Kinetics and mechanism of acid-catalyzed hydrolysis of the diazo functional group of diazophenylacetamide

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epoc ABSTRACT: The acid-catalyzed hydrolysis of diazophenylacetamide giving mandelamide as product was found to occur with a normal ($k_H/k_D > 1$) hydronium ion isotope effect and to be subject to general acid rather than specific hydronium ion catalysis. This shows that the reaction occurs by rate-determining hydron transfer from the catalyzing acid to the diazo carbon atom of the substrate, followed by rapid displacement of the diazo group by water. Comparison of the rate of this reaction with those of the same process for other diazophenylacetic acid functional derivatives, $PhCN_2COX$, reveals that the reactivity of these substrates is controlled by the electron-releasing resonance ability of the group X. Copyright © 2003 John Wiley & Sons, Ltd.
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KEYWORDS: rate data analysis; Brønsted relation; diazo compounds hydrolysis; diazophenylacetamide; general acid catalysis; hydronium ion isotope effect

INTRODUCTION

The acid-catalyzed hydrolysis of aliphatic diazo compounds is a much-studied reaction that has figured prominently in the development of modern ideas on acid–base catalysis (for reviews, see Ref. 1). Diazo compounds are also synthetically useful materials; they can, for example, be transformed, via the Wolff rearrangement, into ketenes, which readily undergo a wide variety of useful reactions.[2] The synthetic utility of diazo compounds, however, is limited by their facile acid-catalyzed hydrolysis, and information on the nature of this acid-catalyzed reaction, and especially on how its rate depends on substrate structure, is consequently of practical value.

We have already reported studies of the kinetics and mechanisms of acid-catalyzed hydrolyses of diazophenylacetic acid, **1**,[3] its carboxylate ion, **2**,[3] and methyl diazophenylacetate, **3**.[4] We now add to that an investigation of the acid-catalyzed hydrolysis of diazophenylacetamide **4**.
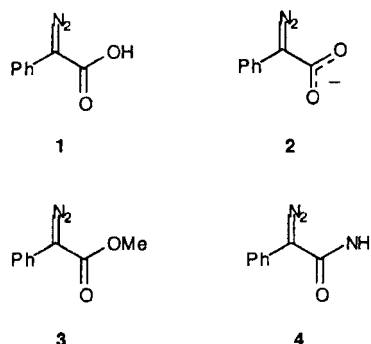
EXPERIMENTAL

Materials. Diazophenylacetamide (**4**) was a sample that had been made for another purpose.[5] All other materials were of the best available commercial grades.

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Kinetics. Rates of reaction of diazophenylacetamide were measured by monitoring the decay of its absorbance at its absorption maximum, $\lambda_{max} = 260$ nm, using initial diazo compound concentrations of the order of 5×10^{-5} M. Measurements were made with a Cary 2200 spectrometer whose cell compartment was thermostatted at 25.0 ± 0.05°C. The data so obtained fit the first-order rate law well, and observed first-order rate constants were calculated by least-squares fitting of a single exponential function.

Product analysis. Product identification was done by high-performance liquid chromatographic (HPLC) analysis using a Varian Vista 5500 instrument with a NovoPak C_{18} reversed-phase column and methanol–water (50 : 50, v/v) as the eluent. The product was characterized by comparing the retention time and UV spectrum with those of an authentic sample.

RESULTS

The acid-catalyzed hydrolysis of the diazo group of diazophenylacetamide (**4**) is expected to produce mandelamide (**5**) as its product:

(1)
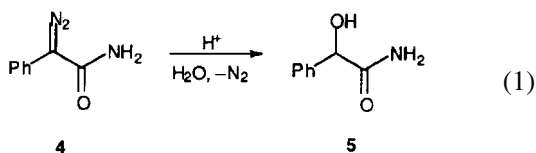
This was found to be the case: HPLC analysis of spent reaction mixtures of hydrolyses conducted in 10^{-4} M aqueous perchloric acid showed the presence of mandelamide and no other product.

