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Rate and equilibrium constants for hydrolysis and isomerization of (*E*)- and (*Z*)-*p*-methoxybenzaldehyde oximes†

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ABSTRACT: The interconversion and hydrolysis of (*E*)- and (*Z*)-oximes of *p*-methoxybenzaldehyde in aqueous solutions of perchloric acid have been studied in the acid concentration range from pH 3 to 11 M. Kinetic measurements confirm that isomerization and hydrolysis proceed through a common tetrahedral intermediate T_0. At low acid concentrations, attack of water on the protonated oxime is rate-determining in the hydrolysis reaction and no separate isomerization is observable. However, as the acid concentration increases the attack of water becomes faster than loss hydroxylamine from T_0 and *E* to *Z* isomerization is observable as a faster reaction in competition with hydrolysis. From kinetic and equilibrium measurements a comprehensive set of rate and equilibrium constants for protonation, hydrolysis and hydration of (*E*)- and (*Z*)-oximes is derived. For the neutral oximes $K_T = [E]/[Z] = 8$ and for the protonated oximes $pK_a = -0.55$ and 0.80 for the *E* and *Z* isomers, respectively. By combining these values with measurements of oxime formation from *p*-methoxybenzaldehyde and hydroxylamine, including $K_{add} = [T_0]/[\text{aldehyde}][NH_2OH] = [T_0]/[\text{oxime}] = 1.8$, values of $pK_R = -3.65$ and -5.90 and $K_{H_2O} = 6.3 \times 10^{-5}$ and 7.9×10^{-6} for (*E*)- and (*Z*)-oximes may also be derived. The values of pK_a, pK_R and K_{H_2O} for the oximes are compared with corresponding values for *p*-methoxybenzaldehyde and its hydrate ($\equiv T_0$). Copyright © 2004 John Wiley & Sons, Ltd.
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KEYWORDS: methoxybenzaldehyde oximes; hydrolysis; *E-Z* isomerization; rate constant; equilibrium constants

INTRODUCTION

Jencks and co-workers have carried out many investigations of the formation and hydrolysis of carbon–nitrogen double bonds and comprehensively reviewed the mechanisms of these reactions.[1,2] Of particular interest for the present paper are their studies of the conversion of aromatic aldehydes to oximes.[2,3] These studies were extended by Sayer and co-workers,[4] and recently have provided a stimulus for investigation by the present authors of the hydrolysis of the oxime of 9-formylfluorene.[5]

One of the best known features of oximes and especially aldoximes is the existence of *syn* and *anti* (*E* and *Z*) isomers.[6] We were surprised, therefore, that kinetic measurements of the hydrolysis of 9-formylfluorene oxime revealed no evidence of an isomerization reaction. The reactant was the *E* (*syn*) isomer and analogy with structurally related oximes[6] suggested that the equilibrium ratio of *syn* to *anti* isomers should be 1:2. Chemical intuition and available experimental evidence[7] suggest that the hydrolysis reaction and interconversion of *E* (**1**) and *Z* (**3**) isomers share a common carbinolamine intermediate (**2**) formed by attack of water on the protonated oximes, as shown in Scheme 1. It might have been expected, therefore, that competing isomerization would lead to detectable departures from first-order kinetics. Despite kinetic measurements over a wide range of acidity (from pH 4 to 11 M $HClO_4$) covering changes in rate-determining step and mechanism of hydrolysis, no such departure was observed.

In so far as (*E*)- and (*Z*)-oximes of aromatic aldehydes may be prepared independently,[8] it seemed worthwhile to study the hydrolysis of the two isomers and to attempt to elucidate the interplay of hydrolysis and isomerization. In this paper, we report measurements for the (*E*)- and (*Z*)-oximes of *p*-methoxybenzaldehyde. These oximes were chosen partly because the isomers differ significantly in basicity and partly because the large spectral change associated with protonation facilitates kinetic studies of isomerization in acid ranges where one isomer is protonated and the other not. Moreover, rate constants for the reverse of the hydrolysis reaction, oxime formation, and an equilibrium constant for the formation of the carbinolamine intermediate (**2**) have already been measured by

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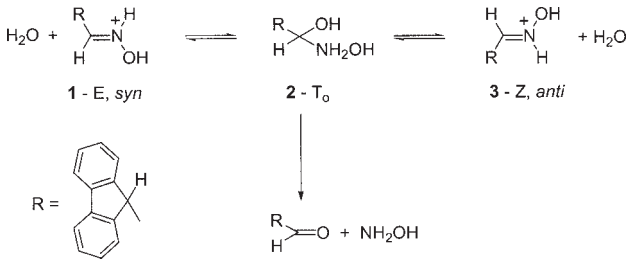
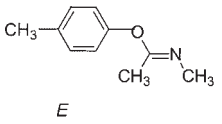


Scheme 1

Calzadilla *et al.*[9] The analysis of kinetic measurements was also considerably assisted by the previous study of the hydrolysis of 9-formylfluorene oxime.[5]

There have been few systematic studies of *syn–anti* isomerization of oximes. However, base- and buffer-catalysed mechanisms have been reported for the oximes of acetaldehyde[10,11] and for the oximes of ring-opened arabinose.[7] Nucleophilic mechanisms have been assigned[7] and the detection of general acid catalysis has been interpreted in terms of general base-catalysed attack of water on the protonated oxime to yield a carbinolamine intermediate (cf. Scheme 1). For stronger bases, especially amines, the base itself may act as nucleophile, directly attacking the protonated oxime.[10] The situation contrasts with *E* to *Z* isomerization of imidate esters (**4** and **5**) studied by Jencks and Satterthwait where nucleophilic mechanisms are precluded by the rapid conversion of tetrahedral intermediates to ester or amide products.[12]



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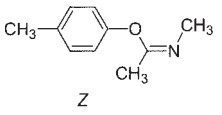

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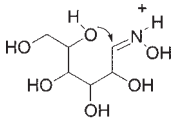
Of interest is the H_3O^+-catalysed isomerization of (*E*)- and (*Z*)-oximes of ring-opened arabinose.[7] This reaction might have been interpreted as nucleophilic attack by water on the protonated oxime as in Scheme 1. However, the high rate of reaction compared with other oximes[7] suggests intramolecular attack by a hydroxyl group of the open-chain sugar, presumably that on the 4- or 5-carbon atom, as in **6**.



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In this paper, we confirm that hydrolysis and isomerization of the *p*-methoxybenzaldehyde oximes in aqueous acidic media occur by competing reactions consistent with Scheme 1. Kinetic and equilibrium measurements yield pK_as for protonation of the isomers and rate constants for attack of water on the protonated species. Combination of these measurements with data from the study of oxime formation by Calzadilla *et al.*[9] yields a 'complete' set of rate and equilibrium constants for hydration and hydrolysis of the (*E*)- and (*Z*)-oximes.

