Smart Solution Chemistry: Prolonging the Lifetime of *ortho*-Phthalaldehyde Disinfection Solutions

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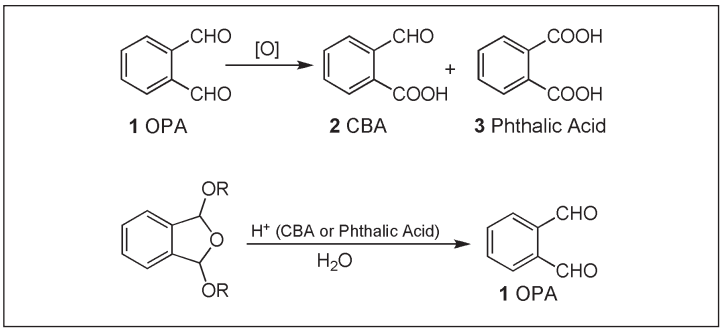

The oxidation of *ortho*-phthalaldehyde to phthalic acid in aqueous solutions can be remedied by the addition of various cyclic acetals, which, when reacted with phthalic acid, yields *ortho*-phthalaldehyde, thus prolonging the lifetime of the *ortho*-phthalaldehyde disinfection solution.

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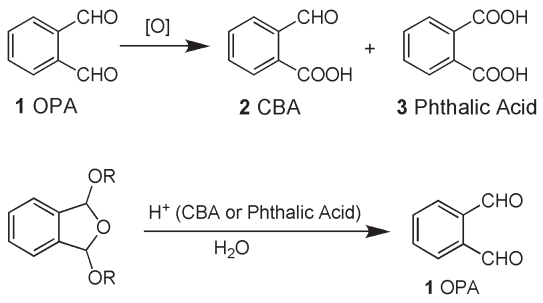
Introduction.

Dilute solutions of *ortho*-phthalaldehyde (OPA) have become preferred over glutaraldehyde for use in hospitals as high-level disinfectants for instrument processing [1]. The lifetime of OPA, **1**, in aqueous media is shortened by oxidation to 2-carboxybenzaldehyde (CBA, **2**) and phthalic acid (**3**) (Scheme 1). This decrease in shelf life can be overcome using "smart solution chemistry." As OPA is oxidized in aqueous environments, concentrations of **2** and **3** increase; by adding cyclic acetals to the solution, the increased concentrations of **2** and **3** can be used to replenish OPA concentrations. Treating a variety of cyclic acetals with phthalic acid in aqueous media readily hydrolyzed these acetals to OPA (Scheme 1). Varying the amount of acid or the pH of the solution allowed the rate of hydrolysis of the cyclic acetal to be controlled. Consequently, the addition of cyclic acetals to an aqueous solution of OPA leads to a "smart solution" that is capable of self replenishment. The ability of this solution to replenish OPA in aqueous solutions prolongs the shelf life and use life of the aqueous OPA solutions.

Scheme 1



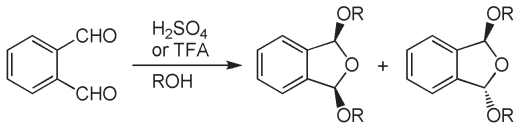
Consumption of OPA by oxidation to CBA and phthalic acid, and conversion of 1,3 dialkyloxyphthalan to OPA.

Results and Discussion.

In aqueous environments, OPA is slowly oxidized to CBA and phthalic acid (see Scheme 1). This oxidation can be easily followed by monitoring the pH and concentration of OPA in idle aqueous solutions. Over a three week period, the pH of the OPA solution decreased from a pH of 6.09 to a slightly more acidic pH of 5.16. The concentration of OPA dropped 10% within the first week. When used as a high-level disinfectant, this oxidation decreases both the shelf life and use life of the OPA solution. OPA is converted to phthalic acid when mixed with hydrogen peroxide at room temperature [2-3]. The potential for contamination of disinfectant solutions with hydrogen peroxide is a common problem in hospitals. Many times instruments are added to disinfection solutions after being in contact with hydrogen peroxide solutions. We have found that when a minimal amount (0.18 mmols) of hydrogen peroxide is added to 30 mL of a 0.5 wt% OPA solution (1.08 mmols), 80% of OPA is oxidized to phthalic acid in just 3 days.

