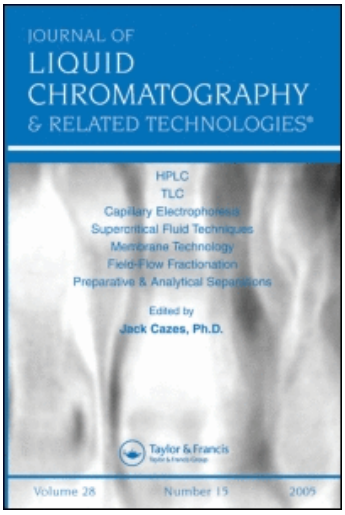

Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

A Coupled Flow Injection-Capillary Electrophoresis System for Kinetic Study of Aspirin Hydrolysis in Aqueous Solution

Zengxuan Cai[a]; Hengwu Chen[a]
[a] Department of Chemistry, Zhejiang University, Hangzhou, P.R. China

Online publication date: 19 June 2003

To cite this Article Cai, Zengxuan and Chen, Hengwu(2003) 'A Coupled Flow Injection-Capillary Electrophoresis System for Kinetic Study of Aspirin Hydrolysis in Aqueous Solution', Journal of Liquid Chromatography & Related Technologies, 26: 11, 1695 — 1707
To link to this Article: DOI: 10.1081/JLC-120021277
URL: http://dx.doi.org/10.1081/JLC-120021277

JOURNAL OF LIQUID CHROMATOGRAPHY & RELATED TECHNOLOGIES®
Vol. 26, No. 11, pp. 1695–1707, 2003

A Coupled Flow Injection-Capillary Electrophoresis System for Kinetic Study of Aspirin Hydrolysis in Aqueous Solution

Zengxuan Cai and Hengwu Chen*

Department of Chemistry, Zhejiang University, Hangzhou, P.R. China

ABSTRACT

A coupled flow injection-capillary electrophoresis (FI-CE) system was developed for automated determination of rate constants of chemical reactions. The system consists of a probe for sampling, a knotted reactor for on-line quenching reaction, an injection valve in combination with a split-flow interface for on-line electrokinetic injection, and a CE unit for separation and detection. Aspirin was used as a model compound to validate the performance of the coupled system. Under the optimized conditions, the coupled system achieved a sampling rate of 20 per hour, and a RSD of 1.1% for 25 consecutive determinations in 75 min. These features of the coupled FI-CE system allowed it to monitor reactions with half-reaction time being no less than 15 min. Several rate constants of aspirin hydrolysis in slightly alkaline media were determined with the developed system.

*Correspondence: Hengwu Chen, Department of Chemistry, Zhejiang University, Xixi Campus, Hangzhou 310028, P.R. China; E-mail: hwchen@mail.hz.zj.cn.

DOI: 10.1081/JLC-120021277
1082-6076 (Print); 1520-572X (Online)

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Key Words: Flow injection; Capillary electrophoresis; Determination of rate constant; Aspirin; Hydrolysis.

INTRODUCTION

Determination of the rate constant of chemical reactions is frequently required in the process of drug development. For instance, estimation of the rate constant of aspirin hydrolysis in various chemical and biochemical media can provide useful information for the production and storage of the drug or its formulations, and for the studies on absorption and disposition of the drug in the body.[1] Among the various analytical techniques used to monitor chemical reactions, UV spectrophotometry is one of the simplest techniques. However, use of UV spectrophotometry requires that the reactant and product do not spectrally interfere with each other. When interference occurs, high performance liquid chromatography (HPLC) is a suitable choice for the kinetic study of chemical reactions.

Due to its inherent analytical merits such as high separation efficiency, fast analytical speed, and less sample and reagent consumption, capillary electrophoresis (CE) has been developed into a complementary technique for HPLC. So far, a great number of papers have been published on the application of the technique for pharmaceutical and biomedical analysis. However, only a few[2–5] reported the application of CE for determination of kinetic constants.

