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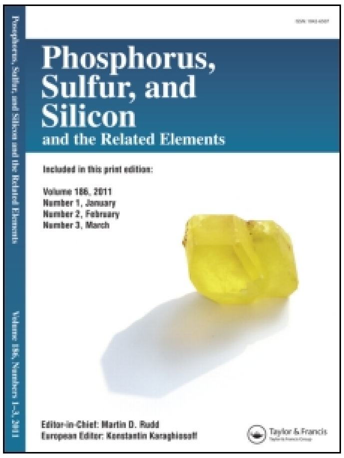

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Spectrophotometric Determination and Kinetic Studies of Condensation of Aromatic Aldehydes with 2-Thiobarbituric Acid

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Online publication date: 27 October 2010

To cite this Article Medien, H. A. A. and Zahran, A. A.(2003) 'Spectrophotometric Determination and Kinetic Studies of Condensation of Aromatic Aldehydes with 2-Thiobarbituric Acid', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 5, 1069 — 1080

To link to this Article: DOI: 10.1080/10426500307859

URL: http://dx.doi.org/10.1080/10426500307859

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Phosphorus, Sulfur and Silicon, 2003, Vol. 178:1069–1080
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1042-6507/03 $12.00 + .00
DOI: 10.1080/10426500390208901

SPECTROPHOTOMETRIC DETERMINATION AND KINETIC STUDIES OF CONDENSATION OF AROMATIC ALDEHYDES WITH 2-THIOBARBITURIC ACID

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(Received August 12, 2002; accepted October 31, 2002)

The condensation reaction of 2-thiobarbituric acid with aromatic aldehydes in ethanol has been investigated spectrophotometrically at 30–50°C. The reaction was catalyzed by HCl solutions. The reaction follows overall second order kinetics, first order each in reactant. Activation parameters have been calculated from the dependence of the rate constants on temperature. The rate of condensation increases with the presence of electron donating groups on the aromatic ring of the aldehyde. The rate-determining step involves dehydration of the aldol intermediate. Based on this reaction, determination of 13 aromatic aldehydes in a concentration range of 0.149–76 μg/ml is proposed.

Keywords: 2-Thiobarbituric acid; aromatic aldehydes; determination; kinetic

Several aromatic aldehydes are present in some natural products. *p*-Dimethylaminobenzaldehyde and syringaldehyde are useful reagents in organic colorimetric analysis[1] and in clinical chemistry.[2] Primary aromatic amines, sulfa drugs, and amino acids frequently have been determined and kinetically studied with these reagents.[3,4] Also, derivatives of barbituric acid are valuable in medicine as soporifics, and they belong to an important class of drugs used as hypnotics, sedatives, and anesthetics. For all these reasons it is desirable to have an accurate method for the analytical determination and kinetic measurements of these compounds (e.g., aromatic aldehydes and derivatives of barbituric acid) through their reaction.

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Many methods are cited in the literature for kinetic studies of reactions of aromatic aldehydes and comprise reactions with chlorodipentylborane,[5] 3-methyl-1-phenylpyrazolin-5-one,[6] phenylhydroxylamine,[7] pyridinium chlorochromate,[8] and phenylhydrazone.[9] Other methods are available for kinetic reactions of aromatic aldehydes.[10–22]

When aldehydes and 2-thiobarbituric acid are condensed through a Knoevenagel condensation, alkylidene or arylidene derivatives of 2-thiobarbituric acid are obtained.[23] This reaction follows the mechanism proposed in Perkin condensation.[24] These derivatives have interesting pharmacological expections, and industrial applications (dyes, photographic sensitizers); they also are significant from the point of view of food technology (test for the rancidity of food).[25] These derivatives also are used as an index of lipid peroxidation in plant materials.[26]

The present investigation aims to study the condensation reaction of aromatic aldehydes and 2-thiobarbituric acid (TBA) kinetically and to study the effect of substituents on the reactivity. This work also aims to introduce a spectrophotometric method for determination of the aromatic aldehydes.

EXPERIMENTAL

Apparatus

Visible absorption spectra were recorded on a Unicam SP 1800 recording spectrophotometer. A SP 6-200 Pye-Unicam spectrophotometer was used for the kinetic spectrophotometry. IR spectra were recorded (KBr) on a Pye-Unicam SP 1000 spectrophotometer. ^{1}H NMR spectra were taken at 270 MHz, using $CDCl_3$ as a solvent.

