.36 ± 0.51
1Eg	26.06	2.36 ± 0.32
1Zh	26.06	7.26 ± 0.58
1Zh	36.60	15.3 ± 1.1
1Zh	44.60	32.6 ± 1.9
1Eh	26.06	0.990 ± 0.104
1Eh	36.06	2.37 ± 0.22
1Eh	44.60	5.27 ± 0.16
1Zi	26.06	10600 ± 700
1Ei	26.06	5680 ± 1020
1Zb	44.60	0.446 ± 0.017
1Zb	48.83	0.684 ± 0.063
1Zb	51.63	0.956 ± 0.035
1Zb	54.48	1.18 ± 0.04
1Zb	57.25	1.52 ± 0.06
1Eb	44.60	0.436 ± 0.013
1Eb	48.83	0.684 ± 0.033
1Eb	51.63	0.894 ± 0.060
1Eb	54.48	1.13 ± 0.11
1Zd	44.60	1.24 ± 0.01
1Zd	48.83	1.98 ± 0.11
1Zd	51.63	2.53 ± 0.07
1Zd	54.48	3.33 ± 0.019
1Ed	44.60	0.858 ± 0.037
1Ed	48.83	1.32 ± 0.07
1Ed	52.89	1.92 ± 0.06
1Ed	54.48	2.25 ± 0.04

[a] In most cases, the rate constants are an average of at least two measurements (see Table 1 in the Supporting Information). [b] Errors were calculated from standard deviations at the 95% confidence level.

TABLE 2. Product Distributions in the Reaction of (*E*)-Hydroximoyl Fluorides with Sodium Methoxide in 9:1 DMSO−Methanol Solution[a,b]

(*E*)-hydroximoyl fluoride	*T*, °C	% *E* product
1Ee	20.25	83
1Ee	26.06	85
1Ee	30.08	85
1Ee	37.30	85
1Ee	40.67	85
1Ef	26.06	88
1Eg	26.06	86
1Eh	26.06	81
1Eh	36.06	84
1Eh	40.60	85

[a] Product distributions were determined by HPLC analysis. [b] The error in the measurement of the product distribution is approximately 5%.

(29) Rappoport, Z.; Topol, A. *J. Chem. Soc., Perkin Trans. 2* **1975**, 863−874.
(30) Bunnett, J. F.; Garbisch, E. W., Jr.; Pruitt, K. M. *J. Am. Chem. Soc.* **1957**, *79*, 385−391.

TABLE 3. Relative Rates and Activation Parameters

compd	rel rate of methoxide substitution at 44.60 °C	E_a (kcal/mol)	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)
1Ze	227	15.7	13.4	−17
1Ee	59.6	17.0	16.3	−9.9
1Za[27]	2.84		18	−10
1Ea[27]	3.26			
1Zh	74.8	15.1	14.5	−15
1Eh	12.1	17.0	16.2	−14
1Zb	1.02	20.7	20.4	−5.0
1Eb	1.00	19.5	19.9	−9.2
1Zd	2.84	20.5	19.9	−4.7
1Ed	1.97	20.2	18.9	−8.5

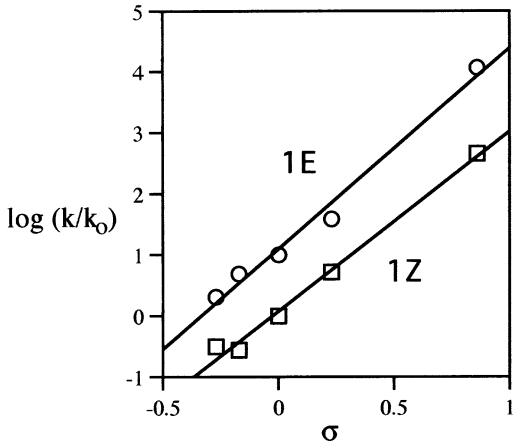


FIGURE 1. Hammett plots (σ) for methoxide substitution of **1Ze-i** and **1Ee-I** in 90:10 DMSO−MeOH at 26.06 °C. Note: For illustrative purposes, the 1E plot is ofset by the addition of one log unit to the log (k/k_o) values.

Interestingly, the hydroximoyl bromides in all instances react approximately 2−3 times faster than the hydroximoyl chlorides. Ab initio molecular orbital calculations have indicated that stabilization of a carbon−carbon double bond by chloride exceeds that by bromide.[35] This might also be true of the carbon−nitrogen double bond, and the difference in rates between the bromide and chloride may reflect a greater stabilization of the double bond of the starting material in the hydroximoyl chloride relative to the hydroximoyl bromide.

A positive correlation with Hammett σ values, a measured negative entropy of activation, and an element effect study that shows rate trends of F ≫ Cl or Br for the reaction of *O*-methylbenzohydroximoyl halides with methoxide in 90:10 DMSO/methanol all support the proposed addition−elimination mechanism. Although we previously[28] have given possible explanations for the stereospecificity of these reactions, it seemed worthwhile to try to obtain a better understanding of these reactions through theoretical calculations.

