Mechanisms of Acid-Catalyzed *Z*/*E* Isomerization of Imines

James E. Johnson,*,† Nora M. Morales,† Andrea M. Gorczyca,† Debra D. Dolliver,‡ and Michael A. McAllister‡,§

Department of Chemistry and Physics, Texas Woman's University, Denton, Texas 76204-5859, and Department of Chemistry, University of North Texas, Denton, Texas 76203

JJohnson@TWU.edu

Received January 18, 2001

The kinetics and mechanism of acid-catalyzed *Z*/*E* isomerization of *O*-methylbenzohydroximoyl chloride (**1Za** and **1Ea**), methyl *O*-methylbenzohydroximate (**1Zb** and **1Eb**), ethyl *O*-methylbenzohydroximate (**1Zc** and **1Ec** and five para and meta substituted derivatives), *O*-methylcinnamohydroximoyl chloride (**2Za** and **2Ea**), and methyl *O*-methylcinnamohydroximate (**2Zb** and **2Zb**) have been investigated. The kinetics of *Z*/*E* isomerization of these imines have been studied in glacial acetic acid (**1Ea** and **1Zc**) and in dioxane solutions containing HCl, trifluoromethanesulfonic acid, or tetrafluoroboric acid (**1Ea**, **1Zb**, **2Ea**, and **2Zb**). The isomerization takes place by either (a) rotation about the carbon−nitrogen double bond of the protonated imine (iminium ion rotation) or (b) nucleophilic attack on the protonated imine to form a tetrahedral intermediate that undergoes stereomutation and loss of the nucleophile (nucleophilic catalysis). The hydroximoyl chlorides **1Ea** and **2Ea** only isomerize by the nucleophilic catalysis mechanism. The hydroximate **1Zb** appears to be capable of isomerizing by either mechanism. The hydroximate **2Zb** may be isomerizing only by iminium ion rotation. Theoretical calculations support the notion that increased conjugation in the protonated imine increases the rate of iminium ion rotation.

Introduction

Over the past decade, the imine functional group has become increasingly important in organic synthesis[1] and as a functional group incorporated into therapeutic agents. The third-generation cephalosporins (cefpodoxime, ceftriaxone, and ceftrazidine)[2] contain an *O*-alkyloxime (*N*-alkoxyimine) functional group and are among the most commonly prescribed antibiotics. The oximidines,[3] which have antitumor activity, and the antidepressant demexiptiline[2] also contain an *O*-alkyloxime moiety (C═NOR). It is likely that the number of drugs containing the imine functional group will continue to increase. For example, the antibiotic gemifloxacin (Factive), which has been developed by SmithKline Beecham King to combat the problem of bacterial resistance to antibiotics, contains an *O*-methyloxime functional group.[4]

For some time, we have been interested in fundamental reaction mechanisms of imines with an emphasis on the kinetics and stereochemistry of these reactions. Because of the remarkable resistance of *O*-alkyloximes and their derivatives to thermal *Z*/*E* isomerization, all of our mechanism studies have been carried out on systems containing this group.

Acid-catalyzed *E*/*Z* isomerization of compounds containing the carbon−nitrogen double bond is a well-known process. Although the mechanism of the isomerization has received some attention,[5−17] the pathway for most of the isomerizations that appear in the literature is not clear.

In simple imines, there are two reasonable mechanisms for *Z*/*E* isomerization:

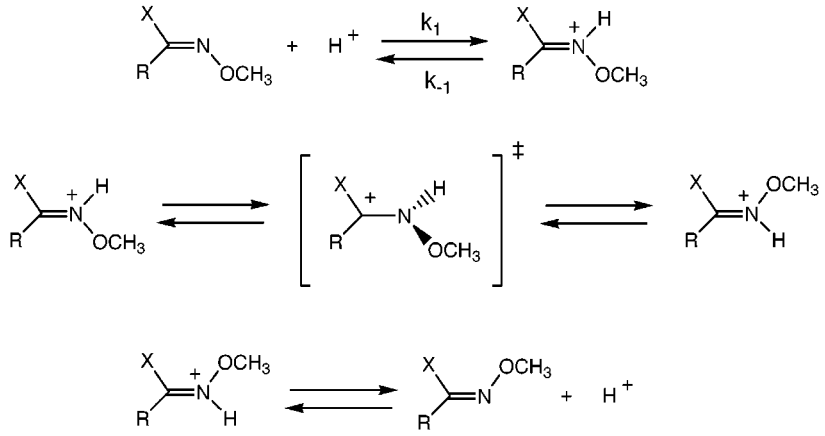
Mechanism 1 (protonation−rotation, Scheme 1): The simplest process that one could envision for acid-catalyzed *E*/*Z* isomerization involves rotation about the carbon−nitrogen double bond of the N-protonated imine. Since protonation could decrease the carbon−nitrogen bond order, it seems reasonable that rotation could take place around the carbon−nitrogen bond axis of the protonated species (an iminium ion). Although it is

* To whom correspondence should be addressed. Phone: 940-898-2567. Fax: 940-898-3198.
† Texas Woman's Universtiy.
‡ University of North Texas.
§ Current address: Agouron Pharmaceuticals, Alanex Division, San Diego, CA 92121-1194.

