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Articles

Mechanism of Hydrolysis of (*Z*)- and (*E*)-*O*-Methylbenzohydroximoyl Chloride

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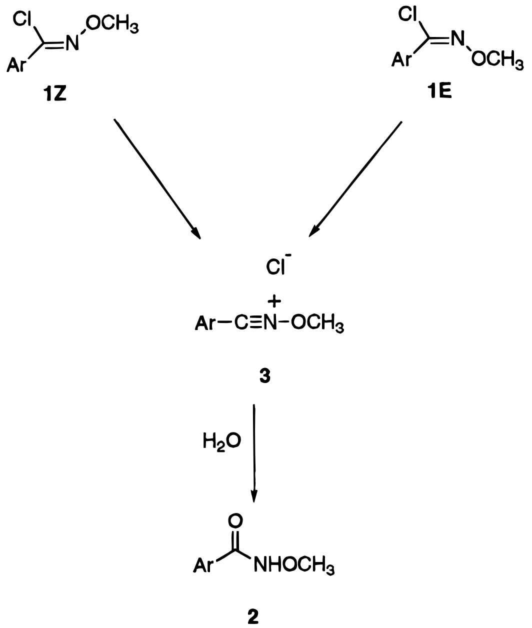
The first-order rate constants for the hydrolysis (1:3 dioxane-water, pH = 7) of (*E*)-*O*-methylbenzohydroximoyl chloride [$C_6H_5C(Cl){=}NOCH_3$, **1Ea**] and several 4-substituted derivatives have been measured. A Hammett plot of these rate constants *vs* σ^+ gave a ρ value of −1.4. Molecular orbital calculations (AM1) have been carried out on (*Z*)-*O*-methylbenzohydroximoyl chloride (**1Za**), a hydrazonyl chloride [$C_6H_5C(Cl){=}NNHCH_3$], and the corresponding nitrilium ions [$C_6H_5C{\equiv}NOCH_3{}^+$ and $C_6H_5C{\equiv}NNHCH_3{}^+$] in an attempt to gain insight into the differences in the reactivities of these two systems. A study of the effect of solvent composition on the rates of hydrolysis of (*Z*)- and (*E*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**1Zb** and **1Eb**) has been carried out using dioxane/water solutions of various compositions. The Grunwald−Winstein *m* values were determined to be 1.1 and 0.95 for the *Z* and *E* isomers, respectively. The activation parameters for the hydrolysis of **1Zb** and **1Eb** are as follows: $\Delta H^{\ddagger} = 34$ kcal/mol and $\Delta S^{\ddagger} = +2$ eu (**1Zb**) and $\Delta H^{\ddagger} = 40$ kcal/mol and $\Delta S^{\ddagger} = +8$ eu (**1Eb**). When plots of ln k/T *vs* $1/T$ were extrapolated to 25 °C, a rate constant ratio for $k_{\mathbf{1Zb}}/k_{\mathbf{1Eb}}$ of about 10^5 was obtained. It is concluded that both (*Z*)- and (*E*)-hydroximoyl chlorides undergo hydrolysis by rate-limiting ionization to a nitrilium ion ($ArC{\equiv}NOCH_3{}^+$). The large difference in ionization rates for **1Zb** and **1Eb** is attributed to a stereoelectronic effect.

Introduction

Some time ago we reported[1] on the rates of hydrolysis (1:3 dioxane/water, pH 7) of (*Z*)- and (*E*)-*O*-methylbenzohydroximoyl halides (**1Z** and **1E**) to methylbenzohydroxamates (**2**, Scheme 1). The rates of hydrolysis of (*Z*)-*O*-methylbenzohydroximoyl chloride (**1Za**) and several *para*-substituted derivatives were studied in 1:3 dioxane/water solutions. The hydrolyses were sluggish and required relatively high temperatures in order to obtain reasonable reaction rates (120 °C for **1Za**). Even higher temperatures (150, 160, and 170 °C) were necessary to study **1Ea** which was found to react much slower than **1Za**. Extrapolation of the **1Ea** rate constant data to 120 °C and comparison with the rate constant for **1Za** at 120 °C revealed that the *Z* isomer reacted about 470 times faster than the *E* isomer. The hydrolysis of **1Za** was found to have characteristics of a unimolecular ionization process ($D_N + A_N$, Scheme 1), including a ρ value of −2.4 with σ^+, common-ion rate depression, and a substantial element effect ($k_{\mathbf{1Zg}}/k_{\mathbf{1Za}} = 41$).

Scheme 1



The difference in the hydrolysis rates of (*Z*)- and (*E*)-*O*-methylbenzohydroximoyl chloride was interpreted by us in terms of a stereoelectronic effect,[2] *i.e.* the *Z* isomer (**1Za**) reacts faster than the *E* isomer (**1Ea**) because it has a nonbonded electron pair antiperiplanar to the nucleofuge (chloride ion).

⊗ Abstract published in *Advance ACS Abstracts,* November 15, 1995.

[1] Johnson, J. E.; Cornell, S. C. *J. Org. Chem.* **1980**, *45*, 4144−4148. The ratio of dioxane to water used in this work was incorrectly reported to be 3:1. The ratio of dioxane to water should have been reported as 1:3.

[2] (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983. (b) Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463−2490. (c) Deslongchamps, P. *Heterocycles* **1977**, *7*, 1271−1317.

