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Generation of *o*-quinone α-carbomethoxymethide by photolysis of methyl 2-hydroxyphenyldiazoacetate in aqueous solution†‡

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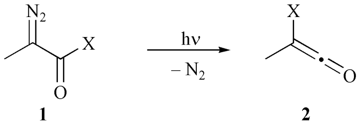
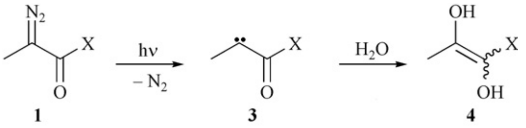
Flash photolysis of methyl 2-hydroxyphenyldiazoacetate (**8**) in dilute aqueous perchloric acid solution and acetic acid and biphosphate ion buffers produced a transient species that was identified as *o*-quinone α-carbomethoxymethide (**9**). This structural assignment is based upon solvent isotope effects, the form of buffer catalysis, UV absorption maxima, and the identity of decay rate constants with those determined for the transient obtained by flash photolysis of other, more conventional, quinone methide precursors, namely the benzyl alcohol methyl 2-hydroxy mandelate (**10**) and its acetate, 2′-acetoxy-2-hydroxyphenylacetate (**11**).

Irradiation of an α-diazocarbonyl compound, **1**, usually leads to a Wolff rearrangement [eqn. (1)] in which loss of nitrogen and migration of the carbonyl group substituent X produces a ketene, **2**.[1]



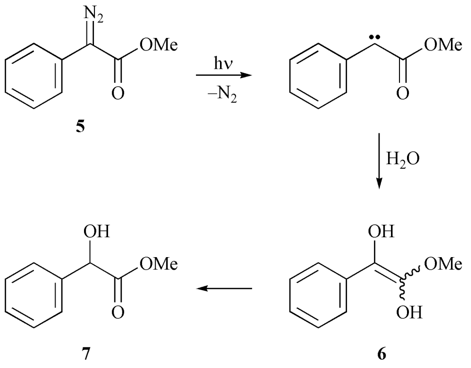
(1)

However, when the migratory aptitude of X is poor, another process [eqn. (2)] takes over, in which loss of nitrogen generates a carbonylcarbene, **3**, that, in aqueous solution, undergoes conjugate addition of water giving an enol, **4**.[2]



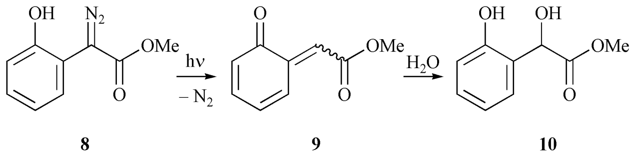
(2)

We have, for example, observed this process in the case of methyl phenyldiazoacetate, **5**, where we were able to substantiate this reaction route [eqn. (3)] by observing the enol intermediate, **6**, and characterizing its ketonization to methyl mandelate, **7**.[3]



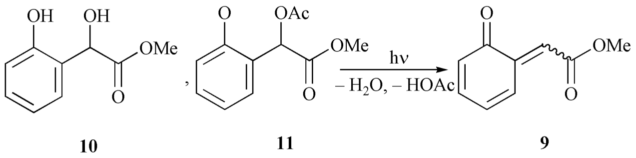
(3)

We now report that still another reaction route becomes available when an *ortho* hydroxyl group is introduced into the benzene ring of methyl phenyldiazoacetate. Irradiation of methyl 2-hydroxyphenyldiazoacetate, **8** [eqn. (4)] in aqueous solution produces methyl 2-hydroxymandelate, **10**, the same final product that would have been obtained if a reaction path analogous to the carbonylcarbene route of eqn. (3) had been followed.



(4)

Now, however, the reaction intermediate observed is not an enol but is rather the quinone methide **9**. We have demonstrated that this is so by monitoring this intermediate and showing that it decays with kinetics characteristic of quinone methide hydration, with rate constants identical to those obtained using quinone methide **9** generated by more traditional routes,[4] namely photolysis of the corresponding benzyl alcohol, methyl 2-hydroxymandelate, **10**, and its acetate, methyl 2′-acetoxy-2-hydroxyphenylacetate, **11** [eqn. (5)]. Because these quinone methide hydration reactions are fast, we used flash photolytic techniques to monitor their course.