RESULTS

Measurements of pK_a

The pK_as of the *E* and *Z* isomers of *p*-methoxybenzaldehyde oxime were determined spectrophotometrically in aqueous solutions of $HClO_4$. The spectra of the neutral forms were similar, with $\lambda_{max} = 263$ nm for the *E*- and 260 nm for the *Z*-isomer, the same was true of the protonated forms, with $\lambda_{max} = 305$ nm for the *E*- and 302 nm for the *Z*-isomer. Both isomers underwent isomerization and hydrolysis, but the reactions were sufficiently slow that absorbances at the beginning of the reactions could be measured directly or extrapolated to the time of mixing of the oximes with acid.

For the less basic (*E*)-oxime, measurements in the acid concentration range 0.1–3 M $HClO_4$ showed that the pK_a increased with increase in acid concentration. A value of $pK_a = -0.55$ in water was extrapolated as the intercept of a plot of pK_a against Cox and Yates's[13] solvent acidity parameter *X*,[14] as shown in Fig. 1. The slope of this plot is $m^* = 1.14$, and it is used below for interpreting the dependence of rates of hydrolysis and isomerization on the acidity of the medium. For the more basic *Z*-isomer a value of $pK_a = 0.80$ was obtained. In this case measurements were confined to the lower acid concentration range 0.01–0.9 M and there was little systematic deviation of K_a from its value in water.

E–Z isomerization

Equilibration of *E*- and *Z*-isomers of *p*-methoxybenzaldehyde oxime could be achieved in $CDCl_3$ as solvent

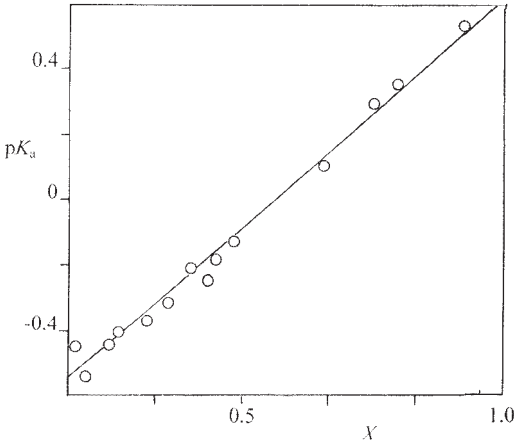


Figure 1. Plot of pK_a against *X* for the dissociation of protonated (*E*)-*p*-methoxybenzaldehyde oxime in solutions of aqueous perchloric acid at 25 °C

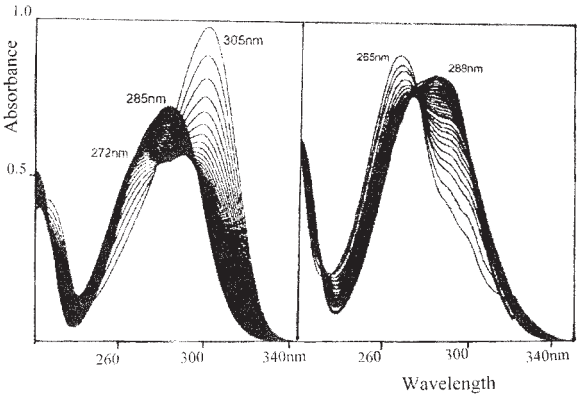


Figure 2. Repetitive scans of UV–visible spectra (time interval 80 s) for the isomerization of *E*- and *Z*-isomers of *p*-methoxybenzaldehyde oxime in 0.58 M aqueous perchloric acid at 25 °C: (a) *Z*-isomer and (b) *E*-isomer

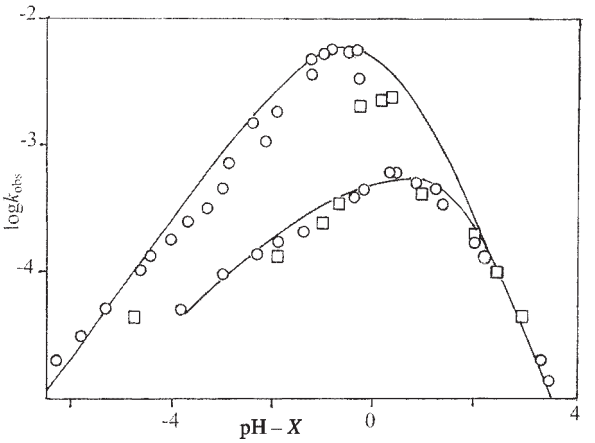


Figure 3. Plot of logarithms of first-order rate constants (k_{obs}) against pH–*X* for isomerization (upper line) and hydrolysis (lower line) of (○) (*E*)- and (□) (*Z*)*p*-methoxybenzaldehyde oximes in aqueous perchloric acid and chloroacetic acid buffers at 25 °C

over a period of 8 days and gave a limiting ratio of *E*- to *Z*-tautomers of 8:1, as judged by NMR measurements.

In aqueous acid solutions, rates of equilibration of *E*- and *Z*-isomers, and also the rate of their hydrolysis, could be monitored spectrophotometrically. Despite the similarity of the spectra of the *E*- and *Z*-isomers (and of their protonated forms), it was generally possible to observe isomerization as a faster reaction than hydrolysis, provided that the less stable isomer was the reactant. Conveniently, the product of hydrolysis, *p*-methoxybenzaldehyde had a chromophore ($\lambda_{max} = 285$ nm) which was easily distinguishable from that of the oximes and could be used to monitor the hydrolysis independently. Moreover, because of the difference in basicity of the (*E*)- and (*Z*)-oximes and sharp differentiation of the spectra of neutral and protonated forms over a range of acid concentrations, isomerization of the *E*- (especially) followed by protonation of the *Z*-isomer is associated with particularly large spectral changes.

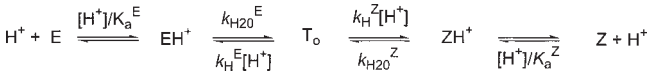
The latter point is illustrated by repetive scans of spectra for reaction of the (*Z*)-oxime in 0.58 M $HClO_4$ shown in Fig. 2(a). At this acid concentration the *Z*-isomer ($pK_a = 0.80$) is completely protonated whereas the *E*-isomer ($pK_a = -0.55$) is substantially unprotonated. The figure shows a rapid decrease in the peak for the protonated species at 305 nm and replacement by that of the unprotonated species at 265 nm. In a slower subsequent reaction (still incomplete) an equilibrium mixture of unprotonated *E*- and protonated *Z*-isomers undergoes hydrolysis to yield *p*-methoxybenzaldehyde with $\lambda_{max} = 285$ nm.

The approach to an equilibrium mixture of protonated and unprotonated isomers starting from the unprotonated *E*-isomer ($\lambda_{max} = 265$ nm) at the same acid concentration is shown in Fig. 2(b). The equilibrium composition of isomers reflects the fact that for the unprotonated species the equilibrium concentration of *E*-isomer is greater by 8-fold than that of the *Z*-isomer but for the protonated species the relative stabilities are reversed so that now the concentration of *Z*-isomer is 1.8-fold greater than that of the *E*-isomer. This is considered in more detail below.

Except for a relatively small range of acid concentrations (close to pH 1), the isomerization reaction was either not observable (above that pH) or occurred more than 10 times faster than hydrolysis (below pH 1). This meant that kinetics for both reactions could be measured independently with little interference of one with the other.

