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Degradation study of unsaturated anhydrides by reversed-phase high-performance liquid chromatography

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Abstract

In this report, the applicability of reversed-phase high-performance liquid chromatography (HPLC) to the degradation and kinetic studies of unsaturated anhydrides is explored. Under the appropriate HPLC conditions, the separation and determination of anhydrides were achieved. After comparing their stabilities in methanol, acetonitrile and pure water, the hydrolytic behavior of anhydrides was further evaluated using varying proportions of aqueous phase and acidity for hydrolysis. On the basis of a nucleophilic-attack pathway, the stability and hydrolytic velocity of the anhydrides were compared. The results showed that the hydrolytic processes of the anhydrides could be described with first-order equations, and the corresponding hydrolytic rate constants were calculated from the experimental data. © 1998 Elsevier Science B.V.

Keywords: Kinetic studies; Stability studies; Anhydrides

1. Introduction

Organic anhydrides are important in the chemical industry. They are used as crosslinking agents, curing agents and co-reagents in organic synthesis [1,2]. In pharmaceutical preparations, they are useful for improving the bioavailability of polymeric drugs [3]. Anhydrides are also used in silk fabric production, as dying assistants [4], and in food science to remove cholesterol and other hydroxyl compounds from fats and oils [5]. The conversion of anhydrides during the processing of drinking water [6] and their effects on human health [7] have also been reported.

Due to their varied uses, the analysis of organic anhydrides is of importance, and has attracted some attention. Published procedures for their measurement have included spectroscopic techniques [8,9], titration [10], colorimetry [11], gas chromatography [12] and liquid chromatography [5].

Among the aforementioned techniques, high-performance liquid chromatography (HPLC) was claimed to be an ideal technique for the analysis of anhydrides, including both indirect and direct determination [5,13,14]. In the indirect analytical methods, hydrolysis or alcoholysis were conducted, and anhydrides were detected in their acidic or esterific forms [5,14]. In the direct methods, HPLC analyses of anhydrides were usually performed under normal-phase conditions. Patterson and Escott [13] have studied some cyclic anhydrides using acetonitrile–

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tetrahydrofuran–hexane mixtures as the mobile phase.

A unique property of anhydrides is their susceptibility to hydrolysis in aqueous solutions and alcohols [5,12–14]. Thus, it seems that normal-phase HPLC, which uses non-aqueous mobile phases, is a good choice. Practically, however, it is rather difficult to conduct analytical experiments under absolutely non-aqueous conditions, as even the commonly used analytical-grade reagents contain 0.01% (v/v) water. Therefore, it is of practical interest to develop HPLC methods in which an aqueous mobile phase can be used for the analysis of anhydrides. Recently, Domb [15] analysed some aliphatic and aromatic anhydrides and their conjugate acids by HPLC using an aqueous mobile phase. After the stability of anhydrides was assessed in acetonitrile–water mixtures (aqueous phase proportions $\leq$50%), quantitative analysis was performed for those anhydrides (benzoic and lauric anhydrides) that did not undergo hydrolysis during the analytical process.

For the purpose of quantitative analysis, one usually needs to know how susceptible anhydrides are to degradation and how fast they degrade. Unfortunately, quantitative descriptions referring to this aspect of anhydrides are not well documented.

HPLC is also an effective approach in chemical kinetics studies. Mizrotsky and Grushka [16] followed the hydrolysis of aspirin by the disappearance and appearance of the relevant peaks. Hisakazu et al. [17] investigated the degradation of acetylsalicylsalicylic acid and salicylsalicylic acid in aqueous solution, and simulated their kinetic processes by pseudo-first-order equations.

The aim of this work was to explore the applicability of HPLC in the study of the degradation of anhydrides and to quantitatively analyse anhydrides in aqueous media. For this purpose, maleic, citroconic, dimethylmaleic, crotonic and methacrylic anhydrides were used as model compounds because of their environmental and industrial importance [7,18,19]. The appropriate chromatographic conditions were developed for the separation and determination of these anhydrides. Their degradation behaviours in acetonitrile, methanol and pure water were compared. After evaluation of the effect of the proportion and acidity of the aqueous phase on their hydrolysis, the hydrolytic kinetics of the anhydrides were compared.

