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Controlled Release of Covalently Bound Organic Molecules by Slow Hydrolysis for Potential Biocide Applications[†]

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A study of the slow hydrolysis of labile acetal groups by low concentrations of lactic acid to release the active molecules is reported. A prototype molecule containing cyclic acetal groups, dimethyl-2,3-O-benzylidene-L-tartrate (DMTAc) and the same molecule incorporated as a pendant group in a polyamide were studied for their hydrolysis by low concentrations of lactic acid. The release of benzaldehyde during slow hydrolysis is monitored by UV-vis and ^{1}H-NMR spectroscopy. This study is very useful to ultimately design and synthesize a polymer with covalently bound insecticidal/anti-microbial/anti-fungal materials for the development of controlled release formulations.

Keywords: slow hydrolysis; lactic acid; controlled release; biocide

1 Introduction

There has been tremendous interest in controlled release formulations for their potential in reducing the use and impact of pesticides/insecticides in the environment. Controlled release of a desired pesticide/insecticide may be achieved by covalently attaching them either as a pendant group or as a part of the polymer backbone through a labile link, to regenerate the biocide by hydrolysis or by enzymatic degradation. The controlled release of the covalently bound active material is dependent on the rate of chemical or biological cleavage of the polymer-active material bonds. This could be normally achieved by acid-base hydrolysis. Schacht and coworkers have synthesized a polyamide containing the pesticide, 2,6-dichlorobenzaldehyde as pendant group through a labile acetal group and studied the controlled release of the pesticide by acid hydrolysis (1). Polymeric pesticides have also been investigated for their potential impact on environmentally safe, efficient and economical crop protection (2).

As part of a project to utilize enzymatic method to synthesize polymers with insecticides as active pendant groups, one of our objectives was to synthesize polymers for the slow release of active molecules upon hydrolysis by human sweat. This could potentially be achieved due to the presence of lactic acid in sweat. However, before taking up multi-step synthesis of incorporating active molecules, we planned to study a simple molecule containing groups that can be easily hydrolyzed by low concentrations of lactic acid. We carried out a detailed study which showed that lactic acid at concentrations as low as 0.1% in water can hydrolyze the acetal groups and release the pendant active molecules which could act as biocides. Due to the low PKa of lactic acid and low percentage (~0.1%) in sweat, it can only hydrolyze chemical bonds slowly, which is desirable for these applications. We monitored by UV-visible absorption and NMR spectroscopy, the hydrolysis process in a monomer containing an acetal group. we then synthesized a modified polyamide or nylon (3, 6) with simple acetal groups linking to a benzene ring. In this paper, we present the synthesis and characterization of the polymer and hydrolysis studies on the monomer and polymer containing acetal groups.

2 Experimental

2.1 Hydrolysis of Acetal Groups

The acid-base hydrolysis of simple and substituted benzaldehyde acetals and their reaction kinetics are well known in

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[†] Dedicated to the memory of Professor Sukant K.Tripathy.

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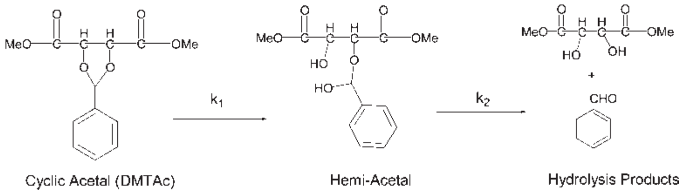
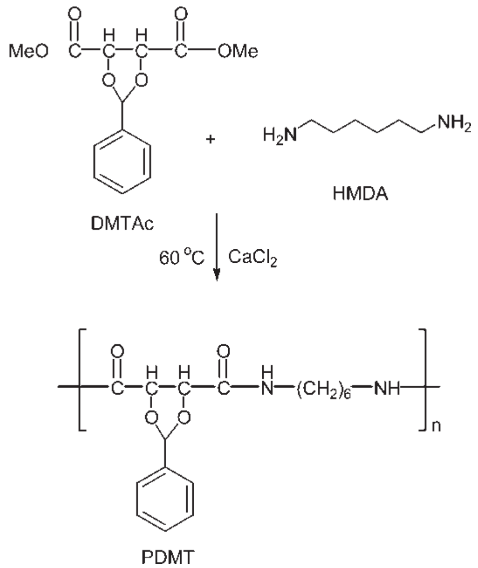


Fig. 1. Hydrolysis of DMTAc.

the literature (3–4). The hydrolysis of acetals is generally accepted to occur via three stage reaction mechanism: (a) generation of an oxocarbonium ion, (b) hydration of this cation to form a hemi acetal, and (c) decomposition of the hemi-acetal into alcohols and aldehydes. We chose a commercially available cyclic acetal, dimethyl-2,3-O-benzylidene-L-tartrate (DMTAc) (Figure 1) for our hydrolysis study purposes. This particular acetal was chosen because it could be a suitable monomer for making the polyamide with a diamine either chemically or biocatalytically. We have monitored the hydrolysis of this cyclic acetal by UV-visible absorption and NMR spectroscopy.