Rate constants for isomerization and hydrolysis of (*E*)- and (*Z*)-oximes at different acid concentrations are recorded in Tables S1–S4 in the supplementary material (available in Wiley Interscience) and are shown in Fig. 3 plotted as logarithms of first-order rate constants against $pH - X$, where *X* is Cox and Yates's solvent acidity parameter.[13] The upper line and experimental points in Fig. 3 refer to the isomerization reaction and the lower to the (slower) hydrolysis. For both reactions the rate constants are independent of the isomer taken as reactant. This is as expected in so far as the isomerization involves an equilibration of reactants and products and the hydrolysis, at least at low pHs where isomerization is a fast reaction, involves reaction of an equilibrated mixture of isomeric reactants. A further point of note is that at lower acid concentrations, where no isomerization is observed, the hydrolytic rate constants appear to be the same. The explanation of this is considered below.

There is significant scatter of the experimental points in Fig. 3, especially for the isomerization reactions, for which the rate constants depend detectably on the wavelength of measurement (cf Table S3). This is because separation of the absorbance changes associated with isomerization and the slower hydrolysis is imperfect and tends to make the measured rate constants for isomerization too low. However, the discrepancies are systematic and not large enough to imply a serious



Scheme 2

deficiency in the quantitative fitting of the data described below.

The lines drawn through the points in Fig. 3 are based on microscopic rate constants chosen to provide a best fit of experimental to calculated data. The microscopic rate contants (and associated equilibrium constants) in turn provide a comprehensive description of the isomerization and hydrolysis reactions.

The isomerization reaction may be described by the reaction steps and rate constants shown in Scheme 2, which is an elaboration of Scheme 1; E and Z denote the isomeric (*E*)- and (*Z*)-oximes, EH^+ and ZH^+ are their conjugate acids and T_0 is the hydroxylamine adduct of the aldehyde. The ionization constants of the protonated oximes are K_a^E and K_a^Z; the rate constants $k_{H_2O}^E$ and $k_{H_2O}^Z$ refer to the attack of water on the protonated oxime and k_H^E and k_H^Z refer to the acid-catalysed dehydration of T_0.

The observed rate constants for isomerization may be expressed in terms of a sum of forward and reverse rate constants k_{obs}^f and k_{obs}^r. The value of k_{obs}^f is then given by

$$k_{obs}^f([E] + [EH^+]) = xk_{H_2O}^E[EH^+] \quad (1)$$

where $x = k_H^Z/(k_H^Z + k_H^E)$. We then obtain for k_{obs}^f

$$k_{obs}^f = \frac{xk_{H_2O}^E}{1 + K_a^E/[H^+]} \quad (2)$$

and for $k_{obs} = k_{obs}^f + k_{obs}^r$

$$k_{obs} = \frac{xk_{H_2O}^E}{1 + K_a^E/[H]^+} + \frac{(1-x)k_{H_2O}^Z}{1 + K_a^Z/[H^+]} \quad (3)$$

To fit Eqn (3) to the kinetic data in Fig. 3, we need to assign values of k_{H_2O}, K_a and x. Values of K_a^E and K_a^Z are known. If we write x as $1/(1 + k_H^E/k_H^Z)$, it can be seen that x is determined if we know k_H^E/k_H^Z. To obtain k_H^E/k_H^Z we use (a) the value of the equilibrium constant $K = 0.125$ for interconversion of *E*- and *Z*-isomers, which is related to k_H^E/k_H^Z by the following relationship based on Scheme 2:

$$\frac{[Z]}{[E]} = \frac{k_{H_2O}^E}{K_a^E}\frac{K_a^Z}{k_{H_2O}^Z}\frac{k_H^Z}{k_H^E} = 0.125 \quad (4)$$

and (b) the fact, noted above and evident from Fig. 3, that at high pH the rates of reaction of both *E*- and *Z*-isomers appear to merge with the rates of hydrolysis. This merging is consistent with the k_{H_2O} step being rate determining for both reactions. However, inspection of Fig. 3 reveals that the rate constants $k_{obs} = k_{H_2O}/K_a$ for the two isomers in this pH range are indistinguishable. This implies that $k_{H_2O}^E/K_a^E = k_{H_2O}^Z/K_a^Z$. From this relationship we obtain $k_H^Z/k_H^E = 0.125$ by substitution in Eqn (4).

To obtain $k_{H_2O}^Z$ and $k_{H_2O}^E$, we take the measured limiting acid-catalysed rate constant at high pH, $3.0 \times 10^{-2}\,M^{-1}\,s^{-1}$. By identifying this with $k_{H_2O}^E/K_a^E = k_{H_2O}^Z/K_a^Z$ we obtain $k_{H_2O}^E = 0.106\,s^{-1}$ and $k_{H_2O}^Z = 4.75 \times 10^{-3}\,s^{-1}$ based on the values of $pK_a^E = -0.55$ and $pK_a^Z = 0.80$.

In principle, we can now calculate the pH dependence of the isomerization reaction. First, however, we should recognize that the change from a reaction which is first order in acid concentration at high pH to one that is no longer acid-catalysed at lower pH is a result of protonation of the oxime reactant as expressed by the $1 + [H^+]/K_a$ term in the denominator of Eqn (3).

However, protonation of the oxime should according to Eqn (3) lead to a pH-independent reaction. In practice, at high acid concentrations, the rate of reaction decreases. This is reasonably interpreted as a medium effect and may be represented in the concentrated acid region by Eqn (5), in which m_2^* is the limiting slope of a plot of $\log k_{obs}$ against X at high acid concentrations[13,14] and describes the acidity dependence for the equilibration of tautomers in this acidity range.

$$k_{obs} = [xk_{H_2O}^E + (1-x)k_{H_2O}^Z] \times 10^{m_2^*} \quad (5)$$

If we now make the approximation that the protonation of both oximes shows the same acidity dependence as determined directly for the *E*-isomer (with $m_1^* = 1.14$), we can modify Eqn (3) to obtain Eqn (6), which is applicable over the entire range of acid concentrations.

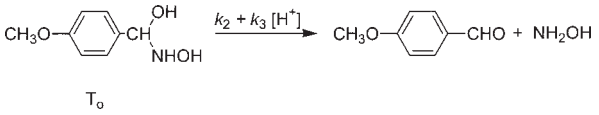
$$k_{obs} = \left\{ \frac{xk_{H_2O}^E}{1 + K_a^E \times 10^{-m_1^* X}/[H^+]} + \frac{(1-x)k_{H_2O}^Z}{1 + K_a^Z \times 10^{-m_1^* X}/[H^+]} \right\} \times 10^{m_2^* X} \quad (6)$$

The line drawn through the experimental points for the isomerization reaction in Fig. 3 is based on Eqn (6) with $m_2^* = -0.58$.

Hydrolysis

The hydrolysis reaction of the *p*-methoxybenzaldehyde oximes may also be described by Scheme 2 if we extend it to include uncatalysed and acid-catalysed reaction paths with rate constants k_2 and k_3 respectively, leading to expulsion of hydroxylamine and formation of aldehyde product from the carbinolamine intermediate T_0, as shown in Scheme 3.

