

# Kinetic Studies of Condensation of Aromatic Aldehydes with Meldrum's Acid

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The condensation reaction of Meldrum's acid with aromatic aldehydes in the presence of a catalyst has been investigated spectrophotometrically at 25–50 °C. The reaction follows overall second order kinetics, first order in each of the reactants. Electron-withdrawing groups accelerate and electron-releasing groups retard the rate of condensation. From the dependence of the rate constants on temperature, the activation parameters have been calculated and also the isokinetic temperature with a value of 403.5 K. Based on this reaction, determination of eight aromatic aldehydes in a concentration range of 1.49 –91 µg/ml is proposed. On the other hand, determination of some aromatic aldehydes with Meldrum's acid is performed in water at 75 °C for 2 h, without adding any catalyst.

## Introduction

Meldrum's acid undergoes standard Knoevenagel condensation with aromatic and heteroaromatic aldehydes furnishing the corresponding arylidene derivatives, which are versatile substrates for different kinds of reactions [1]. They are useful substrates for cycloaddition reactions and for the synthesis of heterocyclic compounds with potential pharmacological activity [2]. The 1,4-addition of nucleophiles to these products has been widely used synthetically and displays some advantages over the acyclic malonate analogues. The conjugated reduction is the way most often used to prepare 5-monoalkyl Meldrum's acids derivatives or analogues, also applied to obtain deuterated carboxylic acids [3].

Methods are cited in the literature for kinetic studies of reactions of aromatic aldehydes, and comprise reactions with chlorodipentylborane [4], 5-*N*-Benzoylamino-1,3,4-thiadiazole-2-acetonitrile [5], 1,3-dimethylbarbituric acid [6], 3-methyl-1-phenylpyrazolin-5-one [7], phenylhydroxylamine [8], pyridinium chlorochromate [9], phenylhydrazine [10], condensation with *o*-phenylenediamine in presence of H<sub>2</sub>O<sub>2</sub> [11] and with cysteine [12]. Other kinetic methods are available for oxidation of aromatic aldehydes [13–23].

This work aims to study the kinetics of the condensation reaction of some aromatic aldehydes with the active methylene compound, 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid, MA), 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.

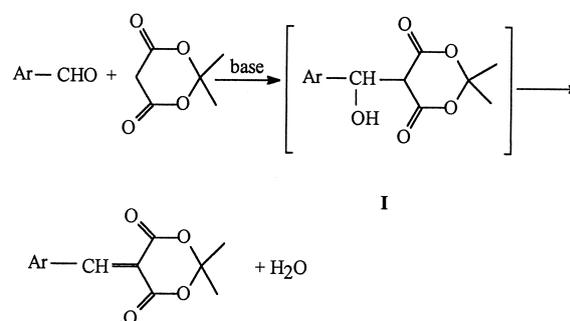
## Results and Discussion

Meldrum's acid like other compounds with an active methylene group [5, 6, 24, 25], interact with aromatic aldehydes through two steps according to Scheme 1.

From the data compiled in Table 1, it was shown that for all aldehydes studied the kinetics is second order overall, first order with respect to each of the reactants, and zero order with respect to piperidine, according to the simple rate law:

$$d[\text{product}]/dt = k_{\text{obs}} [\text{aldehyde}][\text{MA}]$$

From this equation it can not be distinguished if the rate-limiting step is the nucleophilic attack of the carbanion of MA on the aldehyde or the dehy-



Scheme 1.

Table 1. Rate constants of the reaction of *p*-nitrobenzaldehyde with Meldrum's acid (MA) at 298 K (Pip = piperidine) for different concentrations of the reactants.