Materials and Reagents

All aromatic aldehydes used were of AR grade (BDH). Alcoholic solution of 2-thiobarbituric acid (Aldrich) was freshly prepared for each analysis. All other chemicals used were of reagent grade.

Analytical Procedure

A calibration graph for each of the aldehydes [3-hydroxy-4-methoxybenzaldehyde (10^{-3} M), *p*-hydroxybenzaldehyde (10^{-3} M), *p*-dimethylaminobenzaldehyde (10^{-4} M), *p*-methoxybenzaldehyde

(10^{-3} M), vanillin (10^{-3} M), syringaldehyde (10^{-3} M), 2,4-dihydroxybenzaldehyde (10^{-3} M), *m*-methoxybenzaldehyde (10^{-3} M), benzaldehyde (5×10^{-3} M), *p*-chlorobenzaldehyde (5×10^{-3} M), *p*-nitrobenzaldehyde (5×10^{-3} M), *p*-cyanobenzaldehyde (5×10^{-3} M), and *m*-hydroxybenzaldehyde (10^{-3} M) was obtained by transferring (0.1–1.0 ml) aliquots in ethanol to test tubes followed by the addition of 1.0 ml of the (0.1 M) ethanolic solution of 2-thiobarbituric acid (TBA) and 1.0 ml of the (2 M) HCl solution. The mixtures are thermostated at 50°C in water bath for 15 min and then diluted to 10 ml with ethanol and the absorbance of the resulting yellow color is measured at the maximum wavelength of each aldehyde derivative.

The points on standard calibration curves each represent the outcome of three determinations.

Kinetic Procedure

The rate of reaction of some aromatic aldehydes tested (viz: *p*-methoxy-benzaldehyde, *p*-hydroxybenzaldehyde, benzaldehyde, *p*-cyano-benzaldehyde, *p*-chlorobenzaldehyde, and *p*-nitrobenzaldehyde) with 2-thiobarbituric acid in the presence of 2 M HCl was followed by monitoring the increase in the absorbance of the product, at its wavelength of maximum absorption with time.

Freshly solutions of (0.02–0.05 M) of all studied aldehydes, solution of (0.001 M) 2-thiobarbituric acid in ethanol, and (2 M) HCl solution were prepared. To test the reaction order with respect to the aldehydes studied, mixing was carried out by withdrawing 1.0 ml, from each concentration of the aldehydes solutions (0.02–0.05 M) to 10 ml flasks containing 1.0 ml of (2 M) HCl solution, 1.0 ml of (0.001 M) 2-thiobarbituric acid solution and the appropriate volume of ethanol. A portion of the reaction mixture was transferred to a quartz cuvette placed in a thermostated (30°C) cell compartment. A blank solution was similarly prepared without aldehyde and the absorbance readings also were recorded and followed as a function of time. A different sets of experiments were carried out by withdrawing (0.5–3 ml) aliquots of 0.001 M (TBA) solution to different 10 ml flasks containing 1.0 ml of (0.05 M) aldehyde solution and 1.0 ml of (2 M) HCl solution to test the order with respect to (TBA).

Initial rates were determined by the method of initial rates,[27,28] whereby the absorbance (A) was plotted against time for each run. The initial slopes (dA/dt) for each run were determined, and used in the following equation for calculating the rate of the reaction:[27,28]

$$\text{Rate} = \frac{dA}{dt} \times \frac{C_\infty - C_i}{A_\infty - A_i}$$

Where C_i and C_∞ are the initial and final concentrations of the colored reaction products respectively, calculated by using the molar extinction coefficients ε. A_i and A_∞ are the absorbencies of the colored species at the start and the end of the reaction. Since both C_i and A_i are nearly equal to zero at the beginning of the reaction, then the above equation reduced to:

$$\text{Rate} = \frac{dA}{dt} \times \frac{C_\infty}{A_\infty}$$

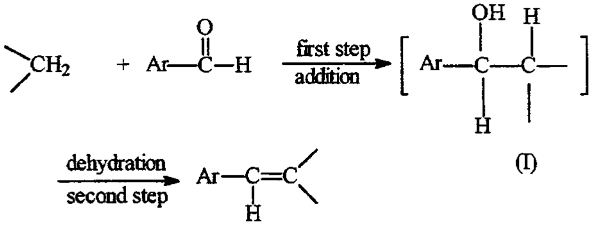
Preparation and Analysis of Reaction Products

