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## VOID-COLUMN LIQUID CHROMATOGRAPHIC REACTOR STUDIES TO DETERMINE REACTION RATES IN MOBILE AND STATIONARY PHASES

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### SUMMARY

A liquid chromatographic reactor system was modified to incorporate a void column, connected between two packed octadecylsilane columns. By varying the void-column volume and the eluent flow-rate, reactant retention times in both the mobile and stationary phases can be decoupled, facilitating the simultaneous measurement of rate constants in both phases. The knowledge of mobile phase rates is of special significance, since this makes it possible to evaluate reaction rates in the stationary phase for a variety of columns. From these phase rates it is possible to obtain information about phase compositions and possibly retention mechanisms. The pseudo-first order base-catalyzed esterification reactions of tetrachloroterephthaloyl chloride were studied in the void-column liquid chromatographic reactor for comparison with earlier studies. Kinetic measurements in the methanol eluent in both the void and packed sections were comparable with those obtained from a batch reactor, indicating no significant external or internal mass transfer effects under moderate operating conditions. The stationary phase kinetic data obtained here support the previous generalized model in which solute molecules interact with both the associated methanol pseudo-layer and the octadecylsilane moieties.

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### INTRODUCTION

In previous studies<sup>1,2</sup> two conclusions were drawn from experiments on the organic base-catalyzed tetrachloroterephthaloyl chloride (TCTPCl<sub>2</sub>) esterification reactions in an octadecylsilane bonded liquid-chromatographic (LC) reactor system, operated with a methanol mobile phase. These were: (1) mass transfer effects on reaction kinetic measurements were negligible; and (2) the reaction rate measurements for reaction in the mobile and stationary phases support a generalized assumption of a stationary phase consisting of hydrocarbon ligands with associated methanol molecules. To explore the homogeneous composition assumption in the mobile phase further and to check the experimental accuracy of the stationary phase rate determination, additional studies were made here on determining the on-column rate constants simultaneously in both phases. In the operation of ordinary chromatographic reactors only an apparent or composite rate constant can be obtained by varying the flow-rate of the mobile phase, if a reaction occurs at comparable rates

in both phases. This is because the residence time ratio,  $t_m/t_s$ , is dependent on the intrinsic phase ratio of the volumes occupied by the mobile (m) phase and the stationary (s) phase ( $f_m/f_s$ ) only. Because reaction rates in bonded stationary phases offer considerable promise for understanding retention mechanisms, methods for decoupling and evaluating these rate constants independently are of special interest. Varying the length of an empty column before an analytical chromatographic reactor is an alternative to changing the column phase ratio<sup>3</sup>, but the formation of product inside this empty tube must be considered. Varying the loading of the stationary phase is another<sup>4</sup>, but this is difficult to implement quantitatively with chemically-bonded LC systems. Here, use of a single void column between two chromatographic reactor columns was selected for study as a means for conveniently obtaining kinetic data in both phases. The single void-column LC reactor appears to be an attractive technique for further development when data on reaction kinetics in the mobile-phase solvent are unavailable or inconvenient to obtain with conventional reactor techniques (e.g. reactants of insufficient purity). For slow reactions, incorporation of the void column into the array can also extend the range of rate-constant measurements due to increasing reactant retention in the system; this is especially attractive because of the limited diffusion occurring with LC as compared to gas chromatography (GC).

Void columns of stainless-steel (ss) tubing of varying lengths and diameters were placed between two high-performance liquid chromatography (HPLC) packed columns, so that product peaks from reaction in the void would then be superimposed upon the eluted product wave. These peaks originate in the void column where reaction continues to proceed in the absence of separation. The area of the void peak is proportional to the reaction rate and the volume of the void column<sup>3</sup>. This approach is also attractive for the separation and isolation of any desired product that is formed continuously in the void-column section of the chromatographic reactor array.

Generally, band-broadening in a well packed efficient micro-particular LC column (5–10  $\mu\text{m}$  particle size) has no significant effect on first-order reaction kinetic measurements, while mass-transfer resistances for slow reactions should not be of concern<sup>1,2,5</sup>. Efficiency can be improved by raising the temperature<sup>6</sup>, since the rates of most processes will increase while mobile phase viscosity decreases.

#### EXPERIMENTAL CONSIDERATIONS AND DESIGN

A schematic diagram of the experimental apparatus is shown in Fig. 1. Detailed information on the packed Altex Ultrasphere ODS columns and associated instruments and hardware (including Waters 6000A pump, Perkin-Elmer LC55 UV-VIS detector, and Spectra-Physics SP4000 data processor) for our LC reactor system are described elsewhere<sup>1</sup>. Several void columns made of ss 316 tubing were available (Alltech Assoc., Deerfield, IL, U.S.A.), all of 1/16 in. O.D.: 30 ft.  $\times$  0.01 in. I.D., 50 ft.  $\times$  0.01 in. I.D., 100 ft.  $\times$  0.01 in. I.D., 30 ft.  $\times$  0.02 in. I.D., 50 ft.  $\times$  0.02 in. I.D., and 30 ft.  $\times$  0.03 in. I.D. The choice of column dimensions depends on two requirements which are:

- (1) production of a maximum conversion in the void volume for accurate response measurements;
- (2) minimization of the effect of dispersion in the void column.