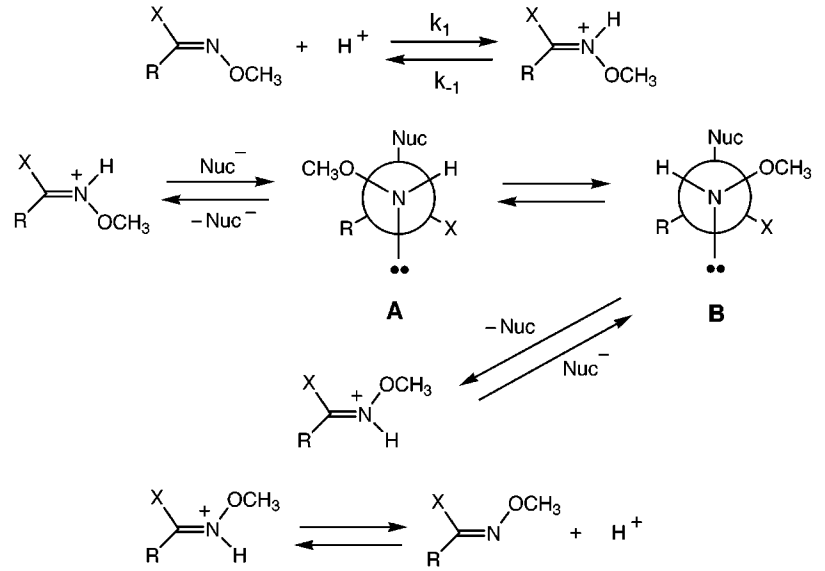
(1) For examples see (a) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421−431. (b) Borg, G.; Chino, M.; Ellman, J. A. *Tetrahedron Lett.* **2001**, *42*, 1433−1436. (c) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12−13.
(2) *The Merck Index* 12th ed.; Merck and Co., Inc.: Whitehouse Station, NJ, 1996.
(3) Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153−155.
(4) Henry, C. M. *Chem. Eng. News*, **2000**, *78*, 41−57.
(5) Idoux, J. P.; Sikorski, J. A. *J. Chem. Soc., Perkin Trans. 2* **1972**, 921−923.
(6) Jennings, W. B.; Al-Showiman, S.; Tolley, M. S.; Boyd, D. R. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1535−1539.
(7) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *96*, 7045−7052.
(8) Conlon, P. R.; Sayer, J. M. *J. Org. Chem.* **1979**, *44*, 262−267.
(9) Holloway, C. E.; Vuik, C. P. J. *Tetrahedron Lett.* **1979**, 1017−1020.
(10) Dignam, K. J.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2*, **1979**, 1437−1443.
(11) Cunningham, I. D.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 537−541.
(12) Pankratz, M.; Childs, R. F. *J. Org. Chem.* **1985**, *50*, 4553−4558.
(13) Childs, R. F.; Dickie, B. D. *J. Am. Chem. Soc.* **1983**, *105*, 5041−5046.
(14) Walter, W.; Meese, C. O.; Schroder, B., *Liebigs Ann. Chem.* **1975**, 1455−1464.
(15) Childs, R. F.; Shaw, G. S.; Lock, C. J. L. *J. Am. Chem. Soc.* **1989**, *111*, 5424−5429.
(16) Johnson, J. E.; Silk, N. M.; Nalley, E. A.; Arfan, M. *J. Org. Chem.* **1981**, *46*, 546−552.
(17) Johnson, J. E.; Silk, N. M.; Arfan, M. *J. Org. Chem.* **1982**, *47*, 1958−1961.

10.1021/jo010067k CCC: $20.00
Published on Web 10/27/2001

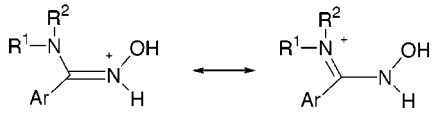
Scheme 1. Mechanism 1: Protonation−Rotation



Scheme 2. Mechanism 2: Nucleophilic Catalysis



generally thought[18] that isomerization of imines takes place by iminium ion rotation, there are only a few examples where experimental evidence[10,11] has been published to support this mechanism. Dignam and Hegarty[10] found that the rates of acid-catalyzed isomerization of benzamidoximes did not increase with increasing total buffer concentration (sodium acetate/acetic acid and other buffers), which demonstrates that the acid counterion does not participate in the reaction. As we have pointed out previously,[16] amidoximes represent a rather special case where resonance delocalization of the positive charge in the conjugate acid through the nitrogen lone pair of the amino group would be expected to be especially important since the resonance structures are equivalent except for substitution:



A similar study on the *Z*/*E* isomerization of the closely related amidines by Cunningham and Hegarty[11] showed that the isomerization was not catalyzed by buffer species.

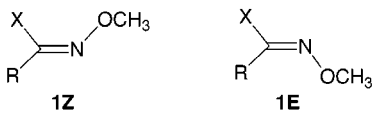
It is interesting that theoretical calculations (MP4SDTQ/6-311G**//6-311G**) on the imine of formaldehyde (CH_2=NH) and its conjugate acid (CH_2=NH_2^+) show that both the σ- and the π-bond strengths are increased when the nitrogen atom of this imine is protonated.[19] A similar study [GVB (6/12)/6-31G*] on formaldehyde imine and the *N*-methylimine of acetaldehyde (CH_3CH=NCH_3) predicts a decrease in the C=N bond length on protonation.[20] Some older calculations (HF/DZ) on the rotational barrier in CH_2=NH_2^+ indicate that the barrier is very high (77 kcal/mol).[21] It appears that the high intrinsic barrier to rotation in iminium ions can be lowered substantially by the addition of groups that stabilize a positive charge.[13]

Mechanism 2 (nucleophilic catalysis, Scheme 2): In this mechanism for *Z*/*E* isomerization, the protonated form of the imine undergoes nucleophilic attack by the acid counterion (Nuc^-) giving a tetrahedral intermediate (**A**). The tetrahedral intermediate undergoes stereomutation by rotation and proton exchange on nitrogen to a conformation (**B**) capable of losing chloride ion to give the other stereoisomer.

(18) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Rowe: New York, 1987; p 491.

(19) Bond, D. *J. Am. Chem. Soc.* **1991**, *113*, 385−387.
(20) Wang, Y.; Poirier, R. A. *J. Phys. Chem. A* **1997**, *101*, 907−912.
(21) Merenyi, G.; Wettermark, G.; Roos, B. *Chem. Phys.* **1973**, *1*, 340−347.

We[16] have published experimental evidence that unambiguously demonstrates that nucleophilic catalysis is responsible for the isomerization of O-methylbenzohydroximoyl chlorides (**1Ea** to **1Za**) when the isomerization is carried out in HCl/dioxane solution.



