Equilibria of formation and dehydration of the carbinolamine intermediate in the reaction of benzaldehyde with hydrazine

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Abstract—Measurement of polarographic limiting currents at equilibria made it possible at pH 3–7 to simultaneously determine concentrations of benzaldehyde, of its hydrazone and of the carbinolamine derivative. The dependence of concentration of carbinolamine at equilibrium on pH indicated presence of its di-, mono-, and unprotonated forms. Acid dissociation constants of the formation ($pK_a^1 \approx 3.2$) of the diprotonated form and of the dissociation of the monoprotonated form of carbinolamine ($pK_a^2 \approx 4.7$) were estimated. The equilibrium constants of formation (K_1) and dehydration (K_2) of the carbinolamine intermediate were determined.
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1. Introduction

Literature dealing with kinetics of reaction of carbonyl compounds with nucleophiles such as hydroxylamine, semicarbazone and its congeners, and hydrazine and its derivatives is voluminous.[1–7] These reactions were assumed to involve two equilibria, with a carbinolamine as intermediate (1):

$$\text{C=O} + \text{RNH}_2 \rightleftharpoons \text{C(OH)(NHR)} \rightleftharpoons \text{C=NR} + \text{H}_2\text{O} \quad (1)$$
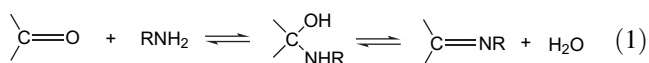
At pH 2–7, where hydrazine is predominantly present in a monoprotonated form, the reaction has to involve several acid–base equilibria (Scheme 1). Little is known about the position and role of these equilibria. The evidence reported[4] for the presence of carbinolamine in such reactions was only qualitative and obtained in unbuffered solutions. The existence of such intermediate was concluded based on a rapid decrease of the carbonyl band in the IR spectrum. This was observed in a reaction mixture containing 0.5 M furfural dissolved in D_2O in the presence of 2.0 M hydroxylamine. This relatively fast reaction was followed in the used unbuffered system by a slower increase of this band with time.
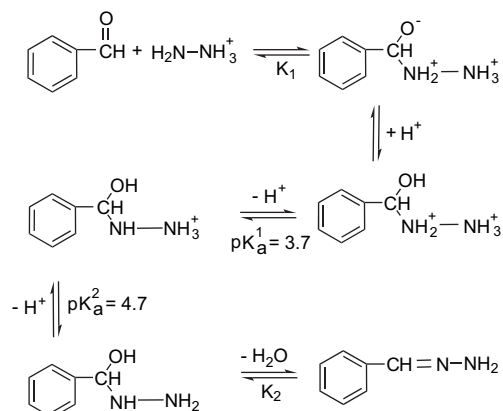
Scheme 1. The reaction mechanism between benzaldehyde and hydrazine.

In a similar experimental approach, the UV absorption in the 250–290 nm range was followed during the reaction of benzaldehyde (in the presence of 25% ethanol) or furfural with an excess of hydroxylamine.[4] A rapid decrease in absorbance in this wavelength range was attributed to the formation of carbinolamine. The following slow increase of the measured absorbance with time was attributed to the formation of the oxime. Reported spectra[4] indicate an overlap of absorption bands of all three aromatic compounds present— the parent carbonyl compound, the carbinolamine, and the resulting oxime.

This demonstrates the limited suitability of spectrophotometry for evaluation of equilibrium constants involved. Because of this situation and the absence of buffers to control the pH during these reactions, the few reported values for experimental equilibrium constants $K'_1 = [\text{C(OH)NHR}]/$

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[CO][RNH$_2$] and K'_2=[C=NR][H$_2$O]/[C(OH)NHR] are not reliable, because the role of the acid–base equilibrium constants has not been taken into consideration. Moreover, no attempt has been made to investigate the role of pH on equilibria involved in Scheme 1.

In later communications from the Jencks' group[8,9] some equilibria between carbonyl compounds and hydroxylamine or semicarbazide have been followed in buffered solutions. The measurements have been carried out at a single pH and only the overall equilibrium constants K'=[>C=NR]/[>C=O][RNH$_2$] were reported.

In this contribution, the advantage has been taken from the possibility of simultaneous determination of the unreacted benzaldehyde and the hydrazone formed. This was possible based on measurements of limiting currents of polarographic *i–E* curves.