The *ortho* arrangement of the two aldehyde groups in OPA favors the cyclic acetal form in aqueous alcoholic solutions. This cyclic acetal form could be used to protect the aldehyde groups. These 1,3-dialkyloxy cyclic acetals are easily prepared by treatment of OPA with either fuming sulfuric acid or trifluoroacetic acid [4] in the corresponding anhydrous alcohol (Scheme 2). Results for the formation of various 1,3-dialkyloxyphthalans are shown in Table 1.

Scheme 2



Formation of 1,3-dialkyloxyphthalans from OPA.

Table 1

Formation of various 1,3-dialkyloxyphthalans from OPA.

Alkyl Group	Acid	Time	% Yield
Methyl	H_2SO_4	4 h	92 [a]
Ethyl	H_2SO_4	6 h	92 [b]
Isopropyl	TFA	24 h	84 [a]
Isopentyl	TFA	24 h	80 [a]

[a] GC Yield; [b] Isolated Yield.

The conversion of 1,3-dialkyloxyphthalans to OPA was first investigated by monitoring the rate of this conversion after the addition of various equivalents of phthalic acid (Scheme 1) [5]. By varying the amount of phthalic acid, the cyclic acetal can be converted to OPA in time periods ranging from a few hours to a few weeks (Table 2). Reactions were stirred at room temperature and concentrations were monitored by GC/MS. Conversion of 1,3-dimethoxyphthalan or 1,3-diethoxyphthalan to OPA with the addition of 0.1 equivalents of phthalic acid was very fast, with conversion occuring in 2 days or less. By adding smaller amounts of phthalic acid, the rate of conversion is slower and the overall conversion time can be increased to between 13 and 24 days.

The rate of conversion of 1,3-dialkyloxyphthalans to OPA can be controlled by varying the pH of the initial solution. Solutions were prepared by dissolving 1,3-diethoxyphthalan in distilled water which was previously adjusted to an initial pH of 3.5, 5.4, 6.9, or 10.8 with either HCl or NaOH (Table 3). Entry 1 shows that at a pH of 3.5, virtually all of the 1,3-diethoxyphthalan is converted to OPA after only 4 days, while at pHs of 5.4 and 6.9 (entries 2 and 3), it takes 20 days to completely convert 1,3-diethoxyphthalan into OPA. At pH 10.8, 1,3-diethoxyphthalan converted to OPA with 89 days required to hydrolyze 95% of the acetal. These different rates of conversion can be useful for prolonging the shelf life and use life of OPA.

Table 2

Conversion of 1,3-dialkyloxyphthalans to OPA by the addition of various equivalents of phthalic acid

Alkyl Group	Acid Equivalents	Conversion Time [a]
Methyl	0.1	2 days
Methyl	0.001	13 days
Ethyl	0.1	1 day
Ethyl	0.05	2 days
Ethyl	0.01	6 days
Ethyl	0.001	24 days

[a] Time required to convert >95% of 1,3-dialkyloxyphthalan to OPA by GC/MS

Table 3

Conversion of 1,3-diethoxyphthalan to OPA at various pHs.

Entry	pH [a]	Conversion Time
1	3.5	4 days
2	5.4	20 days
3	6.9	20 days
4	10.8	89 days

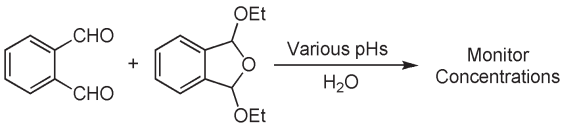
[a] pH indicates the initial pH of the solution.

In basic solutions, the conversion of the cyclic acetal is very slow, thus generating a small amount of OPA over a long period of time. This is desirable if the solution is idle for long periods of time, and the only concentration loss is due to oxidation of OPA to phthalic acid. Alternatively, in acidic environments, the cyclic acetal is converted rapidly to OPA. This is desirable if the solution is being heavily used and the concentration of OPA is diminishing due to its use as a disinfectant.

