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Online Reaction Monitoring and Evaluation of Kinetic Parameters for Dilute Reactions Using Refractive Index Measurements

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Abstract:

This work demonstrates the utility of an online refractometer technique as a simple and accurate tool for monitoring the progress of a reaction and determining its end-point. It is also shown that, for a dilute reaction, the change of refractive index due to reaction is proportional to the extent of reaction. The corresponding kinetic rate coefficient can also be evaluated, provided the kinetic model is known. This proposed methodology was subsequently applied to monitor and study the kinetics of two different model reactions, namely alkaline hydrolysis of methyl paraben and hydrolysis of acetic anhydride. Both reactions were performed in dilute solution and under pseudo-first-order reaction conditions. The rate coefficients determined from the present refractive index measurements were in agreement with those independently determined using calorimetric and spectroscopic methods. Replicate kinetic experiments were also performed in order to confirm the reliability of the present refractive index measurements. For known simple reactions which are repetitively performed, or for continuous online process monitoring of simple reactions, the present approach provides a convenient alternative to spectroscopic and/or calorimetric monitoring.

Introduction

Online process analytical tools have been increasingly utilized to monitor chemical reactions. In comparison to offline analytical tools, online measurements are generally able to collect much more information on the reaction progress, and as such, they can greatly improve the efficiency as well as the accuracy of the process reaction monitoring. Simple, fast, and nondestructive techniques are certainly some of the preferred criteria to monitor most reactions. On the basis of this consideration, many spectroscopic tools, such as IR (near-IR, mid-IR, and far-IR), UV/vis, and Raman have been developed and are widely utilized as online process analytical techniques.

In addition to spectroscopic measurements, several physico-chemical property measurements such as refractive index,[1,2] volume,[3,4] surface tension,[4,5] conductivity,[3] viscosity,[6] heat-flow,[7−11] etc. can also be used to monitor a reaction. The changes in the bulk physico-chemical properties of solution mixtures at fixed temperature and pressure are directly correlated to the reaction progress. Compared to spectroscopic techniques, the measurement and subsequent numerical evaluation of these bulk physico-chemical property measurements are rather simple and quite straightforward, at least for simple reactions.

In the current study, the use of a bulk physico-chemical measurement, namely refractive index, to monitor reaction progress is investigated. This technique certainly deserves more attention since it has several practical features, i.e., ease of use, sensitivity to composition changes, nondestructiveness, rapid data acquisition times, applicability to online measurements, etc. In this regard, an online refractometer is employed in the present study to provide continuous refractive index measurements during reactions. In addition, this study also proposes a novel and rather simple methodology to derive kinetic parameters from the refractive index measurements for dilute reaction systems. The relationship between the changes of refractive index monitored during reaction to the corresponding extent of reaction is provided. Accordingly, given a kinetic reaction model, the kinetic rate coefficient can be directly evaluated from the online refractive index measurements.

In order to demonstrate the present methodology, two different reactions with considerably different reaction times, namely alkaline hydrolysis of methyl paraben and hydrolysis of acetic anhydride, were studied with an online refractometer. These were selected as model reactions since they could be conveniently performed in dilute solution under typically

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pseudo-first-order reaction conditions. The kinetic rate constants determined using the present technique were found to be in good agreement with those determined using other more established techniques, namely spectroscopy and calorimetry. Consequently, the present study indicates that for known simple reactions which are repetitively performed, or for continuous online process monitoring of simple reactions, the present approach provides a potential alternative to spectroscopic and/or calorimetric monitoring.

Methodology

The numerical procedure for obtaining the kinetic rate coefficient from the refractive index measurement of a single reaction performed in a dilute range of concentration is outlined below.

In dilute solution, the refractive index n of a solution can be related to the refractive index of the solvent n_s and the mole fraction of the individual solutes x_i, as shown in eq 1, where α_i is the corresponding coefficient for each individual solute.

$$n = n_s + \sum_{\text{solute-}i} \alpha_i x_i \tag{1}$$

A rather general stoichiometric reaction with stoichiometric coefficients a, b, c, and d can be written as shown in eq 2. Accordingly, the bulk refractive index of the solution at any reaction time t can be related to the mole fractions of the individual reactive substances as shown in eq 3. In this equation, mole fractions are expressed in terms of y_i^0, y_{total}^t, ξ which refer to the initial moles of substance-i, the total moles of the reaction solution at reaction time t, and the extent of reaction, respectively. The total mole of the reaction solution y_{total}^t is given in eq 4 as a summation of the total initial moles y_{total}^0 (i.e., from all the reactive substances y_i^0 as well as the solvent y_S^0) and the change of moles due to reaction.