Currently, the most frequently used technique for investigations of kinetics and equilibria involving organic compounds is spectrophotometry in the UV–visible region. This technique offers in most cases useful information concerning the kinetics of reactions involved. For investigation of equilibria, an application of this technique offers straightforward information, provided that absorption maxima of starting materials, of products and sometimes of intermediates are well separated. Frequently overlaps occur, which can be solved only using time-consuming deconvolution approaches. The usage of another spectroscopic technique, namely NMR, is often limited for reactions in D$_2$O by the insufficient solubility of the starting materials or products.

In DC polarography, used in this study, the investigated solution is placed in a supporting electrolyte in an electrolytic cell, together with a dropping mercury electrode and a reference electrode. To these two electrodes is applied a voltage, gradually increasing by about 0.1 V/min. Currents passing through the investigated solution are recorded as a function of the applied voltage. In the presence of a reducible or an easily oxidized species, the current increases with increasing voltage. The plot of the current as a function of the applied voltage shows an increase of current in the potential region where the species is reduced or oxidized. At a sufficiently high voltage, the current ceases to increase and reaches a limiting value.

Resulting stepwise curve (resembling the plots of integrated areas in NMR) is called a polarographic wave. The potential at the inflection point of such curve, where the current reaches one half of its limiting value, is called the half-wave potential. Its value is characteristic for the nature of the reduced or oxidized species in the given solution. The difference between the current before the wave raise and the top of the step is called 'limiting current'. Such currents are often controlled by the diffusion of the electroactive species to the electrode and are a linear function of concentration (similarly as an absorbance at a given wavelength).

If two species are present in the solution, such as benzaldehyde and its hydrazone, two waves are observed, if the reduction potentials of the two species differ by more than about 0.1 V (Fig. 1). The limiting currents of the two species are additive. Measurements of two (or more) limiting currents, which are a linear function of concentration, enable simultaneous determination of two (or more) electroactive species present in the solution. This makes it possible to determine concentrations of starting materials and products (and sometimes even intermediates) in a much less time-consuming fashion than a deconvolution of spectra.
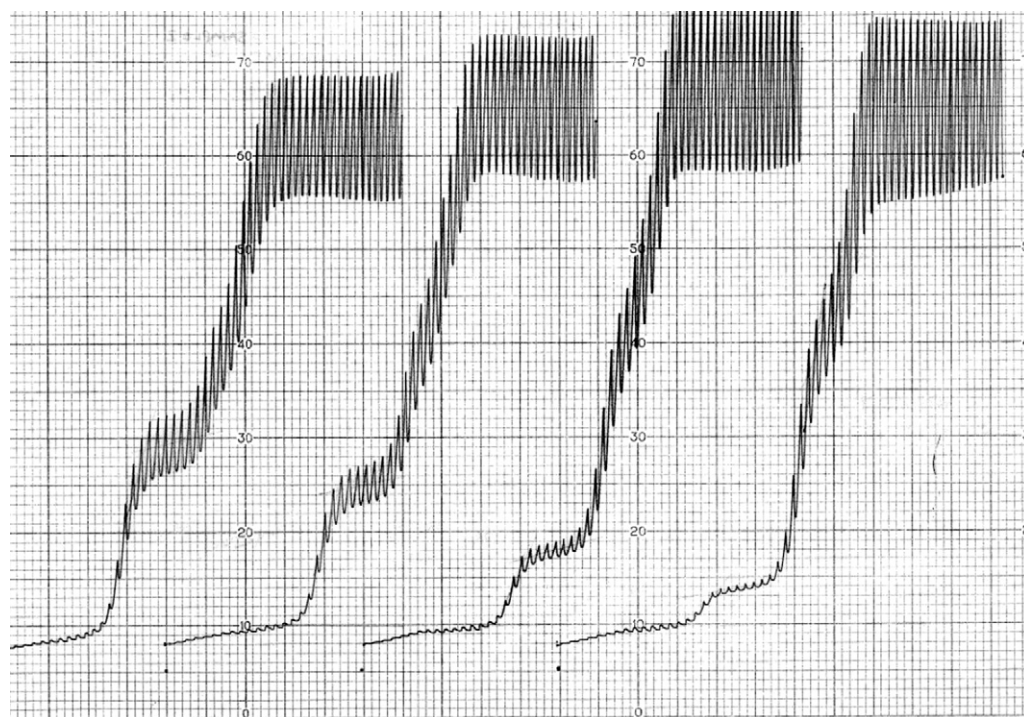
Figure 1. Polarographic curves of benzaldehyde in the presence of hydrazine at equilibrium. The concentration of the amine increases from right to left.

