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Conjugate addition of water to *α*-carbonylcarbenes

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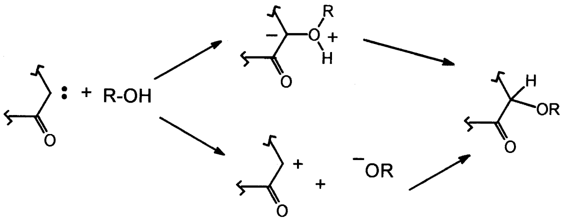
ABSTRACT: α-Carbonylcarbenes (**2a–c**) generated by UV photolysis of 2-diazophenylacetic acid (**1a**), its methyl ester (**1b**) and 4-diazo-3-isochromanone (**1c**) in aqueous solution undergo conjugate addition of water across the entire carbonylcarbene moiety to give enols (**3a–c**) of the corresponding α-hydroxycarbonyl compounds. These carbenes are long-lived, with microsecond lifetimes in aqueous solution. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: Conjugate addition; α-carbonylcarbenes; water

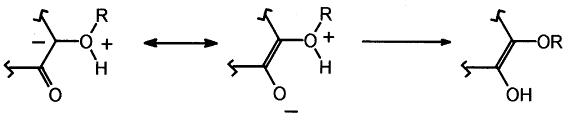
INTRODUCTION

The insertion of α-carbonylcarbenes into O—H bonds is a well known[1,2] synthetically important reaction.[3] This process is thought to proceed via two alternative routes: (a) formation of an ylide through electrophilic attack of the carbene on an unshared electron pair of hydroxylic oxygen, followed by a 1,2-proton shift to give the final product, or (b) initial protonation of the carbene to give a carbocation, which is then rapidly trapped by solvent [Eqn (1)].[2,4,5]



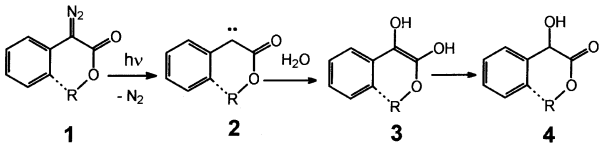
(1)

However, as Eqn (2) illustrates, the proposed oxygen ylide could also undergo proton translocation from hydroxylic oxygen to carbonyl oxygen to give an enol, which would then ketonize, forming the observed α-alkoxycarbonyl compound.



(2)

We have, in fact, observed such an enol-forming reaction in the hydration of α-carbonylcarbenes (**2a–c**) generated by laser flash photolysis from 2-diazophenylacetic acid (**1a**), its methyl ester (**1b**) and 4-diazo-3-isochromanone (**1c**) [Eqn (3)].



(3)

R = H (a), Me (b), -CH₂- (c)

EXPERIMENTAL

Materials. 2-Diazophenylacetic acid (**1a**) was prepared by saponification of methyl 2-diazophenylacetate (**1b**), itself obtained by lead tetraacetate oxidation of the hydrazone of methyl benzoylformate.[6] The diazo acid undergoes rapid acid-catalyzed hydrolysis,[7] and therefore was not isolated; aqueous stock solutions of the acid salt were used instead. These were obtained by allowing a solution of methyl diazophenylacetate, dissolved in an equimolar amount of 0.1 M aqueous sodium hydroxide, to stand at room temperature for 2 days and then washing this solution with methylene chloride to remove any unreacted ester. 4-Diazo-3-isochromanone (**1c**) was prepared by a diazo transfer reaction from *p*-acetamidobenzenesulfonyl azide to 3-isochromanone.[8]

Kinetics. Flash photolysis was performed using a conventional flash lamp system and an excimer-laser system that have already been described.[9] The conventional system produced a 50 μs excitation pulse and the laser system, operating at 248 nm, produced a 20 ns excitation pulse. In both systems the temperature of the reacting solutions was controlled at 25.0 ± 0.05 °C. Rate measurements were carried out by monitoring absorbance changes at 330 nm. Determinations were made in

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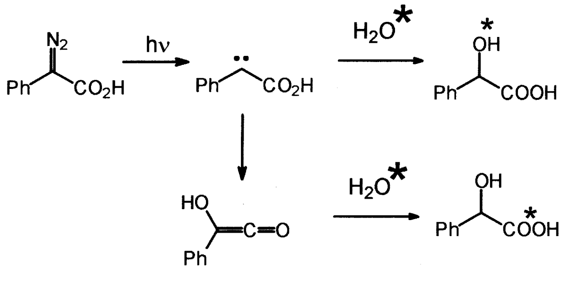
aqueous solutions over the range of acidity $[H^+] = 1.0 - 10^{-12}$ M, using perchloric acid and sodium hydroxide solutions in addition to formic acid, acetic acid, biphosphate ion, hydrogen *t*-butylphosphonate ion and tris(hydroxymethyl)methylammonium ion buffers. The ionic strength of the reaction solutions was maintained at 0.10 M.