$$aA + bB \rightarrow cC + dD \tag{2}$$

$$n^t = n_S + \Big(\alpha_A(y_A^0 - \xi) + \alpha_B\Big(y_B^0 - \frac{b}{a}\xi\Big) + \alpha_C\Big(y_C^0 + \frac{c}{a}\xi\Big) + \alpha_D\Big(y_D^0 + \frac{d}{a}\xi\Big)\Big)/y_{\text{total}}^t \tag{3}$$

$$y_{\text{total}}^t = y_A^0 + y_B^0 + y_C^0 + y_D^0 + y_S^0 + \xi \times \left(\frac{(c+d)-(a+b)}{a}\right) = y_{\text{total}}^0 + \xi\left(\frac{(c+d)-(a+b)}{a}\right) \tag{4}$$

For dilute reactions, the change of moles due to reaction is always small compared to the total initial moles of the reaction solution. Furthermore, since dilute reaction is considered, the total moles y_{total}^t can be assumed to be nearly constant, and therefore substituted by the total initial moles of the reaction solution y_{total}^0. This results in the new expression eq 5. Note that eq 5 is exact when the sum-total stoichiometric coefficients before and after reaction are equal (i.e., $(c + d) - (a + b) = 0$).

$$n^t = n_S + \Big(\alpha_A(y_A^0 - \xi) + \alpha_B\Big(y_B^0 - \frac{b}{a}\xi\Big) + \alpha_C\Big(y_C^0 + \frac{c}{a}\xi\Big) + \alpha_D\Big(y_D^0 + \frac{d}{a}\xi\Big)\Big)/y_{\text{total}}^0 \tag{5}$$

Equation 5 can be factored. The simplified expression is shown in eq 6. In this equation, n^0 is the refractive index of the solution at $t = 0$, and β is the lumped-parameter which takes into account the stoichiometric reaction coefficients, the coefficients α_i and the initial total moles of reaction mixture. It can be noted that the lumped parameter β may not be exactly constant due to the mass balance approximation used as well as possible small changes in the individual refractive indices during reaction.

$$n^t = n^0 + \beta\xi \tag{6}$$

$$n^0 = n_S + (\alpha_A y_A^0 + \alpha_B y_B^0 + \alpha_C y_C^0 + \alpha_D y_D^0)/y_{\text{total}}^0 \tag{7}$$

$$\beta = \Big(\frac{c}{a}\alpha_C + \frac{d}{a}\alpha_D - \alpha_A - \frac{b}{a}\alpha_B\Big)/y_{\text{total}}^0 \tag{8}$$

The evaluation of the parameters in eq 6 from experimental data requires a few steps. First, the initial refractive index of the solution n^0 is most easily obtained by extrapolation of n^t to the initial reaction time (i.e., $\xi \rightarrow 0$). Second, the lumped parameter β can only be evaluated after the reaction model and the extent of reaction as a function of time is defined.

In the case of a first-order reaction or a pseudo-first-order reaction, the fractional conversion X_A is related to the reaction time as given in eq 9. Furthermore, the fractional conversion X_A can be related to the extent of reaction ξ and the change of refractive index Δn as provided in eq 10. Finally, substitution of these two expressions provides the direct relationship between the change of refractive index and the reaction time eq 11.

$$-\ln(1 - X_A) = kt \tag{9}$$

$$X_A = \frac{\xi}{y_A^0} = \frac{(n^t - n^0)}{\beta y_A^0} = \frac{\Delta n}{\beta y_A^0} \tag{10}$$

$$-\ln\left(1 - \frac{\Delta n}{\beta y_A^0}\right) = kt \tag{11}$$

Both the kinetic rate constant k and lumped parameter β can be simultaneously evaluated using a nonlinear minimization procedure. In this work, numerical calculations were performed using Matlab (v. R2007b), with an in-house written algorithm.

Experimental Section

Materials. Acetic anhydride (J.T. Baker, Baker analyzed for HPLC solvent, 99.8%+), methyl 4-hydroxybenzoate or methyl paraben (Sigma Aldrich, Sigma Ultra, 99%+), and sodium hydroxide pellets (Merck, pro analysi, >99%) were used directly without further purification. Deionized ultrapure water was used in this study (Young Lin Instrument, Aquamax - Basic 321 Water Purification System).