As for the isomerization reactions, we can achieve a best fit of calculated to experimental values of k_{obs} by



Scheme 3

deriving a kinetic expression based on Schemes 2 and 3 and using the rate constants already assigned for the isomerization reaction together with optimally adjusted values of k_2/k_3 and $k_2/(k_H^E + k_H^Z)$.

To obtain the appropriate rate expression we rely on the analysis of Scheme 2 [Eqns (3) and (6)] and the previous treatment of the hydrolysis reaction of 9-formylfluorene oxime[5] as guides.

Our starting expression for k_{obs} is the following:

$$k_{obs}([E] + [EH^+] + [Z] + [ZH^+]) = (k_2 + k_3[H^+])[T_0] \quad (7)$$

Applying the steady-state approximation to the carbinolamine adduct, we obtain the following expression for its concentration:

$$[T_0] = \frac{k_{H_2O}^E[EH^+] + k_{H_2O}^Z[ZH^+]}{k_H^E[H^+] + k_H^Z[H^+] + k_2 + k_3[H^+]} \quad (8)$$

Substitution for $[T_0]$ in Eqn (7) and rearrangement then gives

$$k_{obs} = \frac{(k_2 + k_3[H^+])(k_{H_2O}^E + ak_{H_2O}^Z)}{\{(k_H^E + k_H^Z)[H^+] + k_2 + k_3[H^+]\}(1 + a + b/[H^+])} \quad (9)$$

where a and b are given by

$$a = \frac{[ZH^+]}{[EH^+]} = \frac{K_T K_a^E}{K_a^Z} \quad (10)$$

$$b = \frac{([E] + [Z])[H^+]}{[ZH^+]} = (1 + K_T)K_a^E \quad (11)$$

By analogy with the hydrolysis of 9-formylfluorene oxime, Eqn (9) can be expressed in several limiting forms in different ranges of acid concentration. The first of these is at low acid concentrations where $k_2 \gg k_3\,[H^+]$ and $(k_H^E + k_H^Z)[H^+]$ and the oximes are unprotonated so that $b/[H^+] \gg (1 + a)$. Under these conditions, attack of H_2O on the protonated oximes is rate determining and k_{obs} is given by

$$k_{obs} = \frac{(k_{H_2O}^E + ak_{H_2O}^Z)[H^+]}{b} \quad (12)$$

In this range the reaction is first order in acid concentration. At higher acid concentrations, there is a change in rate-determining step from attack of water on the protonated oxime to reaction of T_0 along the k_2 reaction path of Scheme 2. Then $(k_H^E + k_H^Z)[H^+]$ is $\gg k_2$ and the reaction becomes independent of pH with rate constant given by

$$k_{obs} = \frac{k_2(k_{H_2O} + ak_{H_2O})}{b(k_H^E + k_H^Z)} \quad (13)$$

With a further increase in acid concentration, the oximes become protonated and $b/[H^+]$ becomes much smaller than $1 + a$. Under these conditions, k_{obs} is expressed by Eqn (14) and shows an inverse dependence on acid concentration.

$$k_{obs} = \frac{k_2(k_{H_2O}^E + ak_{H_2O}^Z)}{(k_H^E + k_H^Z)(1 + a)[H^+]} \quad (14)$$

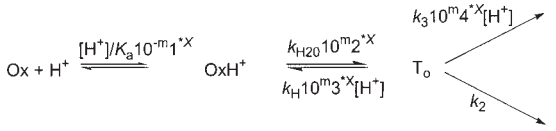
Finally, at the highest acid concentrations, the acid-catalysed reaction of T_0 to form aldehyde becomes important so that $k_3[H^+] \gg k_2$ and Eqn (14) is modified to Eqn (15) with k_{obs} again independent of acid concentration:

$$k_{obs} = \frac{k_3(k_{H_2O}^E + ak_{H_2O}^Z)}{(k_H^E + k_H^Z)(1 + a)} \quad (15)$$

The slopes of plots of k_{obs} versus $[H^+]$ or $1/[H^+]$, or indeed pH-independent values of k_{obs}, implied by Eqns (12)–(15) yield further information on microscopic rate constants which may be evaluated from a best fit of Eqn (9) to the experimental measurements. Values of a and b and $k_{H_2O}^E$ and $k_{H_2O}^Z$ are available from analysis of the isomerization measurements. Combination of Eqns (13) and (14) indicates that $k_2/(k_E^H + k_E^Z)$ is accessible from measurements of k_{obs} at low acid concentrations, whereas combination of Eqns (14) and (15) implies that k_2/k_3 is determinable at higher acid concentrations.

As with the isomerization reactions, there is one further requirement for fitting of calculated to experimental measurements, namely a knowledge of the acidity dependences of rate and equilibrium constants in concentrated acid solutions. As explained above and in more detail for the hydrolysis of the oxime of 9-formylfluorene,[5] this may be expressed by replacing rate and equilibrium constants k and K_a by $k \times 10^{m^*X}$ and $K_a \times 10^{-m^*X}$, where X is Cox and Yates's acidity parameter.[13,14] This is illustrated by Scheme 4 and Eqn (16), which was previously employed for 9-formylfluorene oxime, for which the *E*- and *Z*-tautomerism however was not taken into account and single values of k_{H_2O}, k_H and K_a were used.

$$k_{obs} = \frac{(k_{H_2O}^E + ak_{H_2O}^Z) \times 10^{m_2^*X}(k_2 + k_3 \times 10^{m_4^*X}[H^+])}{\{(k_H^E + k_H^Z) \times 10^{m_3^*X}[H^+] + (k_2 + k_3 \times 10^{m_4^*X}[H^+])\}\left(1 + a + \frac{b \times 10^{-m_1^*X}}{[H^+]}\right)} \quad (16)$$



Scheme 4

Equation (16) may be modified for the presence of equilibrated *E*- and *Z*-isomers by replacing k_{H_2O} by $k^E_{H_2O} + ak^Z_{H_2O}$, k_H by $k^E_H + k^Z_H$ and K_a by b. Factoring the equation into two parts corresponding to low acid (k_2 rate-determining) and high (k_3 rate-determining) acid concentrations gives

$$k_{obs} = \frac{k_2(k^E_{H_2O} + ak^Z_{H_2O}) \times 10^{m^*_2X}}{\{(k^E_H + k^Z_H) \times 10^{m^*_3X}[H^+] + k_2\}\left(1 + a + \frac{b \times 10^{-m^*_1X}}{[H^+]}\right)} + \frac{k_3(k^E_{H_2O} + ak^Z_{H_2O}) \times 10^{(m^*_4+m^*_2-m^*_3)X}}{(k^E_H + k^Z_H)\left(1 + a + \frac{b \times 10^{-m^*_1X}}{[H^+]}\right)} \quad (17)$$

At the highest acidities $b \times 10^{-m^*_1X}/[H^+]$ becomes much smaller than $1 + a$, reflecting complete protonation of the oximes, and a plot of log k_{obs} against X has a limiting slope $m^*_2 + m^*_4 - m^*_3$ and intercept $k_3(k^E_{H_2O} + ak^Z_{H_2O})/[(k^E_H + k^Z_H)(1 + a)]$ at $X = 0$ [(cf. Eqn (15)].