(5)

There is some precedent for the generation of quinone methides by irradiation of suitably constituted diazo compounds: photolysis of the "masked" diazo substrate **12** in an argon matrix at 10 K was shown to give *o*-quinone methide **14** through the diazo compound **13** [eqn. (6)].[5]

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† Dedicated to Professor Dr Z. R. Grabowski and Professor Dr J. Wirz on the occasions of their 75th and 60th birthdays.

‡ Electronic supplementary information (ESI) available. Tables S1–S4 of rate data. See http://www.rsc.org/suppdata/cp/b2/b211444p/

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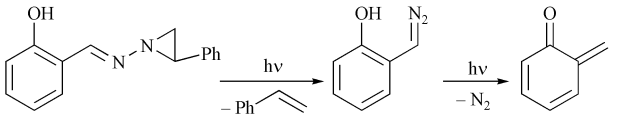


12 **13** **14**

(6)

Experimental

Materials. Methyl 2-hydroxyphenyldiazoacetate, **8**, was synthesized by using triethylamine to cleave the tosyl hydrazone of methyl 2-hydroxyphenylglyoxylate (Bamford–Stevens reaction).[6] This hydrazone was made from tosyl azide and methyl 2-hydroxyphenylglyoxylate,[7] obtained by acid-catalyzed esterification of 2-hydroxyphenylglyoxylic acid, itself prepared by selenium dioxide oxidation of 2-hydroxyacetophenone.[8] This synthesis produced methyl 2-hydroxyphenyldiazoacetate mixed with its ring-closed counterpart, 3-diazobenzofuran-2-one, but the two substances could be separated by column chromatography (silica gel with 4 : 1 hexanes : diethyl ether as the eluent). The diazoester was obtained as yellow needles, mp 88–90°, with the following spectral properties: ^{1}H NMR ($CDCl_3$): δ/ppm = 8.27 (br s, 1H), 7.26–7.17 (m, 1H), 7.05–6.91 (m, 3H), 3.92 (s, H); ^{13}C NMR ($CDCl_3$): δ/ppm = 154.0, 129.4 (2 C), 126.1, 121.1 (2C), 119.5, 111.6, 53.4; HRMS: $m/e = 192.0535$ (calcd. for $C_9H_8N_2O_3$), 192.0536 (found).

Methyl 2-hydroxymandelate,[9] **10**, was prepared by acid-catalyzed esterification of 2-hydroxymandelic acid, itself made by sodium borohydride reduction of 2-hydroxyphenylglyoxylic acid. As reported,[8,9] 2-hydroxymandelic acid could not be obtained completely free of solvent, and it was therefore used as an ethyl acetate solvate.

Methyl 2′-acetoxy-2-hydroxyphenylacetate, **11**, was prepared by treating methyl 2-hydroxymandelate with equimolar amounts of acetic anhydride and boron trifluoride diethyl etherate. The product was purified by column chromatography (silica gel with 10.1 hexanes : diethyl ether as the eluent) to give a slightly yellow liquid with the following spectral properties: ^{1}H NMR ($CDCl_3$): δ/ppm = 7.31–7.23 (m, 3H), 6.94–6.90 (m, 2H), 6.26 (s, 1H), 3.74 (s, 3H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$); δ/ppm = 171.2, 170.8, 155.1, 131.3, 129.9, 120.9, 120.1, 117.3, 71.2, 53.3, 20.9; HRMS: $m/e = 224.0685$ (calcd. for $C_{11}H_{12}O_5$) 224.0685 (found).

All other materials were best available commercial grades.

Product analyses. Product compositions were determined by HPLC using a Varian Vista 5500 instrument with a NovoPak C_{18} reverse-phase column and methanol–water (50 : 50 v/v) as the eluent. Reaction solutions containing substrate at similar concentrations as used for kinetic measurements (2–3 $\times 10^{-5}$ M) were subjected to a single pulse from our microsecond flash photolysis system.[10] Products were identified by comparing retention times and UV spectra with those of authentic samples.