Regardless of the analytical methods used, determination of the rate constant of a reaction usually involves four steps: sampling the reaction solution at pre-determined time intervals, quenching the reaction with a suitable reagent prior to analysis, separating and detecting the objective compound, and analyzing observed data. To obtain a rate constant, at least five aliquots of the reaction solution should be taken at different reaction times and analyzed thereafter. For detail studies on the kinetic behavior of a reaction under different conditions such as temperature, pH, ionic strength, and solvents etc., several tens or even hundreds of analyses may be required, which is labor intensive and time consuming. A few automated analytical systems with UV-spectrophotometric detection[6,7] or HPLC separation and UV-detection[8,9] for kinetic studies of solvent extraction,[6,7] and chemical reaction,[8,9] have been reported.

Recently, the advantages of coupling flow injection (FI) sample introduction to CE have been demonstrated.[10,11] This combination significantly increased sample throughput and improved reproducibility. Furthermore, potentials in coupling FI on-line sample pre-treatment techniques such as dialysis,[12] gas diffusion,[13] filtration,[14] solid-phase extraction,[15,16] and ion

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

exchange[17] to CE have also been exploited, resulting in a great reduction of labor and time consumed for sample pretreatment,[12–14] and significant improvement of detection limits.[15–17]

In this work, an automated FI-CE system was developed for kinetic study of chemical reaction. The developed system was validated with determination of rate constants of aspirin hydrolysis in slightly alkaline media.

EXPERIMENTAL

Apparatus

A Beckman P/ACE 2100 CE system equipped with a UV detector was used to perform separation and detection. The high-voltage power supply equipped internally in the commercial CE system was not used because its anode, the electrode positioned in the capillary-inlet vial, was not grounded. This hampered the capillary inlet from being coupled to the FI system. Thus, a separate high voltage power supply with a grounded anode (Beijing New Technology Institute, Beijing, China) was employed. A fused-silica capillary, 27 cm in length (effective length of 20 cm) and 75 μm in i.d. (Yongnian Optical Fiber, Yongnian, Hebei, China), was used for separation. UV detection was performed at 214 nm. A LZ-2000 programmable FI processor (Zhaofa Instruments, Shenyang, China), equipped with dual variable speed peristaltic pumps and an 8-channel 16-port injector valve, was used to achieve automated sample pre-treatment and injection. A model CS501 thermostat was used to control the temperature of the hydrolysis reaction, and a Beckman Φ200 pH meter was employed to measure the pH values of the reaction media. The schematic diagram of the coupled FI-CE system is illustrated in Fig. 1. The knotted reactor was home-made with a 0.5 mm i.d. × 50 cm PTFE tubing, as described in Ref.[18] All connections were made with 0.5 mm i.d. PTFE tubing.

Reagents

The standard solution of aspirin (4 mg mL^{-1}) was prepared by dissolving 40 mg aspirin (donated by Shenyang Pharmaceutical University, China) in 1 mL 95% ethanol and diluting to 10 mL with water. This solution should be used within 2 hours. Working solutions were step-wise diluted with water. All other reagents used were of analytical grade, and distilled water was used throughout.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