2. Experimental

2.1. Instrumentation

The liquid chromatography system used in this study comprised a Jasco (Tokyo, Japan) PU-980 HPLC pump, equipped with a 5-μl loop, a Rheodyne (Cotati, CA, USA) injection valve, an Applied Biosystems (Foster City, CA, USA) 785A UV–Vis detector (operated at 220 nm) and a Waters (Milford, MA, USA) 746 data acquisition module. The column was an Upchurch Scientific (Oak Harbor, WA, USA) narrow-bore C_{18} cartridge (5 μm, 150×2.0 mm I.D.).

A Shimadzu (Kyoto, Japan) UV-160 UV–Vis recording spectrometer and a Metrohm (Sweden) 691 pH meter were also used.

2.2. Chemicals and standards

Ammonium phosphate [$(NH_4)_2HPO_4$] was purchased from Merck (Darmstadt, Germany), 85% phosphoric acid was obtained from Carlo Erba (Italy), tetrabutylammonium dihydrogenphosphate (TBADP) and HPLC-grade acetonitrile (CH_3CN) were purchased from J.T. Baker (Phillipsburg, NJ, USA).

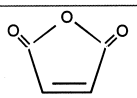
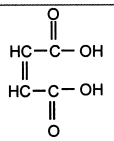
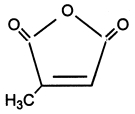
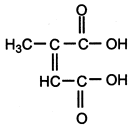
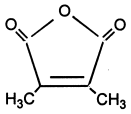
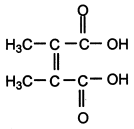
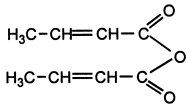
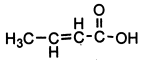
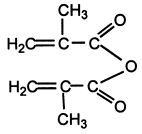
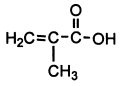
Dimethylmaleic anhydride (DMMA) and acid, maleic anhydride (MALA), crotonic acid and methacrylic acid were obtained from Fluka (Buchs, Switzerland), citroconic anhydride (CICA) and acid, crotonic anhydride (CRTA), maleic acid and methacrylic anhydride (MEAA) were supplied by Aldrich (Milwaukee, WI, USA). Table 1 shows the structures of the above anhydrides and their conjugate acids. MALA, CICA and DMMA are cyclic anhydrides.

The stock solutions of anhydrides (5 m*M* concentration) were prepared in CH_3CN weekly. Their conjugate acids were also prepared, in water, at the same concentration. Deionized water, with a typical resistivity of greater than 18 mΩ/cm, was obtained from a Millipore Milli-Q reagent water system (Bedford, MA, USA).

2.3. Degradation of anhydrides and HPLC analysis

Degradation (alcoholysis or hydrolysis) of anhy-

Table 1
Structure of anhydrides and their conjugate acids

Anhydride	Structure	Acid	Structure
MALA		MAL	
CICA		CIC	
DMMA		DMM	
CRTA		CRT	
MEAA		MEA	

drides was conducted by dissolving the corresponding stock solutions according to the specified conditions. Hydrolysis of anhydrides under different acidity conditions was carried out by mixing the anhydride stock solutions with 10 m*M* $NH_4H_2PO_4$–$(NH_4)_2HPO_4$ buffer solution (pH≤7), 10 m*M* $(NH_4)_2HPO_4$ (pH 8.0) or 10 m*M* NaOH solution (pH 12).

To study the degradation behavior and the kinetics of the anhydrides, the HPLC mobile phase used was composed of a CH_3CN–$NH_4H_2PO_4$–$(NH_4)_2HPO_4$, pH 2.5, buffer solution (30:70, v/v). For simultaneous separation and determination, the mobile phase used was a mixture of 10 m*M* $NH_4H_2PO_4$–$(NH_4)_HPO_4$, pH 2.5 (95:5, v/v) and 10^{-4} *M* TBADP–MeCN (95:5, v/v). Separation was performed at room temperature and a flow-rate 0.18 ml/min. Samples (5 μl) were injected for analysis. Plots of the percentage anhydride vs. time were generated to evaluate the degradation, hydrolysis and stability of the anhydrides.

3. Results and discussion

3.1. Determination and separation

Preliminary experiments showed that all of the anhydrides and their conjugate acids had very similar absorbance curves. Their UV absorbance was in the range 205–235 nm when CH_3CN was used as the solvent. Therefore, a medium wavelength of 220 nm was used in the following investigations for the determination of anhydrides and their conjugate acids.