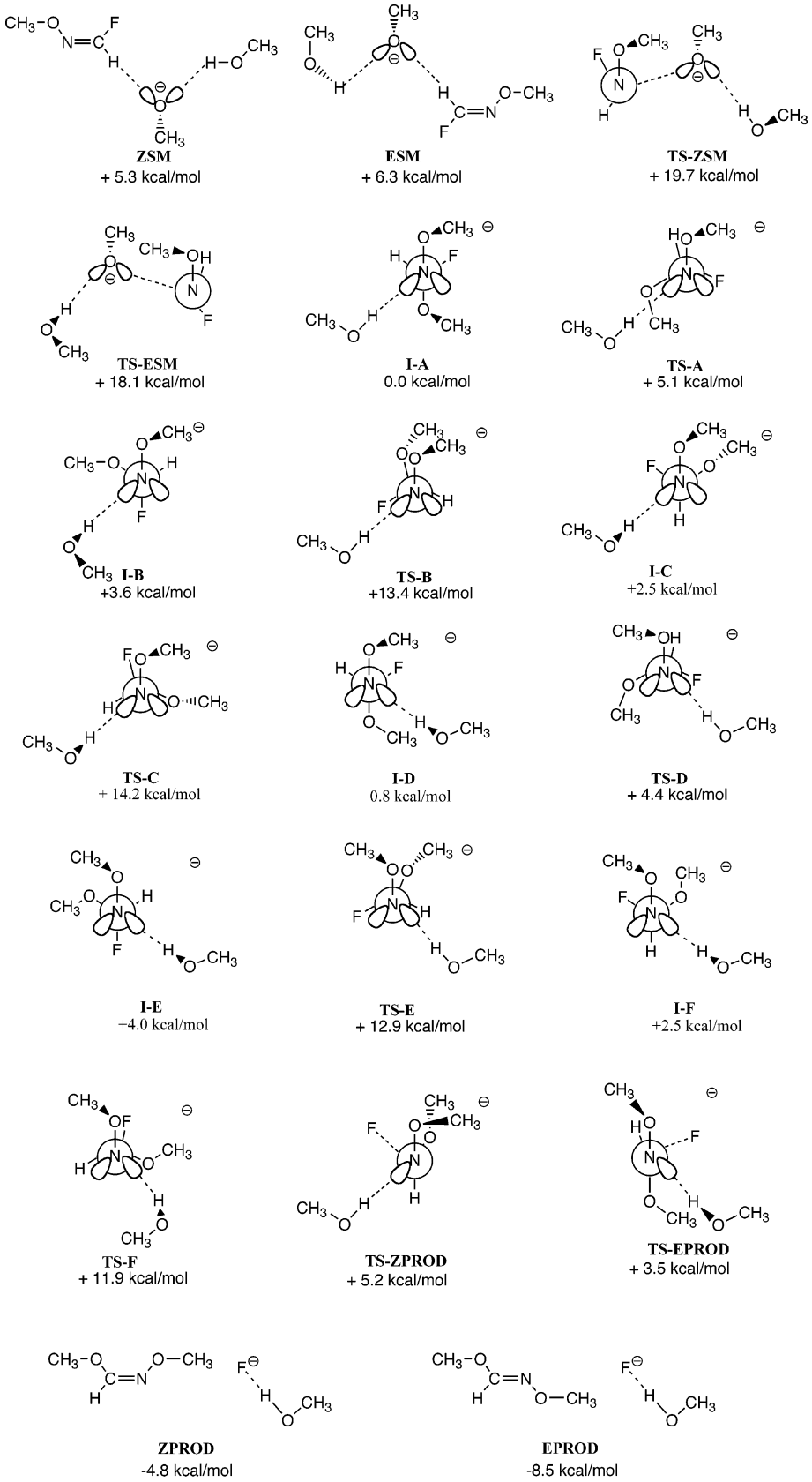
Ab initio calculations were performed on starting materials, transition states for nucleophilic attack by methoxide, all staggered and eclipsed conformers of the tetrahedral intermediate formed by the $A_N^{\ddagger} + D_N$ mechanism, transition states for elimination of fluoride ion, and products. These structures are graphically represented in Chart 2.

In these calculations, the phenyl group has been replaced by a hydrogen for computational expediency and will be referred to as the "simplified system." The phenyl group was included in certain structures to better define the reaction coordinate in calculations that will be discussed later. The Cartesian coordinates and total energies for all structures are included in the Supporting Information. Calculations were performed using Gaussian 94[36] and Gaussian 98[37] at the HF/6-31+G(d), MP2/6-31+G(d)//HF/6-31+G(d), and B3LYP/6-31+G(d)//HF/6-31+G(d) levels of theory.[38,39] In addition, to account for solvent polarity effects, single-point calculations performed using the self-consistent iterative polarizable continuum method (SCIPCM)[40] on the geometry optimized at the HF/6-31+G(d) level with a dielectric constant (ϵ = 47.0) to reflect that of dimethyl sulfoxide [HF(scrf)/6-31+G(d), and B3LYP(scrf)/6-31+G(D)//HF/6-31+G(d)] were also performed. All calculations include a single methanol molecule to mimic minimal immediate solvation effects and to stabilize the intermediate structures. The data for these calculations are also included in the Supporting Information. Qualitatively, there is little difference between the reaction coordinates derived from the different computational levels. Therefore, all discussion referring to the simplified system will refer to calculations done at the HF/6-31+G(d) level keeping in mind that other theory levels provide the same picture of the reaction.