The synthesis of reaction products was undertaken using the same methods cited in the literatures.[29–30] To a solution of TBA (0.004 mmol) in absolute ethanol, aromatic aldehyde (0.004 mmol) was added. The reaction mixture was warmed at 60°C for 2 min and left at room temperature overnight. The crystals obtained were filtered off, dried, and crystallized from ethanol. When *p*-dimethylaminobenzaldehyde was mixed with TBA, the product 5-(p-dimethylaminobenzylidene)-2-thio barbituric acid was obtained, m.p. = 264°C, yield 95% (Found: C, 63.10; H, 5.80; N, 14.80 calculated: C, 62.71; H, 5.92; N, 14.63); IR (KBr) cm^{-1} = 3060, 2920 (NH amide), 1690, (C=O); 1165 (C=S).^{1}H NMR: δ = 3.14–3.28 (s, 6H, $2CH_3$), 11.95–12.05 (s, 2H, NH), 8.15 (s, H, CH) 6.76–6.87 (m, 2H, aromatic protons), 8.40–8.52 (m, 2H, aromatic protons).

Other products have been obtained using different aldehydes by the same preparation method and their structures were confirmed by the spectral data.

RESULTS AND DISCUSSION

Previous work[31,32] showed that the reaction of an active methylene compounds follow the general pattern of nucleophilic addition to a carbonyl group, and Scheme 1 is proposed.



SCHEME 1

TABLE I Observed Rate Constants of the Condensation Reaction Between *p*-Hydroxybenzaldehyde and 2-Thiobarbituric Acid in Presence of 2 M HCl at 303 K

10^3 [Ald] M	10^3 [TMB] M	10^3 k_{obs} sec^{-1}
2.0	0.1	0.36
3.0	0.1	0.52
4.0	0.1	0.73
5.0	0.1	0.90
5.0	0.05	0.46
5.0	0.2	1.18
5.0	0.3	2.69

The rate limiting step can be the formation of a metastable aldol (I) or its dehydration to 5-arylidene-2-thiobarbituric acid, depending on the substitution on aromatic ring and on the experimental conditions (solvent, pH).[33,34]

Preliminary reaction orders were determined from slopes of log (initial rate) versus log (concentration) plots. From the observed results, it was shown that for all aldehydes studied the kinetics is second order overall, first order with respect to each of the reactants, as shown in Table I for *p*-hydroxybenzaldehyde reaction as an example, according to the simple rate law:

$$\mathrm{d[product]/dt} = k_{\mathrm{obs}}[\mathrm{aldehyde}][\mathrm{TBA}]$$

The study of the stoichiometry of the reaction indicates that the products have a maximum absorption at a molar ratio of 1:1 (aldehyde: TBA).

The observed rate constants k_{obs}, calculated from the initial rate (R_i) values are in good agreement with the values calculated from the first order plots [$\ln(A_\infty - A_t)$ against t] where A_t and A_∞ are the values of the absorbance at time t and at the end of the reaction respectively. The second order rate constants calculated by dividing k_{obs} values by the concentrations of the aldehydes. Duplicate kinetic runs showed that the rates are reproducible to within ±4%.

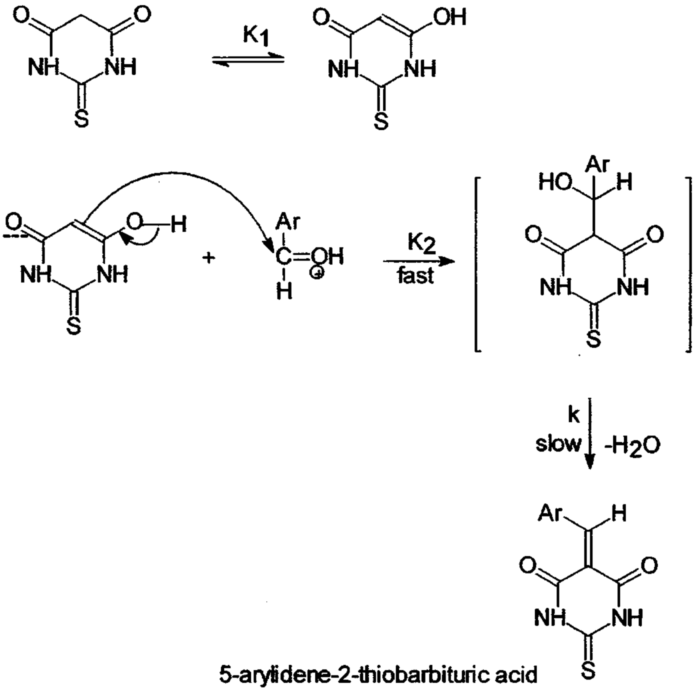
The kinetic results in Table II shows that the rate of the reaction between different substituted benzaldehydes and 2-thiobarbituric acid (TBA) increases by the presence of electron releasing groups in the aromatic aldehyde ring, whereas electron-withdrawing groups suppress it.