Additional assignments of m^* can be made in the same manner as for the oxime of 9-formylfluorene.[5] Thus m^*_1 for protonation of an equilibrium mixture of *p*-methoxybenzaldehyde oximes can be taken as 1.14 as previously determined for the protonation of the *E*-isomer. Following the same reasoning as for 9-formylfluorene oxime, m^*_4 is also taken as 1.14. Since the measured value of m^* in Fig. 2 is $m^*_2 + m^*_4 - m^*_3 = -0.38$, we obtain $m^*_2 - m^*_3 = -1.52$. If we assign m^*_2 as -0.58, as determined for the isomerization reaction above, we can derive $m^*_3 = 0.94$ and then adjust k_2/k_3 and $k_2/(k^E_H + k^Z_H)$ to achieve a best fit of calculated to observed values of k_{obs} (In Ref. 5 the wrong signs are reported for m^* values; these should be $m^*_1 = 0.9$, $m^*_2 = -0.4$, $m^*_3 = 0.8$ and $m^*_4 = 0.9$). It is worth noting that the values of m^*_2 and m^*_3 are similar to those assigned arbitrarily on the basis of measurement of $m^*_2 - m^*_3$ for 9-formylfluorene oxime.[5]

The parameters k_2/k_3 and $k_2/(k^E_H + k^Z_H)$ determine the concentration of acid at which the change in rate-determining step (corresponding to the change from acid-catalysed to uncatalysed reaction) and the change from the uncatalysed k_2 pathway from T_0 to products to the acid-catalysed k_3 pathway occur. As explained in the earlier paper,[5] the results are relatively insensitive to the chosen values of m^* except at high acid concentrations where the value corresponds to $m^*_2 - m^*_3 + m^*_4$ and to a lesser extent at intermediate acid concentration (when the k_2 step is rate-determining) where the value is $m^*_2 - m^*_3$. The value of m^*_1, which refers to protonation of the oxime, is well-defined by equilibrium measurements.

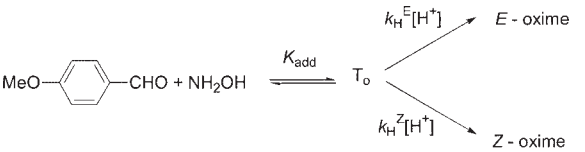
The fit of calculated to measured rate constants is shown in Fig. 3. The derived values of rate constant ratios k_2/k_3 and $k_2/(k^E_E + k^Z_E)$ are 1.9 and 0.014, respectively.

Equilibrium constants

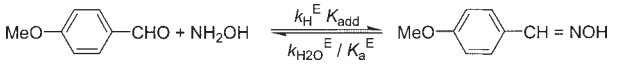
The kinetic and equilibrium data derived from studies of the protonation, isomerization and hydrolysis of the (*E*)- and (*Z*)-oximes may be extended by combining them with rate and equilibrium constants for attack of NH_2OH upon *p*-methoxybenzaldehyde in the reverse of the hydrolysis reaction. The latter measurements have been reported by Calzadilla *et al.*[9] They provide the rate constant $k = 7.77 \times 10^3\ M^{-1}\ s^{-1}$ for the acid-catalysed reaction of NH_2OH with *p*-methoxybenzaldehyde at high pH (2–7) and the equilibrium constant $K_{add} = [T_0]/[NH_2OH][aldehyde] = 1.8$.

The rate constant k corresponds to a reaction in which the carbinolamine T_0 is formed in a pre-equilibrium and undergoes rate-determining acid-catalysed dehydration as shown in Scheme 5. The dehydration of T_0 yields both (*E*)- and (*Z*)-oximes and the measured rate constant may be expressed in terms of a sum of rate constants $k^E_H + k^Z_H$ leading to the two products, i.e. $k = (k^E_H + k^Z_H)K_{add}$. Since, as was shown above, $k^Z_H/k^E_H = 0.125$, it is possible to dissect k into contributions for formation of the individual oximes, $k^E = k^E_H K_{add} = 6.91 \times 10^3$ and $k^Z = k^Z_H K_{add} = 8.64 \times 10^2\ M^{-1}\ s^{-1}$.

The values of k^E and k^Z may now be combined with corresponding rate constants for the reverse hydrolysis reaction, $k^E_{H_2O}/K^E_a$ and $k^Z_{H_2O}/K^Z_a$. The latter rate constants correspond to the acid-catalysed reaction at high pH involving rate-determining attack of water on the protonated oximes. As we have seen, the values for the two oximes are indistinguishable with $k^E_{H_2O}/K^E_a = k^Z_{H_2O}/K^Z_a = 3.0 \times 10^{-2}\ M^{-1}\ s^{-1}$. The ratios of rate constants for the oxime-forming and hydrolysis reactions give the equilibrium constants K^E_{ox} and K^Z_{ox} for oxime formation from the aldehyde and hydroxylamine ($K_{ox} = kK_a/k_{H_2O}$) as shown for the (*E*)-oxime in Scheme 6 (in which k is replaced by $k_H K_{add}$). The values obtained are $K^E_{ox} = 3.0 \times 10^5\ M^{-1}$ and $K^Z_{ox} = 2.88 \times 10^4\ M^{-1}$. Expressed as negative logarithms, these become $pK^E_{ox} = -5.36$ and $pK^Z_{ox} = -4.46$.

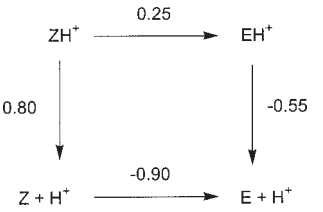


Scheme 5



$$K_{ox} = \frac{k_H^E K_{add} K_a^E}{k_{H2O}^E}$$

Scheme 6



Scheme 8

In a previous paper, equilibrium constants for adduct formation between a number of aldehydes and hydroxylamine, and for hydration and protonation of the corresponding oximes, were compared with equilibrium constants for hydration and protonation of the parent aldehydes.[5] For *p*-methoxybenzaldehyde an equilibrium constant for hydration has been estimated as 3.6×10^{-4} by Fastrez,[15] and this fits reasonably well with free energy correlations between equilibrium constants for hydration of substituted benzaldehydes[16] and for adduct formation with hydroxylamine[9] or HCN[17] based on data from the literature.