Rates of this hydrolysis reaction were measured in aqueous perchloric acid solution, using both H_2O and D_2O as the solvent, at a constant ionic strength of 0.10 M, maintained by the addition of sodium perchlorate as required. The data obtained are summarized in Supplementary Table S1 at the epoc website at http://www.wiley.com/epoc and are also displayed in Fig. 1. It can be seen that the observed first-order rate constants are linearly related to acid concentration. Linear least-squares analysis gave the hydronium ion catalytic coefficient $k_{H^+} = 3.12 \pm 0.02$ and the isotope effect $k_{H^+}/k_{D^+} = 2.22 \pm 0.03$.

Rates of decay of diazophenylacetamide were also measured in aqueous (H_2O) acetic, formic, methoxyacetic and chloroacetic acid buffers, using series of solutions of constant stoichiometric buffer ratio and constant ionic strength (0.10 M), but varying buffer concentration. The data obtained are summarized in Supplementary Table S2 at the epoc website.

In the case of the acetic acid buffers, this technique kept hydronium ion concentrations sufficiently constant along a given buffer solution series to maintain a constant level of hydronium ion catalysis along that series. As
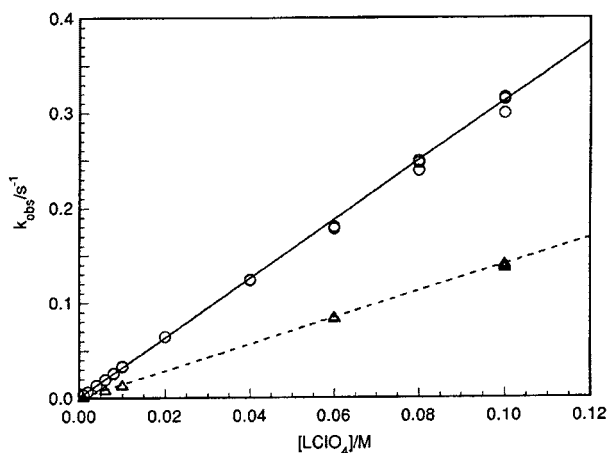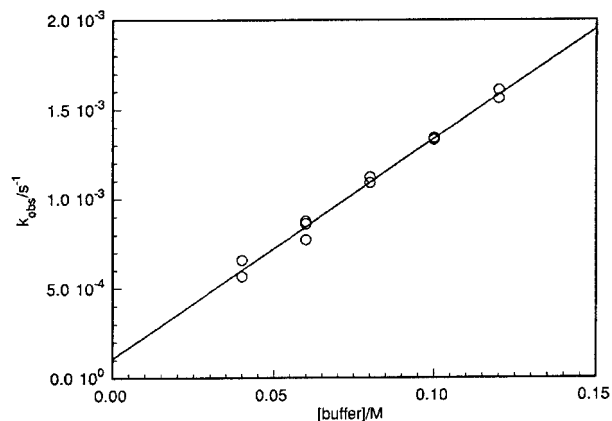
Figure 2. Relationship between observed first-order rate constants and buffer concentration for the reaction of diazophenylacetamide in aqueous acetic acid buffers with buffer ratio = 1.0 at 25°C

Fig. 2 illustrates, buffer catalysis was strong and, since observed first-order rate constants increased linearly with increasing buffer concentration, the data were analyzed by least-squares fitting of the linear buffer dilution expression:

$$k_{obs} = k_{intcp} + k_{buff}[\text{buffer}]$$ (2)

The buffer catalytic coefficients so obtained, k_{buff}, were in turn separated into their general acid, k_{HA}, and general base, k_B, components with the aid of the equation:

$$k_{buff} = k_B + (k_{HA} - k_B)f_A$$ (3)

in which f_A is the fraction of buffer present in the acid form. Figure 3 shows that the data conformed to this relationship well; least-squares fitting gave $k_{HA} = (2.36 \pm 0.03) \times 10^{-2} \, l \, mol^{-1} \, s^{-1}$ and $k_B = (6.13 \pm 3.10) \times 10^{-4} \, l \, mol^{-1} \, s^{-1}$.