RESULTS

Photolysis of diazocarbonyl compounds in aqueous solution

Photodecomposition of α-diazocarbonyl compounds is known to produce α-carbonylcarbenes,[10] which can rearrange into ketenes or, in the presence of water, undergo insertion into O—H bonds. Photolysis of all three α-diazocarbonyl compounds **1a–c** in aqueous solutions gives α-hydroxycarbonyl compounds **4a–c** as the major products. In the case of methyl 2-diazophenylacetate (**1b**) and 4-diazo-3-isochromanone (**1c**), the formation of methyl mandelate (**4b**) and 4-hydroxy-3-isochromanone (**4c**), respectively, indicates that lediazotization of the starting material leads to an α-carbonylcarbene, followed by hydration of the latter. Photolysis of 2-diazophenylacetic acid (**1a**), yielding mandelic acid (**4a**), however, can proceed via two different routes: formation and hydration of carboxyphenylcarbene (**2a**) or Wolff rearrangement of **2a** to hydroxyphenylketene, followed by nucleophilic addition of water [Eqn (4)].



(4)

These two mechanisms can be distinguished by oxygen-18 tracer experiments conducted in isotopically labeled water. The carbonylcarbene route will give mandelic acid with the isotopic label in its α-hydroxy group, whereas hydration of hydroxyphenylketene will give mandelic acid with the isotopic label in its carboxy group [Eqn (4)]. The positions of the label can be determined easily by mass spectrometry, because mandelic acid fragments readily upon electron impact producing the hydroxybenzyl cation as the principal species in its mass spectrum.[11] Our results showed that 96% of the mandelic acid formed from 2-diazophenylacetic acid was labeled in its α-hydroxy group, thus supporting the α-carbonylcarbene route.

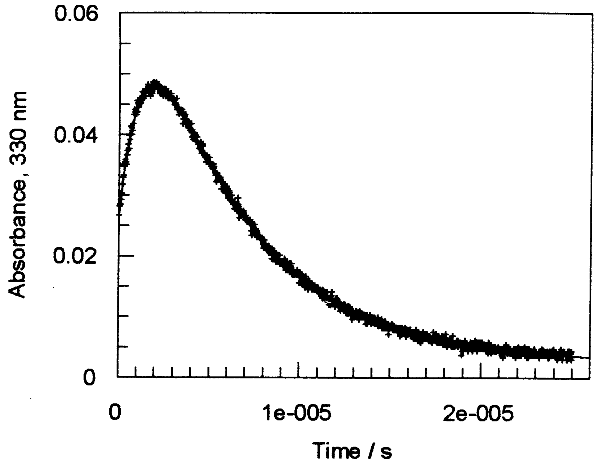
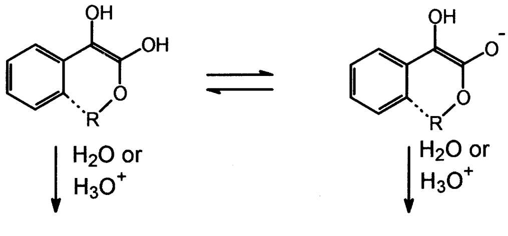


Figure 1. Changes in absorbance at 330 nm observed in laser flash photolysis of 2-diazophenylacetic acid in aqueous solution

Flash photolysis: enol generation

Flash photolysis of diazocompounds **1a–c** produced intermediates that could be observed as a rapid rise and then a slower decay of absorbance at 330 nm (Fig. 1). In all three cases the observed intermediates showed the behavior expected of enols. The rate profiles for reaction through solvent-derived species in the $pC_H{}^+$ range from 0 to 12, shown in Fig. 2 are typical of enol ketonization reactions; the reactions also showed general acid catalysis and had solvent isotope effects in the normal direction ($k_H/k_D > 1$). These features plus the structures of final products allowed us to identify the observed intermediates as enol forms (**3a–c**) of the corresponding -hydroxycarbonyl compounds[12].