The purity of the substrate methyl paraben was checked by ^{1}H NMR after dissolution in $CDCl_3$ (Bruker Avance 400 MHz with 0.5 WB, equipped with a 5 mm TBI probe with *z* gradient, running a standard Bruker supplied pulse sequence). The measurements of the spectra showed that only very minor levels of impurities were found. Integration of the proton resonances provided lower bounds for the purity of methyl paraben (>99.5%).

Equipment. The reactions were carried out in a 50 mL jacketed glass reactor equipped with a magnetic stirrer. The fluid was pumped continuously in a closed loop system from the reactor through a Teflon membrane pump (Cole-Parmer) to the refractometer and recycled back to the reactor. A temperature bath recirculator (Polyscience model 9105, with temperature stability ±0.05 K) was used to maintain the temperature of the reactor. The flow-rate of the pump used in this study was set to ~1 mL/min.

Refractive index measurements were performed with a flow-through Abbemat-HP automatic refractometer using the sodium-D line at 589.3 nm. This refractometer has an accuracy of $\pm 2 \times 10^{-5}$ n_D, a resolution of $\pm$ 10^{-6} n_D, and is thermostatically controlled to within ±0.01 K. Continuous measurements of the refractive index can be automatically recorded every second.

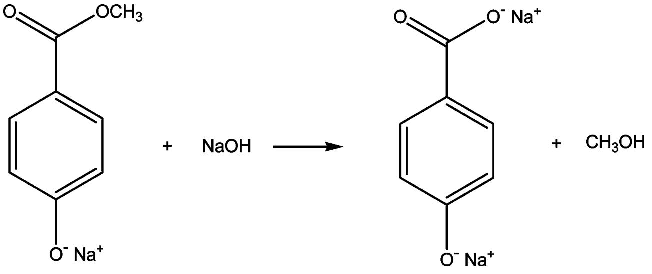
The amount of solid reagents methyl paraben and sodium hydroxide used for the reactions were measured using a balance (GR-200, A&D, Japan) with a precision of $\pm 10^{-4}$ g. The amount of liquid acetic anhydride used in the reaction was determined from the difference in the masses of the gas-tight syringe before and after its injections.

Hydrolysis of Methyl Paraben. An aqueous solution of sodium hydroxide (0.5 M in 50 mL solution) was prepared. Approximately 25 mL of this solution was first transferred into the reactor. The reactor was kept isothermal at the reaction temperature. The stirrer and pump were turned on, and the solution was circulated through the pump, flow-through refractometer and back to the reactor. A certain amount of methyl paraben (~0.38 g) was transferred into the reactor using a funnel, while the pump was turned off. Subsequently, another 25 mL of sodium hydroxide solution was quickly added to the reactor to ensure that no reagents were left in the funnel. The time when methyl paraben was transferred into the reactor was noted as reaction time t_0. After methyl paraben was fully dissolved into solution in the 50 mL jacketed glass reactor, the pump was turned on again. Methyl paraben is only slightly soluble in pure water, but becomes highly soluble in aqueous sodium hydroxide since it is very rapidly transformed into its deprotonated form. Since the sodium hydroxide concentration used is ~10 times greater than the methyl paraben concentration, pseudo-first-order condition can be assumed. The overall reaction for the alkaline hydrolysis of methyl paraben is shown in Scheme 1.

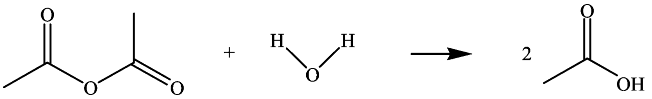
The total time for (1) dissolution of methyl paraben and (2) homogeneous mixing in the present closed-loop experimental setup was ~7 min. Afterwards, good quality and representative data could be acquired. This mixing time can be compared to the typical total reaction times of ~3 h and more.

Hydrolysis of Acetic Anhydride. Approximately 50 mL of water was first transferred into the reactor. The reactor was kept isothermal at the reaction temperature. The stirrer and pump were turned on, and the solution was circulated through the pump and flow-through refractometer and back to the reactor. A certain amount of acetic anhydride (~0.54 g) was directly injected into the reactor using a gas-tight syringe. The time when acetic anhydride was transferred into the reactor was noted as reaction time t_0. The total time for homogeneous mixing in the present closed-loop experimental setup was ~5 min. Afterwards, good quality data could be acquired. This mixing time can be compared to the typical total reaction times of ~45 min. Since the water concentration is ~520 times greater than the acetic anhydride concentration, pseudo-first-order conditions can be assumed. The overall reaction for the hydrolysis of acetic anhydride is shown in Scheme 2.