[Aldehyde], M	[MA], M	[Pip], M	$10^4 k_{\text{obs}}$ , sec <sup>-1</sup>
$2.5 \times 10^{-4}$	0.01	0.01	4.5
$5.0 \times 10^{-4}$	0.01	0.01	9.78
$7.5 \times 10^{-4}$	0.01	0.01	14.5
$10.0 \times 10^{-4}$	0.01	0.01	19.58
0.01	$2.5 \times 10^{-4}$	0.01	2.24
0.01	$5.0 \times 10^{-4}$	0.01	4.48
0.01	$7.5 \times 10^{-4}$	0.01	6.74
0.01	$10.0 \times 10^{-4}$	0.01	9.01

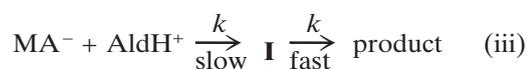
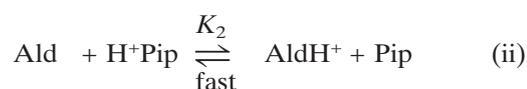
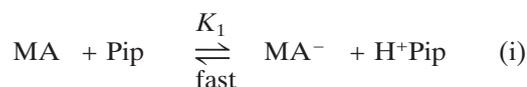
dration of compound I, both steps being consistent with a second order equation. The study of the stoichiometry of the reaction indicates that the products have a maximum absorption at a molar ratio of 1:1 (aldehyde:MA).

The kinetic results in Table 1 show that the rate of the reaction between different substituted benzaldehydes and (MA) decreases in the following order:



It can be noted that electron-withdrawing groups accelerate and electron-releasing groups retard the rate of reaction. In fact, electron-withdrawing groups favor the addition of MA to substituted benzaldehydes (first step), and electron-releasing ones favor the dehydration step (second step). The results for the reaction obtained can then be rationalized considering the first step is the rate-limiting one and the second step is the faster.

Therefore, the reaction process in the presence of piperidine (Pip) as a base, can be represented by equations (i)–(iii) where Ald, MA and **I** refer to the aldehyde, Meldrum's acid and the intermediate **I** in Scheme 1 respectively:



These equations lead to rate expressions (iv) and (v).

$$\text{rate} = k [\text{MA}^-][\text{AldH}^+] \quad (\text{iv})$$

$$\text{rate} = kK_1K_2 [\text{MA}][\text{Ald}]. \quad (\text{v})$$

From equation (v), one can conclude that

$$k_{\text{obs}} = kK_1K_2 [\text{MA}]. \quad (\text{vi})$$

Equation (v) shows that the reaction follows second order kinetics, first order each in aldehyde and MA. The observed pseudo-first order rate constant ( $k_{\text{obs}}$ ) is therefore a product of the equilibrium constants of the first two steps and the rate constant ( $k$ ) of the third step. The rate constant  $k$  could not be evaluated since no data are available for the equilibrium constants  $K_1$  and  $K_2$ . The second order rate constants were calculated using the equation,  $k_2 = k_{\text{obs}}/[\text{MA}]$ .

The rate constants of the reaction of different substituted aldehydes at 298 K correlate well with Hammett's  $\sigma$  values (Hammett's polar substituent constants) for aldehyde, as shown in Fig. 1. The positive  $\rho$  value (1.226) ( $r = 0.9449$ ) means that electron-withdrawing groups enhance the rate of the reaction.

#### Activation parameters

The rates of the reaction of six different benzaldehydes were determined at 298, 303, 313 and 323 K. The activation energies  $\Delta E^\ddagger$  were determined from the slopes of the Arrhenius plots of

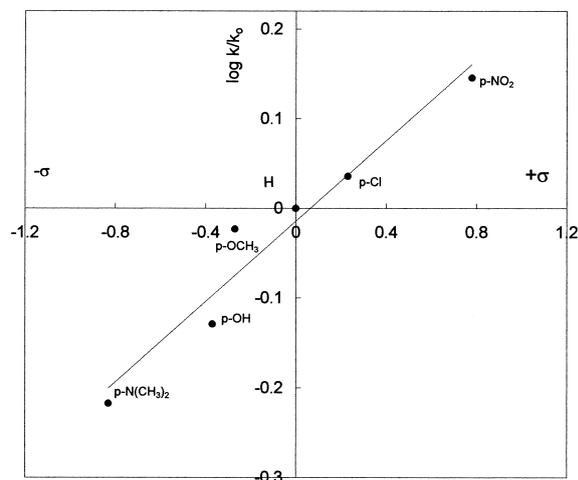


Fig. 1. Hammett plot for the reaction of substituted benzaldehydes with Meldrum's acid.