The above condition is fulfilled in reaction mixtures containing benzaldehyde and its hydrazone. The majority of reductions of azomethine derivatives occur at more positive potentials than the reduction of the parent carbonyl compound.[10] The limiting current of the first wave in Figure 1, which is more positive by about 0.25 V and corresponds to a two-electro reduction of the azomethine bond in the product, increases with increasing concentration of the amine. The limiting current of the second, more negative wave, which corresponds to the two-electron reduction of the formyl group, decreases. Measurements of the limiting currents of the two waves thus enable a simultaneous determination of both species in the given reaction mixture.

2. Results and discussion

In the investigated pH range benzaldehyde is reduced in a single two-electron wave or two one-electron waves to alcohol,[11] whereas benzaldehyde hydrazone is reduced, similarly as other hydrazones,[12,13] in a single four-electron wave to benzylamine. Limiting currents of the waves of these two compounds are a linear function of concentration and individual concentrations were determined using calibration curves. Due to a different number of transferred electrons, a direct comparison of limiting currents would be in this case misleading.

From the difference of the sum of equilibrium concentrations of benzaldehyde $[PhCHO]_e$ and of its hydrazone $[PhCH=NNH_2]_e$ subtracted from the initial concentration of $[PhCHO]_o$, it was at each pH possible to calculate the equilibrium concentration of the carbinolamine $[PhCH(OH)NHNH_2]_e$, using expression $[PhCH(OH)NHNH_2]_e = [PhCHO]_o - ([PhCHO]_e + [PhCH=NNH_2]_e)$.

The possibility of using polarographic limiting currents for following formation of carbinolamine in the course of hydrolysis of benzylidine aniline has been pointed out early.[14] In that communication, which remained undeservedly obscure, the authors did not apply their results for the determination of equilibrium constants of formation and cleavage of carbinolamine nor their pH dependence.

The hydrazine is in aqueous media present in diprotonated, monoprotonated, and unprotonated forms. For the two dissociations, pK_a values of 0.27 and 8.2 have been reported.[15,16] To simplify the data treatment, the reaction of benzaldehyde in this investigation was followed between pH 2.0 and 7.0 where the monoprotonated form of hydrazine predominates. Reactions were followed in the presence of 10-fold excess of hydrazine over benzaldehyde. Under such conditions, the formation of azine is negligible.

To find conditions under which the equilibrium at each pH value was established, the decrease in concentration of benzaldehyde and increase in concentration of the hydrazone formed with time were followed (Fig. 2). At pH higher than about 2.5 the sum of concentration of benzaldehyde and its hydrazone was lower than the analytical concentration of benzaldehyde introduced into solution (Fig. 2). The difference between the sum and initial concentration presents the concentration of carbinolamine at any time during
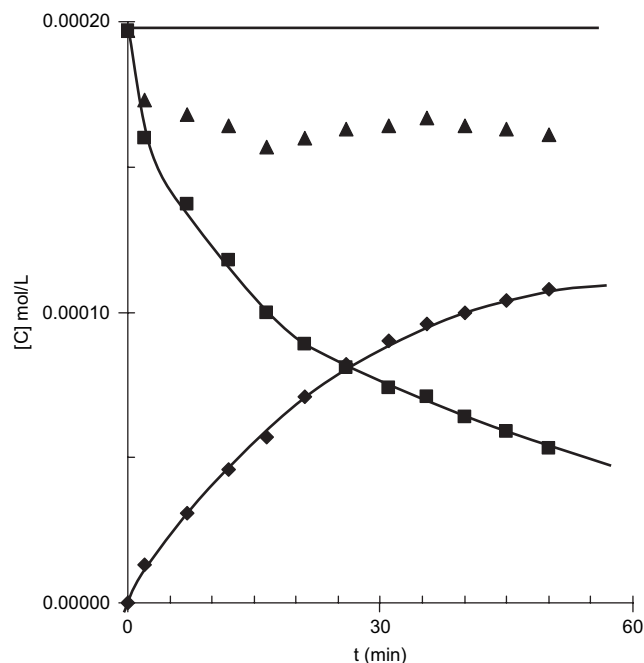

