

## Reaction of Pyruvic Acid with Nitrosobenzenes

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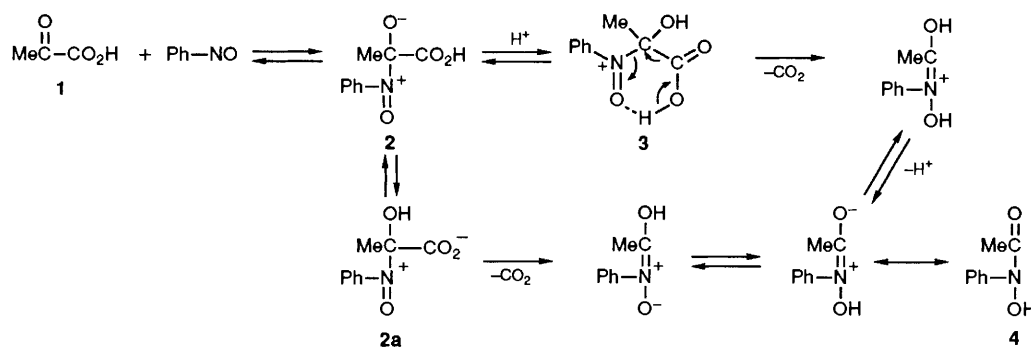
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Pyruvic acid reacts with nitrosobenzenes in both acid-catalysed and uncatalysed reactions giving *N*-phenylacetohydroxamic acids.

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The importance of pyruvic acid arises from the fact that it takes place in many fundamental biochemical processes.<sup>1</sup> The great attention received for the chemistry of hydroxamic acids is, on the other hand, closely connected with the variety of their pharmaceutical and industrial applications, as well as their role as a model system for natural siderophores.<sup>2-5</sup>

It was reported that  $\alpha$ -keto acids, among others pyruvic acid, are converted by the thiamine-catalysed enzymatic reactions with nitrosobenzenes into *N*-phenylhydroxamic acids.<sup>6a,b</sup> However, earlier attempts to obtain hydroxamic acids by direct reaction of pyruvic acid with nitrosobenzenes were unsuccessful.<sup>6c</sup>



Scheme 1

We now report that pyruvic acid reacts with substituted nitrosobenzenes in aqueous acidic medium to give the corresponding *N*-phenylacetohydroxamic acids. The reaction proceeds by nucleophilic attack of the nitroso nitrogen on the carbon atom of the  $\alpha$ -keto group of pyruvic acid **1**, followed by protonation of the zwitterionic intermediate **2** and decarboxylation of the resulting nitrosocarbinol cation **3**, which leads to the product, hydroxamic acid **4**, Scheme 1.

This mechanism is supported by the following observations: (i) The product of the reaction is the corresponding hydroxamic acid **4**, as shown by the spectroscopic evidence and product isolation.

(ii) At constant hydronium ion concentration, the observed reaction kinetics are second order overall, and first order with respect to both pyruvic acid and nitrosobenzene.

(iii) The Hammett plot of  $\log k$  vs.  $\sigma$  values ( $r = 0.988$ ,  $\rho = -1.97$ ) indicates that the order of reactivity of substituted nitrosobenzenes in this reaction is that of the electron-donating properties of the ring substituents, R (see Table 1).

(iv) Linear dependence ( $r = 0.997$ ) of  $k_{\text{obs}}/[\text{Py}]$  ( $\text{Py} = \text{pyruvic acid}$ ) on  $\text{H}_3\text{O}^+$  concentration in the range of  $0.05$ – $1.66 \text{ mol dm}^{-3}$  was obtained. The slope of  $3.60 \times 10^{-4} \text{ dm}^6 \text{ mol}^{-2} \text{ s}^{-1}$  and intercept of  $2.96 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$  are referred to the rates of proton-catalysed and uncatalysed reaction, respectively. This result is in agreement with the rate law, see eqn. (1), derived assuming steady-state conditions for

$$k_{\text{obs}} = k [\text{Py}] [\text{H}^+] + k' [\text{Py}] \quad (1)$$

the reaction system described by Scheme 1. Accordingly, protonation of the intermediate **2** leads to acid catalysis.

(v) The solvent deuterium isotope effects,  $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$  of  $1.15 \pm 0.02$  (in 98% deuterium oxide) and  $1.20 \pm 0.07$  (in 97% deuterium oxide) at hydronium ion concentration of  $0.12$  and  $0.31 \text{ mol dm}^{-3}$ , respectively, were observed. The corresponding isotope effect at  $1.16 \text{ mol dm}^{-3} \text{ H}_3\text{O}^+$  (in 94% deuterium oxide) was  $1.03 \pm 0.01$ . In the closely similar reactions of formaldehyde<sup>7a</sup> and acetaldehyde<sup>7b</sup> with nitrosobenzene, on the other hand, the observed solvent deuterium isotope effects were much greater and inverse,<sup>†</sup> and are related to the protonation of the zwitterionic addition intermediate. However, cancellation of the solvent isotope effect on going from  $0.12 \text{ mol dm}^{-3} \text{ H}_3\text{O}^+$  (where uncatalysed reaction prevails) to  $1.16 \text{ mol dm}^{-3} \text{ H}_3\text{O}^+$  (where at least 60% of reaction is acid-catalysed) indicates that the component of the observed isotope effect pertinent to the acid-catalysed reaction must be inverse. The apparent magnitude of this effect,<sup>‡</sup>

<sup>†</sup> In the reaction of formaldehyde with nitrosobenzene<sup>7a,b</sup>  $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$  are 0.61 to 0.54, and in the reaction of acetaldehyde with nitrosobenzene<sup>7b</sup>  $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$  is 0.38.