Kinetics. Rate measurements were made using a microsecond flash photolysis system that has already been described,[10] and reactions were followed by monitoring absorbance decay at $\lambda = 420$ nm. Initial substrate concentrations were 2–3 $\times$ 10^{-5} M, and the temperature of all reacting solutions was controlled at 25.0 ± 0.05 °C. Observed first-order rate constants were obtained for the most part by least-squares fitting of an exponential function; in some of the slower runs, however, instability of the monitoring light source power supply produced a minor base-line drift, and in these cases a linear term was added to the exponential function.

Results

Product study. HPLC analyses of spent reaction mixtures were performed for flash photolyses of methyl 2-hydroxyphenyldiazoacetate (**8**) carried out in 1×10^{-3} M perchloric acid and sodium hydroxide solutions and in acetic acid ($[H^+] = 3 \times 10^{-5}$ M) and biphosphate ion ($[H^+] = 2 \times 10^{-7}$ M) buffers. Methyl 2-hydroxymandelate (**10**) was found to be by far the major product formed (> 95%) in the perchloric acid solution and in the acetic acid and biphosphate ion buffers, as expected for the quinone methide generation and hydration route of eqn. (4). In the sodium hydroxide solution, however, another process took over: no methyl 2-hydroxymandelate could be detected and only another, unidentified substance was found. Rate data obtained in basic solutions, moreover, no longer conformed to a first-order rate law. This behavior is similar to our experience with *o*-quinone methide itself in basic solution,[4b] and it can be attributed to further reaction of the quinone methide transient with its phenol hydration product, which, in basic solution, exists as the very reactive phenoxide ion.[11]

Kinetics. Rates of decay of *o*-quinone α-carbomethoxymethide, **9**, were measured in dilute aqueous (H_2O and D_2O) solutions of perchloric acid as well as acetic acid and biphosphate ion buffers. The ionic strength of these solutions was maintained at 0.10 M through the addition of sodium perchlorate as needed. These data are summarized in Tables S1 and S2 of the ESI.‡

The rate measurements in buffers were made in series of solutions of fixed buffer ratio, and therefore fixed hydronium ion concentration, but varying total buffer concentrations. Buffer catalysis was weak, but observed first-order rate constants did increase with increasing buffer concentration. The data were therefore analyzed by least-squares fitting of the buffer dilution expression shown as [eqn. (7)].

$$k_{\text{obs}} = k_{\text{int}} + k_{\text{buff}}[\text{buffer}] \quad (7)$$

The zero-buffer-concentration intercepts, k_{int}, obtained in this way, together with the perchloric acid data, were then used to construct the rate profiles shown in Fig. 1. Hydronium ion concentrations, written here as $[L^+]$, of the buffer solutions needed for this purpose were obtained by calculation using

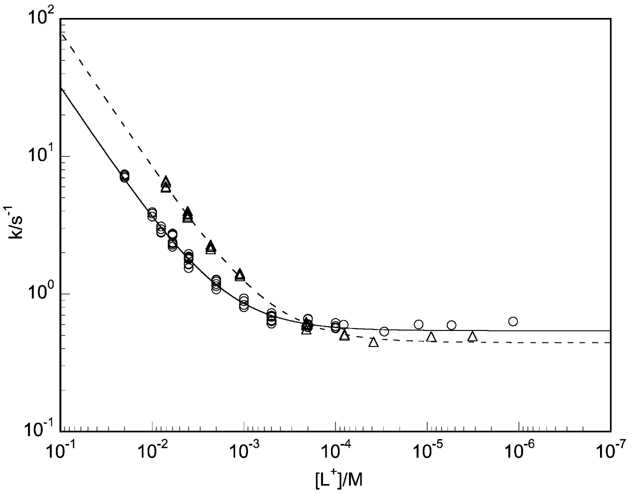


Fig. 1 Rate profiles for the decay of *o*-quinone α-carbomethoxymethide, **9**, in (○) H_2O, and (Δ) D_2O, solution at 25 °C.

thermodynamic acidity constants of the buffer acids from the literature and activity coefficients recommended by Bates.[12]

These rate profiles show acid-catalyzed and uncatalyzed portions; the data were therefore analyzed using the rate law of [eqn. (8)]. Least squares fitting gave the results

$$k_{\text{prof}} = k_{\text{uc}} + k_{\text{L}^+}[\text{L}^+] \qquad (8)$$

$k_{\text{H}^+} = (3.14 \pm 0.05) \times 10^2\ \text{M}^{-1}\ \text{s}^{-1}$, $k_{\text{H}^+}/k_{\text{D}^+} = 0.391 \pm 0.009$, $(k_{\text{uc}})_{\text{H}_2\text{O}} = (5.40 \pm 0.08) \times 10^{-1}\text{s}^{-1}$, $(k_{\text{uc}})_{\text{H}_2\text{O}}/(k_{\text{uc}})_{\text{D}_2\text{O}} = 1.22 \pm 0.03$.