Figure 2. Time dependence of concentration of benzaldehyde, benzaldehyde hydrazone, and their sum at pH 4.15. Initial benzaldehyde concentration was 2×10^{-4} M, that of hydrazine 2×10^{-3} M. (◆) Benzaldehyde hydrazone, (■) benzaldehyde, (▲) the sum of concentrations of benzaldehyde and of benzaldehyde hydrazone. Theoretical curves for first-order kinetics were plotted together with experimental points.

the reaction as well as at equilibrium. The rate of formation of carbinolamine at pH 4.15 is too fast to be followed in this way, but the investigation of kinetics at other pH values and temperatures is under investigation. In the reaction of hydrazine with terephthalaldehyde it was possible using variations of polarographic *i–E* curves to follow concentration changes of two carbinolamines $-4-CH(OH)NHNH_2-C_6H_4-CHO$ and $CH(OH)NHNH_2-C_6H_4-CH=NNH_2$ with time.[17]

The equilibrium concentration of benzaldehyde in the presence of a 10-fold excess of hydrazine decreases with increasing pH (Fig. 3), whereas that of benzaldehyde hydrazone increases. The equilibrium concentration of the carbinolamine increases at pH higher than about 2.5, reaches a maximum at about pH 4.2 and decreases up to about pH 5.5. Between pH 5.5 and 7.0 the equilibrium concentration of the carbinolamine remains constant. This shape of the pH dependence of the equilibrium concentration indicates that carbinolamine is present in three forms—a diprotonated one, a monoprotonated one, and an unprotonated one. The equilibrium concentration of the diprotonated form remains negligible, that of the monoprotonated one is highest, and that of the unprotonated form is somewhat lower.

To estimate the equilibrium constant of the reaction involving the monoprotonated form of the carbinolamine, the pH dependence of the equilibrium concentration of the monoprotonated carbinolamine was approximated by two dissociation curves (Fig. 4), which show that the two acid–base equilibria involving the monoprotonated form of carbinolamine are approximately $pK_a^1 \approx 3.7$ and $pK_a^2 \approx 4.7$.

Different approaches have to be used to estimate the equilibrium constants involving carbinolamine formation in
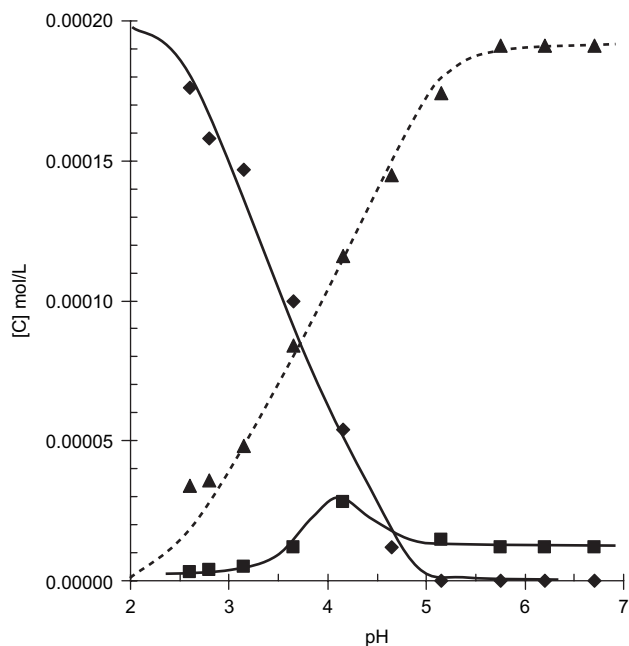
Figure 3. Dependences of equilibrium concentrations of benzaldehyde, benzaldehyde hydrazone, and carbinolamine intermediate on pH in solutions containing 2×10^{-4} M benzaldehyde and 2×10^{-3} M hydrazine. (◆) Benzaldehyde, (▲) benzaldehyde hydrazone, and (■) carbinolamine intermediate.

different pH regions. At pH lower than about 3, the equilibrium concentration of carbinolamine, which is practically completely present in a diprotonated form, is negligibly low. In the given pH range, the concentration of the monoprotonated form is extremely low and cannot be followed. As the equilibrium between the diprotonated form and the starting material is shifted in favor of the parent aldehyde, the reaction can be considered to go directly from the starting materials to the product.