In fact, the addition of (TBA) to substituted benzaldehydes (first step) is favored by electron withdrawing groups, and the dehydration step (second step) is favored by electron donating ones. The results for the

TABLE II Second Order Rate Constants (k_2) and the Activation Parameters of the Reaction Between 2-Thiobarbituric Acid and Aromatic Aldehydes in the Presence of 2 M HCl at 303 K

	k_2 l · mol^{-1} · sec^{-1}			ΔE$^{\#}$	ΔH$^{\#}$	ΔG$^{\#}$	ΔS$^{\#}$
Aldehydes	303K	313K	323K	Kcal · mol^{-1}			Cal · mol^{-1} · K^{-1}
p-Methoxybenzaldehyde	0.25	0.32	0.40	3.82	3.22	18.51	−50.47
p-Hydroxybenzaldehyde	0.18	0.25	0.32	5.60	5.00	18.71	−45.2
Benzaldehyde	0.12	0.23	0.30	8.92	8.32	18.95	−35.1
p-Cyanobenzaldehyde	0.03	0.06	0.10	11.71	11.11	19.78	−28.63
p-Nitrobenzaldehyde	0.02	0.045	0.08	13.5	12.9	20.9	−23.5
p-Chlorobenzaldehyde	0.065	0.12	0.17	9.37	8.77	19.32	−34.82

reaction obtained (Table II) then can be rationalized considering that the second step is rate-limiting and the first step is the faster of the two. Therefore, the reaction process can be represented by the following mechanism:[29,30]



The above equations lead to rate expression (1),

$$\text{Rate} = kK_1K_2[\text{TBA}]\,[\text{Ald}] \qquad (1)$$

Since, [Ald] $\gg$ [TBA], then, Eq. (1) becomes:

$$\text{Rate} = \text{k}\text{K}_1\text{K}_2[\text{TBA}] \tag{2}$$

From Eq. (2), one can conclude that

$$k_{\text{obs}} = \text{k}\text{K}_1\text{K}_2[\text{Ald}] \tag{3}$$

Eq. (1) shows that the reaction follows second order kinetics, first order each in aldehyde and (TBA). The second order rate constants were calculated using the equation, $k_2 = k_{\text{obs}}/[\text{Ald}]$.

Effect of Varying [HCl]

As mentioned above, the reaction involves an addition step followed by dehydration step, which is the rate determining one. The addition step is enhanced by addition of an acid, which facilitate the attack of (TBA) molecule to give the intermediate leading to enhancing the rate of the reaction.

For all aldehydes studied, the reaction was found to be catalyzed by addition of HCl solution. The values of k_{obs} increase in [HCl] from 0.1 M up to 2 M, after which the value of k_{obs} becomes constant.

Effect of Substituents

An attempt has been made to apply the Hammett's equation for the reaction of different substituted benzaldehydes (p-OCH_3, p-OH, p-CN, p-Cl and p-NO_2) at 303 K using the σ values (Hammett's polar substituent constants) for these aldehyde substituents as shown in Figure 1. The negative ρ value (-1.0217) ($r = 0.982$) means that electron-repelling groups enhance the rate of the reaction. This is because the electron repelling groups enhance the dehydration step of the aldol formed (I) and stabilizes the cationic intermediate which is formed after losing a water molecule to give the final product.

Activation Parameters

The rates of the reaction of seven different benzaldehydes were determined at different three temperatures: 303, 313, and 323 K. The activation energies $\Delta E^{\#}$, determined from the slopes of the Arrhenius plots of log k_2 versus T^{-1} and the other thermodynamic parameters $\Delta H^{\#}$, $\Delta S^{\#}$ and $\Delta G^{\#}$ calculated at 303 K and are given in Table II.