Nucleophilic attack of methoxide ion on *O*-methylhydroximoyl fluoride (the simplified system) would form a tetrahedral intermediate with single bond character between carbon and nitrogen. There are three staggered

(31) Marchese, G.; Naso, F.; Modena, G. *J. Chem. Soc. B* **1969**, 290−293.
(32) Silversmith, E. F.; Smith, D. *J. Org. Chem.* **1958**, *23*, 427−430.
(33) Ta-Shma, R.; Rappoport, A. *J. Am. Chem. Soc.* **1977**, *99*, 1845−1858.
(34) Hegarty, A. F.; McCormack, M. T.; Hathaway, B. J.; Hulett, L. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1136−1141.
(35) Hoz, S.; Basch, H.; Wolk, J. L.; Rappoport, Z.; Goldberg, M. *J. Org. Chem.* **1991**, *56*, 5424−5426.
(36) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Repogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Degrees, D. J.; Baker, J.; Head-Gordon, S. M.; Gonzalez, C.; Pople, J. A. *Gaussian 94, Revision D.3;* Gaussian: Pittsburgh, PA, 1996.
(37) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dappich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morojuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98, Revision A.9*; Gaussian: Pittsburgh, PA, 1998.
(38) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley-Interscience: New York, 1986; and references therein.
(39) (a) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974−12979. (b) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989. (c) Dreizler, R. M.; Gross, E. K. V. *Density Functional Theory*; Springer, Berlin, 1990. (d) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3105. (e) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−790.
(40) (a) Forseman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, J. *J. Phys. Chem.* **1996**, *100*, 16098−16102. (b) Tomasi, J.; Bonaccorsi, R.; Cammi, R.; Valle, F. J. O. *THEOCHEM* **1991**, *234*, 401−402.

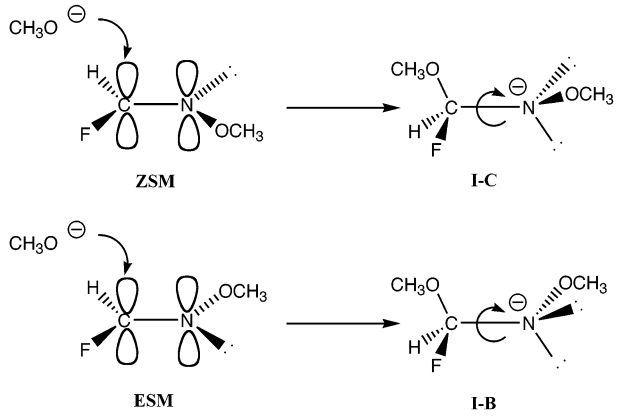
CHART 2[a]



[a] Key for structure numbers in Chart 2: Z and E, configuration of hydroximoyl fluoride or hydroximate; SM, starting materials; PROD, products; TS, transition state; I, tetrahedral intermediate.

conformations (around the C−N bond) for this tetrahedral intermediate that presumably could interconvert by rotation around the carbon−nitrogen single bond. There are two other internal rotors within the intermediates

SCHEME 3



(the oxygen−carbon bond of the C−O−C−N attachment and the oxygen−nitrogen bond of the C−O−N−C attachment). Conformations were investigated by rotation around these rotors also. All conformations reported in this paper resulting from rotation around the C−N bond represent the structures with the most stable arrangement around the other two internal rotors. The conformations **I-A**, **I-B**, and **I-C** represent the lowest energy staggered conformations around the C−N bond with the methanol solvent molecule positioned on the left when facing down the nitrogen−carbon single bond and **I-D**, **I-E**, and **I-F** with the methanol molecule on the right.

The tetrahedral intermediate first formed by methoxide attack on (*Z*)-*O*-methylhydroximoyl fluoride would be **I-C** (Scheme 3 and Chart 2). The tetrahedral intermediate first formed by methoxide attack on (*E*)-*O*-methylhydroximoyl fluoride would be **I-B** (Scheme 3 and Chart 2). Intermediate **I-C** has a lone pair of electrons on nitrogen in an antiperiplanar relationship to fluorine. It is assumed that these electrons in this arrangement could assist in the departure of fluoride ion from the molecule. This would result in the *Z*-isomer of the product (retained stereochemistry). In **I-B**, the lone pair electrons are not in an antiperiplanar relationship, and the barrier to expulsion of fluoride from this intermediate would be prohibitively high. **I-B** must undergo rotation to a conformation in which lone pair electrons on nitrogen fall in an antiperiplanar relationship to fluorine before elimination of fluoride may proceed [either to **I-C** (leading to the *Z* isomer of the product) or **I-A** (leading to the *E* isomer of the product)].