At pH between about 3.7 and 4.7 the predominant form of the carbinolamine is the monoprotonated one. Between pH
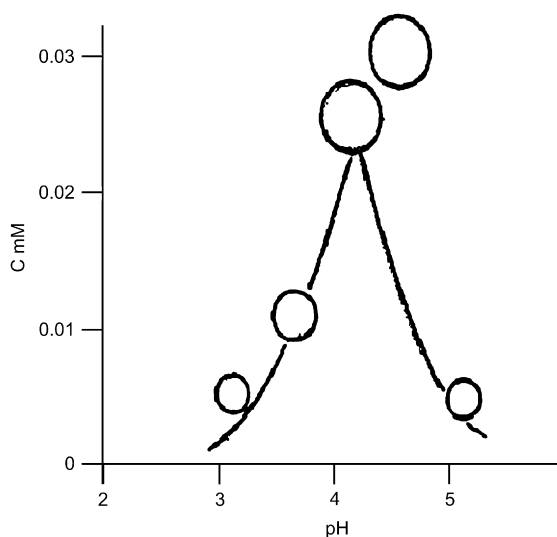
Figure 4. Dependence of concentration of carbinolamine in a solution containing 0.1 mM benzaldehyde and 1×10^{-3} M hydrazine on pH. Experimental points (size indicates experimental error) and theoretical curves for $pK_a^1=3.7$ and $pK_a^2=4.7$.

3.7 and about 5.5 both mono and unprotonated forms are present.

The sequence of reactions is depicted in Scheme 1. Defining $K_a^1=[PhCH(OH)NHNH_3^+][H^+]/[PhCH(OH)NH_2^+NH_3^+]$ and $K_a^2=[PhCH(OH)NHNH_2][H^+]/[PhCH(OH)NHNH_3^+]$ and equilibrium constant for the carbinol formation $K_1=S_{IM}[H^+]^2/(K_a^1K_a^2+K_a^1[H^+]+[H^+]^2)[PhCHO][NH_2NH_3^+]$ and the equilibrium constant of dehydration of the carbinolamine $K_2=[PhCH=NNH_2](K_a^2+[H^+])/S_{IM}K_a^2$ where the determined analytical concentration of the intermediate is defined as $S_{IM}=[PhCH(OH)NH_2^+NH_3^+]+[PhCH(OH)NHNH_3^+]+[PhCH(OH)NHNH_2]$, it was possible to calculate the values of equilibrium constant K_1 for the addition reaction yielding the carbinolamine and equilibrium constant K_2 for the elimination of water from carbinolamine at individual pH values (Table 1).

As the analytical concentration of the carbinolamine (S_{IM}) was obtained as a difference between two large values, the accuracy of values of S_{IM} is limited. This, together with possible contribution of some azine formation, may be responsible for the trend in calculated values of K_1.

The basicity of the O^- group in the primary addition product $PhCH(O^-)NH_2^+NH_3^+$ is so strong that its protonation will not play a role within the studied pH range 2–7. The dependence of concentration of carbinolamine at pH<4 indicates that its monoprotonated form is generated by a dissociation (at pH<4). This rules out the possibility that the conversion of $PhCH(O^-)NH_2^+NH_3^+$ into $PhCH(OH)NHNH_3^+$ would take place by an intramolecular hydrogen ion transfer. Such transfer would be, namely, pH independent and the concentration of the monoprotonated form would remain pH independent at pH lower than about 4. No information is available about the process involved in the dehydration. It is currently not possible to decide, if the elimination of water takes place in two steps—e.g., by protonation of the OH group with a subsequent dissociation of $PhCH=NH^+NH_2$, by initial elimination of the OH^- ion or by an intramolecular proton transfer, followed by the elimination of water.