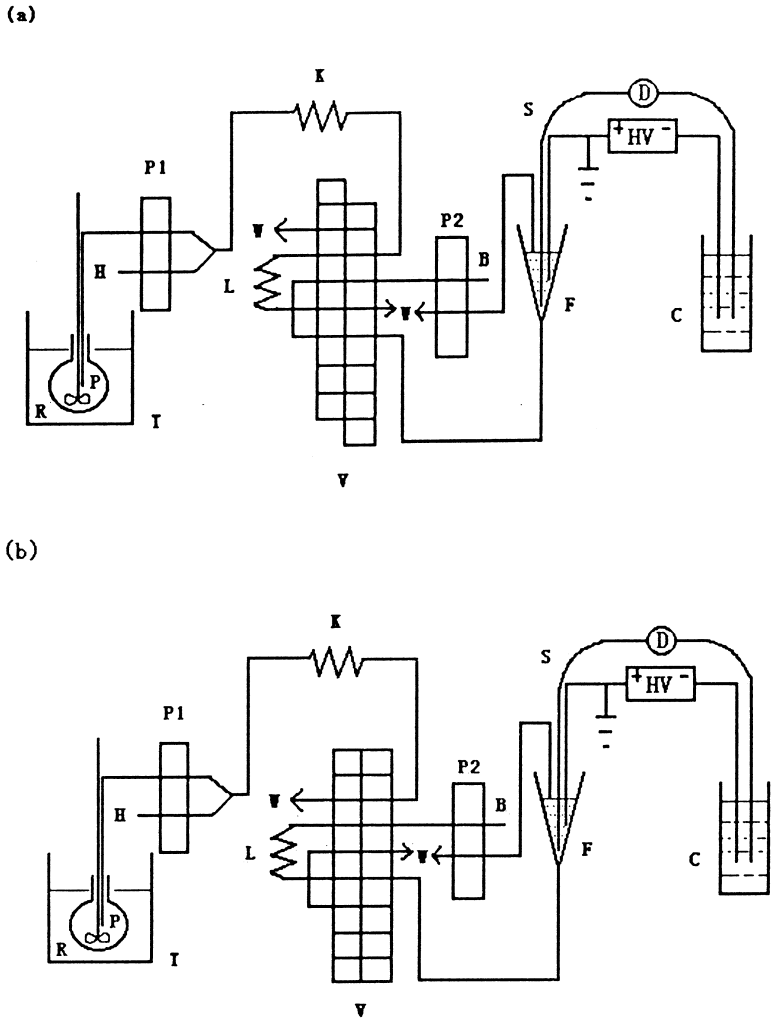

Figure 1. Schematic diagram of the FI–CE system for continuously monitoring the aspirin hydrolysis in aqueous solution. *Key:* B, running buffer; C, cathode vial; D, UV-detector; F, split-flow interface; H, hydrochloric acid solution; HV, high voltage power supply; K, knotted reactor; L, sampling loop; P, sampling probe; P1 and P2, peristaltic pumps; T, thermostat; R, reaction vessel; S, separation capillary; V, switch valve; W, waste. (a) loading; (b) injection.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Procedure for Flow Injection-Capillary Electrophoresis Analysis

Before operation, the separation capillary was washed with 0.1 mol L^{-1} NaOH, water and running buffer, each for 5 min. A 250-mL round bottom flask containing 190 mL of selected reaction medium, and a 25 mL plastic centrifuging tube containing 10 mL of aspirin solution (4 mg mL^{-1}) were positioned in the water-bath of the thermostat, and warmed up to the pre-set temperature. A constant voltage of 15 kV was applied to the capillary before starting the FI program. Immediately after transferring the 10 mL warmed aspirin solution into the 190 mL warmed reaction medium, the FI program was initiated. The FI program included three steps. In step 1 (duration of 25 s), with the valve in loading position and both pumps on, a stream of hydrolysis solution and, a stream of diluted HCl solution (both at a flow rate of 1.0 mL min^{-1}), were pumped by Pump 1 to be mixed in a knotted reactor where the hydrolysis reaction of aspirin was quenched due to neutralization of the reaction medium. The neutralized solution was then loaded into a sampling loop. During this step, carrier solution (also served as the running buffer for CE) was delivered by Pump 2 to pass the split-flow interface at a rate of 1.0 mL min^{-1}. In step 2 (duration of 15 s), with the valve being switched to injection position and Pump 1 stopped and Pump 2 kept running, the sample band stored in the sampling loop was delivered by the carrier solution at 1.0 mL min^{-1} to the split-flow interface, where a small fraction of the sample was electrokinetically injected into the capillary, and the remaining went to waste. In step 3 (140 s), with the rotation speed of Pump 2 being slowed down, the carrier solution was kept passing the interface at a flow-rate of 0.5 mL min^{-1}, while the injected sample was subjected to CE separation and detection until the end of this cycle. Immediately after the completion of one cycle, the next one started. After consecutive running of 5∼20 cycles (depending on the half time, $t_{1/2,}$ of the hydrolysis reaction), the program was terminated at the end of the last cycle.