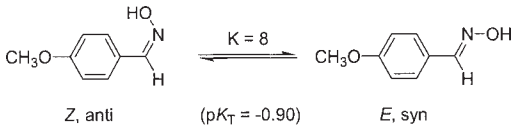
A value of $pK_a = -4.0$ was estimated for protonated *p*-methoxybenzaldehyde based on the correlation of pK_as of substituted benzaldehydes, $pK_a = -1.39\sigma - 4.41$ reported by Sharif and Zalewski.[18]

DISCUSSION

Acid–base and tautomeric equilibria

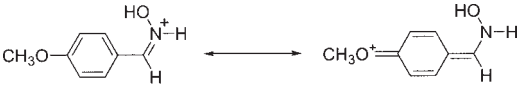
The *E*- and *Z*-isomers of *p*-methoxybenzaldehyde were prepared in the manner described in standard laboratory texts.[8] The *E*-isomer was obtained from reaction of *p*-methoxybenzaldehyde with hydroxylamine. The *Z*-isomer was precipitated as its hydrochloride salt by bubbling dry HCl gas through a solution of the *E*-isomer in diethyl ether. Equilibration of the isomers over 15 days in $CDCl_3$ gave a limiting ratio of 8:1 in favour of the *E*-isomer (Scheme 7). This corresponds to a tautomeric constant (expressed as its negative logarithm) of $pK_T = -0.90$.

Hydrolysis and isomerization of the (*E*)- and (*Z*)-oximes occur sufficiently slowly in aqueous acid for pK_as to be determined spectrophotometrically prior to reaction. The values obtained are −0.55 for the *E*-isomer and 0.80 for the more basic *Z*-isomer. When these are combined with $pK_T = -0.90$ for the *E*–*Z* equilibrium, a value of $pK'_T = 0.25$ for equilibration of the protonated *E*- and *Z*-isomers ($K'_T = [EH^+]/[ZH^+]$) is obtained based on the thermodynamic cycle shown in Scheme 8. This means that protonation reverses the relative stabilities of the isomers from $[E]/[Z] = 8$ to $[EH^+]/[ZH^+] = 0.6$.



Scheme 7

It is not obvious why the *Z*-isomer is more stable in the protonated form. Possibly the hydrogen attached to the positively charged nitrogen atom is more exposed to solvation. However, preliminary measurements for other benzaldehyde oximes yield approximate pK_as for protonated *E*- and *Z*-isomers of −0.6 and −1.0, respectively, for the unsubstituted compound and −1.4 and −1.6 for the *m*-chloro-substituted compounds (R. A. More O'Ferrall and D. M. O'Brien, unpublished measurements). In these cases the *Z*-isomer is less basic than the *E*-isomer. Possibly electron donation from the methoxy group helps relieve steric interaction between the N-OH group and aromatic ring in the protonated form of the *Z*-isomer of the methoxy substituted oximes (**7** ↔ **8**). This is speculative, but Satterthwait and Jencks found that the *Z*-form of the imidate esters **4** and **5** was more basic than the *E*-isomer ($pK_a = 8.0$ compared with 6.5).[12] Here also there is potential for resonance between the iminium ion and an oxygen substituent.



7 **8**

It is worth noting that the preferential precipitation of the (*Z*)-hydrochloride by passing HCl through what is presumably an equilibrating mixture of *E*- and *Z*-substituted benzaldehyde oximes must reflect a lower solubility of this isomer, rather than a higher concentration at equilibrium. There seems no obvious reason why this isomer should be less stable in solution and the most likely explanation would seem to be a greater stability or ease of formation of the crystalline state.

Isomerization and hydrolysis reactions

Except at relatively low acid concentrations, isomerization of the *E*- or *Z*-isomers of *p*-methoxybenzaldehyde oximes may be observed to occur in competition with their hydrolysis reactions. Although there is little difference in UV spectra between the isomers, a change in absorbance is easily measurable provided the less stable isomer is the reactant. Particularly large absorbance changes are observed in the acid range 0.1–2.5 M when the unprotonated *E*-isomer is converted to the protonated

form of the more basic *Z*-isomer with a change in λ_{max} from 265 to 305 nm (Fig. 1).

The most important evidence that isomerization and hydrolysis reactions share a common tetrahedral intermediate, as shown in Scheme 1, comes from measurements at low acidites in the pH range 1.5–4. Under these conditions, hydrolysis occurs with rate-determining attack of water on a low concentration of protonated oxime and the reaction is acid catalysed. In this pH range, in contrast to measurements at higher acidities, no isomerization is observable. This is consistent with a shared tetrahedral intermediate T_0 for the two reactions and a faster reaction expelling hydroxylamine than water from the intermediate in the hydrolysis.

If this interpretation is correct, the rate of isomerization should become faster than hydrolysis when the acid concentration is increased to the pH at which there is a change in rate-determing step in the hydrolysis reaction from water attack on the protonated oxime to expulsion of hydroxylamine from T_0. Below this pH the isomerization reaction should continue to be acid-catalysed while the hydrolysis becomes independent of pH. This indeed is what is observed, as is apparent from the pH profile in Fig. 1 at pH $\geq$ 1.

At pHs above that corresponding to the change in rate-determining step for the hydrolysis reaction, it is noteworthy that the acid-catalysed attack of water upon the two oximes occurs, apparently coincidentally, with the same rate constant. As the acid concentration is increased, at sufficiently high acid concentrations, the isomerization reaction ceases to be acid-catalysed and in principle also becomes independent of pH. This reflects a change of reactant from neutral to protonated oxime. Although the pK_as for the two oxime isomers differ (0.80 and −0.55), separate inflections in the pH profile are not observed because the isomerization is reversible and a sum of rate constants is measured irrespective of which isomer is the reactant. Strictly, the isomerization does not become fully independent of acid concentration for reaction of the protonated oximes because, as discussed above, the reaction is subject to a rate-depressing medium effect at the highest acid concentrations.

The acidity dependence of the hydrolysis reaction represented by the lower correlation line in Fig. 2 is similar to that of the previously studied hydrolysis of the oxime of 9-formylfluorene.[5] Below pH 1, where formation of the tetrahedral intermediate ceases to be rate-determing, the *E*- and *Z*-isomers are equilibrated prior to hydrolysis and the acidity dependence of the reaction is similar to that of the 9-formylfluorene oxime, for which equilibration of isomers was assumed rather than observed.

Equilibria for hydrolysis and hydration

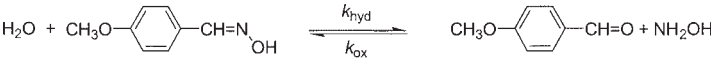
The above measurements lead to evaluation of a comprehensive set of rate and equilibrium constants for *E*- and *Z*-reactants. This is so because it is possible to measure (a) the equilibrium constant K_T for isomerization, (b) pK_as for the two isomers and (c) separate values of the rate constants (k_{H_2O}/K_a) for attack of water on the protonated oximes. The values of k_{H_2O}/K_a are measured at high pH where isomerization is presumed not to compete with hydrolysis.

The measurements may be combined with those of Calzadilla *et al.* for the reverse oxime forming reaction.[9] Thus combination of the values of k_{H_2O}/K_a with rate constants for the reverse rate-determining dehydration of the carbinolamine intermediate to form (*E*)- and (*Z*)-oximes as described above yields equilibrium constants K_{ox}^{E} and K_{ox}^{Z} for oxime formation (Scheme 9).