Anhydrides are susceptible to water and alcohols [20]. When media containing methanol, or water, are used, degradation of anhydrides will occur. Obviously, hydrolysis of anhydrides will also be expected during any HPLC analytical process if aqueous mobile phase is used. Therefore, the variation in the total concentration of any particular anhydride is determined by its hydrolysis off-column (before HPLC analysis) and on-column (during analysis). Both processes are important; the latter, in particular, can cause quantitative problems.

The mobile phase made up of $NH_4H_2PO_4$–$(NH_4)_2HPO_4$ and CH_3CN was used in this work to resolve anhydrides and their degradation products. The proportion of the aqueous phase in the mobile phase was studied over a wide range (0–95%). It was found that increasing the proportion of aqueous phase (%v) in the mobile phase caused prolonged retention for anhydrides and decreased anhydride–acid ratios (measured by peak areas). A mobile phase containing less than 35% (v/v) CH_3CN provided baseline separation for the anhydrides and their degradation products. Typical chromatograms of the five anhydrides and their degradation products are shown in Fig. 1. As can be seen, two main peaks are observed in each chromatogram. The on-column hydrolysis of anhydrides was indicated by the 'tailing' of the acid peaks in the chromatograms, e.g. for MALA, CICA and DMMA. From their increasing retention times, the relative polarity of the five anhydrides was deduced to decrease in the order MALA (strongest)>CICA>DMMA>CRTA>MEAA (weakest). Moreover, the relatively high anhydride–acid ratios show that CRTA and MEAA are more stable than the other anhydrides.

In order to minimize the hydrolysis of anhydrides during the HPLC separation, the mobile phase with

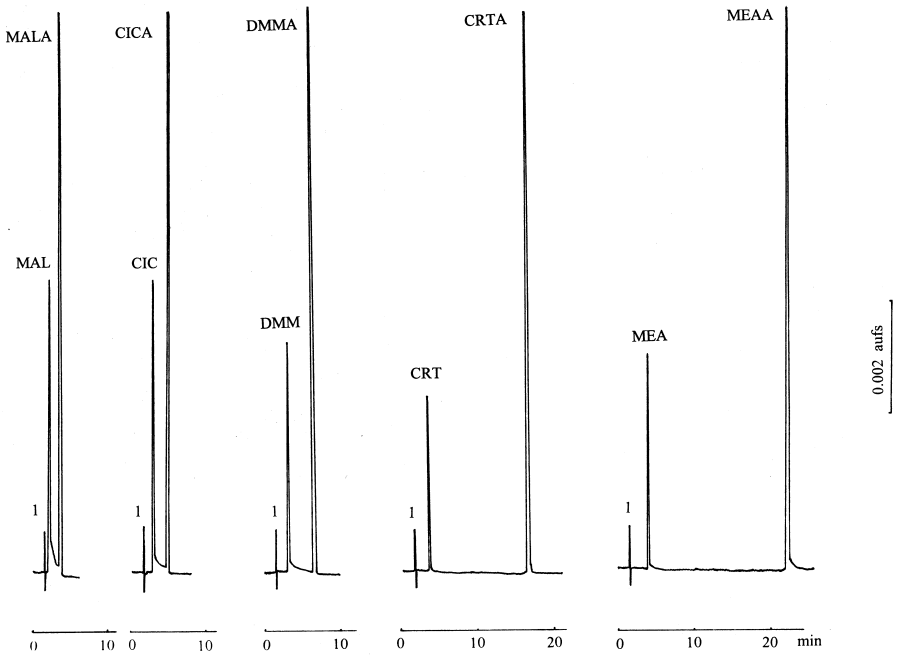


Fig. 1. Chromatograms of anhydrides and their conjugate acids. HPLC conditions: C_{18} column (5 μm, 150×2.0 mm I.D.); Mobile phase, 10 m*M* $NH_4H_2PO_4$–$(NH_4)_2HPO_4$, pH 2.5–CH_3CN (70:30, v/v); flow-rate, 0.18 ml/min; detection, 220 nm; room temperature. Anhydrides were prepared in CH_3CN.

the least amount of aqueous phase was used, provided that the anhydrides could be separated from their degradation products. Simultaneously, in order to compare the stability and degradation behaviors among the anhydrides, a constant mobile phase was required for separation. In this work, a mixture of buffer solution–CH_3CN (30:70, v/v) was found to be appropriate and this was used as the mobile phase in the subsequent experiments. A buffer solution of low pH was needed in the mobile phase, to obtain symmetrical and sharp peaks for the acids.