It appears that upon formation of **I-C** by nucleophilic attack of methoxide on the *Z* isomer of the starting material, the barriers to convert (going through **TS-B** leading to **I-B** or through **TS-C** leading to **I-A**) to the other conformations are relatively high (10.9 and 11.7 kcal, respectively) (Figure 2). This is qualitatively the same with solvation by methanol on the other lobe of nitrogen (10.4 and 9.4 kcal, Chart 2). The barrier to elimination of fluoride from **I-C** is only 2.8 kcal. It appears that after nucleophilic attack by methoxide on (*Z*)-O-methylhydroximoyl fluoride (**ZSM**) forming **I-C**, elimination of fluoride would proceed at a much faster rate than would rotation around the C−N bond. This would lead to completely retained stereochemistry in the product and helps to explain the experimental observations.

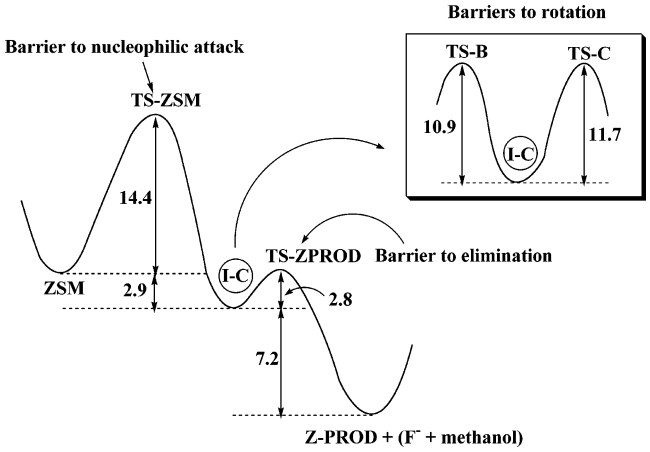


FIGURE 2. Reaction coordinate for the *Z* isomer (HF/6-31+G(d) + ZPVE).

With nucleophilic attack by methoxide on the (*E*)-*O*-methylhydroximoyl fluoride (**ESM**), intermediate **I-B** is formed (Figure 3). This intermediate must undergo rotation to an intermediate in which lone pair electrons on nitrogen are in an antiperiplanar orientation to fluorine. The barrier to rotate to form **I-A** (through **TS-A**, leading to the *E* isomer of the product and retained stereochemistry) is only 1.5 kcal. The barrier to rotate to form **I-C** (through **TS-B**, leading to the *Z* isomer of the product and inverted stereochemistry) is 9.8 kcal. These numbers too look qualitatively the same with solvation by methanol on the other side of the molecule (0.4 kcal to rotate to the intermediate leading to retained stereochemistry and 8.9 kcal to rotate to the intermediate leading to inverted stereochemistry).

By these values, one would anticipate sole formation of the *E* isomer of the product. This is not what is seen experimentally with approximately 15% of the product exhibiting inverted stereochemistry (*Z* isomer of the product). It is likely that the phenyl group that had been eliminated from these calculations might affect the relative heights of these rotational barriers (**TS-A** and **TS-B**). In **TS-A**, the replacement of phenyl by hydrogen possibly artificially lowers that barrier relative to **TS-B**. As seen in Figure 4, there is likely to be steric and electron−electron repulsive interaction present in **TS-A** with a phenyl group (**TS-A-Ph**) that would destabilize this transition state. In **TS-B-Ph**, the effect of the phenyl group would not be as dramatic.

Calculations with the phenyl in place were carried out for **TS-A**, **TS-B**, **I-B**, and **TS-ESM** but only done at the HF/3-21G level because of the complexity of the structures (titled **TS-A-Ph**, **TS-B-Ph**, **I-B-Ph**, and **TS-ESM-Ph** in the Supporting Information). Here, **TS-A** (barrier height = 7.5 kcal) turns out to be only 3.3 kcal lower in energy than **TS-B** (barrier height = 10.8 kcal) as opposed to an 8.3 kcal difference between these two transition states with the phenyl replaced by hydrogen (Figure 3). This barrier difference qualitatively better accounts for the experimental findings of approximately 85:15 *E*/*Z* product distribution.

The calculated barriers for nucleophilic attack of methoxide in the simplified system showed the barrier for attack of methoxide on the *E* isomer of the starting material to be 2.7 kcal lower than that for the *Z* isomer