Table 2. Rate constants and the activation parameters of the reaction of substituted benzaldehydes with Meldrum's acid (MA) using 0.1 M piperidine in chloroform.

Substituent	$10^2 k_2, \text{l} \cdot \text{mol}^{-1} \text{s}^{-1}$				$\Delta E^\ddagger$	$\Delta H^\ddagger$	$\Delta S^\ddagger$	$\Delta G^\ddagger$
	298 K	308 K	313 K	323 K				
<i>p</i> -NO <sub>2</sub>	9.79	14.2	16.9	23.6	8.34	7.74	19.07	-38.02
<i>p</i> -Cl	7.6	13.2	16.0	22.9	8.42	7.83	18.90	-38.57
H	7.0	12.4	15.6	21.6	8.66	8.07	18.95	-36.52
<i>p</i> -OCH <sub>3</sub>	6.64	11.7	15.4	20.8	8.83	8.25	19.19	-36.72
<i>p</i> -OH	5.2	7.50	12.0	16.2	9.06	8.46	19.13	-35.77
<i>p</i> -N(CH <sub>3</sub> ) <sub>2</sub>	4.24	6.50	11.0	14.2	9.70	9.09	19.46	-34.80

$\log k_2$  versus  $T^{-1}$ . The activation parameters  $\Delta H^\ddagger$ ,  $\Delta S^\ddagger$  and  $\Delta G^\ddagger$  were calculated at 298 K and are given in Table 2.

The entropy of activation values are negative as expected for bimolecular or ter-molecular reactions. In this study the entropy of activation ( $\Delta S^\ddagger$ ) is substituent dependent. Since all the substituents are located in *para* position, direct steric interaction is unlikely, so that resonance and/or inductive effects are the operating factors. Within the series, electron-withdrawing substituents in the aromatic aldehyde, through their resonance and/or inductive effects, localize the formal charge in the transition state. This favours the formation of more ordered transition states reflecting high and negative entropies of activation. On the other hand, the presence of electron releasing substituents in the aldehyde alters their nature, leading to much more delocalization of the charge in the transition state, and hence reflecting low and negative entropies of activation.

The linear correlation between  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  (Fig. 2) for the reaction of different substituents of benzaldehyde with MA shows that all the compounds react by the same mechanism [26]. The value of the slope was 403.5 K ( $r = 0.989$ ), which is the value of the isokinetic temperature  $\beta$  (the temperature at which the substituent effects are supposed to be reversed). This value is not the real temperature used in the kinetic runs.

The constancy of  $\Delta G^\ddagger$  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  $\Delta G^\ddagger$  may be more or less constant with relative changes in  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  as pointed out by Leffler [26].

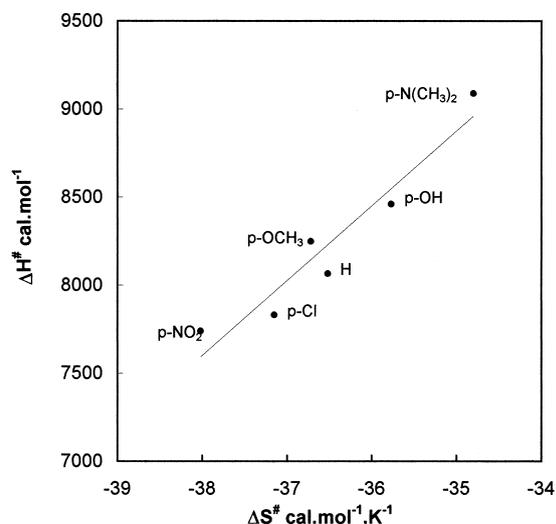


Fig. 2. The linear relationship between  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  for the reaction of Meldrum's acid with different aromatic aldehydes.

The mechanism for the title reaction is common for all members in the series as indicated by (a) the good straight-line plot of  $\Delta H^\ddagger$  versus  $\Delta S^\ddagger$ , (b) the linear plots of  $\log k_2$  at 50 °C against  $\log k_2$  at 25 °C (gradient = 0.658,  $r = 0.95$ ).