The slopes of the buffer dilution plots, k_{buff}, were separated into their general acid, k_{HA}, and general base, k_{B}, components with the aid of the relationship shown as [eqn. (9)], in which f_{A} is the fraction of buffer present in the acid form.

$$k_{\text{buff}} = k_{\text{B}} + (k_{\text{HA}} - k_{\text{B}})f_{\text{A}} \qquad (9)$$

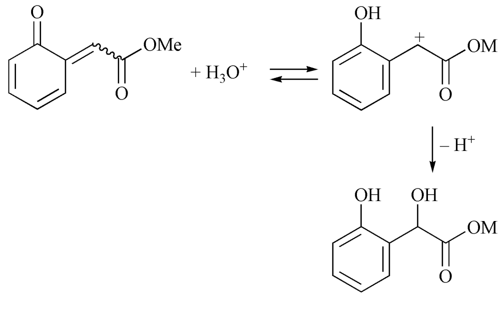
Least squares analysis showed that in the acetic acid solutions the buffer reaction was wholly of the general base type, in both H_2O and D_2O, with $(k_{\text{B}})_{\text{H}_2\text{O}} = (2.27 \pm 0.14) \times 10^1\ \text{M}^{-1}\ \text{s}^{-1}$ and $(k_{\text{B}})_{\text{H}_2\text{O}}/(k_{\text{B}})_{\text{D}_2\text{O}} = 0.92 \pm 0.08$. A similar analysis could not be carried out for the biphosphate buffer solutions because measurements were made at only one buffer ratio.

Rates of *o*-quinone α-carbomethoxymethide, **9**, decay were also measured using methyl 2-hydroxymandelate, **10**, and methyl 2′-acetoxy-2-hydroxyphenylacetate, **11**, as the photochemical substrates. These measurements were made in dilute aqueous (H_2O) perchloric acid only, and the ionic strength was maintained at 0.10 M by adding sodium perchlorate as required. These data are summarized in Tables S3 and S4 of the ESI.‡

Discussion

We have shown in previous studies[4b–c] that the hydration of quinone methides in aqueous solution occurs by acid-catalyzed and uncatalyzed routes. The ketonization of enols, such as those formed by conjugate addition of water to α-carbonylcarbenes in the photolysis of α-carbonyldiazo compounds illustrated in eqn. (3), also occurs by acid-catalyzed and uncatalyzed routes. The mechanisms of the two reactions, however, are quite different, and that gives them distinctive kinetic signatures by which they can easily be distinguished.

Quinone methide hydration catalyzed by the hydronium ion occurs through rapid pre-equilibrium protonation of the quinone carbonyl oxygen atom followed by rate-determining capture of the carbocation so formed by a water molecule [eqn. (10)].[4b–c]



(10)

Because the oxygen–hydrogen bonds of the water molecule formed in the pre-equilibrium step are tighter than those of the hydronium ion reactant,[13] this produces an inverse solvent isotope effect, just like that, $k_{\text{H}^+}/k_{\text{D}^+} = 0.39$ observed here. The corresponding isotope effect on the hydration of the parent *o*-quinone methide itself is $k_{\text{H}^+}/k_{\text{D}^+} = 0.42$.[4b] The hydronium-ion catalyzed ketonization of enols, on the other hand, occurs by rate-determining hydron transfer from the hydronium ion to the β-carbon atom of the enol.[14] The solvent isotope effect on this process therefore contains a primary component and is consequently normal ($k_{\text{H}}/k_{\text{D}} > 1$) rather than inverse; that on the ketonization of mandelic acid enol, for example, is $k_{\text{H}^+}/k_{\text{D}^+} = 3.3$.[15]