1Z **1E**

1Za and **1Ea**: R = C_6H_5; X = Cl
b: R = C_6H_5; X = OCH_3
c: R = C_6H_5; X = OC_2H_5
d: R = 4-$NO_2C_6H_4$; X = OC_2H_5
e: R = 4-ClC_6H_4; X = OC_2H_5
f: R = 4-$CH_3OC_6H_4$; X = OC_2H_5
g: R = 4-$CH_3C_6H_4$; X = OC_2H_5
h: R = 3-ClC_6H_4; X = OC_2H_5
i: R = C_6H_5; X = OCH_2CF_3
j: R = H; X = Cl
k: R = H; X = OCH_3

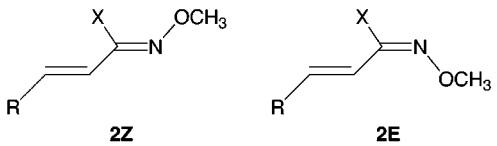
The rates of *E* to *Z* isomerization were compared to the rate of incorporation of radioactive chloride ion ($^{36}Cl^-$) into the *E*-hydroximoyl chloride during the isomerization. It was found that radioactive chloride ($^{36}Cl^-$) is incorporated into the hydroximoyl chloride at a rate equal to one-half the rate of isomerization. This result requires a tetrahedral intermediate that loses ($^{36}Cl^-$ and $^{35}Cl^-/^{37}Cl^-$) with equal probability.

The Hammett ρ value for the HCl-catalyzed isomerization of the *E*-hydroximoyl chloride was relatively small ($\rho = -0.66$). We suggested that the low ρ value was due to offsetting ρ values of the protonation step (negative ρ value) and the nucleophilic attack by the acid counterion (positive ρ value).

In later work,[17] we found a negligible substituent effect on the isomerization of *O*-methylacetophenone oxime in HCl/dioxane. Based on the negligible substituent effect, we suggested that *O*-methyloximes also isomerize by the nucleophilic catalysis mechanism.

Results and Discussion

In the present work, we have investigated *Z*/*E* isomerization of hydroximoyl chlorides **1Za/1Ea** and **2Za/2Ea** and the hydroximates **1Zb/1Eb** and **2Zb/2Eb** in dioxane solutions of HCl, trifluoromethanesulfonic acid (triflic acid), or tetrafluoroboric acid. Our initial qualitative work



2Z **2E**

2Za and **2Ea**: R = C_6H_5; X = Cl
b: R = C_6H_5; X = OCH_3
c: R = H; X = Cl
d: R = H; X = OCH_3

showed that the isomerization of the hydroximates took place in all three acids, while the hydroximoyl chlorides isomerized only in HCl dioxane solution. Since the hydroximoyl chlorides isomerized only with an acid (HCl) that has a nucleophilic counterion, we can conclude that the hydroximoyl chlorides are capable of isomerizing only by the nucleophilic catalysis pathway. These results are in agreement with our earlier work.[16] The hydroximates are capable of isomerizing by the iminium ion pathway since they isomerize in acids with non-nucleophilic counterions (triflic acid and tetrafluoroboric acid).

Table 1. First-Order Rate Constants for the Acid-Catalyzed Isomerization of Hydroximoyl Chlorides and Methyl Hydroximates in Dioxane at 39.5 °C

imine	acid[a]	10^3[imine], M	*Z* isomer at equilibrium (%)	10^4k, s^{-1}
1Ea	HCl	3.06	96	0.154 ± 0.004
2Ea	HCl	2.00	76	$0.0785^b \pm 0.0033$
1Zb	HBF_4	6.68	23	$1.08^b \pm 0.03$
1Zb	HCl	2.78	23	$22.8^b \pm 0.6$
1Zb	CF_3SO_3H	4.80	23	$3.74^b \pm 0.30$
2Zb	HBF_4	3.66	3	0.463 ± 0.038
2Zb	HCl	2.45	3	8.39 ± 0.30
2Zb	CF_3SO_3H	3.42	3	21.5 ± 0.3

[a] Concentration of acid = 0.010 M. [b] Reversible first-order rate constant. The first-order rate constant is a sum of the rate constants for the forward and reverse reactions (ref 26).

To gain additional insight into the isomerization process, we have measured the rates (Table 1) of isomerization of the hydroximoyl chlorides **1Za** and **2Za** in HCl and the hydroximates **1Zb** and **2Zb** in all three of the acids studied. Because the rates of these reactions depend on the concentration of the acid, all of the rate measurements were carried out at the same acid concentration.

The pK_a's of the three acids used in this work relative to water are as follows: CF_3SO_3H (−13),[22] HCl (−7),[23] and HBF_4 (0.05).[24] Furthermore, it is known that *p*-toluenesulfonic acid is a stronger acid than HCl in dioxane.[25] It therefore seems reasonable to assume that triflic acid is a stronger acid that HCl in dioxane. The rates of isomerization (see Table 1) for methyl *O*-methylcinnamohydroximate (**2Zb**) follow the order of acidity of the these acids (triflic acid > HCl > tetrafluoroboric acid). The rates of isomerization of methyl O-methylbenzohydroximate (**1Zb**) follow the order HCl > triflic acid > tetrafluoroboric acid. These results suggest that the primary pathway for isomerization in HCl/dioxane of the cinnamohydroximate is iminium ion rotation. Since the rate of isomerization of the benzohydroximate **1Zb** is higher with HCl than in the stronger acid, triflic acid, it seems likely that the primary pathway for isomerization of **1Zb** in HCl/dioxane is nucleophilic catalysis. It is not possible, however, to rule out some nucleophlic catalysis in the case of **2Zb**, and some iminium ion rotation in the isomerization of **1Zb** in HCl/dioxane.