Figure 1. Rates of hydrolysis of diazophenylacetamide in H_2O (O) and D_2O ($\triangle$) solutions of perchloric acid at 25°C
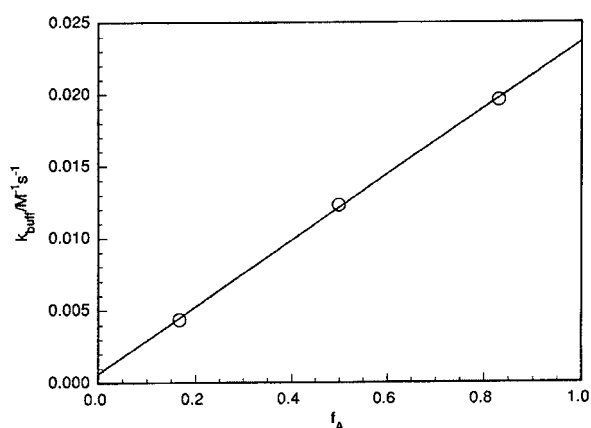
Figure 3. Separation of buffer catalysis into its general acid and general base components for the reaction of diazophenylacetamide in aqueous acetic acid buffers at 25°C

Table 1. Results of analysis according to Eqn (4) for the hydrolysis of diazophenylacetamide in aqueous buffer solutions at 25°C[a]

Buffer acid	pK_a	k_{HA} (10^{-2} l mol^{-1} s^{-1})	k_B (10^{-4} l mol^{-1} s^{-1})	k_{H^+} (l mol^{-1} s^{-1})	k_{H_2O} (10^{-5} s^{-1})
ClCH$_2$CO$_2$H	2.87	40.4 ± 5.2	273 ± 194	3.39 ± 0.55	-171 ± 58
CH$_3$OCH$_2$CO$_2$H	3.57	17.9 ± 0.4	-7.5 ± 18.1	3.54 ± 0.15	1.83 ± 5.43
HCO$_2$H	3.75	9.05 ± 0.19	-9.55 ± 8.95	2.81 ± 0.11	3.57 ± 2.77
CH$_3$CO$_2$H	4.76	2.40 ± 0.04	4.30 ± 2.08	3.51 ± 0.15	1.29 ± 0.62

[a] Ionic strength $= 0.10$ M (NaClO$_4$).

This kind of analysis, unfortunately, could not be applied to data obtained in buffer solutions of the other, stronger buffer acids used here, because hydronium ion concentrations, and therefore f_A, failed to remain sufficiently constant along given buffer solution series. Such 'buffer failure' is a difficulty common to dilute solutions of moderately strong buffer acids, and it can be handled in a variety of ways.[6a] The method used here involved least-squares fitting of the expression:

$$k_{obs} = k_{H^+}[H^+] + k_{HA}[HA] + k_B[A^-] + k_{H_2O} \qquad (4)$$

with the concentrations $[H^+]$, $[HA]$ and $[A^-]$ as independent variables, and k_{H^+}, k_{HA}, k_B and k_{H_2O} as parameters determined by the fit. The concentration variables needed for this purpose were obtained by calculation, using acidity constants of the buffer acids from the literature and activity coefficients appropriate to the ionic strength of the experiments (0.10 M) recommended by Bates.[7] The least-squares fitting was done using GraFit software.[8]

This analysis was carried out for the chloroacetic, methoxyacetic and formic acid buffers, and also for the acetic acid buffers. The results obtained are given in Table 1. It can be seen that the value of k_{HA} for acetic acid obtained in this way agrees very well with that determined using Eqns (3) and (4) as described above, and that values of k_{H^+} acquired from each of the four different buffers are consistent with that determined directly using perchloric acid solutions (see above). The general base catalytic coefficients, k_B, and the rate constants for the water reaction, k_{H_2O}, on the other hand, are not well determined: their statistical uncertainties (standard deviations = 68% confidence intervals) are comparable to their values; this is consistent with expectation (see below).