The form of buffer catalysis is also different for quinone methide decay from that for enol ketonization. In the quinone methide reaction, the buffer base acts as a nucleophile, adding directly to the methide methylene group.[4b,d] The strength of the buffer reaction therefore depends on the nucleophilic strength of the buffer base, and because acetate ion is a weak nucleophile, buffer catalysis in acetic acid buffers is weak, as observed here for *o*-quinone α-carbomethoxy-methide. Enol ketonization, on the other hand, being a rate-determining hydron transfer reaction, is catalyzed by buffers with buffer catalysis increasing in proportion to the acid strength of the buffer acid. Since acetic acid is a moderately strong general acid, it is a good catalyst, and enol ketonization is catalyzed strongly by acetic acid buffers, unlike the weak catalysis observed here for *o*-quinone α-carbomethoxymethide. The absence of general acid catalysis found here is, of course, also consistent with a quinone methide reaction and not with an enol ketonization.

Additional support for identification of the presently observed intermediate species as a quinone methide rather than an enol comes from its UV absorbance. Quinone methides have a cyclohexadienone structure which produces a relatively long wavelength absorption band. *o*-Quinone methide itself, for example, has $\lambda_{\text{max}} \cong 400$ nm, not unlike $\lambda_{\text{max}} = 420$ nm observed for the present intermediate species. β-Phenylsubstituted enols, such as that which might be formed from methyl 2-hydroxyphenyldiazoacetate, will have a styrene-type chromophore with an absorption band at considerably lower wavelengths; for example, $\lambda_{\text{max}} = 268$ nm for β,β-dimethoxystyrene,[16] and $\lambda_{\text{max}} = 275$ for the enol of methyl mandelate.[3]

Perhaps the strongest evidence of all supporting assignment of a quinone methide structure to the intermediate species observed here upon photolysis of methyl 2-hydroxyphenyldiazoacetate, **8**, comes from the results obtained by flash photolysis of methyl 2-hydroxymandelate, **10**, and its acetate derivative, methyl 2′-acetoxy-2-hydroxyphenylacetate, **11**. Benzyl alcohols such as **10** are probably the most commonly used substrates for photochemical generation of quinone methides, and their acetate derivatives, such as **11**, are even better quinone methide precursors.[4] It is not surprising, therefore, that flash photolysis of the benzyl alcohol **10** and its acetate **11** produced a short-lived transient species with a UV spectral band at $\lambda_{\text{max}} = 420$ nm, just like the transient observed upon flash photolysis of the diazo substrate **8**. Fig. 2

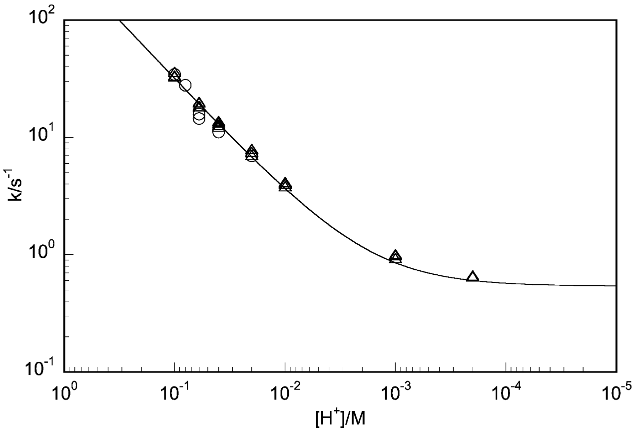


Fig. 2 Comparison of rates of decay of *o*-quinone α-carbomethoxymethide generated from methyl 2-hydroxyphenyldiazoacetate, **8**, (—); methyl 2-hydroxymandelate, **10**, (O); and methyl 2′-acetoxy-2-hydroxyphenylacetate, **11**, (Δ) in aqueous solution at 25 °C.

shows, moreover, that the rate constants for decay of the transients obtained from all three substrates have the same numerical values. The line shown in this figure was drawn using parameters obtained from the least squares analysis of measurements made using diazo substrate **8**, whereas the circles and triangles represent measurements made with the benzyl alcohol substrate **10** and its acetate **11**, respectively. It may be seen that the data obtained with **10** and **11** fit the line representing **8** as well as do the **8** data points themselves displayed in Fig. 1.

Acknowledgements

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