Scheme 1. **Alkaline hydrolysis reaction of methyl paraben (deprotonated)**



Scheme 2. **Hydrolysis reaction of acetic anhydride**



Results and Discussion

Hydrolysis of Methyl Paraben. Refractive index measurements were carried out in order to monitor and evaluate the kinetic rate coefficient for the hydrolysis reaction of methyl

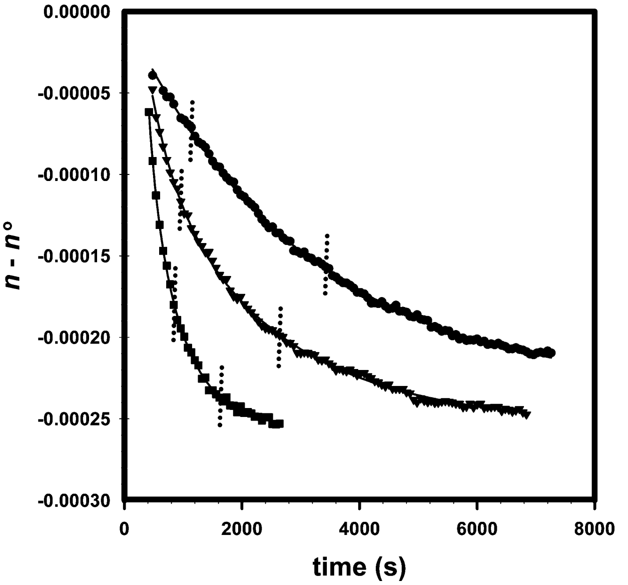


Figure 1. **Changes of refractive index during the hydrolysis reaction of methyl paraben at 298 K (•), 308 K (▼), and 318 K (■). A good fit of the data was obtained with a third-order polynomial. Outlier measurements due to bubble formation have been omitted. The interval data of changes of refractive index used for subsequent kinetic analysis are indicated by the dotted lines.**

Table 1. **Summary of pseudo-first-order rate constants for hydrolysis of methyl paraben, obtained from on-line refractometer method as well as other techniques of measurements**

	k (10^{-4} s^{-1})[a]		
T (K)	refractometer (this study)	FTIR spectroscopy	calorimetry
298	3.3 ± 0.1	3.08 ± 0.01[b]	3.35 ± 0.03[c] 3.15 ± 0.22[d]
308	6.9 ± 0.1		6.78 ± 0.03[e]
318	13.5 ± 0.3		13.9 ± 0.19[e]

[a] Standard deviations are reported as 2σ. [b] Evaluated directly from concentration data (obtained using FTIR spectroscopy) as reported in ref 8. [c] Evaluated directly from heat flow data (obtained using flow-through Thermal Activity Monitor (TAM) III microcalorimeter) as reported in ref 8. [d] Reference 10. [e] Independently measured using TAM III microcalorimeter with ampoule measurements. Detailed procedure can be found in ref 10.

paraben. Reactions at three different temperatures (298.15, 308.15, and 318.15 K) were performed in order to demonstrate the utility of the present online refractive index measurement. The changes of refractive index observed during reactions in these three different experimental runs are shown in Figure 1.

An initial period of ~400 s was typically needed to ensure the homogeneity of the reaction solution in the present online setup. The measurements obtained from this initial period are not representative of the intrinsic reaction kinetics and, hence, were omitted from further analysis. The refractive index changes presented in Figure 1 clearly show the progress of the reaction.

Since the hydrolysis reaction of methyl paraben in the presence of excess sodium hydroxide can be represented by pseudo-first-order kinetics,[10] eq 11 can be readily used to simultaneously evaluate both the pseudo-first-order rate constant k and the lumped parameter β. Only intermediate reaction times (indicated by dotted lines in Figure 1) which ensure solution homogeneity and have relatively higher signal-to-noise ratios were used in the kinetic analysis. The pseudo-first-order rate constants obtained are reported in Table 1. These values are also compared to those previously and independently determined using FTIR spectroscopy as well as calorimetric measurements.[8,10] The results show that the rate constants determined from the present refractive index method are in good agreement with those determined from other techniques. It is also noted, however, that the standard deviations of the rate constants determined from the present refractive index measurements are typically greater than those determined from both spectroscopic and calorimetric measurements.