RESULTS AND DISCUSSION

Principles

Aspirin hydrolyzes rapidly in aqueous solution, producing salicylic acid and acetic acid. To monitor this reaction, either aspirin or salicylic acid can be used as the target species, due to both compounds having strong absorbance in UV region. In the present study, aspirin instead of salicylic acid was selected as the target species, because the concentration of salicylic acid during the

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

early stage of hydrolysis was too low to be detected by a UV detector equipped in the CE system. The pH and temperature dependent hydrolysis reaction has been recognized as pseudo-first order.[19,20] For a pseudo-first order reaction, the rate constant k is expressed by:

$$\ln C_t = -kt + \ln C_0$$

where C_0 is the initial concentration of aspirin and C_t is the concentration of the species at reaction time t. Within linear calibration range, C_0 and C_t can be substituted by their corresponding absorbance signals. Thus, if peak height is used as the signal response, the rate constant can be expressed by the equation

$$\ln H_t = -kt + \ln H_0 \tag{1}$$

where H_0 is the peak height of aspirin observed before hydrolysis and H_t is the peak height of the species at reaction time t. Also, the active energy (E_a) of the hydrolysis reaction may be estimated according to the equation

$$\ln k = -\frac{E_a}{\mathrm{R}T} + \ln A \tag{2}$$

where T represents the temperatures at which the reaction occurs, R is the gas constant, and A is the pre-exponential factor.

Method Development

An automated analytical system for determining rate constants of chemical reactions should be capable of (1) sampling of the reaction solution automatically at pre-set times; (2) on-line quenching of the chemical reaction; (3) injecting the reaction-quenched sample automatically into the separation unit; (4) separating and detecting the target species rapidly and consecutively. Based on these considerations, a coupled FI-CE system was designed, as shown in Fig. 1 and described in profexure for FI-CE analysis. The overall speed of the total analytical system was determined by CE separation time, and the reliability of the system depended, in most part, on the efficiency of the on-line quenching. Therefore, optimization of CE separation and on-line quenching were performed.

Capillary Electrophoresis Separation Conditions

The conditions used for CE separation should ensure that the monitored species (aspirin) is stable enough so that no detectable change in its concentration occurs during separation. Edwards[19] reported, that at a temperature of

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

10–35°C, the hydrolysis rate of aspirin was very slow ($k_{obs} < 1$ day^{-1}) in aqueous solution of pH range 5–8. Thus, CE separation was restricted within this pH range. Tests showed that aspirin and salicylic acid could be baseline separated in a 40 mmol L^{-1} phosphate buffer of pH 6.8. Therefore, it was used as both the carrier solution of FI system and the running buffer of CE separation.

The maximum sampling frequency of the coupled system was restricted by the time duration for CE separation. Short capillary and high voltage are favorable to perform rapid separations. Therefore, a fused-silica capillary of 27 cm long, the shortest length required by the capillary cartridge, was used. It should be pointed out that in the present coupled FI-CE system, the voltage applied for separation was also used for electrokinetic injection. Applying a higher voltage may increase separation speed, but it may also cause sample overloading that seriously deteriorates separation efficiency. As a result, a moderate voltage of 15 kV was selected for compromise between the separation efficiency and separation speed. Under these experimental conditions, aspirin and salicylic acid could be baseline separated within 3 min, resulting in a total sampling rate of 20 per hour. With this sampling frequency, hydrolysis reactions with $t_{1/2}$ no less than 15 min could be followed by the coupled FI-system to produce at least five data points within 15 min. For this reason, slightly alkaline reaction media were selected to ensure the hydrolysis reaction proceeding at reasonable rate.

