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# Ketonization of the unusually acidic elongated enol generated by flash photolytic decarboxylation of *p*-formylphenylacetic acid in aqueous solution

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**Abstract**: Rates of photolysis of *p*-formylphenylacetic acid were measured flash photoytically in perchloric acid and sodium hydroxide solutions, and also in acetic acid, biphosphate ion, and tris-(hydroxymethyl)methaneammonium ion buffers, using H<sub>2</sub>O and D<sub>2</sub>O as solvents. The results provide rate profiles and solvent isotope effects, which indicate that photolysis occurs through an elongated enol intermediate. This enol is unusually strongly acidic, by some two to three  $pQ_a$  units, when compared with simple non-elongated enols.

Key words: flash photolysis, elongated enols, rate profiles, solvent isotope effects.

**Résumé :** Faisant appel à la photolyse éclair, on a mesuré les vitesses de photolyse de l'acide *p*-formylphénylacétique dans des solutions aqueuses ou dans le l'eau lourde d'acide perchlorique et d'hydroxyde de sodium ainsi que dans l'acide acétique en présence d'ion biphosphate et de tris(hydroxyméthyl)méthaneammonium comme tampons. Les résultats permettent d'obtenir des profils de vitesse et des effets isotopiques de solvant qui indiquent que la photolyse se produit par le biais d'un intermédiaire énolique allongé. Cet énol est particulièrement acide, par des valeurs de  $pQ_a$  de deux à trois unités supérieures à celles d'énols simples non allongés.

Mots-clés : photolyse éclair, énols allongés, profils de vitesse, effets isotopiques de solvant.

[Traduit par la Rédaction]

# Introduction

Photodecarboxylation of p-benzoylphenylacetic acid (1) when carried out in aqueous solution, gives p-methylbenzophenone (2) as its reaction product (eq. [1]) (1).



This substance is formed through a carbanion intermediate, whose negative charge is delocalized from methylene carbon (3) onto carbonyl oxygen (4) (eq. [2]).



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This article is dedicated to the memory of Keith Yates.

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Product formation could therefore occur either by direct protonation of methylene carbon (eq. [3]) or by protonation of carbonyl oxygen to give an elongated enol intermediate, **5**, whose ketonization would afford the observed product (eq. [4]). In previously reported work (2), we carried out this decarboxylation flash photolytically and detected a short-lived transient species that we identified as elongated enol **5**. This enol has proved to be an unusually strong acid, several orders of magnitude more acidic than other simple enol analogs without the elongating cyclohexadienyl spacer.



We have now added to that previous study a companion investigation of the photodecarboxylation of p-formyl-phenylacetic acid (6) (eq. [5]). We found that this reaction



also occurs through an elongated enol intermediate, which is also unusually strongly acidic.

# **Experimental Section**

## Materials

p-Formylphenylacetic acid was prepared by a Sommelet reaction (3) on 4-chloromethylphenylacetic acid, itself synthesized by chloromethylation of phenylacetic acid (4).

#### 4-Chloromethylphenylacetic acid

A 10 mL capacity vial, equipped with septa and stirring bar, was purged with argon, and 0.8 mL (1.78 g, 0.0068 mol) of SnCl<sub>4</sub> was introduced through a syringe. Dry phenylacetic acid (1.36 g, 0.010 mol) was dissolved in 2 mL (2.12 g, 0.026 mol) of monochloromethyl ether (ClCH<sub>2</sub>OCH<sub>3</sub>) at room temperature and the solution was slowly added into the vial within 20 min upon vigorous stirring at 0 °C. The reaction mixture was left at room temperature for 1 h under argon and then quenched with 30 mL of ice-cold water upon vigorous stirring. An amorphous white precipitate was separated. This was washed with water and dissolved in 20 mL of CHCl<sub>3</sub>, and the solution was dried over MgSO<sub>4</sub>. The solvent was evaporated to dryness, and the residue was recrystallized from a mixture of CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and hexane (20 mL) to afford 0.82 g (44%) of a product whose melting point (149-151 °C) was consistent with the literature (4). Its <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) had the following signals:  $\delta$ : 3.65 (s, 2H, CH<sub>2</sub>), 4.57 (s, 2H, CH<sub>2</sub>Cl), 7.26 (d, 2H, J = 9 Hz, p-C<sub>6</sub>H<sub>4</sub>), 7.35 (d, 2H, J =9 Hz, *p*-C<sub>6</sub>H<sub>4</sub>).