3.2. Degradation of anhydrides

The degradation of anhydrides was studied in pure CH_3CN, water and methanol. Results showed that all of the anhydrides of interest were stable in CH_3CN. In water, hydrolysis occurred and the anhydrides were converted to acids. In methanol, due to methanolysis, ester and acid were produced, as is well known [20]. Fig. 2 shows typical chromatograms generated from the methanolysis of CICA and CRTA. It was observed that the esters were eluted between the corresponding acids and anhydrides.

3.3. Hydrolysis of anhydrides

Since both off-column and on-column processes account for the total hydrolysis of anhydrides, in order to calculate the net amount of hydrolyzed anhydride under different hydrolytic conditions, correction is required to eliminate the contribution from the hydrolysis of anhydrides from the on-column process. Because the mobile phase used in all experiments was kept constant and anhydrides were stable in CH_3CN, we first injected the anhydride solution in CH_3CN under the working HPLC conditions. Then, the hydrolyzed amount of anhydrides from on-column hydrolysis could be derived by comparing the obtained peak areas of their acidic forms with those of standard solutions. Because the total amount of acid generated was the sum of that from off-column and on-column processes, the net amount of acid from the former could be calculated. Consequently, the amount of hydrolyzed anhydrides

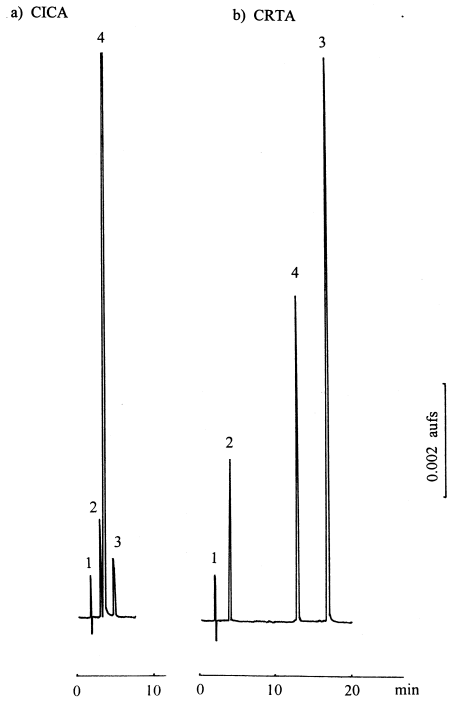


Fig. 2. Chromatograms generated on methanolysis of CICA and CRTA; (a) 2=CIC, 3=CICA; (b) 2=CRT, 3=CRTA. Peak 1, solvent; peak 4, the corresponding ester of the anhydride. HPLC conditions are the same as for Fig. 1.

under different hydrolytic conditions could be obtained from their hydrolytic equations and the original concentrations.

Because the proportion of aqueous phase and the acidity of the hydrolytic conditions play important roles in the hydrolytic process, their influence was investigated in detail.

3.4. Effect of the proportion of aqueous phase on hydrolysis

Fig. 3a,b illustrate the hydrolysis of anhydrides in different aqueous–CH_3CN mixtures. On increasing the proportion of aqueous phase, i.e. from 5 to 100%, the anhydrides underwent hydrolysis faster, as expected. MALA is the most susceptible anhydride, and its existence could not be detected after 20 min under conditions of >50% aqueous phase. However, its hydrolysis slowed down on decreasing the proportion of aqueous phase, e.g., 90% MALA could be detected after 30 min when the percentage of aqueous phase was 5%. CICA has a similar structure to MALA, except for a β-substituted methyl group. It is the second most reactive anhydride. It also underwent hydrolysis very fast under conditions where there were higher proportions of aqueous phase. DMMA, with two β-substituted methyl groups, was the slowest of the three cyclic anhydrides to undergo hydrolysis.