The conclusions concerning the isomerization of **1Zb** and **2Zb** in HCl/dioxane are reasonable in light of the structures of these two hydroximates. Because of the increased conjugation in cinnamohydroximate (**2Za**), it seems likely that the positive charge in the conjugate acid

(22) Perrin, D. D. *Dissociation Constants of Inorganic Acids and Bases in Aqueous Solutions*, 2nd ed.; Pergamon: Oxford, 1982.
(23) Serjeant, E. P.; Dempsey, B. *Ionization Constants of Organic Acids in Aqueous Solutions*; Pergamon: Oxford, 1979.
(24) Lide, D., Ed. *CRC Handbook of Chemistry and Physics*, 79th ed.; CRC Press: Boco Raton, FL, 1998.
(25) Smagowski, H *Roczniki Chemii* **1972**, *46*, 1500−1606.

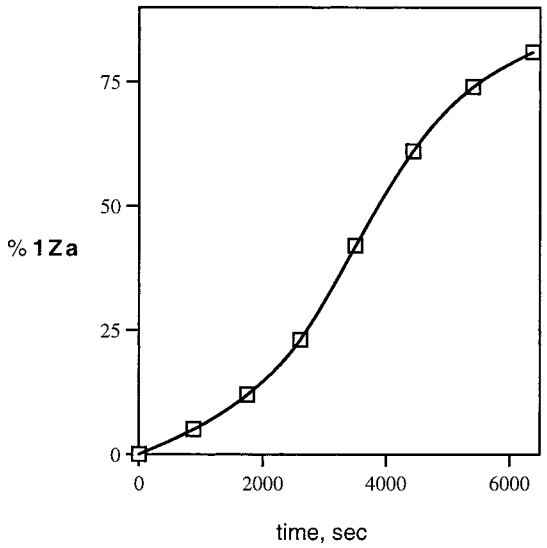
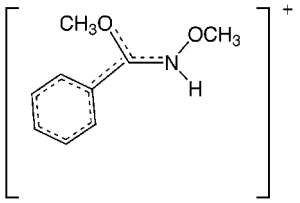
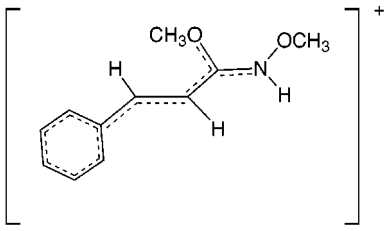


Figure 1. Isomerization of **1Ea** to **1Za** in glacial acetic acid at 80.0 °C.

of the cinnamohydroximate (**2ZH**$^+$) is more delocalized than the positive charge in the benzohydroximate (**1ZH**$^+$).



1ZbH$^+$



2ZbH$^+$

This should have two effects: (1) the C−N bond order in the conjugate acid of cinnamohydroximate should be less than in the benzohydroximate and (2) the magnitude of the positive charge on the carbon atom of the carbon−nitrogen double bond should be less in the conjugate acid of the cinnamohydroximate than in the benzohydroximate. Both effects should enhance the rate of iminium ion rotation over the nucleophilic catalysis pathway in the cinnamohydroximate (as compared to the benzohydroximate).

At one time, we thought it would be possible to use the Hammett ρ values for these isomerizations to determine which mechanism is operating. Our premise was that the Hammett ρ value should be more negative for the protonation−rotation mechanism than the nucleophilic catalysis process. To test this premise, we have measured rates of *Z*/*E* isomerization of the hydroximates **1Zd**−**h** in glacial acetic acid, a medium of low nucleophilicity where we would expect the isomerization to take place by the iminium ion rotation mechanism (Table 2). There was a slight improvement in the correlation with

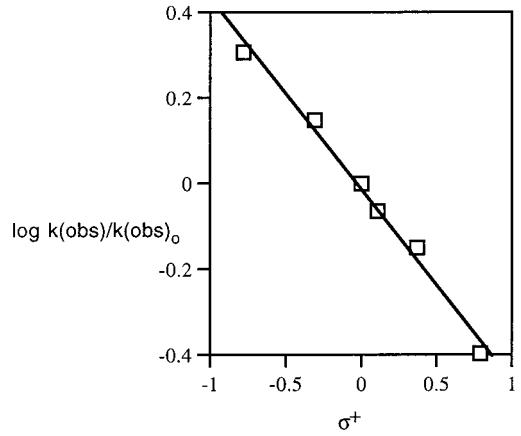


Figure 2. Hammett plot (σ^+) for the isomerization of **1Ec** to **1Zh** in glacial acetic acid at 80.0 °C.

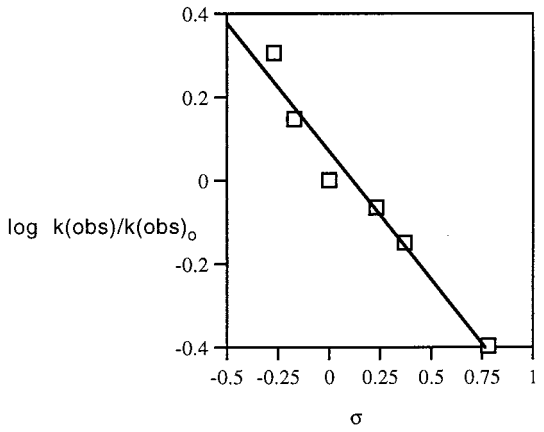


Figure 3. Hammett plot (σ) for the isomerization of **1Ec** to **1Zh** in glacial acetic acid at 80.0 °C.

σ^+ (r = 0.994, Figure 2) as compared with σ (r = 0.982, Figure 3) for these isomerizations. The Hammett ρ value for this isomerization is −0.45 with σ^+ (−0.61 with σ) which is close to that reported by us for the hydrogen chloride isomerization of hydroximoyl chlorides (ρ = −0.66 with σ). The improved correlation with σ^+ over σ may be indicative of the iminium ion rotation mechanism since one would expect that through resonance groups would have a greater effect on both the preequilibrium protonation step and the rotation step than is accounted for by σ values. Based on the fact that glacial acetic acid is a solvent of low nucleophilicity, it seems likely that the hydroximates **1Zd**−**h** are isomerizing by the protonation−rotation mechanism. It is clear from this work, however, that using the Hammett correlation as a probe for distinguishing between these two mechanisms is not possible.