#### 4-Formylphenylacetic acid

Hexamethylenetetramine (840 mg, 0.0060 mol) and 4chloromethylphenylacetic acid (740 mg, 0.0044 mol) were heated under reflux for 1 h in 20 mL of chloroform. The solvent was then evaporated to one half of its initial volume, and 990 mg (75%) of a colorless quaternary ammonium salt separated. This was dried and then heated under reflux in 10 mL of 50 vol% aqueous acetic acid for 1.5 h under an argon atmosphere. Upon cooling to ambient temperature, the mixture was quenched with a solution of 10 g of NH<sub>4</sub>Cl in 40 mL of H<sub>2</sub>O and was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$ 15 mL). The extract was washed with a solution of  $NH_4Cl$ (1.0 g) and 0.5 mL of concd. HCl in 10 mL of H<sub>2</sub>O and was dried over MgSO<sub>4</sub>. The solvent was removed under vacuum to afford 460 mg (70%) of crude product, which was chromatographed on a column containing 8 g of silica gel with mobile phase MeCN–CH<sub>2</sub>Cl<sub>2</sub> (1:1 v/v). The main fraction furnished 330 mg (44%) of a relatively pure (>90%, NMR) compound. The course of the separation was monitored by TLC on SIL-G/UV 254 plates with acetoneacetonitrile (3:1) as the mobile phase. Further, an analytical sample (80 mg) with no detectable impurities (HPLC, TLC) and mp 128 to 129 °C was obtained, starting from 150 mg of the material, by recrystallization (2 times) from  $CH_2Cl_2$ -hexane (1:3  $\nu/\nu$ ) under an argon atmosphere. (Baker et al. (5), who originally obtained 4-formylphenylacetic acid with a very poor yield, reported mp 131 °C). The spectroscopic data (NMR, MS) listed here confirm the structure.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$ : 3.75 (s, 2H, CH<sub>2</sub>), 7.46 (d, 2H, J = 8 Hz, p-C<sub>6</sub>H<sub>4</sub>), 7.86 (d, 2H, J = 8 Hz, p-C<sub>6</sub>H<sub>4</sub>), 10.01 (s, 1H, CHO). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$ : 41.05 (CH<sub>2</sub>), 130.09, 130.19, 135.56 and 140.30 (C<sub>Ar</sub>), 176.51 (CO<sub>2</sub>H), 191.90 (C=O). MS (EI) *m*/*z*: 164 M<sup>+</sup> (85), 119 M<sup>+</sup> - CO<sub>2</sub>-H (55), 91 M<sup>+</sup> - CO<sub>2</sub>-OH (100). HRMS (EI) calcd. for (M<sup>+</sup>) C<sub>9</sub>H<sub>8</sub>O<sub>3</sub>: 164.0473; found 164.0476.

All other materials were best available commercial grades.

#### Kinetics

Rate measurements were made using either a conventional flash lamp (microsecond) flash photolysis system (6), or an eximer laser (nanosecond) system (7) operating at  $\lambda_{exc}$  = 248 nm, which have already been described (6, 7). This revealed a short-lived transient species, subsequently identified as an elongated enol intermediate (vide infra) with broad UV absorbance centered at  $\lambda = 330$  nm. Decay of this absorbance, for the most part, followed the first-order rate law well, and rate constants were obtained by least-squares fitting of a single exponential function. In some cases, however, the data fit a double exponential function better than a single exponential function, and a double exponential was therefore used. In this situation, one of the two rate constants obtained changed its value when the reacting solution was degassed, and the other unchanging rate constant was then taken to be that for ketonization of the elongated enol intermediate.

#### **Product identification**

The reaction investigated was shown to be the decarboxylation of eq. 5 by HPLC analysis using an authentic sample of the expected product p-methylbenzaldehyde (7).