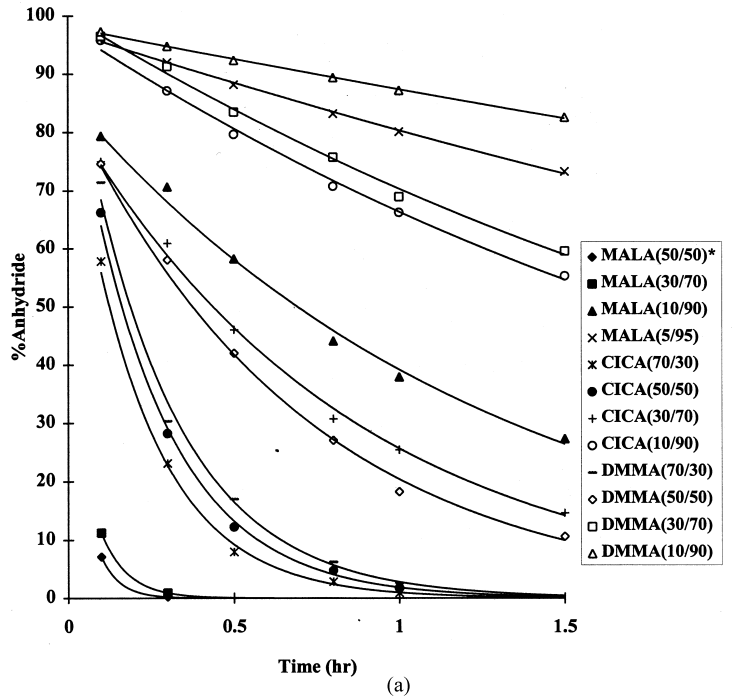
Compared to the cyclic anhydrides, both CRTA and MEAA underwent hydrolysis slower, indicated by their much longer existence, denoted by times of hydrolysis and higher anhydride–acid ratios. Hydrolysis was very slow when the proportion of aqueous phase was below 30% (Fig. 3b). The amount of MEAA that was hydrolyzed was less than 2% in the first 30 min; while for CRTA, it was less than 0.5%. In other words, if a standard error of 5% is acceptable for practical applications, the quantitative analysis of CRTA and MEAA is feasible under the present reversed-phase HPLC conditions, without the need to correct for on-column hydrolysis.

3.5. Effect of pH on the hydrolysis of anhydrides

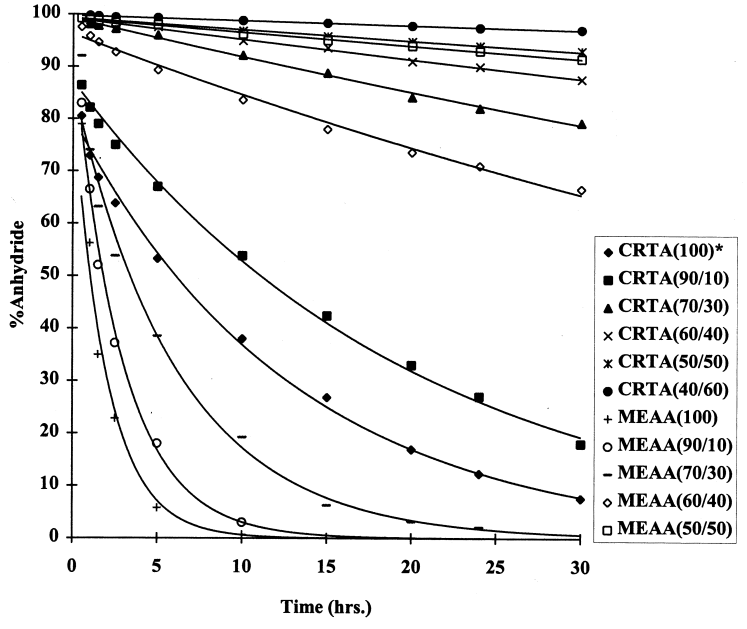
The effects of acidity on the hydrolysis of anhydrides were evaluated at different pH values, i.e. pH 2.5, 4.0, 5.6, 7.0, 8.0 and 12.0. From the % anhydride vs. pH curves of CICA and CRTA (Fig. 4), we found that the least hydrolyzing medium for all of the anhydrides of interest was at neutral pH. Increasing or decreasing the pH of the solution resulted in faster hydrolysis. Under strongly basic conditions (pH 12), both CICA and CRTA were almost completely converted to their conjugate acids within 18 min. Differences were noticed for the cyclic anhydride (CICA) and the non-cyclic anhydride (CRTA). The stability of CICA did not extend beyond 1 h over the range of pH values studied, whereas the hydrolysis of CRTA was negligible at neutral pH. Similar results to those for CICA and CRTA were obtained for MALA and DMMA, and MEAA, respectively.