On-Line Quenching Hydrolysis Reaction

After the hydrolysis solution was sampled from the reaction vessel at pre-set time intervals, the hydrolysis of aspirin in the sampled solution should be immediately quenched. In the present system, automated quenching was carried out by on-line mixing the sample stream and a diluted hydrochloric acid stream. The concentration of the hydrochloric acid solutions was pre-determined, with acid–base titration, to ensure that sample solution was neutralized to ca. pH 7 after thoroughly mixing. Since the reactor geometry affected the homogeneity of mixing and, in turn, the precision of analytical results, it was optimized by using a 100 μg L^{-1} salicylic acid solution prepared in 20 mmol L^{-1} borate buffer (pH 9.74) and a 55 mmol L^{-1} hydrochloric acid solution as quenching reagent. Here salicylic acid, rather than aspirin, was used as a target species because the former was stable in aqueous solution. The investigated reactors included both coiled and knotted reactors made with PTFE tubing of different lengths. The results, listed in Table 1, showed that the knotted reactor made with 50 cm PTFE tubing provided the best precisions (RSD < 3% for both peak height and peak area, $n = 6$). With this knotted reactor being employed,

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Table 1. The influence of reactor geometry on the signal precision of the FI-CE system.

		RSD of measurements (%, $n = 6$)	
Tubing length	Reactor type	Peak height	Peak area
10	Coiled	6.9	8.4
30	Coiled	4.8	6.6
30	Knotted	3.0	3.2
50	Coiled	4.6	5.2
50	Knotted	2.7	2.8

Note: Salicylic acid concentration:100 μg mL^{-1}.

analysis of two other salicylic acid solutions prepared in reaction media of different pH values produced RSD ($n = 6$, peak height) of 1.7% and 1.1%, respectively. Thus, the knotted reactor fabricated with 0.5 mm (i.d.) × 50 cm PTFE tubing was used throughout the work.

Analytical Performance of the Coupled System

Long time stability is a basic requirement for continuous process monitoring system. The long time stability of the coupled FI-CE system was evaluated by consecutively sampling a mixed aspirin and salicylic acid solution in 20 mmol L^{-1} borate–HCl buffer (pH 6.81), and measuring the CE signals of both aspirin and salicylic acid in a period of 80 min. Figure 2 is a typical recording trace of the measured signals. The relative standard deviations of 25 determinations of aspirin were 1.1% for both peak area and peak height, and that of salicylic acid were 1.3% for peak area and 1.1% for peak height. The relatively larger RSD for peak areas of salicylic acid may be ascribed to the integration errors caused by the software selection of integration boundaries. Even so, these results illustrated that the long time stability of the developed system was quite good. Since the precision for peak height is better than that for peak area, it was employed for the evaluation of the reaction rate in the kinetic studies.

Other characteristic data of the developed system are listed in Table 2. From the data such as the detection limit, dynamic linear range of the calibration curve, sample throughput rate, and long time stability, one can conclude that the analytical performance of the present FI-CE system can meet the requirements for automated determination of the rate constant of chemical reactions with moderately quick reaction speed.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