At the studied temperatures, an electron-withdrawing substituent in the *para* position of the aldehyde increases the reaction rates, while a *para* positioned electron releasing or donating substituent decreases it. This behaviour could be explained by the observation that the ratio  $k_{p\text{-NO}_2}/k_{p\text{-N(CH}_3)_2}$  which was 2.31, 2.18, 1.53, and 1.66 at 25, 35, 40, and 50 °C, respectively (Table 2). 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 chloroform is  $p\text{-NO}_2 > p\text{-Cl} > \text{H} > p\text{-OCH}_3 > p\text{-OH} > p\text{-N(CH}_3)_2$ . This order of decrease in magnitude of the substituent effect is expected on the basis of both inductive and resonance effects.

### Quantitative Determination of the Aldehydes Tested

The absorbance of the color due to reaction of the aldehydes tested with excess MA in the presence of 0.1 M piperidine in chloroform had reached a maximum intensity after 15 min at 50 °C.

Table 3 shows a 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 ( $\mu\text{g/ml}$ ) in the final solution. The points on standard calibration curves each represent the outcome of three determinations. The relative standard deviations (*r.s.d.*) vary between 0.69 and 1.0% for  $10 \mu\text{g ml}^{-1}$  of each aldehyde used ( $n = 3$ ), and the reproducibility varies between 95.8 and 101% for each aldehyde. Fig. 3 shows the relationship between absorbance vs. concentration (calibration graph) for  $p$ -dimethylaminobenzaldehyde as an example.

No interference is caused by the presence of formaldehyde (10 mM), acetone (5.17 mM), benzoic acid (2.46 mM), acetaldehyde (6.82 mM) and aniline (3.2 mM). In summary, thirteen aromatic aldehydes have been shown to be assessable with a new simple analytical method.

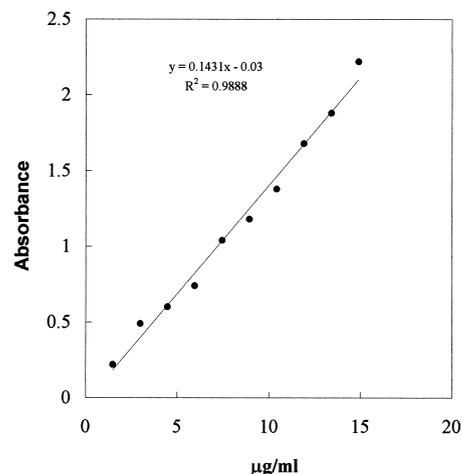


Fig. 3. The calibration graph of  $p$ -dimethylaminobenzaldehyde through its reaction with Meldrum's acid in chloroform in the presence of piperidine as a catalyst.

### Determination of aromatic aldehydes without catalyst in water

The use of water as a solvent in organic chemistry was rediscovered in the 1980s by Breslow [27, 28] who showed that hydrophobic effects could strongly enhance the rate of several organic reactions. Previously the scant solubility of the reactants was the main reason that ruled this solvent out from studies. Bigi et al [29] have investigated the condensation reaction of Meldrum's acid and aldehydes as a clean synthesis in water.

In the present investigation, the concentrations of three aromatic aldehydes ( $N,N$ -dimethylaminobenzaldehyde, 3,5-dimethoxy-4-hydroxybenzaldehyde and  $p$ -chlorobenzaldehyde) were determined

Table 3. Statistical analysis of the calibration graphs for the determination of some aromatic aldehydes by reaction with Meldrum's acid (M) in chloroform at 50 °C in the presence of piperidine.