The results in Table 1 also show that the values of k_{HA} decrease with decreasing strength of the catalyst acid; this also is as expected. The data, in fact, give a reasonably good Brønsted relation (Fig. 4), with the Brønsted exponent $\alpha = 0.66 \pm 0.06$; this is a reasonable value of α for a reaction with the present velocity. The hydronium ion catalytic coefficient falls below this Brønsted relation by a considerable margin (two orders of magnitude), as is usually the case for reactions such as the present one involving rate-determining proton transfer to carbon.[9]
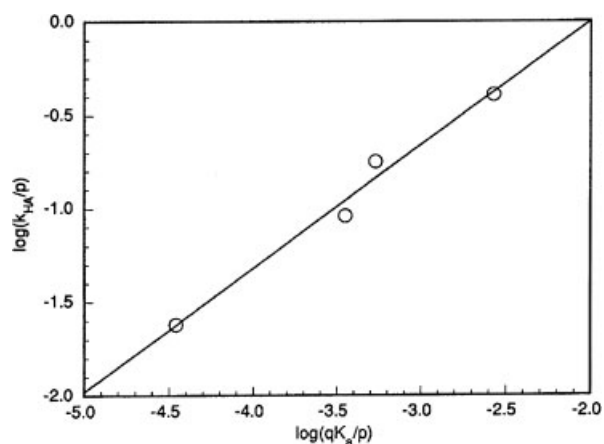
Figure 4. Brønsted relation for the reaction of diazophenylacetamide in aqueous solution at 25°C. The catalysts, from right to left, are ClCH$_2$CO$_2$H, CH$_3$OCH$_2$CO$_2$H, HCO$_2$H and CH$_3$CO$_2$H

DISCUSSION

The acid-catalyzed hydrolysis of α-diazocarbonyl compounds such as the substrate investigated here may occur by either one of three principal reaction mechanisms.[1] Two of these involve rapid pre-equilibrium protonation of the substrate, either on carbonyl oxygen or on diazo carbon, followed by rate-determining displacement of the diazo group by water; the third mechanism consists of rate-determining diazo carbon protonation followed by rapid diazo group displacement.

The two pre-equilibrium reaction mechanisms can be expected to give hydronium ion isotope effects in the inverse direction, $k_{H^+}/k_{D^+} < 1$. This is because the pre-equilibrium step produces a water molecule:

$$H_3O^+ + S \underset{}{\overset{fast}{\rightleftharpoons}} H_2O + HS^+ \xrightarrow{r.d} product \qquad (5)$$
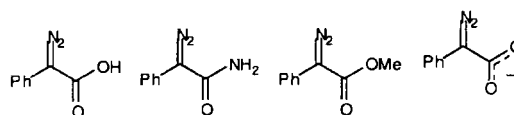
k_{H^+}/ M^{-1} S^{-1}:   0.345   3.12   0.142   226

Scheme 1
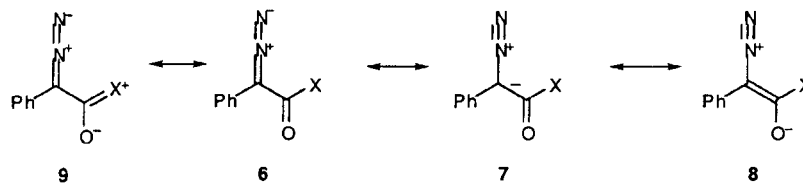
Scheme 2

whose O—H bonds are stronger than the O—H bonds of the hydronium ion.[6b,10] The reaction therefore proceeds with a tightening up of the isotopically substituted bonds, which leads to an inverse isotope effect. Since the isotope effect determined here for the present reaction, $k_{H^+}/k_{D^+} = 2.22$, is not inverse, these pre-equilibrium reaction mechanisms may be dismissed.