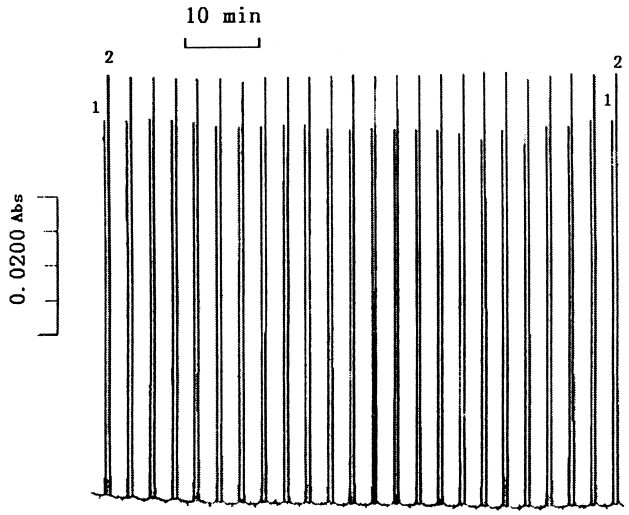

Figure 2. A recording trace of the electropherograms obtained by consecutive injection of an aspirin–alicylic acid (both in $100\,\mu g\,mol^{-1}$) solution prepared in 20 mM borate–HCl buffer of pH 6.81. *Key:* 1, aspirin; 2, salicylic acid.

Kinetic Studies of Aspirin Hydrolysis

The applicability of the FI-CE system for the kinetic studies of chemical reactions was demonstrated by determination of rate constants of aspirin hydrolysis in slightly alkaline media (pH 9.7–12.0), and in the temperature range 30–47°C. Figure 3 is a typical recorded trace of the electrophoregram

Table 2. Analytical performances of the coupled FI-CE system for automated determination of aspirin.

RSD (%, $n = 6$, for $100\,\mu g\,mL^{-1}$ aspirin)	0.3
Detection limit (3σ, $\mu g\,mL^{-1}$)	1.0
Linear regression equation	$A = -0.0002 + 8.0 \times 10^{-5} \times C$[a]
Determination coefficient (R^2)	0.9993
Linear range ($\mu g\,mL^{-1}$)	0–200
Sample throughout rate (h^{-1})	20
Sample consumption per run (mL, including to waste)	1.3

[a]Aspirin concentration in $\mu g\,mL^{-1}$.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

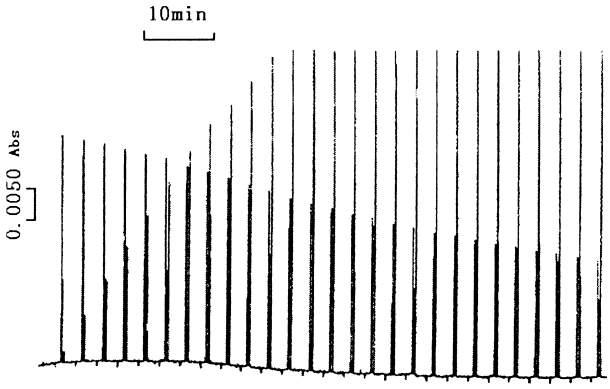

Figure 3. A typical recording trace of electropherogram showing the hydrolysis degradation of aspirin. Reaction medium, 0.020 mol L^{-1} $Na_2B_4O_7$–0.025 mol L^{-1} NaOH (pH 9.89). Temperature, 42°C. Aspirin concentration, 200 μ mL^{-1}.

obtained by on-line monitoring the hydrolysis reaction with the FI–CE system. Figure 4 shows the relationships of logarithmic aspirin concentration against hydrolysis time at constant temperature and varying pH values. This figure clearly illustrates the loss of aspirin being pseudo first-order. The calculated pseudo first-order rate constants of aspirin hydrolysis at different pH and temperature are listed in Table 3. For comparison, previously

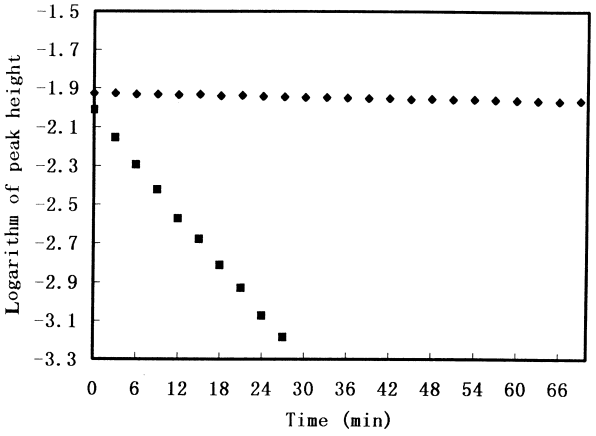

Figure 4. The effect of pH on the aspirin hydrolysis at a fixed temperature (30°C). The pH values of reaction media: *Key:* black diamond, pH 9.7; black square, pH 12.0.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Table 3. Rate constants of hydrolysis of aspirin in alkaline media.