# Results

Rates of decay of the broad UV absorption band centered at  $\lambda_{max} = 330$  nm, generated by flashing 4-formylphenylacetic acid, were determined in aqueous perchloric acid and sodium hydroxide solutions, and also in acetic acid, biphosphate ion, and tris-(hydroxymethyl)methaneammonium ion buffer solutions, using H<sub>2</sub>O as solvent; some rate measurements were made as well in perchloric acid and sodium hydroxide solutions and biphosphate ion buffers, using D<sub>2</sub>O as solvent. The ionic strength of all reacting solutions was kept constant at 0.10 mol/L with sodium perchlorate as the inert electrolyte. The results are summarized in Tables S1–S3.<sup>2.3</sup>

<sup>&</sup>lt;sup>2</sup> Supplementary data for this article are available on the journal Web site (canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5207. For more information on obtaining material refer to cisti-icist.nrc-cnrc.gc.ca/irm/unpub\_e.shtml.

<sup>&</sup>lt;sup>3</sup> In perchloric acid solutions the absorbance from the transient species of interest here diminished as the acid concentration increased, consistent with decarboxylation occurring through the carboxylate form of the substrate, and HPLC analysis showed the formation of other (uninvestigated) products. These interferences could be diminished somewhat by using deoxygenated solutions and accumulating data from several replicate flash photolysis shots.

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The measurements in buffers were made in a series of solutions of constant buffer ratio, and therefore constant hydronium ion concentration, but varying total buffer concentration. Buffer catalysis was strong, and observed rate constants within a given buffer solution series were accurately proportional to buffer concentration. The data were therefore analyzed by least-squares fitting of the linear buffer dilution expression shown in eq. [6]. The zero buffer concentration intercepts,  $k_{\rm int}$ , obtained in this way, plus the rate constants determined in perchloric acid and sodium hydroxide solution, are displayed as the rate profiles shown in Fig. 1.

[6] 
$$k_{obs} = k_{int} + k_{buff}$$
[buffer]

The shape of these rate profiles is characteristic of enol ketonization reactions, which are known to occur by ratedetermining  $\beta$ -carbon hydronation of either the enol or its enolate ion by any available acid (8). Because these profiles refer to solvent-related species, the available acids will be either the hydronium ion, written here as L<sup>+</sup>, or a solvent water molecule, L<sub>2</sub>O, as shown in the reaction scheme of eq. [7].<sup>4</sup> The acid-catalyzed descending diagonal portions at the high acidity ends of these profiles then represent  $\beta$ -carbon hydronation of the enol by hydronium ion. These sections are followed by short "uncatalyzed" horizontal portions, which could be due either to  $\beta$ -carbon hydronation of enol by solvent water or to the ionization of enol to enolate and hydronium ions followed by  $\beta$ -carbon hydronation of the enolate ion by hydronium ion. This latter process generates hydronium ions in its rapid preequilibrium ionization step and then uses them up in its ratedetermining step, to give an overall reaction independent of hydronium ion concentration.



These short horizontal sections are followed by basecatalyzed ascending diagonal portions that can be assigned to the ionization of enol to enolate ion followed by hydronation of enolate by solvent water. This process produces hydronium ions in its rapid pre-equilibrium step but does not use then up in its rate-determining step, to give an overall reaction whose rate is inversely proportional to hydronium ion concentration and has the appearance of hydroxide ion catalysis. Finally at sufficiently low acidity, the position of the enol–enolate equilibrium shifts over to the side of the enolate ion, and the process reduces to simple hydronation of enolate  $\beta$ -carbon by solvent water. This gives the final horizontal rate profile plateau.

The rate law that applies to this reaction scheme is shown in eq. [8], where  $k_{uc}$  is used to designate the process of an uncertain mechanism represented by the central short horiFig. 1. Rate profiles for the ketonization of elongated enol 8 in  $H_2O(\bigcirc)$  and  $D(\triangle)$  solutions.



zontal sections of the rate profiles, and the other rate and equilibrium constants are defined by eq. [7].