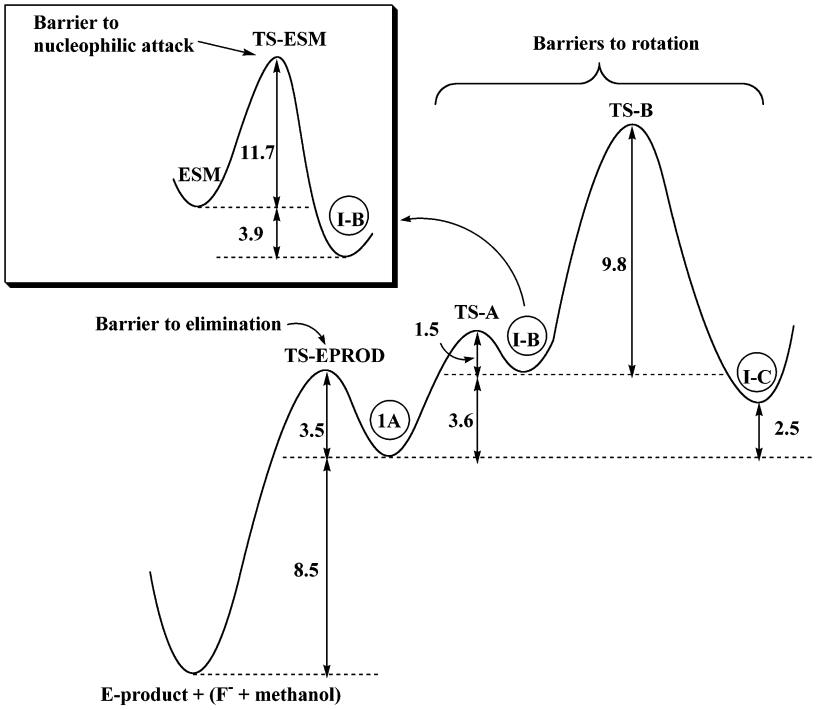


FIGURE 3. Reaction coordinate for the *E* isomer (HF/6-31+G(d) + ZPVE).

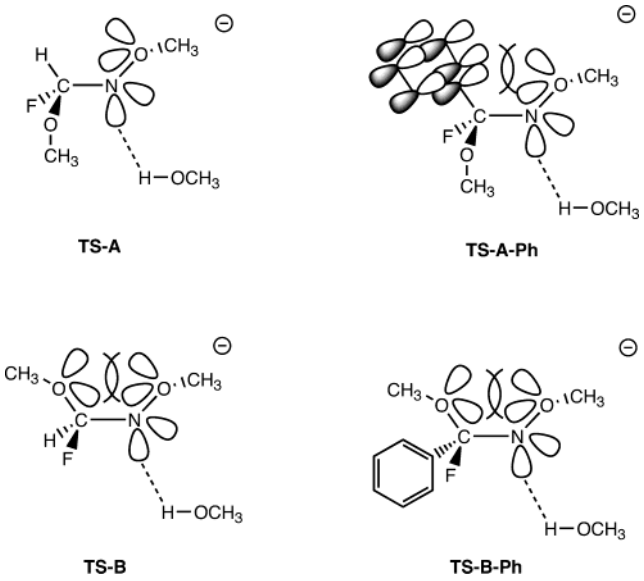


FIGURE 4. Effect of the phenyl group on transition state A vs transition state B.

of the starting material. This does not appear to support experimental findings as the *Z* isomer was found to react faster than the *E* isomer in all cases. Calculations with the phenyl group in place, however, appear to help explain this discrepancy.

As noted before, it appears that once the *E* isomer undergoes nucleophilic attack to form the tetrahedral intermediate (**I-B**), it faces sizable barriers to rotation to form product (10.8 kcal to the *Z* product and 7.5 kcal to the *E* product). Interestingly, the barrier for loss of the attacking nucleophile (back reaction of **I-B** to **ESM**) is 13.1 kcal. This is only 2.2 kcal higher than the barrier to rotation to the conformation that leads to *Z* product. While these numbers quantitatively would predict essentially no back reaction, these numbers would also predict essentially no formation of the *Z* product. It is felt that the low level of theory, the lack of electron correlation, and the neglect for the full solvent effects in these calculations force one to view the data strictly in a qualitative sense. If one looks at this reaction surface qualitatively, it appears that **I-B** sits at the bottom of a rather deep well, and it does appear that back reaction of **I-B** to form starting material could occur a small percentage of the time. Therefore, despite a lower barrier to nucleophilic attack in the *E* isomer, back reaction could slow the rate of final product formation. This argument could also account for the smaller experimental element effect found for the *E* isomer relative to the *Z* isomer. In other words, back reaction of the *E* isomer could negate to a degree the influence of the halogen in increasing the rate of the addition step of the mechanism. With this interpretation, the experimental and computational findings would be in complete agreement.

In summary, upon nucleophilic attack of methoxide on the *Z*-hydroximoyl fluoride, the tetrahedral intermediate that is formed is oriented such that fluoride ion can be readily expelled (Figure 2). The barrier for elimination of fluoride from the simplified intermediate is approximately 7 kcal lower in energy than either barrier to rotation. Therefore, the elimination step is so much faster than the rotation that the reaction proceeds with complete retention of stereochemistry.

In the *E* isomer, the tetrahedral intermediate initially formed from methoxide attack must rotate into a conformation from which fluoride ion can be eliminated. The calculated barriers including the phenyl indicate that the first-formed tetrahedral intermediate sits in a fairly deep well. There is competition at this point between rotation to the intermediate that leads to *E* product, rotation to the intermediate that leads to *Z* product, and loss of

methoxide to reform starting material. The lowest barrier to rotation is the route that leads to the *E* product, and this is the product that is preferentially formed experimentally. The competing back reaction to starting material slows the reaction down and diminishes the rate enhancement of replacing the leaving group from chlorine (or bromine) to fluorine.