The entropy of activation values are negative as expected for bimolecular or ter-molecular reactions. In this study the entropy of activation $\Delta S^{\#}$ is substituent dependent. Since all the substituents are located in *para* position, direct steric interaction is unlikely, so that resonance

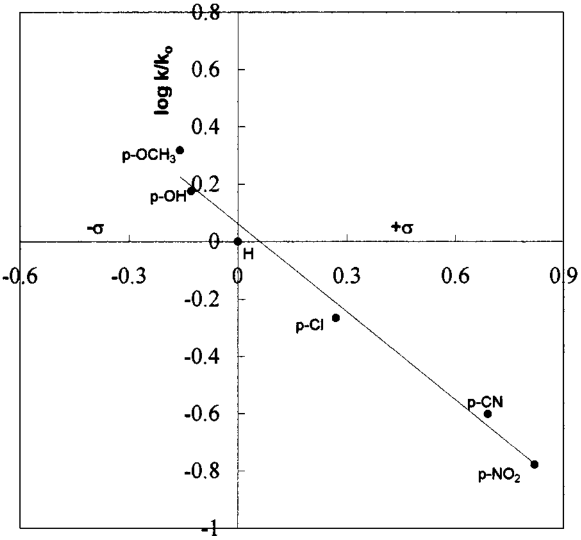


FIGURE 1 Hammett plot for the reaction of substituted benzaldehydes with thiobarbituric acid at 303 K.

and/or inductive effects are the operating factor. Within the series, electron-releasing substituents in the aromatic aldehyde, through their resonance and/or inductive effects, localize the formal charge on the T.S. This favors the formation of more ordered transition states reflecting high and negative entropies of activation. On the other hand, the presence of electron withdrawing substituents in the aldehyde alters their nature, leading to much more delocalization of the charge in T.S., and hence reflecting low and negative entropies of activation.

The linear correlation between $\Delta H^{\#}$ and $\Delta S^{\#}$ (Figure 2) for the reaction of different substituents of benzaldehyde with (TBA) shows that all the compounds react by the same mechanism.[35,36] The value of the isokinetic temperature β obtained was 360.45 K, (r = 0.998). This value is not the real temperature used in the kinetic runs.

The constancy of $\Delta G^{\#}$ may be explained on the basis of an isokinetic relationship that exists for a series of compounds of slightly different structures but undergoing reaction essentially by the same mechanism; the $\Delta G^{\#}$ may be more or less constant with relative changes in $\Delta H^{\#}$ and $\Delta S^{\#}$ as pointed out by Leffler.[37]

The mechanism for the title reaction is common for all members in the series as indicated by (a) the good straight-line plot of $\Delta H^{\#}$ versus $\Delta S^{\#}$, (b) the linear plots of log k_2 at 323 K against log k_2 at 303 K (gradient, 0.657, $r = 0.987$).

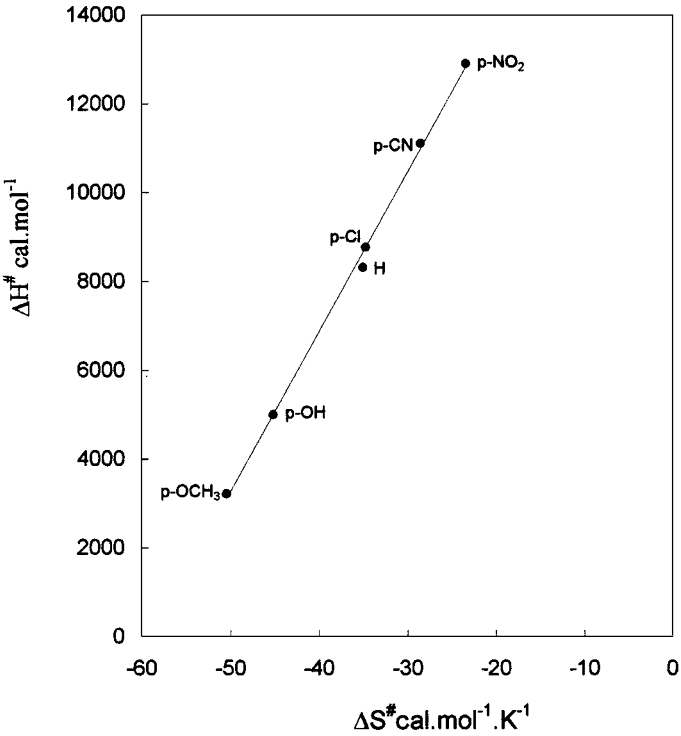


FIGURE 2 The linear relationship between $\Delta H^{\#}$ and $\Delta S^{\#}$.