3.6. Stability and hydrolytic velocity of anhydrides

The stability and hydrolytic behavior of the anhydrides can be explained by their hydrolytic pathways. As is known, the hydrolysis of anhydrides



(a)



(b)

Fig. 3. Effect of the proportion of aqueous phase on hydrolysis. HPLC conditions are the same as for Fig. 1. Figures in brackets denote proportions of CH_3CN and water, respectively.

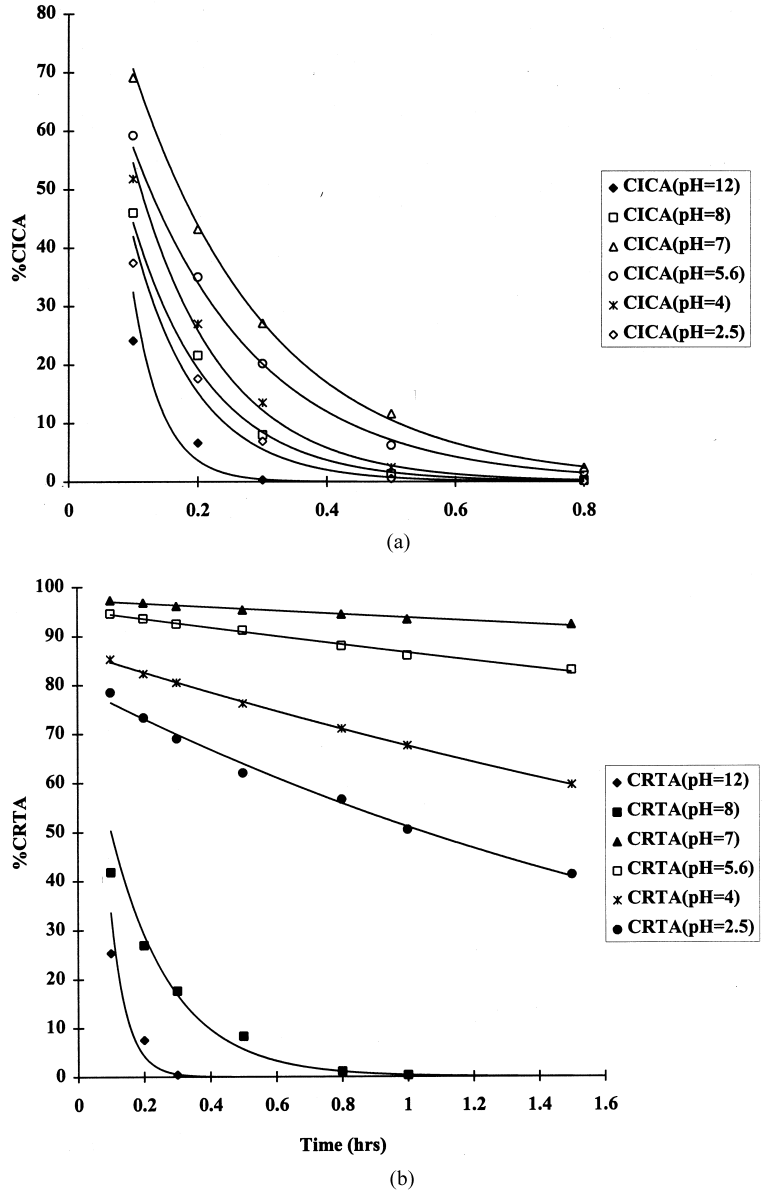


Fig. 4. Effect of pH on hydrolysis. HPLC conditions are the same as for Fig. 1.

follows the nucleophilic substitution pathway [21]. When anhydrides undergo nucleophilic substitution reactions at the carbonyl group, two steps are involved. The first step is attack on the anhydride by the nucleophile at the carbonyl carbon, which leads to localization of the electrons of the π bond on the oxygen atom in a tetrahedral intermediate. The second step is the recovery of the carbonyl group when a leaving group is lost. In basic, and neutral or acidic solutions, the hydroxide ion or water molecule acts as the nucleophile, respectively. Because the hydroxide ion has stronger nucleophilicity than the water molecule, more rapid hydrolysis of anhydrides is observed in basic solutions than in neutral or acidic solutions. It should be noted that the difference in hydrolytic velocity between neutral and