Aldehydes	$\lambda_{\text{max}}$ [nm]	Concentration range [ $\mu\text{g/ml}$ ]	$\epsilon$ [ $\text{l mol}^{-1} \text{cm}^{-1}$ ]	Slope (b)	Intercept (a)
$p$ -Dimethylamino-benzaldehyde	445	1.49–14.9	21327.27	0.1431	–0.03
3,5-Dimethoxy-4-hydroxybenzaldehyde	365	9.1–91	3030	0.0167	–0.009
$p$ -Methoxybenzaldehyde	365	6.8–68	2199	0.016	0.0087
$p$ -Hydroxybenzaldehyde	370	6.1–61	4015	0.033	0.021
$p$ -Nitrobenzaldehyde	340	7.55–75.5	1648	0.0109	–0.003
$m$ -Nitrobenzaldehyde	340	7.55–75.5	1000	0.0066	0.00
$p$ -Chlorobenzaldehyde	325	7.025–70.25	569	0.004	0.0033
Benzaldehyde	360	5.3–53	1000	0.0063	0.00

with Meldrum's acid in water at 75 °C after 2 h without adding any catalyst. A calibration graph for  $5 \times 10^{-3}$  M each of the aldehydes, was obtained by transferring (0.1–1.0 ml) aliquots in water to test tubes followed by the addition of 1.0 ml of the 0.1 M solution of Meldrum's acid (MA) in water. The mixtures were thermostated at 75 °C in a water bath for 2 h and then diluted to 10 ml with water, and the absorbance of the resulting yellow color was measured at the maximum wavelength of each aldehyde derivative.

The points on standard calibration curves each represent the outcome of three determinations. Table 4 shows a linear regression analysis of the data obtained from calibration graphs of the aldehydes tested from the relation  $A = a + bc$ . Fig. 4 shows the relationship between absorbance vs. concentration (calibration graph) for *p*-dimethylaminobenzaldehyde as an example.

In conclusion it is shown that the determination of aldehydes with Meldrum's acid efficiently occurs in water as a solvent without adding any catalyst, by heating at 75 °C for 2 h. Thus this reaction can be used to remove aldehydes from wastewater produced in the fine chemicals industry.

## Materials and Methods

### Apparatus

Visible absorption spectra were recorded on a Unicam SP 1800 recording spectrometer. 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.  $^1\text{H}$  NMR spectra were taken at 270 MHz using  $\text{CDCl}_3$  as a solvent.

### Reagents

All aromatic aldehydes used were of AR grade (BDH). The Meldrum's acid used was of AR grade (Aldrich). Chloroform (Analar) was used as

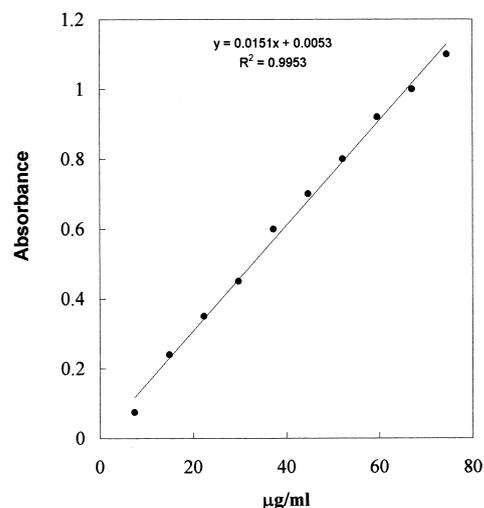


Fig. 4. The calibration graph for *p*-dimethylaminobenzaldehyde through its reaction with Meldrum's acid in water without catalyst.

a solvent. The standard solution of piperidine (E. Merck) was directly prepared in chloroform.

### Kinetic procedure

The rate of reaction of the aldehydes tested (*p*-dimethylamino-benzaldehyde, *p*-nitrobenzaldehyde, *p*-hydroxybenzaldehyde, *p*-methoxybenzaldehyde, *p*-chlorobenzaldehyde, and benzaldehyde) with MA in the presence of piperidine was followed by monitoring the increase in the absorbance of the product, at its wavelength of maximum absorption, with time.

Freshly prepared samples of aldehydes ( $5 \times 10^{-3}$  M), piperidine (0.1 M) and 0.1 M MA (0.1 M) in chloroform were allowed to equilibrate to 25 °C for 10 min in a thermostat. Mixing was carried out by withdrawing 0.5–2.0 ml aliquots of the aldehyde solution to 10 ml flasks containing 1.0 ml of 0.1 M piperidine, 1.0 ml of 0.1 M MA solution, and the appropriate volume of chloroform. A portion of the reaction mixture was transferred to a quartz

Table 4. Statistical analysis of the calibration graphs for the determination of some aromatic aldehydes by reaction with Meldrum's acid in water at 75 °C for 2 h without catalyst.