The effect of added nucleophilic salts (Table 2) on the rates of isomerization of **1Zc** in glacial acetic acid support the notion that these isomerizations are proceeding by the iminium ion rotation mechanism. This study showed that addition of equivalent amounts of halide ion did not change the rates of isomerization in comparison to added perchlorate ion. When the isomerization of **1Zc** was carried out with a large amount of iodide ion relative to **1Zc** (**1Zc**/iodide ion = 1:124), the first-order rate constant was about 60% higher than the corresponding rate constant with added perchlorate ion. This suggests that

Table 2. Reversible First-Order Rate Constants[a] for the Isomerization of Ethyl *O*-Methylbenzohydroximates in Glacial Acetic Acid at 80.0 °C

imine	10^3[imine], M	added salt	10^3[salt], M	*Z* isomer at equilibrium (%)	10^3k, s^{-1}
1Zc	9.01			50	2.37 ± 0.19
1Zc	8.90	$NaClO_4$	9.10	49	2.09 ± 0.42
1Zc	8.90	NaI	9.10	49	2.29 ± 0.83
1Zc	8.94	$NaClO_4$	111	59	6.68 ± 0.35
1Zc	8.94	NaI	111	55	10.7 ± 1.8
1Zc	250	$NaClO_4$	100	42	2.78 ± 0.51
1Zc	250	$(C_2H_5)_4NCl$	100	43	2.99 ± 0.34
1Zd	8.90			51	0.952 ± 0.022
1Ze	9.09			45	2.04 ± 0.47
1Zf	8.90			36	4.79 ± 0.27
1Zg	8.90			44	3.33 ± 0.23
1Zh	8.90			46	1.68 ± 0.16
1Zi	8.90			60	0.245 ± 0.047

[a] The first-order rate constant is a sum of the rate constants for the forward and reverse reactions (ref 26).

the isomerization mechanism has shifted, at least in part, to the nucleophilic catalysis mechanism.

It is noteworthy that the hydroximate **1Zb** isomerizes by the nucleophilic catalysis mechanism in HCl/dioxane, but the hydroximate **1Zc** undergoes isomerization by iminium ion rotation in glacial acetic acid even in the presence of modest amounts of chloride ion or ioidide ion. We attribute this difference in behavior to the difference in nucleophilicitiy of chloride ion in glacial acetic acid and dioxane. Chloride ion should be highly solvated and less nucleophilic in acetic acid as compared to dioxane.

Interestingly, the hydroximoyl chloride **1Za** undergoes a slow autocatalyzed[26] isomerization in glacial acetic acid (Figure 1). Our interpretation of this result is that the isomerization takes place by the ionization of the *Z*-hydroximoyl chloride [as a minor contaminant (ca. 1%) in the starting material] to give chloride ion that then catalyzes the isomerization. A large difference in the rates of ionization of **1Za** and **1Eb** would be expected in glacial acetic acid since we have shown[27] that the para methoxy derivative of the *E*-hydroximoyl choride **1Ea** undergoes ionization to a nitrilium ion and chloride ion about 10^5 times slower than the corresponding *Z* isomer in 1:3 dioxane−water solution at 25 °C.

We have carried out ab initio calculations, using the Gaussian 94 and Gaussian 98 series of programs,[28] on the C═N rotation barriers of the conjugate acids of hydroximates and hydroximoyl chlorides (Table 3). Geometries were fully optimized at the Hartree−Fock (HF) level of theory using the 6-31+G(*) basis set.[29] Single-point energy calculations using the hybrid density functional (B3LYP and Moller−Plesset (MP2) levels of theory[30] were completed to help account for electron correlation effects. For computational expediency the calculations were carried out on compounds in which the phenyl was replaced by a hydrogen atom (**1ZjH**$^+$, **1EjH**$^+$, **1ZkH**$^+$, **1EkH**$^+$, **2ZcH**$^+$, **2EcH**$^+$, **2ZdH**$^+$, and **2EdH**$^+$ in Table 3). The energies for these compounds were optimized with different conformations around the nitrogen−oxygen bond, the imine carbon−oxygen bond (**1ZkH**$^+$, **1EkH**$^+$, **2ZdH**$^+$, and **2Ed H**$^+$) and the imine carbon-vinyl carbon bond (**2ZcH**$^+$, **2EcH**$^+$, **2ZdH**$^+$, and **2EdH**$^+$). Table 3 shows only the lowest rotational barriers (HF/6-31+G*+ZPVE) acquired for each compound, although the trends remain true for all conformations investigated. In some cases there is a conformational change in a vinyl group or a methoxy group that accompanies the rotation about the protonated carbon−nitrogen double bond.

Table 3. Calculated Energies for Rotation about the Carbon−Nitrogen Double Bond of Iminium Ions (kcal/mol)[a]

iminium ion[c]	HF + ZPVE[b]	MP2/HF + ZPVE[b]	B3LYP + ZPVE[b]
1ZjH$^+$	47.2	46.4	43.3
1EjH$^+$	47.6	45.7	43.4
1ZkH$^+$	30.3	31.3	32.0
1EkH$^+$	31.0	31.6	32.6
2ZcH$^+$	30.3	32.1	30.3
2EcH$^+$	31.9	33.1	31.4
2ZdH$^+$	20.4	20.1	20.7
2EdH$^+$	21.5	21.2	22.0
1ZaH$^+$	23.4		
1EaH$^+$	23.3		
1ZbH$^+$	17.6		
1EbH$^+$	16.7		
2ZaH$^+$	17.1		
2EaH$^+$	19.5		

[a] All calculations used the 6-31+G* basis set. [b] All ZPVEs were scaled by 0.9. [c] Iminium ions are designated by adding H^+ to the number used in this paper for the imine.