Moreover, Calzadilla *et al.*'s measurement of the equilibrium constant $K_{add} = 1.8$ for formation of the adduct T_0 between *p*-methoxybenzaldehyde and hydroxylamine[9] may be combined with K_{ox} and K_a for the appropriate (*E*)- or (*Z*)-oxime to provide a network of equilibrium constants consisting of thermodynamic cycles associated with the formation, ionization and hydration of the oxime. This network is shown [for the (*E*)-oxime] in Scheme 10 with the equilibrium constants expressed as negative logarithms (p*K*s) and the equilibria denoted by single rather than double arrows to show the direction of reactions to which the p*K*s refer.

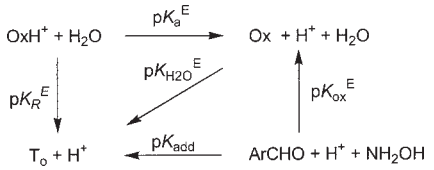
Most importantly, the network of Scheme 10 extends the measurement of a pK_a for the protonated oxime to yield a value of pK_R and, characteristically, as a third arm of this cycle, pK_{H_2O}, the equilibrium constant for hydration of the oxime. Analogous cycles have been extensively considered for deprotonation and hydration of carbocations.[19]

The equilibrium constants from Scheme 10 are shown as p*K*s for *E*- and *Z*-isomers in Table 1. Corresponding values for 9-formylfluorene, *p*-chorobenzaldehyde and acetone oximes,[5] and indeed *O*-methyl oximes of substituted benzaldehydes,[3] have been similarly tabulated (without separation of *E*- and *Z*-isomers). The equilibrium constants K_R^E and K_R^Z may be used to dissect rate constants k_H and k_{H_2O} for the acid-catalysed conversion



$$K_{ox} = k_{ox} / k_{hyd}$$

Scheme 9

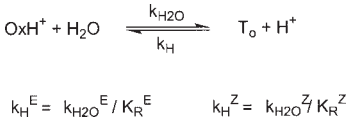


Scheme 10

Table 1. Rate and equilibrium constants[a] for hydration and protonation of *p*-methoxybenzaldehyde and its (*E*)- and (*Z*)-oximes

Parameter	(*E*)-Oxime	(*Z*)-Oxime	Aldehyde
pK_{H_2O}	4.20	5.10	3.4[b]
pK_a	−0.55	0.80	−4.0[c]
pK_R	3.65	5.90	−0.6
pK_{ox}	−4.46	−5.36	
pK_{add}			−0.26[d]
k_H	3.8×10^3	4.8×10^2	
$k_{H_2O}(s^{-1})$	4.8×10^{-3}	0.106	
k_{NH_2OH}			7.76×10^3
k'_{NH_2OH}			6.0×10^5[e]

[a] Units of rate constants $M^{-1} s^{-1}$ except as indicated.
[b] Ref. 15.
[c] Extrapolated from data in Ref. 18.
[d] Ref. 9.
[e] Rate constant for attack of NH_2OH on protonated aldehyde. An incorrect value for the corresponding rate constant for NH_2OMe was given as 1.1×10^8 in Ref. 5 by not recognizing that k_{H_2O} was the rate-determining step in the reaction considered.

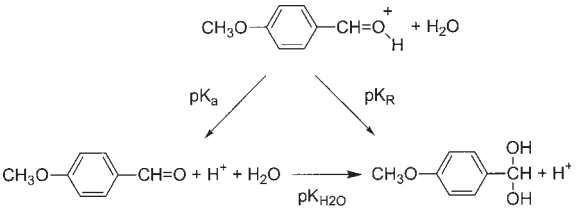


Scheme 11

of T_0 to the respective protonated oximes and the reverse hydration reactions (Scheme 11). This is possible because individual values of $k^E_{H_2O}$ and $k^Z_{H_2O}$ are accessible from the measurements at high pH for the hydrolysis reactions where there is no competing isomerization. Values of k_H can then be derived as shown in Scheme 11. It may be noted that k_H and k_{H_2O} are the only rate constants associated with oxime formation or hydrolysis which depend on the configuration of the oxime.

This completes the set of rate and equilibrium constants for the *E*- and *Z*-isomers of *p*-methoxybenzaldehyde oxime in Table 1. However, also included in the Table are equilibrium constants pK_a, pK_R and pK_{H_2O} for the analogous protonation and hydration of the parent aldehyde as described in the thermodynamic cycle of Scheme 12, together with rate constants for attack of hydroxylamine on the aldehyde and its conjugate acid, k_{NH_2OH} and k'_{NH_2OH} respectively.

Previous measurements of rate and equilibrium constant for oximes have normally provided apparent values, usually corresponding to equilibrated isomers. For example, Koehler *et al.* measured pK_as of oximes of substituted benzaldehydes in the presence of excess



Scheme 12

hydroxylamine.[20] For the *p*-methoxybenzaldehyde oxime they obtained a value of −0.25, which may be compared with our values of 0.80 and −0.55 for *E*- and *Z*-isomers, respectively. Their value is close to the calculated value of $pK_{app} = -0.15$ predicted for an equilibrated mixture of isomers where ($1/K_{app} = 1/K^Z_a + 1/K^E_a$). It is possible that the excess hydroxylamine (hydrochloride) contributed to the equilibration.

The analysis in this paper shows that in principle existing measurements may be dissected into *E*- and *Z*-values if a limited number of additional measurements are undertaken. However, they also suggest that the *p*-methoxybenzaldehyde oxime presents a case of extreme difference of *E*- and *Z*-isomers. Normally, therefore, there may be little advantage in dealing with single rather than equilibrated isomers.

On the other hand, it should be noted that the conditions under which the isomers are equilibrated are limited to fairly acidic media (at least in the absence of buffers). Some care in the interpretation of results for mixtures of isomers is therefore required. Synthesis will usually yield a single *E*, *syn*) isomer, which is also predominant in the solution equilibrium between neutral isomers of aldoximes. A pK_a measurement will yield a value for this isomer therefore unless care is taken to ensure equilibration. Moreover, the hydrolysis rate constant at high pH corresponding to attack of water on the protonated oxime (k_{H_2O}/K_a) will refer to this isomer. Only at higher acid concentrations, where the protonated oximes are the reactants, will the isomers be likely to be equilibrated. Of course, at an intermediate acid concentration isomer equilibration and hydrolysis will occur at comparable rates and the assumption made here, that either isomerization is much faster than hydrolysis or that it does not occur at all, will break down.

These considerations apply to the only other kinetic studies of the hydrolysis of oximes known to us, namely the oximes of 9-formylfluorene[5] and acetophenone.[21] It has been mentioned already that the former hydrolysis revealed no evidence of competing *E–Z* isomerization. This was at least in part because the reaction was monitored from formation of the hydrolysis product rather than disappearance of isomeric reactants. Only where isomerization occurred at a rate comparable to hydrolysis would its influence have been detectable. Particularly if the reactant (*E*) isomer was faster reacting this would easily have escaped detection. Minor discrepancies in fitting observed to calculated rate constants in

acetate and hydroxylamine buffers[5] may, however, have arisen from this source.

Despite the complexity of the above analysis, we believe that the present paper clarifies the influence of *E–Z* isomerization on the hydrolysis (and formation) of oximes and offers a straightforward guide to analysing when and how the existence of isomers may be taken into account in the interpretation of existing or new kinetic and equilibrium measurements.