2.2 *Synthesis of Polyamide with Pendant Acetal Groups*

The commercially available diester, DMTAc was added to a solution of hexamethylenediamine (HMDA) (1:1 ratio) in methanol and catalytic amount of $CaCl_2$ was added (Scheme 1). The mixture was stirred at 60°C for 24 h. The solvent was evaporated to dryness under vacuum to obtain a light yellow colored crystalline compound. The polymer, PDMT was purified by a precipitation method from methanol. The polymer was highly soluble in chloroform and partially soluble in THF and methanol and insoluble in hexane.



Sch. 1. Synthesis of PDMT.

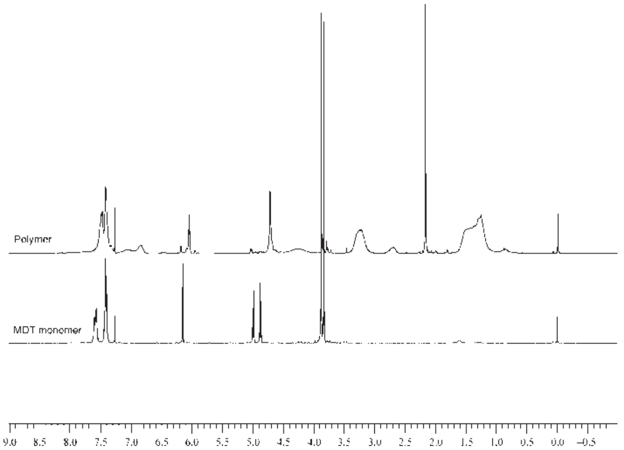


Fig. 2. ^{1}H-NMR spectra of the monomer, DMTAc and the polymer, PDMT.

^{1}H-NMR spectrum of the DMTAc monomer and polymer are shown in Figure 2. As can be seen from the ^{1}H-NMR spectrum, the ester methyl protons at 3.7 ppm have disappeared in the product, the ortho protons on the benzene ring shifted upfield due to the change from ester to amide environment. ^{13}C-NMR: δ (ppm) = 169 (carbonyl); 137–128 (aromatic); 106 (benzylidene), 80 (ethylinic); 40–25 (aliphatic on HMDA). GPC, M_n: 3,000 Da.

3 Results and Discussion

3.1 *UV-Visible Absorption Study*

We first prepared a stock solution of DMTAc (Aldrich, 1.95×10^{-2}M) in methanol and recorded its absorption spectrum. We have also measured the absorption spectrum of benzaldehyde in methanol. The absorption maximum and extinction coefficients of DMTAc and benzaldehyde (Aldrich) were found to be 284 nm ($\varepsilon = 8$ $M^{-1}cm^{-1}$) and 290 nm ($\varepsilon = 680$ $M^{-1}cm^{-1}$), respectively. The large difference in extinction coefficients is advantageous for studying the hydrolysis of DMTAc. The samples for hydrolysis monitoring were prepared using the stock solution of DMTAc and different concentrations of lactic acid (Aldrich, 85%, 11.32 M) as follows: (1) 0.4 ml of DMTAc was mixed with 2.5 ml of 10% lactic acid (final concentration of DMTAc = 2.7×10^{-3} M and lactic acid = 0.9 M); (2) 0.4 ml of DMTAc and 2.5 ml of 0.1% lactic acid (9×10^{-3} M) and the absorption maxima at 284 nm was monitored at frequent intervals. The absorption spectra of both samples are shown in Figure 3 (a–b). As can be seen from the spectra, the absorbance at around 288 nm increased significantly due to the release of benzaldehyde after complete hydrolysis by lactic acid. This suggests that lactic acid even in low concentrations can indeed hydrolyze the acetal groups.

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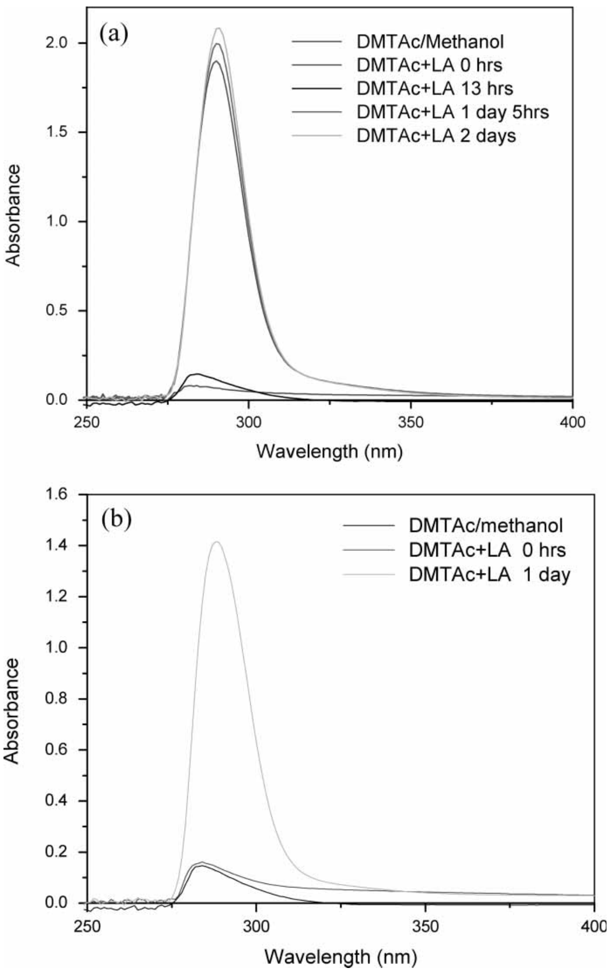