Aldehydes	$\lambda_{\text{max}}$ [nm]	Concentration range [ $\mu\text{g}/\text{ml}$ ]	$\epsilon$ [ $\text{l mol}^{-1} \text{cm}^{-1}$ ]	Slope (b)	Intercept (a)	$r$
<i>p</i> -Dimethylamino-benzaldehyde	445	7.45–74.5	2247.88	0.0150	0.0053	0.995
3,5-Dimethoxy-4-hydroxybenzaldehyde	365	9.1–91	1564	0.0086	0.002	0.992
<i>p</i> -Chlorobenzaldehyde	325	7.025–70.25	413	0.003	–0.001	0.975

cuvette placed in a thermostated (25 °C) cell compartment. A blank solution was similarly prepared without aldehyde and the absorbance readings were also recorded and followed as a function of time. Other set of runs were carried out in a similar manner using MA ( $5 \times 10^{-3}$  M) and aldehyde (0.1 M) solution.

Initial rates were determined by the method of initial rates [30, 31], 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 [30, 31].

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

$C_i$  and  $C_{\infty}$  are the initial and final concentrations of the colored reaction products respectively, calculated by using the molar extinction coefficients  $\epsilon$ ,  $A_i$  and  $A_{\infty}$  are the absorbencies of the colored species at the initial and the end of the reaction. Since both  $C_i$  and  $A_i$  are nearly equal to zero at the beginning of the reaction, the above equation reduced to:

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

The observed rate constants  $k_{\text{obs}}$  using excess MA, calculated from the initial rate ( $R_i$ ) values by dividing it by the concentrations of the aldehydes.

The method of initial rates was employed in order to avoid complications from product decomposition at high catalyst concentrations. Duplicate runs were made at each concentration. Preliminary reaction orders were determined from slopes of  $\log$  (initial rate) *versus*  $\log$  (concentration) plots. Because of the difficulty in estimating ionic strength in chloroform, the influence of ionic strength was not investigated.

The first order rate constants were also calculated from the plots of  $\log (A_{\infty} - A_t)$  *versus* time (where  $A_{\infty}$  and  $A_t$  are the values of the absorbance at the end of the reaction and at time  $t$  respectively) which are in good agreement with those values calculated from the initial rate method indicated above. The second order rate constants  $k_2$  calculated from the equation  $k_2 = k_{\text{obs}}/[\text{MA}]$ .

### Analytical Procedure

1.0 ml of Meldrum's acid solution (0.1 M) and 1.0 ml of a 0.1 M piperidine solution in chloroform were transferred into 10 ml volumetric flasks. 0.1–1.0 ml aliquots of stock solution ( $5 \times 10^{-3}$  M) of the aldehydes (*p*-nitrobenzaldehyde, *p*-hydroxybenzaldehyde, *p*-methoxybenzaldehyde, 3,5-dimethoxy-4-hydroxybenzaldehyde, *m*-nitrobenzaldehyde, benzaldehyde, *p*-chloro-benzaldehyde,  $10^{-3}$  M *p*-dimethylaminobenzaldehyde) was added.

The mixtures were thermostated at 50 °C in a water bath for 15 min and then diluted to 10 ml with chloroform. The absorbance of the resulting yellow color at the maximum wavelength of each aldehyde derivative was measured against an appropriate blank. The calibration graphs were constructed by plotting the final concentration of each aldehyde against the absorbance values. The points on standard calibration graphs each represent the outcome of three determinations.

### Preparation and analysis of reaction products

To a solution of MA (0.004 mol) in chloroform, aromatic aldehyde (0.004 mol) was added. To the reaction mixture 5 ml of 0.1 M piperidine were added. The reaction mixture was warmed at 50 °C for 5 min and left at 25 °C overnight. The crystals obtained were filtered off, dried and crystallized from chloroform. The physical properties, spectra and elemental analyses are given in Table 5.

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