In the rate-determining carbon protonation reaction mechanism, on the other hand, there will be a hydron in flight in the reaction's transition state, and the isotope effect in this case will therefore have a primary component; it will consequently be in the normal direction, $k_{H^+}/k_{D^+} > 1$. The magnitude of this isotope effect, however, will be reduced by a minor inverse component produced by tightening of the 'non-reacting' O—H bonds of the hydronium ion as they are transformed into O—H bonds of a water molecule.[10,11] The isotope effect observed here is in fact a typical value for such a process.[11]

Reactions that occur by rate-determining proton transfer from the hydronium ion generally also take place by rate-determining proton transfer form other acids. This leads to general acid catalysis rather than specific hydronium ion catalysis, just as is observed here. The catalytic efficacy of the general acids, moreover, usually decreases with decreasing general acid strength, producing a Brønsted relation with exponent in the normal $\alpha = 0$–1 range,[9,12] again as found here.

The reaction mechanism established here for acid-catalyzed hydrolysis of diazophenylacetamide, consisting of rate-determining proton transfer from acid catalyst to diazo carbon, is also the mechanism by which acid-catalyzed hydrolysis of diazophenylacetic acid itself occurs,[3] and also that of its carboxylate ion[3] and its methyl ester.[4] The hydronium ion catalytic coefficients (k_{H^+}, $1\,mol^{-1}\,s^{-1}$) for all four reactions are shown in Scheme 1.

The considerable variation in reactivity along this series may be understood in terms of the fact that these diazo carbonyl compounds are resonance hybrids of several canonical forms that delocalize negative charge from the diazo group, as shown in structure **6**, on to the diazo carbon atom, as shown in **7**, and also on to the carbonyl oxygen atom, as shown in **8** (Scheme 2). This delocalization of negative charge onto the carbonyl oxygen, however, is opposed by negative charge delocalization on to the same atom from the group X, as shown in **9**. The stronger this opposing delocalization, the weaker is the delocalization on to this oxygen atom from the diazo group, and consequently the stronger is the negative charge density on the diazo carbon atom. On the reasonable assumption that the rate of protonation of the diazo carbon atom is determined by the negative charge density on this atom, rates of reaction will be controlled by the negative charge-releasing ability of the group X. This ability as measured, for example, by the Hansch, Leo and Taft resonance substituent constants R^+, rises in the order $OMe < OH < NH_2 < O^-$,[13] which is the same as the rising order of the hydronium ion catalytic coefficients. These R^+ substituent constants, in fact, as shown by Fig. 5, give a reasonably good quantitative correlation of the rate data.
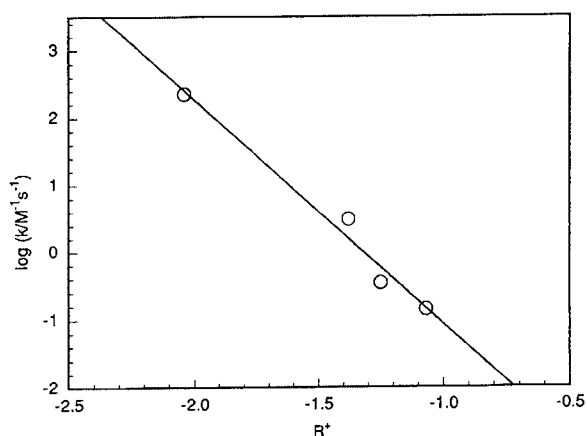
Acknowledgement

Figure 5. Correlation of hydronium ion catalytic coefficients for the hydrolysis of diazophenylacetic acid and its carboxyl group functional derivatives using R^+ resonance substituent constants

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