[8] 
$$k_{\text{obs}} = k_{\text{L}}[\text{L}^+] + k_{\text{uc}} + k_{\text{o}}'Q_{\text{a}}^{\text{E}}/(Q_{\text{a}}^{\text{E}} + [\text{L}^+])$$

Least-squares fitting using this expression gave for H<sub>2</sub>O solutions:  $k_{\rm H} = (8.11 \pm 0.48) \times 10^3 \, ({\rm mol/L})^{-1} {\rm s}^{-1}$ ,  $k_{\rm uc} = (2.62 \pm 0.28) \times 10^1 {\rm s}^{-1}$ ,  $Q_a^{\rm E} = (9.20 \pm 0.58) \times 10^{-9} {\rm mol/L}$ ,  $pQ_a^{\rm E} = 8.04$ , and  $k_o' = (2.82 \pm 0.05) \times 10^5 {\rm s}^{-1}$ , and results for D<sub>2</sub>O solutions that, when combined with their H<sub>2</sub>O counterparts, gave the isotope effects:  $k_{\rm H}/k_{\rm D} = 4.49 \pm 0.09$ ,  $(k_o')_{\rm H}/(k_o')_{\rm D} = 7.74 \pm 0.36$ , and  $(Q_a^{\rm E})_{\rm H}/(Q_a^{\rm E})_{\rm D} = 3.41 \pm 0.14.5$  The lines through the data points shown in Fig. 1 were drawn using these results. It may be seen that the data fit the reaction scheme of eq. [7] well and thus provide strong evidence that the process under observation is an enol ketonization reaction.

Further support for the assignment of the rate profiles of Fig. 1 to enol ketonization comes from the isotope effects obtained by comparing results determined in H<sub>2</sub>O solution with those obtained in D<sub>2</sub>O. The rate constants  $k_{\rm L}$  and  $k_{\rm o}'$ refer to rate-determining substrate hydronation, and isotope effects on these quantities can therefore be expected to contain primary isotope effect components in the normal direction  $(k_{\rm H}/k_{\rm D} > 1)$  of appreciable magnitude. These isotope effects, however, will also contain secondary components, with that on  $k_{\rm L}$  in the inverse direction ( $k_{\rm H}/k_{\rm D} < 1$ ) and that on  $k_0'$  in the normal direction  $(k_H/k_D > 1)$  (9). This will make the isotope effect on  $k_0'$  considerably stronger than that on  $k_{\rm H}'$ , which is nicely consistent with our observation, i.e.,  $(k_{o}')_{\rm H}/(k_{o}')_{\rm D} = 7.7$  whereas  $k_{\rm H}/k_{\rm D} = 4.5$ . The isotope effect on  $Q_{\rm a}^{\rm E}$  is also consistent with this quantity being the acidity constant of an enol ionizing as an oxygen acid. Such equilibrium isotope effects lie in the normal direction and generally fall in the range 3–5 (8); that of course agrees well with the observed value  $(Q_a^E)_H/(Q_a^E)_D = 3.4$ .

Thus, both solvent isotope effects and rate profiles agree that decarboxylation of p-formylphenylacetic acid occurs through an elongated enol intermediate, **8**, as shown in eq. [9].

<sup>4</sup> The symbol "L" is used to denote either protium or deuterium, "H" is used specifically for protium, and "D" specifically for deuterium. <sup>5</sup> This is a concentration equilibrium constant applicable at the ionic strength (0.10 mol/L) of the solutions in which it was determined.



## Discussion

The present results show the elongated enol **8** with  $pQ_a^E = 8.04$ , to have an unusually strongly acidic hydroxyl group; simple enols ionizing as oxygen acids ordinarily have acidity constants in the range  $pQ_a^E = 10-11$  (8). An especially apt comparison of the present system can be made with the enol of acetaldehyde **9**, which lacks the elongating cyclo-



hexadienyl spacer

of enol 8; acetaldehyde enol has  $pQ_a^E = 10.50$  (6), some two and a half pQ units weaker than the acidity constant of elongated enol 8. This striking difference is a result of the fact that ionization of enol 8 (eq. [10]) creates an anion whose negative charge can be delocalized from enolate oxygen 10 onto methylene carbon 11 (eq. [10]); this converts a cyclohexadienyl moiety into a benzene ring and thus benefits from a gain in benzene resonance energy. A similar shift of negative charge density is of course possible in the unionized enol, but that involves generation of charge and is consequently not as energetically advantageous. The anion is consequently stabilized more than the unionized enol, and that reduces the energy gap between the enol and enolate ion, making the enol a stronger acid than it would otherwise be.



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