At studied temperatures, an electron-withdrawing substituent in the *para* position of the aldehyde decreases the reaction rates, while a similarly positioned electron releasing or donating substituent increases it. This behavior could be explained by the observation that the ratio $k_{p\text{-}OCH_3}/k_{p\text{-}NO_2}$ was 12.5, 7.1 and 5.0 at 303, 313 and 323 K respectively (Table II). Consequently, the variation of the rate constant depends on the nature of the substituent in the aldehyde. The order of decreasing reactivity of substituted aldehyde in ethanol is p-OCH$_3$ > p-OH > H > p-Cl > p-CN > p-NO$_2$. This order of decrease in magnitude of the substituent effect is expected on the basis of both inductive and resonance effects.

Determination of the Aldehydes Tested

Effect of Time and Temperature

The absorbance of the color due to reaction of the aldehydes tested with excess (TBA) in the presence of 2 M HCl in ethanol had reached a maximum intensity after 15 min at 50°C. It is observed that the

TABLE III Statistical Analysis of the Calibration Graphs for the Determination of Some Aromatic Aldehydes by Reaction with 2-Thiobarbituric Acid in the Presence of 2 M HCl

Aldehydes	$\lambda_{\max}$ nm	Concentration range μg /ml	ε $(\mathrm{l\ mol^{-1}\ cm^{-1}})$	Slope (b)	Intercept (a)
3-Hydroxy-4-methoxy-benzaldehyde	425	7.6–76.0	10900	0.0144	−0.0164
p-Dimethylaminobenzaldehyde	460	0.149–1.49	19670	0.132	−0.0003
Syringaldehyde	440	1.82–18.2	15730	0.086	−0.024
Vanillin	400	1.521–15.215	14850	0.0976	0.004
p-Methoxybenzaldehyde	400	1.36–13.60	16650	0.122	−0.009
p-Hydroxybenzaldehyde	410	1.22–12.2	15380	0.126	−0.018
m-Hydroxybenzaldehyde	410	1.22–12.2	520	0.042	0.005
Benzaldehyde	360	10.6–53	550	0.0052	0.0
p-Chlorobenzaldehyde	360	6.93–69.25	1840	0.0133	−0.01
2,4,-Dihydroxybenzaldehyde	420	1.38–13.8	12200	0.089	−0.01
p-Cyanobenzaldehyde	360	5.95–59.5	980	0.008	0.003
p-Nitrobenzaldehyde	355	7.55–75.5	1560	0.0103	0.009
m-Methoxybenzaldehyde	400	1.36–13.6	6610	0.048	−0.023

absorbance is nearly constant with increasing the temperatures from 50 to 70°C.

Accuracy and Precision

Table III shows linear regression analysis of the data obtained from calibration graphs of the aldehydes tested from the relation $A = a + bc$, where A is the absorbance at the relevant peak in a 1.0 cm quartz cell, a and b are the intercept and the slope of the calibration graphs, respectively, and c is the concentration of the aldehyde in μg/ml in the final solution.

Five replicate determinations at different concentration levels of *p*-hydroxybenzaldehyde as a representative aldehyde were carried out to test the precision and accuracy of the proposed method. The recovery was 96.98%. The relative standard deviation R.S.D. ($n = 5$) at 12.2 μg/ml and the percentage relative error were 0.96 and 0.43 respectively. The figures obtained point out to the good accuracy and repeatability of the method. The ruggedness of the proposed method was studied by evaluating the coefficient of variation (five replicates) at 12.2 μg/ml for *p*-hydroxybenzaldehyde determination during one and five days. It was found to be 0.96 and 1.023% respectively.

Selectivity

The effects of various compounds on the determination of 10^{-4} M *p*-hydroxybenzaldehyde were studied. The results are summarized in

TABLE IV Effect of Various Foreign Species on the Determination of 10^{-4} M of *p*-Hydroxybenzaldehyde at the Optimum Conditions

Substance	Tolerance Limit Ratio (mol/mol)
Formaldehyde, acetaldehyde	100
Acetone, benzoic acid	50
Aniline	30

Table IV. The tolerance limit was defined as the concentration of added substance causing less than ±3% relative error.

Conclusion

In summary, 13 aromatic aldehydes have been shown to be assessable with a simple analytical method. The present method of determination offers the advantages of: (a) reagent availability and stability; (b) reasonable selectivity in the presence of many other C=O containing compounds; (c) less time consumption; and (d) high sensitivity compared to other spectrophotmetric methods.

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