A comparison of the experimental data and the pseudo-first-order model (eq 11) is shown in Figure 2. The consistency of the results confirms that a pseudo-first-order kinetic model is appropriate for this hydrolysis reaction.

Hydrolysis of Acetic Anhydride. Refractive index measurements were carried out in order to monitor and evaluate the kinetic rate coefficient for the hydrolysis reaction of acetic anhydride at 293.15 and 298.15 K. It can be noted that this reaction is faster than the hydrolysis reaction of methyl paraben and also provides a smaller change of refractive index (i.e., ~1 × 10^{-4} n_D). The changes of refractive index due to reaction performed at two different temperatures are shown in Figure 3.

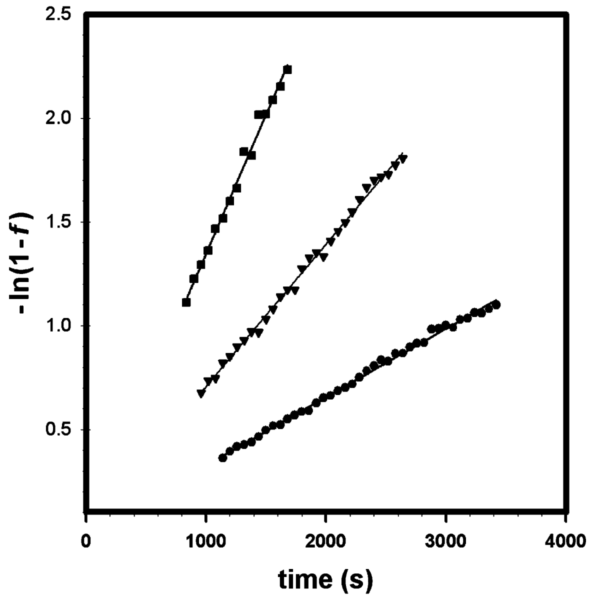


Figure 2. **Kinetic plot of methyl paraben hydrolysis at 298 K (•), 308 K (▼), and 318 K (■) using eq 11 where $f = (\Delta n)/(\beta y_A^0)$. The pseudo-first-order reaction constants are provided by the slopes of the regression lines (solid line).**

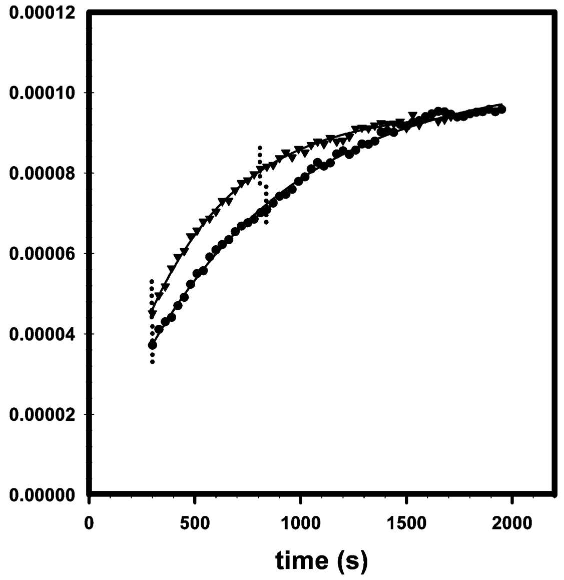


Figure 3. **Refractive index changes during the hydrolysis reaction of acetic anhydride at 293 K (•) and 298 K (▼). Smoothing lines are shown. A good fit of the data was obtained with a third-order polynomial. Outlier measurements due to bubble formation have been omitted. The interval data of changes of refractive index used for subsequent kinetic analysis are indicated by the dotted lines.**

The refractive index changes in Figure 3 clearly reflect both the extent of reaction as well as the approach to a reaction end-point. The initial period of time (i.e., $t < 300$ s) before the reaction solution has attained homogeneity is not shown.