acidic conditions is that the carbonyl oxygen atom of anhydrides, in the latter, will be protonated prior to hydrolytic reaction, and this results in an increase in the electrophilicity of the carbonyl group and, subsequently, the hydrolytic velocity [21], as indicated by the % anhydride vs. pH curves in Fig. 4. Under conditions of constant pH, a higher proportion of aqueous phase means a higher water concentration, so rapid hydrolysis should also be feasible. The differences in the molecular structures of anhydrides also account for their stability and hydrolytic velocity. For example, when compared with the cyclic CRTA and MEAA, rapid hydrolysis of the cyclic anhydrides maybe attributed to their being capable of forming stable tetrahedral intermediates, resulting in the higher velocities in the first step of the nucleophilic pathway and, consequently, their hydrolytic velocities. Among the three cyclic anhydrides, electrophilicity at the carbon atom of the carbonyl group decreases from MALA to CICA to DMMA, with an increase in the number of substituted methyl groups [20]. As a result, the hydrolytic velocities were also observed to decrease correspondingly. Between CRTA and MEAA, a possible reason for the faster hydrolysis of the latter is that the isopropylene in MEAA acts as a better leaving group than the propylene of CRTA.

The stability of the anhydrides was found to increase in the following order: MALA<CICA< DMMA<MEAA<CRTA.

3.7. Kinetic description of the hydrolysis of anhydrides

The hydrolysis of the anhydrides can be depicted as in Fig. 5.

Based on the use of standard solutions of their conjugate acids, the process of hydrolysis can be described indirectly. Considering both the anhydride concentrations that undergo and do not undergo hydrolysis, we have:

$$C_{anh} = C_0 - f(C_{aci}, t) \quad (3)$$

where C_0 denotes the original concentration of a particular anhydride; C_{anh} and C_{aci} indicate the concentration of anhydride that does not undergo hydrolysis and of the generated acid during the hydrolysis.

Practically, compared to the anhydride, the proportion of water in the hydrolytic conditions is in great excess and can be treated as a constant during the hydrolytic reactions. So, we can assume that the hydrolysis of an anhydride is a pseudo-first-order reaction and Eq. (3) should have the following expression [22]:

$$C_{anh} = C_0 e^{-kt} \quad (4)$$

where t is the time and k is the observed rate constant. In this work, simulation involved the use of the exponential regression on the experimental data shown in Fig. 3. Pseudo-first-order reactions were confirmed, for the hydrolysis of anhydrides, by the corresponding coefficient factor (r^2) (Table 2). It was noticed that the rate constants of CRTA and MEAA were small, i.e. 0.0022 and 0.0027/h, under conditions in which the proportion of aqueous phase was lower than 50%. This indicates that both anhydrides are stable, and direct quantitative analysis of them can be carried out under reversed-phase HPLC conditions, whereas corrections were required, to exclude their hydrolyzed amounts (formed during passage from the column), for the other anhydrides.

Fig. 6 is a typical chromatogram showing the simultaneous separation of the five anhydrides and their conjugate acids. Baseline separation was achieved for all components. Because the analytes were prepared in CH_3CN, the mobile phase was the only factor responsible for the hydrolysis of the anhydrides. Their concentrations after this on-column process can be estimated from the kinetic equations ($C_0 = 5 \cdot 10^{-5}$ M; velocity constants are given in Table 2). Also, their concentrations can be calculated from the variations in the concentrations of their conjugate acids (Section 3.3). Comparisons

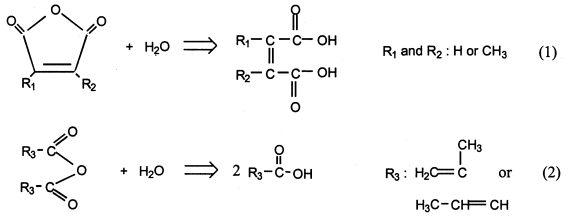


Fig. 5. Hydrolysis of anhydride.