Fig. 3. UV-Visible absorption study of hydrolysis of DMTAc by (a)10% lactic acid and (b) 0.1% lactic acid.

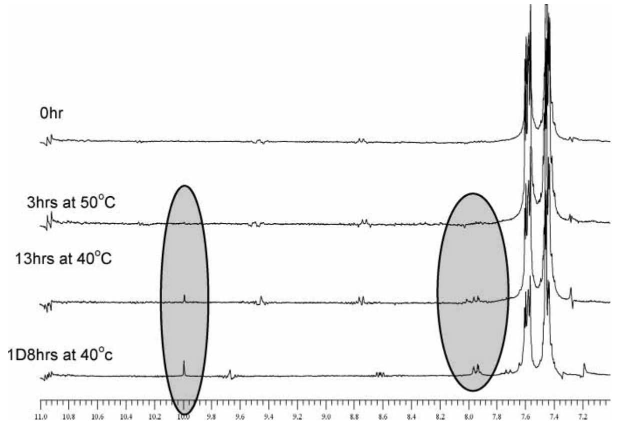

Fig. 4. ^{1}H-NMR spectra of DMTAc during lactic acid hydrolysis. The peaks of aldehydic and aromatic protons of benzaldehyde which was released by hydrolysis are highlighted.

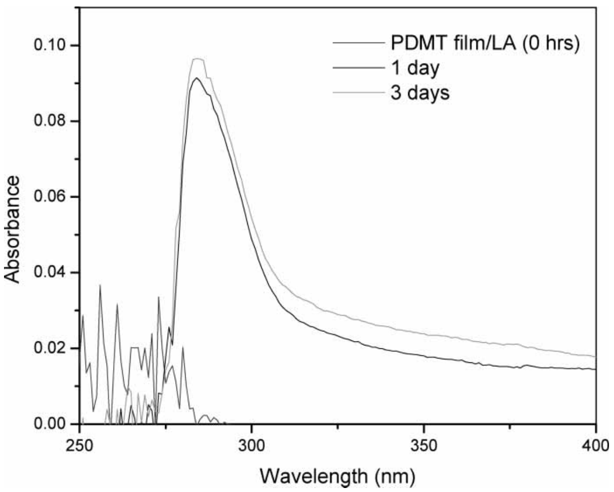

Fig. 5. UV-visible absorption spectra of PDMT film in 1% aqeous lactic acid.

3.2 ^{1}H-NMR Study

Although UV-visible spectra indicated the hydrolysis clearly, it was felt essential to gather other evidence to show the presence of benzaldehyde in the hydrolyzed products. We thus monitored the hydrolysis of DMTAc by ^{1}H-NMR spectroscopy. The sample for NMR measurements was prepared by dissolving DMTAc in 0.5 ml CD_3OD and 0.05 ml D_2O, 0.1 ml of lactic acid was added to the solution. (final concentration of lactic acid was 1.74 M or 15%). D_2O was added to enhance the ionization of lactic acid in the solution. As can be seen clearly from the NMR spectrum (Figure 4), the appearance of the benzaldehyde proton at $\delta = 10$ ppm and its aromatic protons at $\delta = 7.7–8$ ppm indicates that the slow hydrolysis is occurring.

3.3 Hydrolysis of PDMT Films by UV-Visible Absorption

The monitoring of hydrolysis of PDMT polymer in the solid state was also studied. The films of PDMT were prepared from chloroform solution and dried under vacuum overnight. The films were immersed in 1% aqueous lactic acid and the absorption spectra at different times were recorded. As can be seen from Figure 5, the aqueous solution has no absorption in the beginning and after keeping the solution with films at 40°C for a day, a benzaldehyde peak appeared at 288 nm. This observation could be attributed to the release of benzaldehyde from the surface of PDMT films.

4 Conclusions

In this study, it was demonstrated that lactic acid in very low concentrations or human sweat can hydrolyze the labile acetal groups either in the monomers or in the polymers. Thus this study provides a significant approach and useful methodology for further investigation on covalently linked specific active molecules to prepare other controlled release insecticide/anti-microbial/anti-fungal formulations for agriculture and civilian applications.

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