The calculations show that the protonated hydroximoyl chloride **1ZjH**$^+$ has a rotational barrier almost 17 kcal/mol higher than the hydroximate **1ZkH**$^+$. Increasing the conjugation by adding a vinyl group lowers the rotational barrier by at least 17 kcal/mol for the hydroximoyl chloride and about 10 kcal/mol for the hydroximate. The calculations indicate that the rotational barrier in the conjugated hydroximoyl chloride **2ZcH**$^+$ (**2EcH**$^+$) is essentially the same as the barrier in the hydroximate **1ZkH**$^+$, whose phenyl substituted counterpart (**2Zb**)

(26) Moore, J. W.; Pearson, R. G. *Kinetics and Mechanism*, 3rd ed.; Wiley: New York, 1981, p. 26 (autocatayzed reactions) and p 304 (reversible first-order reactions).

(27) Johnson, J. E.; Riesgo, E. C.; Jano, I. *J. Org. Chem.* **1996**, *61*, 45−50.

(28) 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.; Zakrzewski, 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.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, J. S.; Baker, J.; Head-Gordon, S. M.; Gonzalez, C.; Pople, J. A. *Gaussian 94 (Revision D.3)*; Gaussian, Inc.: Pittsburgh, PA, 1996.

(29) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; and Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley-Interscience: New York, 1986; and references therein.

(30) (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 Universtiy 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.

isomerizes by the iminium ion rotation mechanism in the absence of a nucleophilic counterion.

Calculations were performed in a similar manner on the phenyl-substituted compounds to verify the above trends (Table 3). Again, the hydroximoyl chlorides **1EaH**$^+$ and **1ZaH**$^+$ have higher barriers to rotation than the hydroximates (**1EbH**$^+$ and **1ZbH**$^+$), differing by at least 5.7 kcal (**1EaH**$^+$ compared to **1ZbH**$^+$).

The rate of isomerization by the iminium ion pathway is also dependent upon the concentration of the protonated species. Since the calculated rotational barriers for the conjugated hydroximoyl chloride and the hydroximate are essentially the same, it is assumed that the difference in isomerization rates is due to different basicities of these two compounds. The hydroximate must be more basic. Its concentration in the protonated form at equilibrium is therefore higher, and the reaction by the iminium ion rotation pathway is fast enough to be measured by the techniques described in this paper. The conjugated hydroximoyl chloride, being less basic, has a lower concentration of the protonated species at equilibrium, and isomerization by the iminium ion pathway is too slow to be observed. When a nucleophilic counterion is present, the isomerization increases to an observable rate.

Conclusions

We have clearly shown that the hydroximoyl chlorides **1Ea** and **2Ea** undergo E/Z isomerization only by the nucleophilc catalysis mechanism. We have also shown that the hydroximates **1Zb** and **2Zb** are capable of isomerizing by iminium ion rotation. It is likely that the predominate pathway for isomerization of the benzohydroximate **1Zb** in HCl/dioxane is nucleophilic catalysis, while the more highly conjugated cinnamohydroximate isomerizes by iminium ion rotation in HCl/dioxane solution.

Experimental Section

Melting points are uncorrected. The ^{1}H NMR spectra were recorded at 90, 200, or 300 MHz, and ^{13}C NMR spectra were recorded at 50 or 75 MHz. Unless otherwise noted, all NMR spectra were recorded in $CDCl_3$ using either TMS or residual $CHCl_3$ as an internal standard. Chemical shifts are given in ppm downfield from TMS. Infrared spectra were recorded on Midac and Nicolet Magna 560 FT infrared spectrophotometers.

All chemicals used in this research were reagent grade and unless otherwise specified were used without further purification. The silver tetrafluoroborate and trifluoromethanesulfonic acid were purchased from Aldrich and were used as received. The synthesis and identification of compounds **1Za**, **1Ea**, **1Zb**, **1Eb**, **1Zc**, and **1Ec** are described elsewhere.[31−34] Unless otherwise noted, the separation of the *Z* and *E* isomers of liquid hydroximates was carried out by preparative gc as described previously.[31] Separation of solid mixtures of *Z* and *E* isomers was accomplished by column chromatography using silica gel (MN-Kieselgel 60, 70−130 mesh) that had been dried at 95 °C for approximately 1 h before use. The experimental proceedures used for the preparation of **1Zd**−**h** and **1Ed**−**h** are in the Supporting Information. The preparation of the HCl−dioxane solution and the procedure for determination of the HCl concentration have been described previously.[16] Temperatures of the constant-temperature baths used in this work were measured with a Hewlett-Packard model 2804A quartz thermometer.

Purification of Dioxane. The dioxane used in this work was purchased from Aldrich. A small amount of benzophenone was added to the dioxane, and the solution was refluxed over sodium until a dark blue color was obtained. The dioxane was then distilled through a fractionating column. The dioxane was stored in a flask under a blanket of dry nitrogen.

Preparation of Terafluoroboric Acid in Dioxane. The dioxane solution of tetrafluoroboric acid was prepared in a glovebox under a nitrogen atmosphere. Silver tetrafluoroborate (0. 228 g, 0.00117 mol) was weighed into a 100 mL volumetric flask, and the flask was filled to the mark with 0.010 M hydrogen chloride in dioxane. The resulting mixture was filtered through a fine fritted funnel to remove suspended silver chloride.

Kinetic Method (HCl, Triflic Acid, and HBF_4). A 10 mL volumetric flask was modified so that it had a 14/20 outer joint at the top. The volumetric flask was fitted with an adapter that contained a nitrogen inlet, a drying tube, and a syringe septum inlet. The syringe inlet was positioned directly above the neck of the volumetric flask. For each kinetic run, a sample of the imine (5−10 mg) was weighed into the 10 mL volumetric flask. Another flask containing the acid (0.010 M) in dioxane was warmed in a sand bath to approximately 39.5 °C in a glovebox purged with dry nitrogen. The volumetric flask containing the imine was transferred to the glovebox and the acid-dioxane solution was added to the mark. Because the HCl−dioxane stock solution was of higher concentration than 0.010 M, two flasks, one containing the stock solution of HCl in dioxane and another containing only dioxane, were warmed in a sand bath to approximately 39.5 °C in a glovebox. The HCl−dioxane stock solution was pipetted into the volumetric flask containing the imine, and the flask was filled to the mark with dioxane. Immediately after the acid was added to the volumetric flask, it was fitted with the adapter and transferred from the glovebox to a water bath at 39.50 ± 0.04 °C. The apparatus was purged during the kinetic run witha slow flow of dry nitrogen. Aliquots (1 mL) were taken with a Teflon syringe needle through the syringe septum inlet. The aliquots were transferred into flasks containing sodium hydroxide solution (1 mL) of the same molarity (0.010 M) as the acid−dioxane solution. Each aliquot was analyzed by injecting 20 μL into an HPLC column (Burdick and Jackson OD5 octadecyl column with a mobile phase of acetonitrile/water) and determining the areas (UV detector with the wavelenth set at 254 nm) of the *Z* and *E* isomers. The ratios of the areas of the *Z* and *E* isomers were corrected by determining the response ratios using known quantites of pure samples. The rate constants are an average of at least two experiments. The rate constants were calculated using the linear least-squares regression method, and the error limits were calculated at the 95% confidence level.