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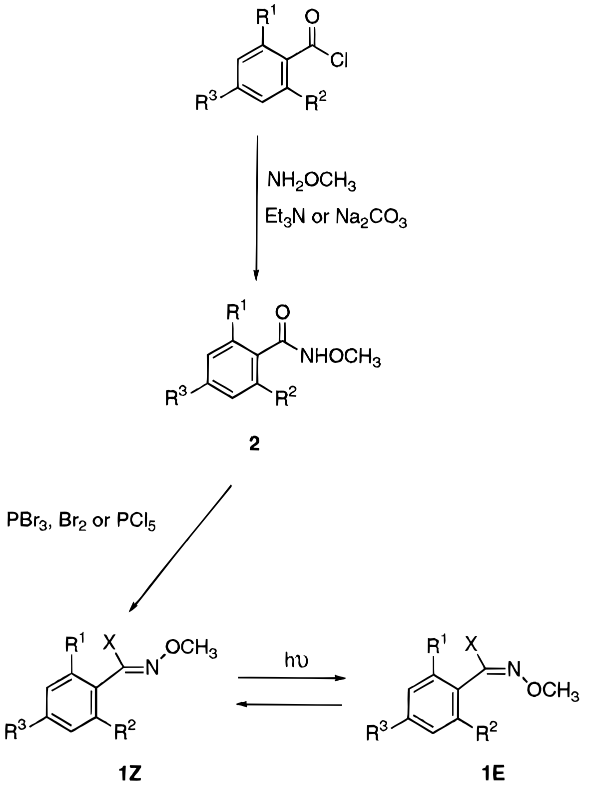
Scheme 2



2a, 1Za, and 1Ea: $R^1 = R^2 = R^3 = H$; $X = Cl$

b: $R^1 = R^2 = H$; $R^3 = OCH_3$; $X = Cl$

c: $R^1 = R^2 = H$; $R^3 = CH_3$; $X = Cl$

d: $R^1 = R^2 = H$; $R^3 = C_6H_5$; $X = Cl$

e: $R^1 = R^2 = OCH_3$; $R^3 = H$; $X = Cl$

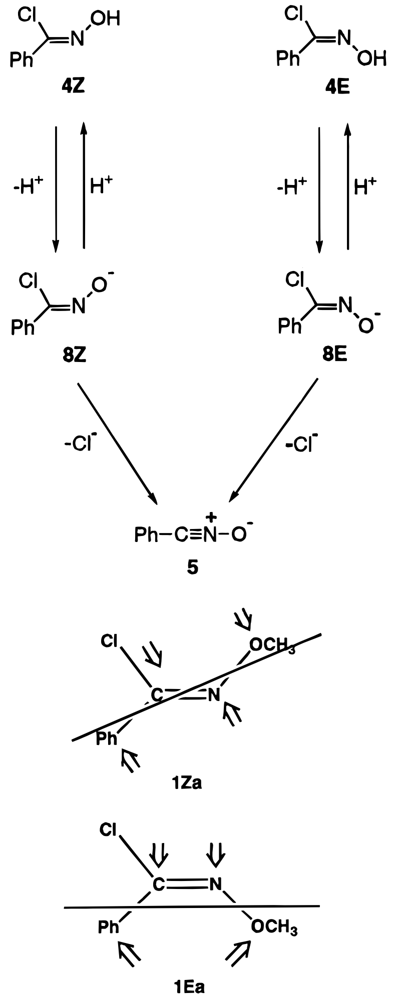
f: $R^1 = R^2 = H$; $R^3 = OCH_3$; $X = Br$

g: $R^1 = R^2 = R^3 = H$; $X = Br$

In a review[3] on least nuclear motion and stereoelectronic effects, Sinnott claims the "modest" *Z*/*E* rate ratio observed by us is not due to a stereoelectronic effect. He argues that a rate ratio of 470 is what one would expect from the differences in nuclear motion between the *Z* and *E* isomers when they undergo ionization to a linear nitrilium ion (**3**). The principle of least nuclear motion (PLNM) states that reactions involving the least motion of nuclei are favored. The nuclear motion necessary for the (*E*)-*O*-methylbenzohydroximoyl chlorides to achieve the linear geometry expected for the nitrilium ion intermediate is more than that of the *Z* isomers:

Hegarty and Mullane[4] have examined the rate of elimination of chloride ion from (*Z*)- and *(E)*-benzohydroximoyl chlorides (**4Z** and **4E**) to benzonitrile oxide (**5**) and found that the rate ratio k_{4Z}/k_{4E} was about 10^7 at 25 °C (Scheme 3). Hegarty and Mullane suggested that the lower rate ratio reported by us[1] could be accounted for by thermal isomerization of the *E* isomer to the more thermodynamically stable *Z* isomer at the high temperatures used to measure the rates of hydrolysis (150−170 °C).

Scheme 3



Sinnot[3] has questioned whether the system studied by Hegarty and Mullane[4] is a good model for elimination reactions. His criticism centers on the fact that the (*Z*)- and (*E*)-hydroximoyl chlorides (**4Z** and **4E**) must be deprotonated in order for the rate of ionization to be measured. From our viewpoint the deprotonation should enhance the rate of ionization by allowing the reaction to avoid formation of an unstable protonated benzonitrile oxide ($PhCNOH^+$). Furthermore, a negatively charged oxygen in **8Z** should repel the nonbonded electron pair on nitrogen and enhance its effect on the ionization process.