In order to further evaluate the effect of pH on the solution, mixtures of OPA and 1,3-diethoxyphthalan were evaluated at various pHs in non-buffered solutions (Scheme 3). The purpose of these experiments was to determine what affect the presence of OPA in solution and subsequent oxidation to phthalic acid has on the rate of hydrolysis. Solutions were prepared at concentrations of 0.037 M OPA and 0.005 M 1,3-diethoxyphthalan in distilled water which was previously adjusted to a wide range of initial pH values with either NaOH or HCl. Entries 1 thru 3 in Table 4 show that all 1,3-diethoxyphthalan is converted to OPA in six days or less in acidic aqueous media in the presence of OPA. At more neutral pHs (entries 4, 5 and 6 in Table 4) conversion times vary from as little as 8 days up to 41 days. The conversion of 1,3-diethoxyphthalan to OPA is generally quicker in the presence of OPA due to the simultaneous oxidation of OPA to phthalic acid, which decreases the pH

as more CBA and phthalic acid are formed. In basic environments (entries 8 and 9), 1,3-diethoxyphthalan is still present even after 91 days at room temperature. By varying the initial pH of the solution, the rate of conversion of 1,3-diethoxyphthalan to OPA can be controlled.

Scheme 3



Evaluation of OPA, 1,3-diethoxyphthalan mixtures at an assortment of pHs.

Table 4
Conversion of 1,3-diethoxyphthalan to OPA in aqueous solutions at a variety of pHs.

Entry	pH [a]	Conversion Time
1	3.03	1 day
2	3.96	5 days
3	5.08	6 days
4	6.03	8 days
5	6.95	23 days
6	8.04	41 days
7	8.9	54 days
8	9.84	> 84 days
9	11.01	> 84 days

[a] pH indicates the initial pH of the solution.

A mixture of cyclic acetals (methyl 0.02 *M*, ethyl 0.02 *M*, and isopropyl 0.02 *M*) was monitored to evaluate their different rates of conversions to OPA in aqueous environments with the addition of 0.01 equivalents of phthalic acid (Scheme 4). Table 5 shows that the relative percentages of 1,3-dimethoxyphthalan and 1,3- diethoxyphthalan drop by 56.3% and 53.5%, respectively, in the first 24 hours, while the relative percentage of 1,3-diisopropoxyphthalan drops by as much as 73.5%. All of the cyclic acetals are readily converted to OPA in just 48 hours.

In conclusion, we have demonstrated that the addition of cyclic acetals to an aqueous solution of OPA, leads to a self-replenishing "smart solution" with no adverse effects on the OPA solution. The ability of cyclic acetals to be used as OPA precursors in aqueous disinfection solutions prolongs both the shelf life and use life of the aqueous OPA solutions.

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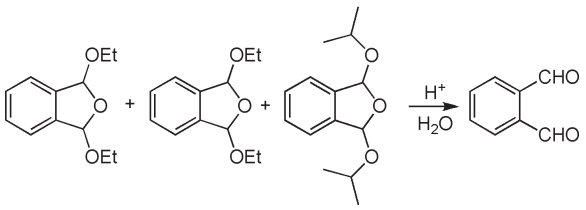
Scheme 4



Evaluation of the formation of OPA from a mixture of acetals.

Table 5
Formation of OPA from a solution of mixed acetals.

Time	Methyl [a]	Ethyl [a]	Isopropyl [a]	OPA [a]
1 h	42.6	32.5	23.8	1.1
24 h	18.6	15.1	6.3	60
48 h	4.4	0.8	2.8	92

[a] Values reported are relative percents of each component in solution determined from the GC/MS chromatogram. Each component had a starting concentration of 0.02 *M*.

General Procedure.

OPA (136 mg, 0.829 mmol) was dissolved in 4.2 mL of pure anhydrous ethanol and fuming sulfuric acid (4 drops) was added to the solution dropwise. The reaction was then stirred at room temperature for 6 h and monitored by GC/MS. The reaction was quenched with the addition of a few drops of saturated aqueous sodium bicarbonate. The mixture was then extracted with ether and the organic phase was washed with H_2O and brine. The organic layer was collected and dried over $MgSO_4$. Pure 1,3-diethoxyphthalan was isolated by silica gel chromatography (hexane:EtOAc, 15:1) as a colorless oil (160 mg, 92%).

REFERENCES AND NOTES

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[5] The concentration of all 1,3-diethoxyphthalan solutions was 0.03 *M* in distilled water for each of the acid and pH studies.