The difference between $pK_a^1=3.2$ used in calculation of constants K_1 and K_2 in Table 1 and $pK_a^1=3.7$ used for a good fit in Figure 4 is within experimental error in both approaches. The observed dependence of the concentration

Table 1. Equilibrium constants of addition of hydrazine to benzaldehyde (K_1) and of the dehydration of carbinolamine yielding benzaldehyde hydrazone (K_2) obtained at different pH values

pH	K_1	K_2
3.15	9.1	—
3.65	15.2	—
4.15	22.4	18.6
5.15	—	14.7
5.75	—	17.7
6.2	—	16.4
6.7	—	16.1
Average	15.6±6.6	16.7±1.5

Benzaldehyde (1×10^{-4} M) and hydrazine (1×10^{-3} M) in phosphate and acetate buffers at 20 °C. pK_a^1 used was 3.2 and that for pK_a^2 was 4.7.

of the carbinolamine intermediate on pH and the possibility of finding the equilibrium constants of both the formation of this intermediate and of its elimination might be proved useful in re-interpretation of the mechanism of formation of addition compounds of some carbonyl compounds.

3. Conclusion

Based on measurements of polarographic limiting currents of separate waves of benzaldehyde and its hydrazone, it was possible to follow changes in concentration of the intermediate carbinolamine at equilibria in the reaction between benzaldehyde and hydrazine as a function of pH. The variations of the equilibrium concentrations of the carbinolamine with pH indicated that the equilibrium concentration of carbinolamine is limited by two acid–base equilibria. The equilibrium between the diprotonated form of the carbinolamine and the starting materials is shifted in favor of the benzaldehyde and the monoprotonated form of hydrazine. The equilibrium between the unprotonated form of the carbinolamine and hydrazone is strongly shifted in favor of the product. Only the monoprotonated form of the carbinolamine exists in reaction mixtures containing a 10-fold excess of hydrazine in measurable equilibrium concentrations in the presence of the starting materials and the product (Scheme 1). This reaction scheme offers more detailed information, enabling a better understanding of the mechanism of this reaction. It represents a starting point for investigation of kinetics of this reaction, which is in process. For benzene derivatives bearing another electroactive group acting as a substituent, it is possible to follow concentration changes of carbinolamines directly, as has been recently demonstrated for the reaction of hydrazine with terephthalaldehyde,[17] where the second formyl group or hydrazone group act as substituents.

4. Experimental

4.1. Electrochemical instrumentation

Current–voltage curves were recorded by using a polarograph as well as capillary electrodes with characteristics of $m=2.0$ mg/s, $t_1=3.0$ s at $h=64$ cm. A two-electrode electrolytic cell is used with a saturated calomel electrode (SCE) separated by a liquid junction (Kalousek cell).

4.2. Chemicals

The chemicals used for the preparation of simple phosphate, acetate, bicine, and borate buffers were of analytical quality and supplied by Baker and Fisher Sci. Company. Benzaldehyde and hydrazine sulfate were supplied by J.T. Baker Chemical Co. (Phillipsburg, NJ). All chemicals were used without further purification. Stock solutions (0.01 M) of the studied aldehydes were prepared in acetonitrile and stored in the dark for up to 3 days, and 0.01 M and 0.1 M stock solutions of hydrazine sulfate were prepared freshly in water.

4.3. Procedures

Polarographic experiments were carried out by using a total of 10 mL buffer solution with concentrations of the benzaldehyde and hydrazine in ratios suitable for individual equilibria. For a preliminary investigation of kinetics for testing the establishment of the equilibria were used reaction mixtures containing 2×10^{-4} M benzaldehyde and 2×10^{-3} M hydrazine. For the investigation of the equilibria, 2×10^{-4} M benzaldehyde was reacted with hydrazine with concentrations varying between 2×10^{-4} and 2×10^{-2} M. Such an excess of hydrazine was to achieve a suitable conversion of the benzaldehyde to the product at the given pH. The conversions of polarographic limiting currents into concentrations for benzaldehyde and the reaction product, needed in evaluation of equilibrium constants, were achieved by using calibration curves for these species recorded under identical experimental conditions as those used in investigations of equilibria. The concentration of the free hydrazine was calculated by subtracting the product concentration from the initial hydrazine concentration and the concentration of intermediate was calculated by subtracting the sum of equilibrium concentrations of the product and benzaldehyde from the initial concentration of benzaldehyde.

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