Although the rate ratio of 470 reported by us[1] is considerably smaller than Hegarty's value of 10^7, the *O*-methylbenzohydroximoyl chloride system appears to have the greatest potential for an unequivocal interpretation of the importance of stereoelectronic effects on elimination reactions from a trigonal center to give an sp-hybridized intermediate.

Results and Discussion

In this report we describe a reinvestigation into the hydrolysis of (*Z*)- and (*E*)-*O*-methylbenzohydroximoyl halides. In an attempt to minimize the possibility of *E* → *Z* isomerization, several new *O*-methylbenzohydroximoyl halides (**1Zd**−**1Zf**, **1Eb**−**1Ed**, and **1Ef**) were synthesized (Scheme 2) which should be more reactive toward hydrolysis than most of those studied previously. These hydroximoyl halides along with **1Ea**, **1Zb**, and **1Zc** were used in this study.

The attempted synthesis of (*E*)-*O*-methyl-2,6-dimethoxybenzohydroximoyl chloride (**1Ee**) was unsuccessful due

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[3] Sinnott, M. L. *Adv. Phys. Org. Chem.* **1988**, *24*, 113−204.

[4] Hegarty, A. F.; Mullane, M. *J. Chem. Soc., Perkin Trans. 2* **1986**, 995−1001.

Table 1. First-Order Rate Constants for the Hydrolysis of *O*-Methylbenzohydroximoyl Halides in 1:3 Dioxane/Water (0.10 M Sodium Perchlorate)

no.	*T*, °C	pH	$10^5 k$, s^{-1}
1Zb	80.0	7.00	2.20 ± 0.13
1Zb	85.0	7.00	4.35 ± 0.20
1Zb	90.0	7.00	6.43 ± 0.28
1Zb	95.0	7.00	10.8 ± 0.6
1Eb	135.0	7.00	1.30 ± 0.14
1Eb	140.0	7.00	2.27 ± 0.34
1Eb	150.0	7.00	7.67 ± 0.49
1Eb	150.0	4.50	8.05 ± 0.86
1Eb	150.0	6.65	7.71 ± 0.51
1Eb	150.0	6.80	7.88 ± 0.49
1Eb	150.0	7.30	7.52 ± 0.77
1Eb	150.0	8.30	7.36 ± 0.79
1Eb	150.0	11.2	7.10 ± 0.60
1Ec	150.0	7.00	1.66 ± 0.18
1Ed	150.0	7.00	1.29 ± 0.28
1Ea	150.0	7.00	0.652 ± 0.078
1Zf	80.0	7.00	82.5 ± 6.9
1Ze	80.0	7.00	129 ± 17

to the low yield of isomerized material and the difficulty in isolating the desired isomer from the crude photolysis mixture. The photoisomerization reaction yielded a significant amount of 2,6-dimethoxybenzonitrile as a byproduct which had about the same retention time in column chromatography as **1Ee**.

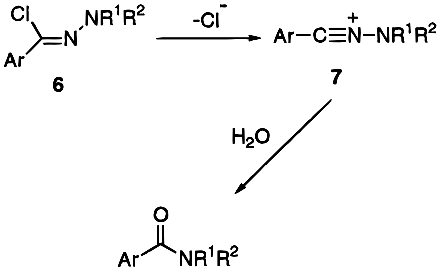
The rates of hydrolysis of **1Ze**, **1Zf**, **and 1Eb−1Ed** were studied in 1:3 dioxane/water (v/v). The solutions were buffered to pH 7, and a constant ionic strength was maintained by addition of sodium perchlorate. The hydrolyses, which give methyl benzohydroxamates, were followed using a high performance liquid chromatography (HPLC) analytical method.

At the higher temperature used to measure the hydrolysis of the *E* isomers (150 °C), there was another product detected in the HPLC analysis of the reactions. This product was determined by HPLC coinjection to be a *para*-substituted benzoic acid which presumably results from hydrolysis of the corresponding methyl benzohydroxamate. More acid formation was observed for (*E*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**1Eb**) than for the other derivatives of (*E*)-*O*-methylbenzohydroximoyl chloride studied.

In all cases the reactions followed first-order kinetics. The kinetic data for the hydrolysis of the hydroximoyl halides in 1:3 dioxane/water are given in Table 1. The hydrolysis rates of (*E*)-*O*-methylbenzohydroximoyl chlorides were found to be unaffected by a change in the pH of the solutions (Table 1), which is consistent with the findings reported by us[1] for the *Z* isomer.

Consistent with a unimolecular process and the experimental results reported by us previously on **1Zg** and **1Za**,[1] (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl bromide (**1Zf**) underwent hydrolysis 38 times faster at 80 °C than the (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**1Zb**) (Table 1). Although an element effect of 38 is on the low end of the range of values (30−440) observed for reactions that involve cleavage of a carbon−halogen bond in the rate-determining step in imidoyl halides,[5−7] our value is likely to be smaller because of the elevated temperature used to make the kinetic measurements. An attempt to measure the element effect for the hydrolysis of (*E*)-hydroximoyl halides was not successful, because (*E*)-4-methoxybenzohydroximoyl bromide (**2Ef**) underwent thermal isomerization to the *Z* isomer faster than it underwent hydrolysis.