Kinetic Method (Glacial Acetic Acid). The imine was weighed into a 25 mL volumetric flask and placed in a constant-temperature bath at 80.00 ± 0.04 °C for 15 min. Glacial acetic acid (Baker) that was thermostated at 80.00 °C was added to the volumetric flask to the mark. Aliquots (2 mL) were withdrawn and added to an equivalent amount of 6 N sodium hydroxide solution. The resulting solution was analyzed by HPLC (see the previous kinetic method).

2,2,2-Trifluoroethyl (*Z*)-*O*-Methylbenzohydroximate (1Zi). A solution of sodium 2,2,2-trifluoroethoxide prepared from 0.45 g of sodium and 2,2,2-trifluoroethanol (20 mL) was added to **1Za** dissolved in dimethyl sulfoxide (90 mL). The solution was heated at 50 °C for 14 h and then poured into ice−water (90 mL). Enough sodium chloride was added to saturate the aqueous layer, and the mixture was extracted several times with ether. The ether extracts were dried over anhydrous magnesium sulfate, and the ether was evaporated to give 1.71 g (64%) of an oil. After distillation (bp 65 °C/0.5 Torr), the ^{1}H NMR spectrum of the oil showed that it contained

(31) Johnson, J. E.; Nalley, E. A.; Kunz, Y. K.; Springfield, J. R. *J. Org. Chem.* **1976**, *41*, 252−259.
(32) Johnson, J. E.; Nalley, E. A.; Weidig, C.; Arfan, M. *J. Org. Chem.* **1981**, *46*, 3623−3629.
(33) Bertolasi, V.; Socerdoti, J. A.; Tassi, D. *Cryst. Struct. Commun.* **1977**, *6*, 335−341.
(34) Johnson, J. E.; Ghafouripour, A.; Haug, Y. K.; Cordes, A. W.; Pennington, W. T.; Exner, O. *J. Org. Chem.* **1985**, *50*, 993−997.

81% **1Zi** and 19% **1Ei**. A sample of **1Zi** was obtained by preparative GC. ^{1}H NMR (90 MHz) (δ): 3.95 (s, 3H), 4.72 (q, 2H, J = 8 Hz), 7.40 (m, 3H), 7.80 (m, 2H). IR (neat, cm^{-1}): 1622, 1614, 1576. Anal. Calc*d* for $C_{10}H_9NO_2F_3$: C, 51.51; H, 4.32; N, 6.01; F, 24.44. Found: C, 51.31; H, 4.31; N, 5.95; F, 24.24.

2,2,2-Trifluoroethyl (*E*)-*O*-Methylbenzohydroximate (1Ei). A glacial acetic acid (15 mL) solution of **1Zi** and **1Ei** (1.00 g) obtained from the previous procedure was heated at 80 °C for 3.5 h. The solution was poured into 6 N sodium hydroxide solution (50 mL), and the resulting mixture was extracted with ether. The ether extracts were dried over magnesium sulfate and evaporated to give a clear oil. GC analysis of the oil showed that it was a mixture of **1Zi** and **1Ei** in a ratio of 57:43. The E isomer (**1Ei**) was obtained by preparative GC. ^{1}H NMR (δ): 3.83 (s, 3H), 4.52 (q, 2H, J = 8 Hz), 7.45 (m, 3H), 7.85 (m, 2H). IR (neat, cm^{-1}): 1633, 1603, 1578. Anal. Calcd for $C_{10}H_9NO_2F_3$: C, 51.51; H, 4.32; N, 6.01; F, 24.44. Found: C, 51.65; H, 4.41; N, 5.87; F, 24.28.

(*Z*,*E*)-*O*-Methylcinnamohydroximoyl Chloride (2Za). This compound was recently reported,[35] but it was isolated only as a crude product. Methyl cinnamohydroxamate[35] (18.01 g) in carbon tetrachloride (25 mL) was placed in a 250 mL round-bottomed flask fitted with a condenser and a solid addition funnel. Phosphorus pentachloride (21.17 g) was added slowly, with stirring, through the addition funnel. With continued addition of phosphorus pentachloride, the solution progressively turned to a vivid yellow color. The temperature of the solution was maintained between 37 and 43 °C. After the addition of the phosphorus pentachloride, the solution was heated to 68 °C and this temperature was maintained for 6 h. The resulting liquid was allowed to cool to room temperature and was then slowly poured into ice-cold water. The mixture was extracted with ether. The ether extracts were then extracted with saturated sodium bicarbonate solution and dried with anhydrous magnesium sulfate. The solvent was removed by rotary evaporation under aspirator pressure to yield a yellow semisolid. The crude product was distilled to give an amber-colored liquid (12.71 g, 64%). Bp: 90−93 °C/0.05 mmHg. ^{1}H NMR (300 MHz) (δ): 4.04 (s, 3H), 6.81−6.87 (d, J = 16 Hz, 1H,), 7.28−7.23 (d, J = 16 Hz, 1H), 7.34−7.48 (m, 5H); ^{13}C NMR (75 MHz) (δ): 62.99, 120.40, 127.08, 128.61, 128.93, 135.02, 137.11, 137.96; IR (neat, cm^{-1}) 1631.2; Anal. Calcd for $C_{10}H_{10}NCl$: C, 61.39; H, 5.15; N, 7.16; Cl, 18.12. Found: C, 61.60; H, 5.18; N, 7.24; Cl, 17.94.