Table 2
Kinetics for the hydrolysis of anhydrides

Anhydride	%v of aqueous phase[a]	Rate constant (h^{-1})			
		H_2O–MeCN mixture		pH 2.5 solution[b]	
		k	r^2	k	r^2
MALA	10	0.789	0.9937		
	5	0.1947	0.9978		
CICA	95	–	–	10.13	0.9924
	70	4.5152	0.9848		
	50	3.947	0.9816		
	30	1.1863	0.997		
	10	0.3901	0.9961		
DMMA	95	–	–	5.8511	0.9942
	70	3.5642	0.9862		
	50	1.4262	0.9929		
	30	0.3545	0.9955		
	10	0.1124	0.9985		
CRTA	100	0.0776	0.9981		
	95	–	–	0.4532	0.9991
	70	0.0077	0.9952		
	50	0.0022	0.9963		
MEAA	100	0.4903	0.9918		
	95	–	–	1.6255	0.9961
	70	0.161	0.9933		
	50	0.0027	0.9966		

The HPLC conditions are the same as those given in Fig. 1.
[a]Conditions for off-column hydrolysis.
[b]10 m*M* $NH_4H_2PO_4$–$(NH_4)_2HPO_4$ buffer, pH 2.5–CH_3CN (95:5, v/v).

of the results (Table 3) shows good agreement between both methods.

4. Conclusions

This study demonstrated that reversed-phase HPLC could be applied to the degradation and hydrolysis of anhydrides. Under the appropriate HPLC conditions, separation and determination of anhydrides and their conjugate acids were achieved. The three cyclic anhydrides, MALA, CICA and DMMA, were found to undergo hydrolysis more rapidly than the two non-cyclic anhydrides, CRTA and MEAA. The effects of the proportion of aqueous phase and of the acidity on the hydrolysis were illustrated, and the differences in hydrolytic velocity and stability of the anhydrides were explained by the nucleophilic pathway. Results showed that the hydrolysis of these anhydrides involved a pseudo-first-order processes, and their kinetics were simulated from the experimental data. Due to their stability in pH-neutral aqueous solution, direct analysis of CRTA and MEAA could be performed under reversed-phase HPLC conditions. For the other three anhydrides (MALA, CICA and DMMA) or, in

Table 3
Quantitative analysis of anhydrides

Anhydride	Concentration ($\times 10^{-6}$ mol/l)	
	Kinetic equations	Indirect method[b]
MALA	–[a]	0.75±0.094
CICA	8.6	6.4±0.67
DMMA	4.6	4.4±0.38
CRTA	36.9	39±1.61
MEAA	13.4	12.8±0.11

[a]Velocity constant is not available.
[b]Triplicate measurements.

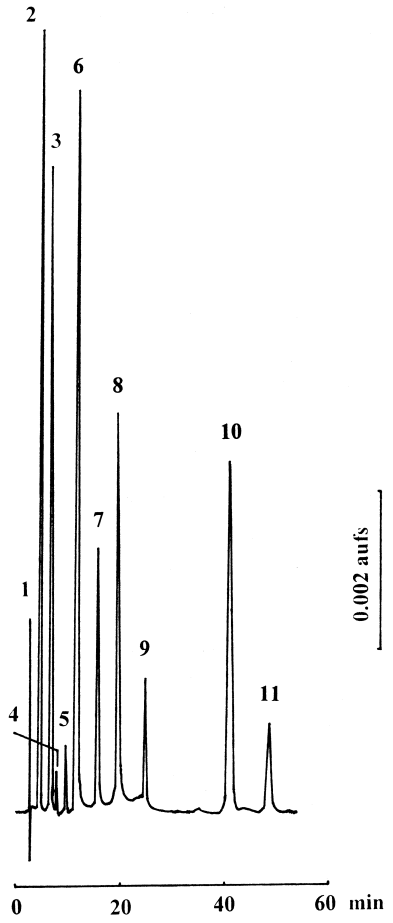


Fig. 6. Separation of the five anhydrides and their conjugate acids. Mobile phase, 10 m*M* $NH_4H_2PO_4$–$(NH_4)_2HPO_4$, pH 2.5 + 10^{-4} *M* TBADP–CH_3CN (95:5, v/v) at a flow-rate of 0.18 ml/min; concentration of the anhydrides injected: $5 \cdot 10^{-5}$ *M*. Peaks: 1, MeCN; 2, MAL; 3, CIC; 4, MALA; 5, CICA; 6, DMM; 7, CRT; 8, MEA; 9, DMMA; 10, CRTA and 11, MEAA; Other conditions are the same as for Fig. 1.

general, for those that are prone to hydrolysis, knowledge of their kinetic behavior in aqueous solution (pertaining to their hydrolysis to acids) can be exploited to determine them quantitatively.

Acknowledgements

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