Experimental Section

A. General Procedures. All chemicals used in this research are reagent grade except as noted. (*Z*)-*O*-Methyl-4-methoxybenzohydroximoyl bromide (**1Zd**) and (*Z*)- and (*E*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**1Eb**) were synthesized by procedures described by Johnson et al.[19] Isomerization of the hydroximoyl bromide **1Zd** and separation of the isomers to prepare **1Ed** were performed by procedures described by Sakamoto et al.[41] Isomerization of the hydroximoyl chloride **1Zb** to form **1Eb** was performed as outlined by Johnson et al.,[19] substituting hexane for the solvent. The hydroximoyl fluorides **1Ze**, **1Ee**, **1Zf**, **1Ef**, **1Zg**, **1Eg**, **1Zh**, and **1Eh** were synthesized as previously published.[42] The benzohydroximates **1Zj**−**m** and **1Ej**−**l** were prepared according to literature procedures (**1Zj**,[44] **1Ej**,[44] **1Zk**,[45] **1Ek**,[45] **1Zl**,[44] **1El**,[44] and **1Zm**[45]). Compounds **1Zi**, **1Ei**, **1Em**, **1Zn**, and **1En** have not been previously prepared and are described below. One of the isomers of methyl *O*-methyl-*p*-methoxybenzohydroximate was prepared by Beart and Ward[45] from the reaction of diazomethane with *p*-methoxybenzohydroxamic acid. Although Beart and Ward did not assign the configuration of their product (**1Zm** or **1Em**), it is likely to be the *Z* isomer since a recent report by Liguori et al.[46] (who did not cite the work of Beart and Ward) has shown that the reaction of diazomethane with benzohydroxamic acids gives *Z*-hydroximates (such as **1Zk**). The configurational assignments for **1Zm** and **1Em** prepared in this work were made by comparing the chemical shifts of the hydroximate methoxy groups (further downfield in the *Z* isomer)[47] and the ortho hydrogens of the aromatic ring (further downfield in the *E* isomer) of the two isomers.

Photochemical isomerizations of hydroximoyl chlorides and fluorides were carried out in quartz tubes placed in a photochemical reactor fitted with low-pressure lamps (254 nm). Melting points are uncorrected.

B. Preparation of Solutions and Solvents Used for Kinetics. Dimethyl sulfoxide (HPLC grade) was stored over dried 4A molecular sieves in a dried three-neck round-bottomed flask fitted with a $CaCl_2$ drying tube (which was sealed to the outside environment when solvent was not being transferred) and two greased ground glass stoppers.

The sodium methoxide solutions were prepared by reaction of sodium with methanol (distilled from magnesium metal). The sodium methoxide solutions were titrated with standardized HCl solutions.

C. Kinetic Method. This method was used for all runs except those measured on either (*Z*)- or (*E*)-(3,5)-bistrifluoromethyl-*O*-methylbenzohydroximoyl fluoride.

One 50 mL, one 25 mL, and one 10 mL volumetric flask were dried in a 100 °C oven. The 50 mL flask was removed from the oven, quickly capped, and brought to room temperature. The hydroximoyl halide was weighed into this 50 mL flask. The previously prepared DMSO (38 mL) was added to this 50 mL flask by gently blowing nitrogen into the sealed DMSO container as DMSO was being removed with volumetric pipets. The 10 and 25 mL volumetric flasks were removed from the oven and quickly capped. Standardized sodium methoxide solution (7 mL) was placed in the 10 mL volumetric flask, and dry DMSO (10 mL) was placed in the 25 mL volumetric flask under nitrogen.

All three volumetric flasks were thermally equilibrated for 15 min in a water bath regulated to ±0.04 °C which was checked with a quartz thermometer. The sodium methoxide solution (5 mL) was pipetted into the 50 mL volumetric flask containing the hydroximoyl halide and DMSO. Upon emptying of the pipet, timing was started. The 50 mL volumetric flask was quickly shaken and filled to the mark with the thermostated DMSO.

Aliquots were taken at regular intervals and were quenched with an approximately equal volume of an HCl solution of approximately the same molarity as the sodium methoxide solution in the 50 mL volumetric flask. A 20 μL portion of each aliquot was injected onto an octadecyl HPLC column for all reactions except those involving (*E*)-*O*-methylbenzohydroximoyl fluorides. For these reactions, two octadecyl HPLC columns linked in sequence were necessary to get baseline separation of the compounds in the reaction mixture. The mobile phase for each reaction was made of various acetonitrile and water mixtures. Compounds were detected by a UV−vis detector set at 254 nm. Normalization factors for peak areas were previously determined by analysis of samples containing known amounts of reactants and products. Errors were calculated from standard deviations at the 95% confidence level. In most cases, rate constants correspond to an average of a least two measurements. The errors reported in Table 1 correspond to the highest error of the averaged measurements.

D. Kinetic Method for Reaction of Sodium Methoxide with 1Zi and 1Ei. The rates of reaction of the bis-trifluoromethyl compounds **1Zi** and **1Ei** with methoxide ion were too fast to follow using the method described in part C. The rate constants for **1Zi** and **1Ei** were obtained by competition experiments with (*Z*)- or (*E*)-*O*-methyl-4-chlorobenzohydroximoyl fluoride (**1Zf** or **1Ef**). The following equation[43] was used to calculate the rate constants for **1Zi**:

$$k_{\mathbf{1Zf}}/k_{\mathbf{1Zi}} = \text{log of fraction of } \mathbf{1Zf} \text{ remaining}/\text{log of fraction of } \mathbf{1Zi} \text{ remaining}$$

A similar equation was used to calculate the rate constant for **1Ei**.