EXPERIMENTAL

Spectrophotometric measurements made use of Phillips PU8600, Perkin-Elmer Hitachi 124 and Genesys 2PC UV–visible spectrophotometers. Measurements of pH were made with a Metrohm 744 pH meter and NMR spectra were recorded on a Jeol JNM-GX270 instrument.

The (*E*)- and (*Z*)-*p*-methoxybenzaldehyde oximes were prepared as described previously and were recrystallized from petroleum spirit (b.p. 40–60 °C) to give white, needle-like crystals. They showed the characteristically different chemical shifts for the CH hydrogen of the oxime group, δ 8.13 for the *E*-isomer and δ 7.26 for the *Z*-isomer.

Values of the pK_as for the two isomers were based on UV absorbance measurements at $\lambda_{max} = 305$ nm for the *E*-isomer and $\lambda_{max} = 302$ nm for the *Z*-isomer. The extinction coefficients at these wavelengths were found to be the same, with $\varepsilon = 1.6 \times 10^4$. Measured absorbances at the indicated concentrations of perchloric acid for the *E*-isomer were as follows: 0.075, 0.061 M; 0.10, 0.122 M; 0.335, 0.451 M; 0.50, 0.722 M; 0.64, 0.902 M; 0.855, 1.13 M; 0.850, 1.22 M; 0.965, 1.32 M; 1.09, 1.50 M; 1.52, 2.23 M; 1.71, 2.63 M; 1.78, 3.01 M;1.87, 3.38 M. Corresponding absorbances and acid concentrations for the *Z*-isomer were as follows: 0.250, 0.01 M; 0.715, 0.059 M; 0.725, 0.075 M; 0.875, 0.104 M; 1.34, 0.232 M; 1.51, 0.293 M; 1.44, 0.301 M; 1.54, 0.383 M; 1.68, 0.439 M; 1.78, 0.754 M; 1.85, 0.928 M. For the *E*-isomer the pK_a was determined from a plot of calculated pK_a values $(K_a = [H^+](A_a - A)/(A - A_b)$, where A is the measured absorbance at the appropriate value of $[H^+]$ and $A_a = 2.0$ and $A_b = 0.22$ are limiting absorbances at high and low acidities for a substrate concentration of 1.3×10^{-4} M) against the solvent acidity parameter X as shown in Fig. 1. The p$K_a = -0.55$ in water corresponds to the intercept of the plot at $X = 0$; the slope of the plot $m^* = 1.14$. For the *Z*-isomer the pK_a was determined in the same way with $A_a = 2.04$ and $A_b = 0.035$, but in the dilute acid concentration range studied (0.01–0.93 M) departures from the aqueous value of the pK_a ($= 0.80$) were small.

Kinetic measurements were carried out by conventional methods. Stock solutions $\sim 10^{-2}$ M in (*Z*)- or (*E*)-oximes were prepared in acetonitrile or methanol and kinetic measurements were initiated by injection of 20 µl of stock solution into 2 ml of aqueous perchloric acid or chloroacetic acid buffer contained in the thermostatted cell compartment of a spectrophotometer. Rate constants for hydrolysis of the oxime were monitored from the limiting rate of increase in absorbance of the *p*-methoxybenzaldehyde product at 285 nm (λ_{max}). Rate constants for isomerization were usually measured starting with the E-isomer because in the acid concentration range studied the *Z*-isomer (and usually the *E*-isomer) was fully protonated and the protonated *Z*-isomer was the most stable species. Because the spectra for the isomers were similar, it was important that measurements of rates of isomerization should maximize the change in absorbance by starting with the less stable form.

Equilibration of (*E*)- and (*Z*)-oximes was carried out over 8 days in $CDCl_3$. The relative concentrations of the two isomers was determined from the intensities of the CH═N proton peaks as 8:1 in favour of the *E*-isomer. It was assumed that this equilibrium was not significantly affected by changing the solvent from chloroform to water.

REFERENCES

1. Jencks WP. *Prog. Phys. Org. Chem.* 1964; **2**: 63–128; Jencks WP. *Catalysis in Chemistry and Enzymology.* McGraw-Hill: New York, 1969.
2. Reiman JE, Jencks WP. *J. Am. Chem. Soc.* 1966; **86**: 3973–3982; Jencks WP. *J. Am. Chem. Soc.* 1959; **81**: 475–481.
3. Rosenberg S, Silver SM, Sayer JM, Jencks WP. *J. Am. Chem. Soc.* 1974; **96**: 7986–7998.
4. Sayer JM, Pinsky B, Schonbrunn A, Washtien W. *J. Am. Chem. Soc.* 1974; **96**: 7998–8009; Sayer JM, Conlon P. *J. Am. Chem. Soc.* 1980; **102**: 3592–3600.
5. More O'Ferrall RA, O'Brien DM, Murphy DG. *Can. J. Chem.* 2000; **78**: 1594–1612.
6. Karabatsos GJ, Taller RA. *Tetrahedron* 1968; **24**: 3347–3360.
7. Finch P, Merchant ZM. *J. Chem. Soc., Perkin Trans 2* 1982; 199–203.
8. Vogel AI. *Practical Organic Chemistry.* Longman: London, 1961.
9. Calzadilla M, Malpica A, Cordova T. *J. Phys. Org. Chem.* 1999; **12**: 708–712.
10. Holloway CE, Vuik CPJ. *Tetrahedron Lett.* 1979; **12**: 1017–1020.
11. Cocivera M, Fyfe CA, Effio A, Vaish SP, Chen HE. *J. Am. Chem. Soc.* 1976; **98**: 1573–1578.
12. Satterthwait AC, Jencks WP. *J. Am. Chem. Soc.* 1974; **96**: 7045–7052.
13. Cox RA, Yates K. *Can. J. Chem.* 1981; **59**: 2116–2124; Cox RA. *Adv. Phys. Org. Chem.* 2000; **34**: 1–66.
14. Bagno A, Scorrano G, More O'Ferrall RA. *Rev. Chem. Intermed.* 1987; **7**: 313–352.
15. Fastrez J. *J. Am. Chem. Soc.* 1977; **99**: 7004–7013.
16. Guthrie JP. *J. Am. Chem. Soc.* 2000; **122**: 5529–5538.
17. Wei-Mei C, Kallen RG. *J. Am. Chem. Soc.* 1978; **100**: 6119–6124.
18. Shariff MR, Zalewski RI. *Bull. Acad. Pol. Sci.* 1982; **29**: 385–391.
19. Richard JP, Rothenburg MEE, Lin S-S, O'Donoghue AC, Toteva MM, Tsuji Y, Williams KB. *Adv. Phys. Org. Chem.* 2000; **34**: 67–115; MacCormac AC, McDonnell CM, More O'Ferrall RA, O'Donoghue AC, Rao SN. *J. Am. Chem. Soc.* 2002; **124**: 8575–8583.
20. Koehler K, Sandstrom W, Cordes EW. *J. Am. Chem. Soc.* 1964; **80**: 2413–2419.
21. Gregory BJ, Moodie RB. *J. Chem. Soc. B* 1970; 862–866.