Reaction media	pH	Temperature, °C	Rate constants, day^{-1}
Observed by present work			
0.020 mol L^{-1} $Na_2B_4O_7$–0.020 mol L^{-1} NaOH	9.70	30	2.04
0.020 mol L^{-1} $Na_2B_4O_7$–0.050 mol L^{-1} NaOH	12.00	30	143
0.020 mol L^{-1} $Na_2B_4O_7$–0.025 mol L^{-1} NaOH	9.93	37	7.34
0.020 mol L^{-1} $Na_2B_4O_7$–0.047 mol L^{-1} NaOH	11.41	40	246
0.020 mol L^{-1} $Na_2B_4O_7$–0.025 mol L^{-1} NaOH	9.89	42	12.5
0.020 mol L^{-1} $Na_2B_4O_7$–0.030 mol L^{-1} NaOH	9.93	47	21.1
Reported by previous works			
0.1052 mol L^{-1} H_3BO_3–0.0948 mol L^{-1} NaOH	10.1	27	3.75[a]
0.1052 mol L^{-1} H_3BO_3–0.0948 mol L^{-1} NaOH	9.7	29.8	1.8[b]
0.05 mol L^{-1} KH_2PO_4–0.1 mol L^{-1} NaOH	11.9	30	379[a]
NaOH (only)	12.0	29.8	153[b]
0.1052 mol L^{-1} H_3BO_3–0.0948 mol L^{-1} NaOH	9.94	37	11.5[a]
0.0556 mol L^{-1} KH_2PO_4–0.0889 mol L^{-1} NaOH	8.46	40	450[a]
0.1052 mol L^{-1} H_3BO_3–0.0948 mol L^{-1} NaOH	9.89	42	18.1[a]
0.1052 mol L^{-1} H_3BO_3–0.0948 mol L^{-1} NaOH	9.84	47	32.4[a]

[a]From Ref.[19]
[b]From Ref.[20]

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

reported constants obtained in similar conditions (pH and temperature) are also given in the table. The rate constants obtained by this work are slightly lower than those obtained with UV spectrophotometry by Edwards,[19] but close to that obtained with UV spectrophotometry by Broxton.[20] The slight discrepancy in the rate constants between this work and Edwards's work is most possibly due to inconsistency in such experimental conditions as buffer types (borate in this work against phosphate in Edwords's work) and ionic strengths. Analysis of the data at pH 9.91 ± 0.03 observed in this study gave a value of $8.75 \times 10^4\,\mathrm{kJ\,mol^{-1}}$ for the active energy, which is in agreement with that ($8.55 \times 10^4\,\mathrm{kJ\,mol^{-1}}$) obtained by analysis of the data reported by Edwards[19] at the same pH values.

ACKNOWLEDGMENTS

Natural Science Foundation of Zhejiang Province is thanked for funding this work. Ms. Vera Verdree is thanked for improving the English writing for our manuscript.