Scheme 4



The hydrolysis of (*Z*)-*O*-methyl-2,6-dimethoxybenzohydroximoyl chloride (**1Ze**) was found to be faster than that of **1Zb** by a factor of 59 at 80 °C. The increased rate of hydrolysis of **1Ze** is likely to be due to a combination of two factors. First, the two *o*-methoxy groups should provide enhanced stabilization of the transition state leading to nitrilium ion formation. Second, the *o*-methoxy groups in **1Ze** should cause the benzene ring to twist out of the plane of the Cl−C=N−OCH_3 group to a greater extent than in **1Za**, resulting in a destabilization of the ground state.

The rates of hydrolysis of (*E*)-*O*-methylbenzohydroximoyl chloride (**1Ea**) and three *para*-substituted derivatives (**1Eb−d**) were measured in order to study substituent effects (Table 1) on this reaction. The *para* substituents chosen for this study were all capable of stabilizing a developing positive charge in the transition state (nitrilium ion formation) which made it possible to measure hydrolysis rates at reasonable time intervals. The rates of hydrolysis of these compounds were all measured at 150 °C. A Hammett plot of the first-order rate constants *vs* σ^+ gave a ρ value of −1.4 which is similar to that reported by us[1] for the hydrolysis of the (*Z*)-hydroximoyl chlorides [$\rho = -2.4(\sigma^+)$].

The sign and magnitude of the ρ value for the (*E*)-hydroximoyl chloride reaction indicate the development of a positive charge in the transition state which is consistent with nitrilium ion formation. In accordance with that reported by us[1] on the hydrolysis of the *Z* isomer, a better correlation was achieved with σ^+ ($r = 0.998$) than with σ ($r = 0.915$). This further supports the formation of a nitrilium ion in the transition state for the hydrolysis of **1E** since a σ^+ correlation indicates that the positive charge is in conjugation with the aromatic ring.

The rate constants[7] for hydrolysis of hydrazonoyl chlorides **6** [$R^1 = CH_3$, 2,4-$(NO_2)_2C_6H_3$], which react by the $D_N + A_N$ mechanism (nitrilium ion **7** in Scheme 4), correlate better with σ than with σ^+; it is possible that this difference is due to an increased amount of positive charge on the carbon in the transition state for nitrilium ion formation in hydroximoyl chlorides as compared to that of hydrazonoyl chorides. The larger positive charge on the carbon in **3** as compared to that on the carbon in the nitrilium ion from hydrazonoyl chlorides may be due to the destabilizing effect of the hydroxylamine oxygen on any positive charge buildup on the adjacent nitrogen atom in **3**. An alternate explanation for this difference, suggested by Rowe,[7] is that the phenyl group attached to the carbon in hydrazonoyl chlorides **6** is coplanar with the carbon−nitrogen π bond. As the chlorine atom

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(5) Ta-Sha, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1977**, *99*, 1845−1858.

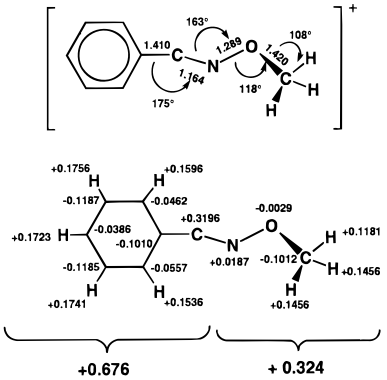
(6) Scott, F. L.; Cronin, D. A.; O'Halloran, J. K. *J. Chem. Soc. C* **1971,** 2769−2775.

(7) Rowe, J. E. *Aust. J. Chem.* **1991**, *44*, 463−468.

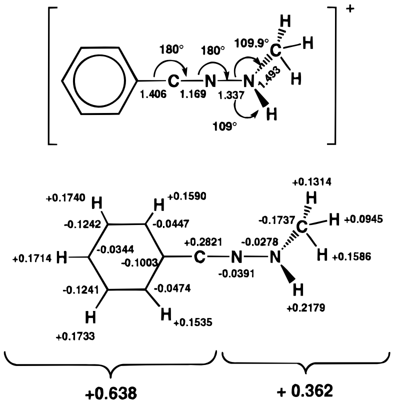
undergoes ionization, the developing positive charge is orthogonal to the phenyl group. Consequently there is no direct resonance interaction of the phenyl group and the developing positive charge. Since the interaction between the phenyl group and the developing positive charge is primarily inductive, the rate constants correlate with Hammett σ values. Implicit in Rowe's argument is that the torsion angle between the phenyl group and the C=N−O plane is larger in **1Z** and **1E** than the corresponding torsion angle in **6**. If this were the case, one would expect a direct resonance interaction of the developing positive charge in **1Z** and **1E** with the phenyl group. Consequently the hydrolysis rate constants for the hydrolysis of **1Z** and **1E** should correlate better with σ^+ than with σ.

Molecular orbital calculations (AM1)[14] appear to rule out the argument that there is a significant difference in the charge distribution in the nitrilium ions **3** (Ar = C_6H_5) and **7** (Ar = C_6H_5, R^1 = H, and R^2 = CH_3). These calculations show little difference in geometry or charge distribution between these two ions:

Molecular Orbital Calculations (AM1) on the Nitrilium Ion 3



Molecular Orbital Calculations (AM1) on the Nitrilium Ion 7



Molecular orbital calculations on **6** (Ar = C_6H_5, R^1 = H, and R^2 = CH_3) and **1Za** indicate that the torsion angle (38°) of the phenyl plane with respect to the C=N−N plane in **6** is larger than the angle (27°) between the phenyl plane and the C=N−O plane in **1Za**. It appears that Rowe's suggestion for the differences in the Hammett correlations for the hydrolysis of hydroximoyl chlorides *vs* hydrazonoyl chlorides is not viable either.