E. Preparation of New Compounds. (*Z*)-*O*-Methyl-3,5-bistrifluoromethylbenzohydroximoyl Chloride (1Zo). Methyl 3,5-bistrifluoromethylbenzohydroxamate (4.00 g, prepared from 3,5-bistrifluoromethylbenzoyl chloride and methoxylamine) was placed in a 50-mL three-neck round-bottomed flask fitted with a condenser, a calcium chloride drying tube, and a solid addition funnel. Phosphorus pentachloride (3.12 g) was added through the solid addition funnel with stirring. The mixture was stirred and heated at 100 °C for 3 h. After the mixture was allowed to cool to room temperature, it was poured into cold water (50 mL). The solution was extracted with chloroform (3 × 150 mL). The chloroform extracts were dried, and the chloroform was removed. The residual oil was vacuum distilled to give a clear liquid (1.02 g, 23%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.15 (s, 3H), δ 7.85 (s, 1H), δ 8.30 (s, 2H); IR (neat) 1619 cm^{-1}; Anal. Calcd for $C_{10}H_6NOF_6Cl$: C, 39.30; H, 1.98; N, 4.58; F, 37.30; Cl, 11.60. Found: C, 39.38; H, 1.89; N, 4.37; F, 37.08; Cl, 11.90.

(*Z*)-*O*-Methyl-3,5-bistrifluoromethylbenzohydroximoyl Bromide (1Zp). Methyl 3,5-bistrifluoromethylbenzohydroxamate (10.02 g) was placed in a 250-mL three-neck round-bottomed flask fitted with a condenser, a calcium chloride

(41) Sakamoto, T.; Okamoto, K.; Kikugawa, Y. *J. Org. Chem.* **1992**, *57*, 3245−3248.
(42) Rowe, J. E.; Lee, K.; Dolliver, D. D.; Johnson, J. E. *Aust. J. Chem.* **1999**, *52*, 807−811.
(43) Gould, E. S. *Mechanism and Structure in Organic Chemistry*; Holt, Rinehart, and Winston: Chicago, 1959; p 173.
(44) Johnson, J. E.; Nalley, E. A.; Kunz, Y. K.; Springfield, J. R. *J. Org. Chem.* **1976**, *41*, 252−259.
(45) Beart, P. M.; Ward, A. D. *Aust. J. Chem.* **1974**, *27*, 1341−1349.
(46) Leggio, A.; Liguori, A.; Sicilliano, C.; Sindona, G. *J. Org. Chem.* **2001**, *66*, 2246−2250.
(47) Johnson, J. E.; Springfield, J. R.; Hwang, J. S.; Hayes, L. J.; Cunningham, W. C.; McClaugherty, D. L. *J. Org. Chem.* **1971**, *36*, 284−294.

drying tube, and a solid addition funnel. The solid was stirred as phosphorus pentabromide (15.08 g) was added through the solid addition funnel. The mixture was stirred and heated at 80 °C for 3 h. After the mixture was allowed to cool to room temperature it was poured into cold water (100 mL). The solution was extracted with ether. The ether extracts were dried, and the ether was removed. The residual oil was vacuum distilled to give a clear liquid (7.40 g, 60%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.19 (s, 3H), 7.92 (s, 1H), 8.30 (s, 2H); IR (neat), 1618 cm^{-1}. Anal. Calcd for $C_{10}H_6NOF_6Br$: C, 34.31; H, 1.73; N, 4.00; F, 32.56; Br, 22.83. Found: C, 34.28; H, 1.74; N, 3.95; F, 32.19; Br, 22.91.

(*Z*)-*O*-Methyl-3,5-bistrifluoromethylbenzohydroximoyl Fluoride (1Zi). (*Z*)-*O*-Methyl-3,5-bistrifluoromethylbenzohydroximoyl bromide (3.01 g) was dissolved in 20 mL of DMSO. Potassium fluoride (2.00 g) was dissolved in DMSO (60 mL) and placed in a 250-mL three-neck round-bottomed flask fitted with a condenser and a calcium chloride drying tube. The hydroximoyl bromide was then added into the reaction flask. The mixture was stirred and heated at 100 °C for 22 h under a slow nitrogen purge. After the reaction was complete, 80 mL of saturated sodium chloride solution was added into the flask. The solution was extracted with ether. The ether extracts were dried, and the diethyl ether was removed. The residual oil was vacuum distilled to give a clear liquid (2.41 g, 97%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.03 (s, 3H), 7.95 (s,1H), 8.20 (s, 2H); IR (neat) 1648 cm^{-1}. Anal. Calcd for $C_{10}H_6NOF_7$: C, 41.54; H, 2.09; N, 4.84; F, 45.90. Found: C, 41.36; H, 2.18; N, 4.84; F, 45.80.