The ketonization of enols is known to occur by rate-determining protonation of the β-carbon atom of either the enol or the enolate ion, according to Eqn (5).



(5)

The rate profiles (Fig. 2) provide good evidence for this mechanism. They contain acid-catalyzed portions at low $pC_H{}^+$, as expected for carbon protonation of the non-ionized enol by the hydronium ion. This is then followed by a short 'uncatalyzed' region at $[H^+] = 10^{-1}–10^{-3}$ M, which represents either protonation of enol by a water molecule or ionization of the enol to the much more reactive enolate ion followed by carbon protonation of enolate by hydronium ion; in the latter case, the fraction of enolate anion is inversely proportional to $[H^+]$, thus

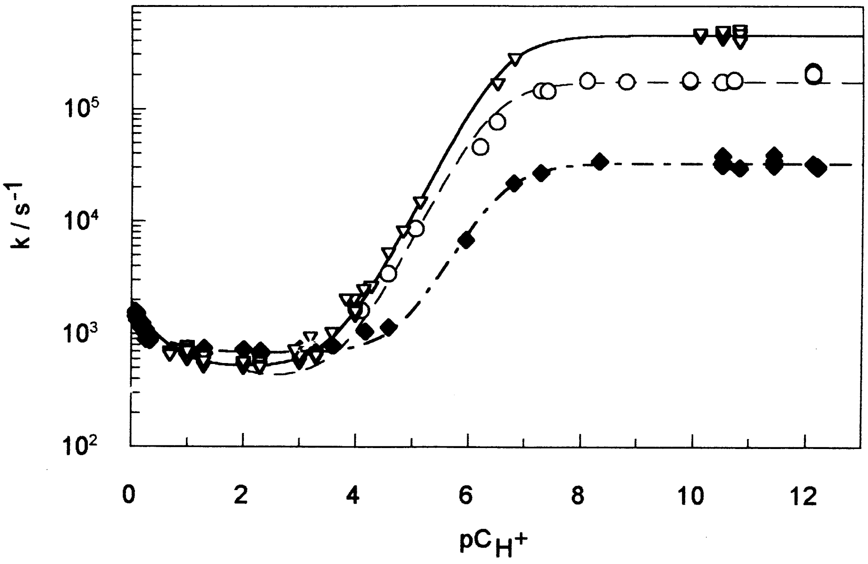


Figure 2. Rate profiles for the ketonization of the enols of (○) mandelic acid (**3a**), (▽) methyl mandelate (**3b**) and (◆) 4-hydroxy-3-isochromanone (**3c**)

giving the overall process the appearance of an 'uncatalyzed' reaction. This portion of the rate profile is followed by a region of apparent hydroxide ion catalysis in which enolate is carbon protonated by a water molecule; the fraction of ionized substrate is still inversely proportional to [H$^+$], and so is the rate. Finally, when the position of the enol–enolate pre-equilibrium shifts over to enolate ion, this apparent hydroxide ion catalysis becomes saturated and another 'uncatalyzed' portion of the rate profile, corresponding to simple rate-determining carbon protonation of enolate by water, results. Comparison of rates of reaction in H_2O and D_2O gave isotope effects in the normal direction ($k_H/k_D > 1$), as expected for rate-determining hydron transfer to carbon.

Interpretation of the rate profiles in Fig. 2 in terms of the reaction Eqn (5) allows the assignment of the breaks in the profiles at $[H^+] \approx 10^{-6}$ M to acid ionization of the enols.

The enol of mandelic acid was also generated independently by photolysis of benzoylformic acid esters, and it shows the same behavior as that generated from 2-diazophenylacetic acid.[12a]

Carbene hydration reaction route

α-Carbonylcarbenes **2a–c** generated from diazo compounds **1a–c** in aqueous solution add water to form O—H insertion products **4a–c** [Eqn (3)]. Formation of the enol