The results of our molecular orbital calculations have been used to calculate the energy change, ΔE, for the ionization of a hydroximoyl chloride (**1Za**) and a hydrazonoyl chloride (**6**) to the corresponding nitrilium ion (**3** or **7**) and chloride ion. The change in energy for the ionization of **1Za** into **3** and a chloride ion was calculated as follows:

$$\Delta E = \Delta E(\mathrm{g}) - \Delta E(\mathrm{sol})$$

where $\Delta E_{(\mathrm{g})}$ is the energy change in the gas phase, calculated using the AM1 method,[14] and $\Delta E_{(\mathrm{sol})}$ is the difference in solvation energy between the ions **3** and Cl^- and the unionized molecule **1Za**. The solvation energy was calculated using the generalized Born model.[15] One-center integrals, (ss/ss), in this model were calculated with Slater-type s orbitals, having standard ζ's. Two-center Coulomb integrals were approximated as the inverse distance between the two centers. Chloride ion was considered a spherical ion with a radius of 1.81 Å, and a simple Born formula was used to calculate its energy of solvation. The result of the calculation for the ionization of **1Za** is

$$\Delta E = 175.33 - 139.35(1 - 1/D)\ \mathrm{kcal/mol}$$

where D is the dielectric constant of the solvent. The effective dielectric constant would be somewhere between 2.2 (for pure dioxane) and 80 (for pure water). The value for ΔE is, therefore, in the range between 99.0 and 37.7 kcal/mol, depending on the composition of the solvent. This, of course, ignores the effect of the added sodium perchlorate and buffer on the dielectric constant of water/dioxane solutions used in this work.

In a similar fashion the change in energy for the ionization of the hydrazonoyl chloride **6** into the nitrilium ion **7** and the chloride ion was calculated as follows:

$$\Delta E = 155.88 - 139.66(1 - 1/D)\ \mathrm{kcal/mol}$$

In this ionization ΔE would be between 79.4 and 18.0 kcal/mol, depending on the ratio of dioxane to water in the solvent.

Although the solvent has a considerable effect on the stabilization of the ions, the difference between the systems is evidently due to mainly the difference in energy in the gaseous state, ΔE(g), while ΔE(sol) is approximately the same in the two reactions. That is

$$\Delta\Delta E = \Delta E(\mathbf{1Za} \rightarrow \mathbf{3}) - \Delta E(\mathbf{6} \rightarrow \mathbf{7}) \approx 175.33 - 155.88 = 19.5\ \mathrm{kcal/mol}$$

Since these ionization reactions should have late transition states, a comparison of the theoretically calculated $\Delta\Delta E$ value to the difference in the experimentally observed free energies of activation should give some insight into the validity of our calculations. The free energy of activation for the ionization of **1Zb** is about

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(8) (a) Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948**, *70*, 846−854. (b) Fainberg, A. H.; Winstein, S. *J. Am. Chem. Soc.* **1956**, *78*, 2770−2777.

(9) Johnson, J. E.; Ghafouripour, A.; Haug, Y. K.; Cordes, A. W.; Pennington, W. T.; Exner, O. *J. Org. Chem.* **1985**, *50*, 993−997.

(10) Johnson, J. E.; Nalley, E. A.; Kunz,Y. K.; Springfield, J. R. *J. Org. Chem.***1976**, *41*, 252−259. The *Z* and *E* assignments for the hydroximoyl chlorides described in this paper are incorrect (see ref 9).

(11) Brit. Patent 1,221,280; 1971; *Chem. Abstr.* **1971**, *75*, 5515e.

(12) Sakamoto, T.; Okamoto, K.; Kikugawa, Y. *J. Org. Chem.* **1992**, *57*, 3245−3248.

(13) Johnson, J. E.; Ghafouripour, A.; Arfan, M.; Todd, S. L.; Sitz, D. A. *J. Org. Chem.* **1985**, *50*, 3348−3355.

(14) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909.

(15) (a) Jano, I. *Chem. Phys. Lett.* **1984**, *106*, 60−64. (b) Jano, I. *Compt. Rend* **1965**, *261*, 103−105.

Table 2. First-Order Rate Constants for the Hydrolysis of (*Z*)- and (*E*)-*O*-Methyl-4-methoxybenzohydroximoyl Chlorides in Various Dioxane/Water (v/v) Mixtures (pH = 7.00)

no.	*T*, °C	% water	10^5k, s^{-1}
1Zb	95.0	90	49.6 ± 1.1
1Zb	95.0	70	5.72 ± 0.18
1Zb	95.0	50	0.514 ± 0.015
1Eb	140.0	90	4.62 ± 0.24
1Eb	140.0	80	2.28 ± 0.13
1Eb	140.0	50	0.0792 ± 0.0010

33 kcal/mol at 30 °C (*vide infra*) which we estimate to be about 12 kcal/mol higher than the activation energy for the ionization of a similarly substituted hydrazonoyl chloride **6** [$k = 6.00 \times 10^{-3}$ s^{-1}at 30 °C in 40% methanol/water; Ar = 4-$CH_3OC_6H_5$, $R^1 = CH_3$, R^2 = 2,4-$(NO_2)_2C_6H_3$].[7] Although our calculated value, $\Delta\Delta E$, is substantially larger (8 kcal/mol) than the difference in the experimentally observed free energies of activation, the calculations correctly predict that hydrazonoyl chlorides should be more reactive in reactions that proceed by the $D_N + A_N$ mechanism than hydroximoyl chlorides.