REFERENCES

1. Baker, S.K.; Niazi, S. Stability of aspirin in different media. J. Pharm. Sci. **1983**, *72* (9), 1024–1026.
2. Okafo, G.N.; Cutler, P.; Knowles, D.J.; Camilleri, P. Capillary electrophoresis study of the hydrolysis of a β-lactamase inhibitor. Anal. Chem. **1995**, *67* (20), 3597–3701.
3. Ye, J.-N.; Zhao, X.-W.; Sun, Q.-X.; Fang, Y.-Z. Capillary electrophoresis as a method for determining dissociation constants of aldohexose isomers. Mikrochim. Acta **1998**, *128*, 119–123.
4. Ye, J.-N.; Jin, W.; Zhao, X.-W; Fang, Y.-Z. Studies of the rate constants of sucrose hydrolysis by capillary electrophoresis with electrochemical determination. Chem. J. Chinese Univ. **1998**, *19* (1), 31–34.
5. Christy, A.A.; Egeberg, P.K. Oxidation of thiocyanate by hydrogen peroxide—a reaction kinetic study by capillary electrophoresis. Talanta **2000**, *51* (6), 1049–1058.
6. Wataral, H.; Cunningham, L.; Freiser, H. Automated systems for solvent extraction kinetic studies. Anal. Chem. **1982**, *54* (13), 2390–2393.
7. Chen, T.-Y.; Zhang, G.-Y.; Zhang, H. Automatic flow injection analysis system for the extraction—kinetic studies. Huaxue Tongbao **1991**, (5) 27, 30–32.
8. Sauter, F.J. Sampling and HPLC analysis on an automated reactor. Am. Lab. **1992**, *24* (October), 33–35.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

9. Shah, K.P.; Zhou, J.; Lee, R.; Schowen, R.L.; Elsbernd, R.; Ault, J.M.; Stobaugh, J.F.; Slavik, M.; Riley, C.M. Automated analytical systems for drug development studies I. System for the determination of drug stability. J. Pharm. Biomed. Anal. **1994**, *12* (8), 993–1001.
10. Kuban, P.; Karlberg, B. Interfacing of flow injection pre-treatment systems with capillary electrophoresis. Trend Anal. Chem. **1998**, *17* (1), 34–41.
11. Fang, Z.-L; Chen, H.-W.; Fang, Q.; Pu, Q.-S. Developments in flow injection-capillary electrophoresis systems. Anal. Sci. **2000**, *16* (2), 197–163.
12. Kuban, P.; Karlberg, B. On-line dialysis coupled to a capillary electrophoresis system for determination of small anions. Anal. Chem. **1997**, *69* (6), 1169–1173.
13. Kuban, P.; Karlberg, B. On-line coupling of gas diffusion to capillary electrophoresis. Talanta **1998**, *45* (3), 477–484.
14. Chen, H.-W.; Fang, Z.-L. Combination of flow injection with capillary electrophoresis: part 4. Automated multicomponent monitoring of drug dissolution. Anal. Chim. Acta **1998**, *376* (2), 209–220.
15. Chen, H.-W.; Fang, Z.-L. Combination of flow injection with capillary electrophoresis: part 5. Automated preconcentration and determination of pseudoephedrine in human plasma. Anal. Chim. Acta **1999**, *394* (1), 13–22.
16. Luo, J.-W.; Chen, H.-W.; He, Q.-H. Determination of cimetidine in human plasma by use of coupled-flow injection, solid-phase extraction, and capillary zone electrophoresis. Chromatographia **2001**, *53* (5–6), 295–300.
17. Arce, L.; Kuban, P.; Rios, A.; Valcarcel, M.; Karlberg, B. On-line ion-exchange preconcentration in a flow injection system coupled to capillary electrophoresis for the direct determination of UV absorbing anions. Anal. Chim. Acta **1999**, *390*, 39–44.
18. Fang, Z.-L; Welz, B. High efficiency low sample consumption on-line ion-exchange pre-concentration system for flow injection flame atomic absorption spectrometry. J. Anal. At. Spectrom. **1989**, *4*, 543–546.
19. Edwards, L.J. The hydrolysis of aspirin. Part II. Trans. Faraday Soc. **1952**, *48* (2), 696–699.
20. Broxton, T.J. Micellar catalysis of organic reactions. VIII, kinetic studies of the hydrolysis of 2-acetyloxybenzoic acid (aspirin) in the presence of micelles. Aust. J. Chem. **1982**, *35*, 1357–1363.

Received September 18, 2002
Accepted January 15, 2003
Manuscript 5966

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016