(*E*)-*O*-Methyl-3,5-bistrifluoromethylbenzohydroximoyl Fluoride (1Ei). (*Z*)-*O*-Methyl-3,5-bistrifluoromethylbenzohydroximoyl fluoride (2.00 g) was dissolved in benzene (80 mL) and placed in six 20-mL quartz test tubes. The test tubes were irradiated at 254 nm for 6 h. Immediately after irradiation, the benzene solution was extracted with a saturated solution of sodium carbonate (2 × 100 mL). The benzene extract was dried, and the benzene was removed. A GC−MS analysis showed that it was a mixture of **1Zi** and **1Ei** in a ratio of 60:40, respectively. The *E* isomer (**1Ei**) was separated from the mixture by preparative GC.[44] A clear liquid product was collected (0.51 g, 26%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.00 (s, 3H), 8.00 (s,1H), 8.45 (s, 2H); IR (neat), 1737 cm^{-1}. Anal. Calcd for $C_{10}H_6NOF_7$: C, 41.54; H, 2.09; N, 4.84; F, 45.90. Found: C, 41.39; H, 2.10; N, 4.81; F, 45.41.

Methyl (*Z*)-*O*-Methyl-3,5-bistrifluoromethylbenzohydroximate (1Zn). Sodium metal (0.88 g) was dissolved in methanol (30 mL) in a 250-mL three-neck round-bottomed flask fitted with a condenser and a calcium chloride drying tube. The hydroximoyl chloride **1Zo** (1.15 g) was dissolved in DMSO (30 mL) and added to the reaction flask. The mixture was stirred and heated for 2 h at 50 °C under a slow purge of nitrogen gas. After the reaction was complete, ice−water (60 mL) was added into the flask, and the mixture was extracted with ether. The ether extract was dried, and the ether was removed. The residual oil was vacuum distilled to give a clear liquid (0.86 g, 76%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.78 (s, 3H), 4.00 (s, 3H), 7.72 (s,1H), 8.10 (s, 2H); IR (neat) 1632 cm^{-1}. Anal. Calcd for $C_{11}H_9NO_2F_6$: C, 43.87; H, 3.01; N, 4.65; F, 37.85. Found: C, 43.73; H, 3.04; N, 4.57; F, 37.69.

Methyl (*E*)-*O*-Methyl-3,5-bistrifluoromethylbenzohydroximate (1En). The *E*-hydroximate **1Zn** (1.50 g) was dissolved in glacial acetic acid (30 mL) and placed in a 50 mL round-bottomed flask. The reaction solution was stirred and heated at 80 °C for 4 h. After reaction was complete, the reaction solution was neutralized with 6 N sodium hydroxide in an ice−water bath. The solution was then extracted with ether. The ether extract was dried, and the ether was removed. An analysis of the mixture by GC−MS showed that it was a mixture of **1Zn** and **1En** in a 50:50 ratio. The *E* isomer (**1En**) was separated from the mixture by column chromatography (silica gel, 70−130 mesh) using 1:6 chloroform/hexane as the mobile phase. After column chromatography, the solvent was removed, and the residual oil was vacuum distilled to give a clear liquid (0.64 g, 42%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.88 (s, 6H), 7.90 (s, 1H), 8.26 (s, 2H); IR (neat) 1613 cm^{-1}. Anal. Calcd for $C_{11}H_9NO_2F_6$: C, 43.87; H, 3.01; N, 4.65; F, 37.85. Found: C, 43.82; H, 3.09; N, 4.68; F, 37.76.

Methyl (*Z*)-O-Methyl-4-methoxybenzohydroximate (1Zm). Reaction of (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl bromide with sodium methoxide in DMSO/methanol solution gave **1Zm**[46] as a colorless liquid (purified by column chromatography): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.815, 3.898 (two s, 6H), 3.903 (s, 3H), 6.89 (d, 2H, J = 9.1 Hz), 7.58 (d, 2H, J = 9.1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 55.16, 59.14, 62.13, 113.67, 122.47, 155.32, 160.93); IR (Nujol) 1609 cm^{-1}.

Methyl (*E*)-*O*-Methyl-4-methoxybenzohydroximate (1Em). Isomerization of **1Zm** in glacial acetic acid gave a mixture of **1Zm** and **1Em**. Separation of the isomers by column chromatography gave **1Em** as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.806, 3.812, 3.815 (three s, 9H), 6.90 (d, 2H, J = 8.9 Hz), 7.76 (d, 2H, J = 8.9 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 54.45, 55.20, 62.05, 113.15, 121.84, 130.54, 158.45, 160.71; IR (neat) 1609 cm^{-1}. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.70; H, 6.79; N, 7.13.

Acknowledgment is made to the Minority Biomedical Research Support Program of the National Institutes of Health (NIH-MBRS Grant No. GM08256), The Robert A. Welch Foundation, and the Texas Woman's University Research Enhancement Program for support of this work. J.E.R. thanks the Texas Woman's University for hospitality during the completion of part of this work.

Supporting Information Available: Rate constants for reactions of sodium methoxide with *O*-methylbenzohydroximoyl halides. Coordinates of all optimized HF/6-31+G(d) and HF/3-21G structures (ground states and transition states) and their energies. This material is available free of charge via the Internet at http://pubs.acs.org.

JO030299E