Solvent composition effects on the hydrolysis of (*Z*)- and (*E*)-*O*-methyl-4-methoxybenzohydroximoyl chlorides (**1Zb** and **1Eb**) were studied using dioxane/water solutions of various compositions (Table 2). The log *k* values obtained were plotted against Grunwald and Winstein[8] *Y* values to obtain the corresponding *m* values. One would expect that the *m*-value for the ionization of **1Zb** or **1Eb** to a nitrilium ion would be close to unity whereas the rate constants for *E* to *Z* isomerization should not be affected much by the composition of the solvent ($m \approx 0$). The *m* values obtained for the *Z* and *E* isomers were 1.1 and 0.95, respectively, which supports an ionization mechanism for both isomers.

In order to obtain activation parameters for a pair of *Z* and *E* isomers, the hydrolysis rate constants for (*Z*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**1Zb**) were measured at 80, 85, 90, and 95 °C and the hydrolysis rate constants for (*E*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**1Eb**) were measured at 135, 140, and 150 °C (Table 1). The activation parameters calculated for **1Zb** and **1Eb** are as follows: $\Delta H^{\ddagger} = 34$ kcal/mol and $\Delta S^{\ddagger} = +2$ eu for **1Zb** and $\Delta H^{\ddagger} = 40$ kcal/mol and $\Delta S^{\ddagger} = +8$ eu for **1Eb**.

When the plots of ln *k*/*T* vs 1/*T* for **1Zb** and **1Eb** were extrapolated to 120 °C, a rate constant ratio ($k_{\mathbf{1Zb}}/k_{\mathbf{1Eb}}$) of 720 was obtained. This is about the same rate ratio that we reported[1] for the hydrolysis of **1Za** and **1Ea** ($k_{\mathbf{1Za}}/k_{\mathbf{1Ea}} = 470$). In order to compare our rate data with that of Hegarty and Mulane,[4] the plots of ln *k*/*T* *vs* 1/*T* for **1Zb** and **1Eb** were extrapolated to 25 °C; a rate constant ratio ($k_{\mathbf{1Zb}}/k_{\mathbf{1Eb}}$) of about 10^5 was obtained. This ratio is about 100 times smaller than the ratio found by Hegarty and Mullane[4] for the rates of elimination of chloride ion from (*Z*)- and (*E*)-benzohydroximoyl chlorides (**4Z** and **4E**) to give benzonitrile oxide (**5**).

In summary, it is concluded that the ρ value of $-1.4(\sigma^+)$ obtained for the hydrolysis of the (*E*)-*O*-methylbenzohydroximoyl chlorides along with the *m* values of 1.0 and 0.95 observed for (*Z*)- and (*E*)-*O*-methyl-4-methoxybenzohydroximoyl chloride (**1Zb** and **1Eb**), respectively, provides strong evidence that these compounds undergo rate-limiting ionization through a nitrilium ion intermediate. The possibility that the *E* isomer isomerizes to the *Z* isomer before it undergoes hydrolysis has been ruled out. Furthermore, the k_Z/k_E rate ratio of 10^5 at 25 °C calculated for **1Zb** and **1Eb** seems too large to be attributed to the principle of least nuclear motion, and it is better explained by a stereoelectronic effect.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Spectra of solid samples were determined from Nujol mulls between sodium chloride plates. NMR spectra were obtained at 90 (^{1}H only), 200, or 300 MHz. Low-resolution mass spectra were obtained on a Varian Saturn 3 ion-trap GC−mass spectrometer.

The photoisomerization of the (*Z*)-hydroximoyl chlorides (except **1Ef**) to a mixture of the *Z* and *E* isomers was carried out using a procedure described previously.[10] The isomers were separated[10] by either preparative GLC or column chromatography.

The synthetic procedures used for the preparation of the methyl benzohydroxamates **2a**−**c** are included in this section. These compounds have been prepared previously by us,[10] by the methylation of the corresponding potassium benzohydroxamates. For this work **2a**−**c** were prepared by the reaction of a carboxylic acid chloride with methoxylamine. The methods used for the conversion of **2a**−**c** to the (*Z*)-hydroximoyl chlorides **1Za**−**c**, the photoisomerization of the (*Z*)-hydroximoyl chlorides, and the chromatographic separation of **1Ea**−**c** from the *Z* isomers have been described previously by us.[9,10] The preparation of the new hydroximoyl chlorides (**1Zd**, **1Ed**, and **1Ze**) used in this study are described in this section. The photoisomerization of **1Zf** to **1Ef** and the chromatographic separation of **1Ef** from **1Zf** were carried out according to procedures reported by Sakamoto *et al.*[12]

Kinetic Method. The dioxane used for kinetic measurements was purchased from Burdick and Jackson (distilled in glass). The dioxane was refluxed over sodium metal until the metal became shiny; the dioxane was then fractionally distilled from the round-bottomed flask containing the sodium. The solvent mixtures of dioxane/water (v/v) were made up at room temperature. The solutions were buffered to pH 7, using 0.01 M potassium dihydrogen phosphate and 0.01 M sodium hydroxide. A constant ionic strength was maintained by the addition of solid sodium perchlorate to a 1:3 dioxane/water (v/v) solution so that the concentration of the sodium perchlorate was 0.10 M. The other solvent compositions used (90, 80, 70, and 50% water) did not contain sodium perchlorate due to solubility limitations. The procedures for degassing the samples and carrying out the kinetic runs have been described previously.[1] The constant temperature bath was maintained at ±0.1 °C, and the temperature of the bath was monitored with a Hewlett-Packard Model 2804A quartz thermometer.