The hydrolysis reaction of acetic anhydride in the presence of excess water can be approximated by a pseudo-first-order kinetic model.[8,11] Accordingly, eq 11 can be readily used. Using the smoothed refractive index changes, both the pseudo-first-order rate constant k and the lumped parameter β were simultaneously determined. Only intermediate reaction times (indicated by dotted lines in Figure 3) which ensure solution

Table 2. **Summary of pseudo-first-order rate constants for hydrolysis of acetic anhydride, obtained from on-line refractometer method as well as other measurement techniques**

	k (10^{-3} s^{-1})^a		
T (K)	refractometer (this study)	Raman spectroscopy	calorimetery
293	1.6 ± 0.07 (run 1) 1.5 ± 0.08 (run 2)		
298	2.1 ± 0.2 (run 1)	2.13 ± 0.03^a	2.24 ± 0.01^b
298	2.2 ± 0.3 (run 2)		2.23^c

[a] Standard deviations are reported as 2σ. Calculated directly from the concentration profile data (obtained using Raman spectroscopy) as reported in ref 8. [b] Evaluated directly from the heat flow data (obtained using flow-through TAM III microcalorimeter) as reported in ref 8. [c] ref 11.

homogeneity and have relatively higher signal-to-noise ratios were used in the kinetic analysis. The pseudo-first-order rate constants obtained are reported in Table 2.

The presently obtained pseudo-first-order rate constants can be compared to those previously determined using Raman spectroscopy and calorimetric measurements. The results show that the rate constants determined using the refractive index method are in good agreement with those evaluated from other measurement techniques. Replicate measurements were also carried out for each temperature in order to validate the present approach. The kinetic rate coefficients determined from replicate measurements compare favorably. In Table 2, the standard deviations of the kinetic rate constants obtained from the refractive index measurement are greater than those obtained from Raman and TAM microcalorimeter measurements. This indicates that the accuracy of the refractometer method is somewhat less than that of the other techniques used to monitor the present reaction. A comparison of the experimental data and the pseudo-first-order model (eq 11) is shown in Figure 4. The consistency of the results confirms that a pseudo-first-order kinetic model is appropriate for the acetic anhydride reaction.

Additional Comments. It should be noted that the present mathematical treatment relies on additivity of refractive indices (eq 1) and hence a linear dependence between change of refractive index and extent of reaction (eq 6) and that this can only be guaranteed in the case of dilute reactions. Extension to more concentrated reactive solutions is potentially more complex, and the relationship between refractive index and extent of reaction would have to be clarified on a case-by-case basis. In practice, this could be further investigated by performing independent but simultaneous online spectroscopic or calorimetric measurements and comparing the resulting extents of reactions obtained by the various methods. If the extents of reactions are not consistent, a calibration involving the concentration dependence of refractive indices could be included in the mathematical model.

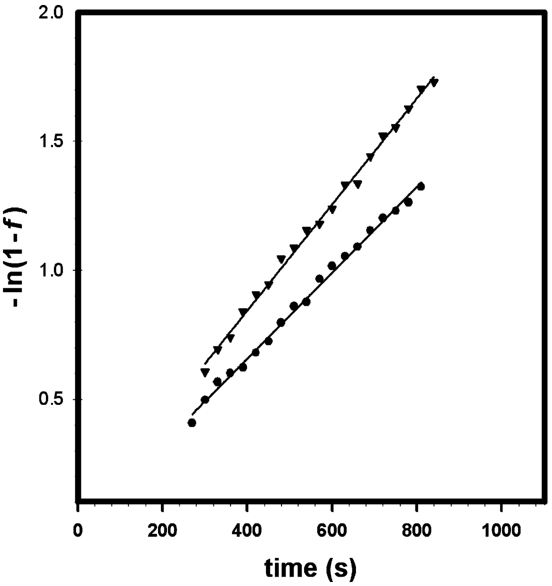


Figure 4. **Kinetic plot of acetic anhydride hydrolysis at 293 K (•) and 298 K (▼) using eq 11 where $f = (\Delta n)/(\beta y_A^0)$. The pseudo-first-order reaction constants are provided by the slopes of the regression lines (solid line).**

On a more practical level, it is also important to ensure as far as possible that bubble formation during the online refractive index measurements are avoided or at least minimized. In addition, it is useful to minimize temperature and/or flow-rate fluctuations during measurements.

Conclusions

This work demonstrates the utility of an online refractometer technique as a simple and accurate tool to monitor the progress of reactions as well as to determine the end-point of reactions. For known reactions, the present approach represents a more economical method compared to using online spectroscopic or calorimetric determinations. Therefore, for reactions which are repetitively performed, or for continuous online processes, this approach provides an attractive alternative to spectroscopic/calorimetric determinations. Although the present study focused on hydrolysis reactions, the proposed methodology is certainly applicable to much wider range of liquid-phase reactions.

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