<sup>‡</sup> Any solvent deuterium isotope effect in reaction of pyruvic acid presumably is complicated with solvent isotope effect on hydration of pyruvic acid.

Table 1 Rates of the reaction of pyruvic acid with substituted nitrosobenzenes<sup>a,b</sup>

Substituent	$k_{\text{obs}}^{c,d}/10^4$ $\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
H	3.37(0.01)
<i>p</i> -Me	12.37(0.014)
<i>p</i> -Br	1.79(0.03)
<i>p</i> -Cl	1.93(0.03)
<i>m</i> -Cl	0.99(0.04)

<sup>a</sup> In water, at 25 °C and ionic strength of  $0.4 \text{ mol dm}^{-3}$  ( $\text{HClO}_4$ – $\text{NaClO}_4$ ) and in the presence of  $\text{Fe}^{3+}$  ion ( $5 \times 10^{-3} \text{ mol dm}^{-3}$ ).

<sup>b</sup> Kinetics are performed spectrophotometrically by following the appearance of the absorbance of mono-*N*-phenylacetohydroxamate iron(III) complex at 520 nm. <sup>c</sup> Rates are expressed as pseudo-first-order rate constants,  $k_{\text{obs}} = k [\text{pyruvate}]$ , according to the rate law established where there is constant concentration of  $\text{H}_3\text{O}^+$ : rate =  $k [\text{pyruvate}] [\text{Ph-NO}]$ . ( $\text{Ph-NO} = \text{nitrosobenzene}$ ). <sup>d</sup> Average of 3–5 runs. Numbers in parentheses are standard deviation of the mean. Concentrations of total pyruvic acid and  $\text{H}_3\text{O}^+$  ( $\text{HClO}_4$ ) are  $0.050$  and  $0.357 \text{ mol dm}^{-3}$ , respectively. Initial concentration of R–Ph–NO was usually  $5 \times 10^{-4} \text{ mol dm}^{-3}$ .

as compared with the corresponding effects in similar reactions,<sup>7a,b</sup> seems unexpected. It may be explained, however, in terms of the model proposed by Swain *et al.* for the proton transfer between electronegative elements, accompanying heavy atom reorganisation.<sup>8</sup> We have applied it to the transfer of carboxylic proton in the decarboxylation process, assuming that the transition state is somewhat like the intermediate **3**. If this is the case, then the transfer of carboxylic proton may not be part of the reaction coordinate motion and only a small isotope effect should result.<sup>8§</sup> Hence, the apparent solvent isotope effect in acid-catalysed reaction of pyruvic acid with nitrosobenzene could be the result of the isotope effect on protonation of intermediate **2** and the isotope effect for carboxylic proton transfer in transition state for decarboxylation. In addition, the mechanism of decarboxylation involving unimolecular decomposition through a cyclic transition state is generally accepted for  $\beta$ -keto acids.<sup>9</sup> Also, intramolecular proton transfer as an integral part of the reaction mechanism was proposed for numerous other decarboxylation reactions.<sup>10</sup>

Finally, it seems reasonable to expect that the solvent isotope effect in the uncatalysed reaction reflects mainly the isotope effect on hydration of pyruvic acid.

(vi) General acid catalysis with dichloroacetic and trichloroacetic acid was observed. This is consistent with the expectation of the existence of zwitterionic addition intermediate **2**.

<sup>§</sup> If proton transfer is part of the reaction coordinate, a sizeable isotope effect should result.<sup>13</sup> Solvent deuterium isotope effects of ca. 1.3 were observed in decarboxylation of benzoylactic acids.<sup>9</sup>

As expected, the intermediate **2** could be trapped not only by a proton, but also by general acids in the cases where proton transfer from general acid to the intermediate **2** is thermodynamically favourable.

The added neutral salt increases the rate of reaction of pyruvic acid with nitrosobenzene. Linear increase was observed in the ionic strength range of 0.4–5.2 mol dm<sup>-3</sup>. Probably, this is the consequence of both salt and dehydration effects on the activity of pyruvic acid.¶ The addition of organic cosolvent decreases the reaction rate, but rather less than in the similar reactions.<sup>6c,12</sup> It should be noted that the reaction may serve as an easy and convenient route to *N*-phenylaceto-hydroxamic acids in high yields. Particularly interesting is our observation that ferric ions catalyse the reaction of pyruvic acid with nitrosobenzene. Following the preliminary evidence, it seems obvious that chelation of ferric ions by pyruvate has an important role in catalysis.

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¶ Pyruvic acid is, under employed conditions, about 60% hydrated.<sup>11</sup>