The rate constants were calculated using a linear regression program. The error limits were calculated at the 95% confidence level.

Hydrolysis Product Analysis. The hydrolyses of the *O*-methylbenzohydroximoyl halides were followed using an HPLC apparatus equipped with an integrator. The detector was set at a wavelength of 260 nm. The hydrolysis product analysis was carried out on a 25-cm Whatman Partisil ODS-3 C18 column with various acetonitrile/water (v/v) compositions as mobile phases. Mobile phases were buffered at pH 4.5 by the addition of glacial acetic acid to obtain chromatograms of better resolution. Peak ratios were normalized by running acetonitrile solutions containing known amounts of reactant and product.

Methyl Benzohydroxamate (2a). A solution of methoxylamine hydrochloride (6.25 g, 0.0728 mol) in water (20 mL) was placed in a 125-mL Erlenmeyer flask. The solution was brought to pH 7 by addition, with stirring, of anhydrous sodium carbonate. Benzoyl chloride (10.54 g, 0.074 98 mol) was added dropwise while the pH was kept at 7 with the addition of more sodium carbonate and more water. The resulting mixture was stirred for 20 min at room temperature and then acidified at 0 °C with 6 M hydrochloric acid. The mixture was extracted with chloroform (3 × 200 mL). The chloroform extracts were dried over anhydrous magnesium sulfate, and the chloroform was removed on a rotary evaporator at aspirator pressure. The residue was an oil which slowly crystallized. The crystals were purified by washing with cold diethyl ether under suction filtration to give colorless crystals (4.78 g, 0.0316 mol, 42%): mp 61−62 °C (lit.[10] mp 61−62 °C); ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.80 (s, 3H), 7.20−7.90 (m, 5H); IR (Nujol) 3237, 1655, 1595, 1576 cm^{-1}.

Methyl 4-Methoxybenzohydroxamate (2b). This compound was prepared as described for the hydroxamate **2a**. Recrystallization from water gave colorless crystals (60%): mp 102−103 °C (lit.[10] mp 102−103 °C); ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.75 (s, 6H), 6.81−7.74 (dd, $J = 6$ Hz, 4H), 10.17 (s, 1H); IR (Nujol) 3179, 1653, 1574 cm^{-1}.

Methyl 4-Methylbenzohydroxamate (2c) This compound was prepared as described for the hydroxamate **2a**. Recrystallization from ether/hexanes gave colorless crystals (73%): mp 70−71 °C (lit.[10] mp 70−71 °C); ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.80 (s, 3H), 7.10−7.74 (dd, $J = 8$ Hz, 4H); IR (Nujol) 3470, 3407, 1659 cm^{-1}.

Methyl 2,6-Dimethoxybenzohydroxamate (2e). Methoxylamine hydrochloride (6.26 g, 0.0750 mol) was placed in a 500-mL three-neck round-bottomed flask fitted with a condenser, a calcium chloride drying tube, and an addition funnel. Triethylamine (15.18 g, 0.1500 mol) in chloroform (HPLC grade, 10 mL) was added with stirring to the solid methoxylamine hydrochloride. Additional chloroform (10 mL) was added to rinse the addition funnel. The reaction mixture was stirred at room temperature for 30 min. A solution of 2,6-dimethoxybenzoyl chloride (19.37 g, 0.0917 mol) in chloroform (125 mL) was then added dropwise with stirring. The solution was stirred for 1 h at room temperature. The mixture was then washed successively with water, a 10% sodium bicarbonate solution, and a 15% sodium hydroxide solution. The aqueous layer obtained from the sodium hydroxide extraction was acidified with concentrated hydrochloric acid at 0 °C and then extracted with chloroform (2 × 100 mL). The chloroform extracts were dried over anhydrous magnesium sulfate, and the chloroform was removed on a rotary evaporator at aspirator pressure. The residue was recrystallized from chloroform/hexanes to give colorless crystals (6.54 g, 0.0324 mol, 43%): mp 134−135 °C (lit.[11] mp 126−128 °C); ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.79 (s, 9H), 6.52 (d, $J = 6$ Hz, 2H), 7.27 (t, $J = 6$ Hz, 1H), 8.51 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 55.8, 64.2, 103.8, 111.8, 131.5, 157.9, 164.0; IR (Nujol) 3192, 1655, 1597 cm^{-1}. Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.85; H, 6.20; N, 6.60.

Methyl 4-Phenylbenzohydroxamate (2d). This compound was prepared as described for the hydroxamate **2e**. Recrystallization from methanol gave colorless crystals (84%): mp 179−180 °C; ^{1}H NMR (90 MHz, DMSO-d_6) δ 3.80 (s, 3H), 7.40−8.00 (m, 9H); ^{13}C NMR (200 MHz, DMSO-d_6) δ 63.2, 126.6, 126.8, 127.7, 128.1, 129.0, 131.0, 139.0, 143.1, 163.1; IR (Nujol) 3188, 1653 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.05; H, 5.82; N, 6.18.