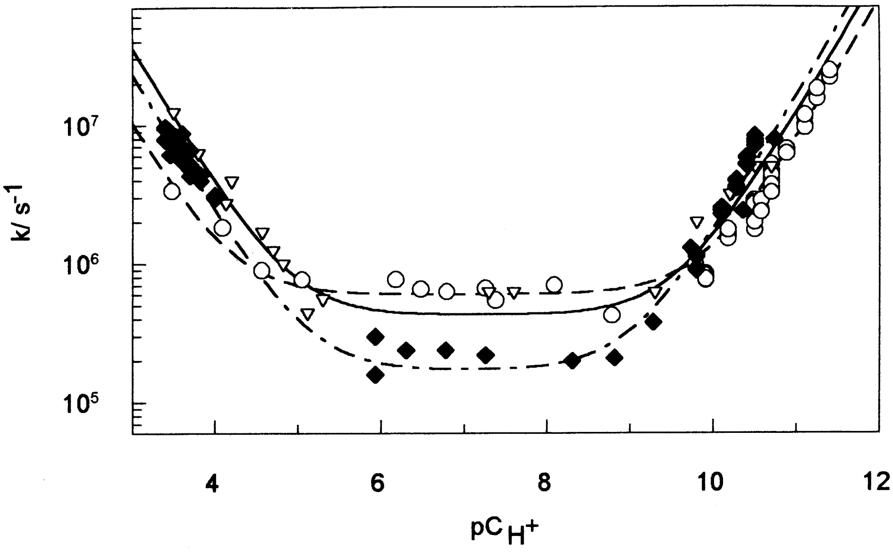
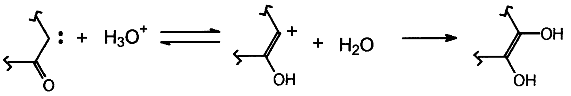


Figure 3. Rate profiles for the hydration of α-carbonylcarbenes (○) (**2a**), (▽) (**2b**) and (◆) (**2c**)

intermediates **3a–c** in this reaction rules out the carbocation-generating and ylide mechanisms of Eqn (1), because such processes would not produce an enol. Our results are consistent, on the other hand, with the enol-generating ylide mechanism of Eqn (2), especially since the very rapid oxygen-to-oxygen proton transfer that converts the ylide to an enol should render the ylide invisible on the timescale of our experiments. We also cannot exclude a concerted addition of water to α-carbonylcarbenes which avoids an ylide intermediate. At any rate, our observation of enol intermediates in the formation of O—H insertion products from α-carbonylcarbenes **2a–c** shows that hydration of these species is not a direct reaction of the carbenic carbon atom only, but that it also involves the carbonyl group of the carboxylic acid function, and is more in the nature of a conjugate addition of water across the entire α-carbonylcarbene moiety [Eqn (3)].

The carbene hydration reactions were observed as a fast rise of absorbance at 330 nm (Fig. 1). These reactions are catalyzed by both acids and bases, and both catalyses are general in type. The rate profiles, shown in Fig. 3 share common features: they contain long ‘uncatalyzed’ regions at $[H^+] = 10^{-5}$–10^{-9} M where the carbene presumably reacts with water, followed by regions of hydroxide ion catalysis where hydroxide ion takes over the role of attacking nucleophile. At $pC_H{}^+ < 5$, investigation of the carbene hydration reactions becomes more difficult: the signal of carbene **2c** becomes very weak, and 2-diazophenylacetic acid (**1a**) undergoes rapid acid-catalyzed decomposition.[7] We nevertheless still managed to observe acid-catalyzed hydration of carbenes **2a–c** (Fig. 3). It is likely that this acid-catalyzed reaction proceeds via pre-equilibrium protonation on the carbonyl oxygen atom followed by rapid attack of water on resulting vinyl cation [Eqn (6)]. Detailed investigation of the mechanism of these reactions is under way.



(6)

It is noteworthy that the lifetimes of the present carbonylcarbene intermediates, reaching 2 μs in neutral solutions, are considerably longer than those of other carbonylcarbenes without phenyl substituents that have been inferred from recent studies in non-aqueous solvents.[4,13] On the other hand, a previous investigation of the phenyl-substituted carbonylcarbene **2b** in some of the same non-aqueous solvents[14] reported lifetimes for this substance approaching those found here.

CONCLUSION

Flash photolysis of each of the α-diazocarbonyl compounds **1a–c** in aqueous solutions shows the formation and decay of an intermediate. On the basis of standard mechanistic criteria this intermediate has been identified as the enol of the corresponding α-hydroxycarbonyl compound. Our investigation of the precursors of these enols indicates that the enols are formed by direct conjugate addition of water to α-carbonylcarbenes, thus representing a new enol-forming reaction.

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