(*E*,*E*)-*O*-Methylcinnamohydroximoyl Chloride (2Ea). A solution of (*Z*,*E*)-*O*-methylcinnamohydroximoyl chloride (4.03 g) in hexane (84 mL) was placed in six quartz tubes. The test tubes were irradiated in a Rayonet photochemical reactor (254 nm) for 6 h. Immediately after irradiation, the hexane solution was extracted with a saturated solution of sodium carbonate. The hexane extracts were dried over anhydrous magnesium sulfate, and the hexane was removed in a rotary evaporator at aspirator pressure. Analysis of the resulting oil by GC-MS showed that the oil contained **2Za** and **2Ea** in a ratio of 35:65. The hydroximoyl chloride **2Ea**[36] was separated by column chromatography using a solution of hexane and chloroform in a ratio of 10:2. The oil was further purified by distillation. Bp: 33−34/0.05 mmHg. ^{1}H NMR (300 MHz) (δ): 4.00 (s, 3H), 7.25−7.30 (d, J = 16 Hz, 1H), 7.33−7.54 (m, 6H). ^{13}C NMR (75 MHz) (δ): 62.97, 113.82, 127.81, 128.64, 129.68, 134.79, 139.0.86, 147.60. IR (neat, cm^{-1}): 1619.81. Anal. Calcd for $C_{10}H_{10}NCl$: C, 61.39; H, 5.15; N, 7.16; Cl, 18.12. Found: C, 61.13; H, 5.14; N, 7.19; Cl, 18.20.

Methyl (*Z*,*E*)-*O*-Methylcinnamohydroximate (2Zb).[36] Sodium metal (3.85 g) was dissolved in methanol (70 mL) in a 250 mL round-bottomed flask fitted with a condenser, and a dropping funnel. A solution of (*Z*,*E*)-*O*-methylcinnamohydroximoyl chloride (5.58 g) in dimethyl sulfoxide (100 mL) was added through the dropping funnel with stirring. The mixture was stirred and heated at 50 °C for 24 h. The flask was allowed to cool to room temperature and then poured into ice-cold water (300 mL). The mixture was extracted with ether, and the ether extracts were dried over anhydrous magnesium sulfate. The ether was removed by rotary evaporation under aspirator pressure to give a yellow oil. The oil was microdistilled to yield **2ZB** as a light yellow liquid (2.8 g, 51%). Bp: 80−84 °C/0.05 mmHg. ^{1}H NMR (300 MHz) (δ): 3.89 (s, 3H), 3.99 (s, 3H), 6.45−6.50 (d, J = 16 Hz, 1H), 7.10−7.15 (d, J = 16 Hz, 1H), 7.30−7.46 (m, 5H). ^{13}C NMR (75 MHz) (δ): 59.30, 62.25, 117.75, 126.87, 127.97, 134.90, 135.46, 155.77. IR (neat, cm^{-1}): 1627.9. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.18; H, 6.83; N, 7.38.

Methyl (*E*,*E*)-*O*-Methylcinnamohydroximate (2Eb).[36] A solution of methyl (*Z*,*E*)-*O*-methylcinnamohydroximate (2.80 g) and glacial acetic acid (100 mL) was heated at 80 °C for 4 h. The reaction mixture was quenched with 6 M NaOH (400 mL) at the end of the reaction period. The resulting solution was extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, and the ether was evaporated under aspirator pressure. The resulting oil was analyzed by GC−MS and found to contain **2Zb** and **2Eb** in a ratio of 45:55. The *E*-hydroximate **2Eb** was separated by column chromatography using a mixture of hexane and chloroform in a ratio of 2:1. The oil was further purified by distillation. Bp: 73−74/0.1 mmHg. ^{1}H NMR (300 MHz) (δ): 3.79 (s, 3H), 3.83 (s, 3H), 7.10−7.05 (d, J = 16 Hz, 1H), 7.24−7.19 (d, J = 16 Hz, 1H), 7.32−7.52 (m, 5H). ^{13}C (75 MHz) (δ): 54.08, 61.82, 111.60, 127.37, 128.46, 128.89 135.63 136.13 159.20. IR (neat, cm^{-1}) 1638.05. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.94; H, 6.87; N, 7.49.

Acknowledgment is made to the Minority Biomedical Research Support Program of the National Institutes of Health (NIH-MBRS Grant GM08256), The Robert A. Welch Foundation, and the Texas Woman's University Research Enhancement Program for support of this work.

Supporting Information Available: Tables giving the Cartesian coordinates for **1ZjH**$^+$, **1EjH**$^+$, **1ZkH**$^+$, **1EkH**$^+$, **2ZcH**$^+$, **2EcH**$^+$, **2ZdH**$^+$, **2EdH**$^+$, **1ZaH**$^+$, **1EaH**$^+$, **1ZbH**$^+$, **1EbH**$^+$, **2ZaH**$^+$, and **2EaH**$^+$ at the HF6-31+G(*) + ZPVE level of theory and experimental procedures including spectral data (^{1}H and ^{13}C NMR and infrared spectra) for **1Zd-h** and **1Ed-h** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

JO010067K

(35) Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Aoe, K.; Okamura, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 6922−6931.

(36) The isomer produced by ultraviolet irratdiation of **2Za** was determined to be the result of isomerization about the carbon−nitrogen double bond (rather than isomerization about the carbon−carbon double bond) from its ^{1}H NMR spectrum; i.e., the CH=CH coupling constant in both **2Za** and **2Eb** is 16 Hz which is consistent with a trans configuration at the carbon−carbon double bond (see ref 37). Similarily, the configurations of **2Zb** and **2Eb** at the carbon−carbon double bond are trans (J = 16 Hz).

(37) Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*; VCH: New York, 1991; pp 77−82.