(*Z*)-*O*-Methyl-2,6-dimethoxybenzohydroximoyl Chloride (1Ze). Methyl 2,6-dimethoxybenzohydroxamate (5.00 g, 0.0237 mol) was placed in a 250-mL three-neck round-bottomed flask fitted with a condenser, a calcium chloride drying tube, and a solid addition funnel. Phosphorus pentachloride (5.19 g, 0.0249 mol) was added through the solid addition funnel with stirring. The mixture was heated and stirred for 6 h at 56−60 °C. The liquid product was allowed to cool to room temperature and was then slowly added to cold water (40 mL). The precipitate that formed was filtered under suction, and two additional recrystallizations from methanol gave the analytical sample (3.08 g, 0.0134 mol, 59%): mp 120−121°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.80 (s, 6H), 4.10 (s, 3H), 6.56 (d, $J = 6$ Hz, 2H), 7.32 (t, $J = 6$ Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 55.9, 62.7, 103.9, 112.0, 131.1, 132.1, 158.8; IR (Nujol) 1594 cm^{-1}; UV−vis (methanol) λ_{max} 285 (3.47), 237 sh (3.80) nm. Anal. Calcd for $C_{10}H_{12}NClO_3$: C, 52.30; H, 5.27; N, 6.10; Cl, 15.44. Found: C, 52.19; H, 5.14; N, 6.22; Cl, 15.66.

(*Z*)-*O*-Methyl-4-phenylbenzohydroximoyl Chloride (1Zd). A suspension of methyl 4-phenylbenzohydroxamate (6.00 g, 0.0264 mol) in carbon tetrachloride (100 mL) was placed in a 250-mL three-neck round-bottomed flask fitted with a condenser, a calcium chloride drying tube, and a solid addition funnel (Kontes No. 299400). Phosphorus pentachloride (5.50 g, 0.0264 mol) was added through the solid addition funnel with stirring. The mixture was stirred and heated at 65 °C for 24 h. The flask was allowed to cool to room temperature, and then the contents were poured into cold water (100 mL). The mixture was cooled to 0 °C and then filtered under suction to collect part of the product that was suspended. The carbon tetrachloride layer was washed successively with a saturated sodium bicarbonate solution, water, a 6 M sodium hydroxide solution, and water. The carbon tetrachloride extract was dried over anhydrous magnesium sulfate, and the carbon tetrachloride was evaporated on a rotary evaporator at aspirator pressure. The solid residue was recrystallized from methanol to yield colorless crystals (6.32 g, 0.0257 mol, 97%): mp 110−111 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.10 (s, 3H), 7.30−8.00 (m, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 63.2, 127.0, 127.1, 127.5, 127.9, 128.9, 131.4, 137.0, 140.0, 143.2; IR (Nujol) 1576 cm^{-1}. Anal. Calcd for $C_{14}H_{12}NOCl$: C, 68.44; H, 4.92; N, 5.70; Cl, 14.43. Found: C, 68.52; H, 4.93; N, 5.74; Cl, 14.49.

(*E*)-*O*-Methyl-4-phenylbenzohydroximoyl Chloride (1Ed). (*Z*)-*O*-Methyl-4-phenylbenzohydroximoyl chloride (2.62 g, 0.0107 mol) was dissolved in benzene (80 mL) and placed in seven 20-mL quartz tubes. The test tubes were irradiated[10] at 254 nm for 6 h. Immediately after irradiation, the benzene solution was extracted with a saturated solution of potassium carbonate (3 × 70 mL). The benzene extract was dried over anhydrous magnesium sulfate, and the benzene was removed on a rotary evaporator at aspirator pressure. The ^{1}H NMR spectrum of the oil residue showed that it was a mixture of the (*Z*)- and (*E*)-*O*-methyl-4-phenylbenzohydroximoyl chlorides in a ratio of 59:41 respectively. The residue (1.90 g, 0.007 73 mol) was fractionated by column chromatography (190 g of MN-Kieselgel 60, 70−130 mesh ASTM silica gel). Elution with benzene/hexanes (1:4) afforded starting material first (0.75 g, 0.0031 mol, 39% based on 1.90 g of the mixture) and then (*E*)-*O*-methyl-4-phenylbenzohydroximoyl chloride (0.56 g, 0.0023 mol, 29% based on 1.90 g of the mixture, 72% recovery based on the amount of *E* isomer present in the mixture). Recrystallization from methanol yielded colorless crystals of **1Ed** (0.26 g, 0.0011 mol, 46%): mp 63−64 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.00 (s, 3H), 7.40−8.00 (m, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 63.4, 126.7, 127.1, 128.0, 128.9, 129.6, 129.8, 139.9, 143.5, 146.1; IR (Nujol) 1568 cm^{-1}. Anal. Calcd for $C_{14}H_{12}NOCl$: C, 68.44; H, 4.92; N, 5.70; Cl, 14.43. Found: C, 68.33; H, 4.93; N, 5.66; Cl, 14.34.

(*Z*)-*O*-Methyl-4-methoxybenzohydroximoyl Bromide (1Zf). The procedure used for this synthesis was that of Johnson *et al.*[13] in their synthesis of (*Z*)-*O*-methyl-4-nitrobenzohydroximoyl bromide. The hydroximoyl bromide **1Zf** was recrystallized from hexanes to give colorless crystals (67%): mp 59−60 °C (lit.[12] mp 58−59 °C); ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.10 (s, 3H), 6.80−7.70 (dd, $J = 8$ Hz, 4H); IR (Nujol) 1607 cm^{-1}.

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