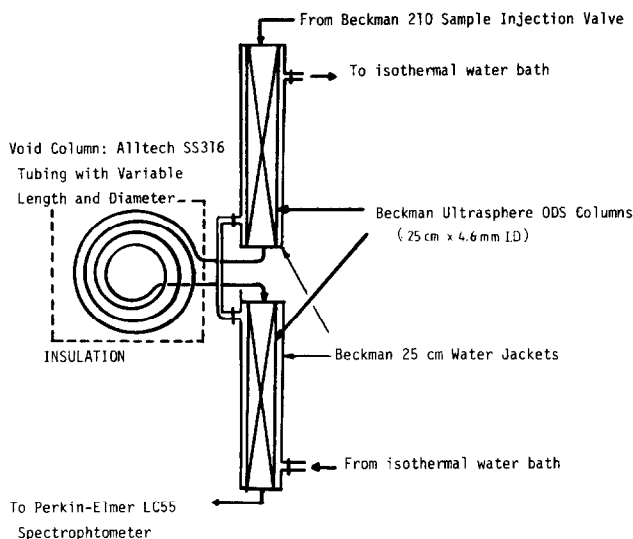


Fig. 1. The design of the single void-column LC reactor. The void column is placed between two Ultrasphere ODS columns, which are encased with water jackets to maintain constant temperature. They are connected in series. (See ref. 1 for description of other related chromatographic equipment.)

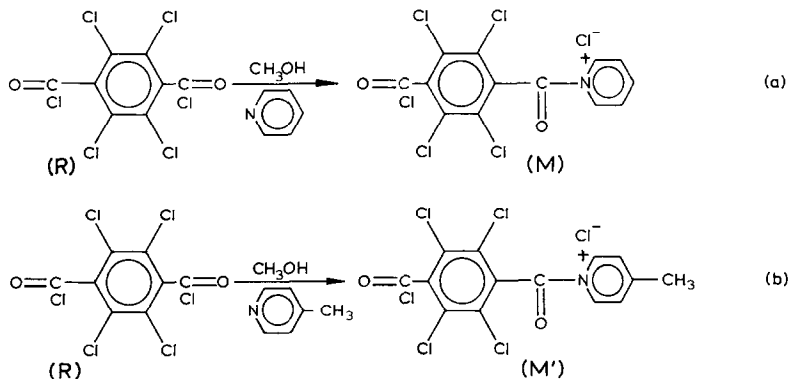
The dispersion effect for this proposed single void-column LC reactor assembly has been examined experimentally. Dispersion in tubes of larger inner diameter (*e.g.*, 30 ft.  $\times$  0.03 in. I.D.) was serious, because laminar or convective dispersion is more pronounced in tubes with large diameters; on the other hand, use of tubings of lesser diameter (*e.g.*, 30 ft.  $\times$  0.01 in. I.D.) did result in insufficient conversion for adequate void-peak response, particularly at relatively fast flow-rates, where there was limited residence time in the void column. Although first order kinetic measurements should not be affected by dispersion good peak resolution is still important for accurate chromatogram interpretation (see Fig. 5). The end and wall effects in chromatographic and empty columns should be minimized, since they can be detrimental to the performance of LC systems<sup>7,8</sup>. Coq *et al.*<sup>5</sup> have found that the variance of band-broadening due to trans-column effects between columns with different inner diameters is proportional to the square of the packed column diameter and the square of the ratio of the diameter of connecting empty tubing and column diameter. The permeability and thickness of the porous frits in the column ends and the mobile phase flow-rate can further contribute to this variance. The spreading, resulting from velocity variations associated with end effects, can be several hundred times higher than that due to velocity inequalities due to laminar flow or convective dispersion in a packed bed<sup>9,10</sup>. We found from the preliminary tests that void columns of both 100 ft.  $\times$  0.01 in. I.D. and 50 ft.  $\times$  0.02 in. I.D. gave reasonable chromatograms, suitable for analysis (*cf.* Figs. 3 and 4) in the operating flow range between 0.10 and 0.90 ml/min.

The connections between the empty tubing and the packed columns were made with low-dead-volume (LDV) female Swagelok nuts (Beckman Instruments, Berkeley, CA, U.S.A.) to minimize further resolution loss. The analytical columns were

two (Beckman) 5- $\mu\text{m}$  Ultrasphere ODS reversed-phase columns (dimension 25 cm  $\times$  0.46 cm I.D.) encased by Beckman water jackets to provide reaction temperature control. The void column was well insulated or immersed in the isothermal water-bath to minimize temperature fluctuations. Other equipment, reagents, and experimental methods employed in this LC reactor system have been described earlier<sup>1,2</sup>.

### Choice of reaction

The reaction choice must match the situation. Since the void peak is superimposed on the eluted product wave, the reaction should be relatively selective with respect to product formation in order to minimize problems in interpretation of reactor chromatograms. Secondly, the reaction rate should be fast enough to produce a significant amount of response for product formed in the void zone. Finally, all the participating species should be resolved in the chromatographic column to minimize any interference and to facilitate the required measurement of peak areas. Here, we have chosen tetrachloroterephthaloyl chloride (TCTPCl<sub>2</sub>), R, as reactant because of familiarity with its reactions<sup>1,11</sup>. With organic bases (pyridine or 4-picoline) in methanol, monoquaternary ammonium salts are formed initially.



The initial intermediate products have been identified earlier as quaternary pyridinium (M) or picolinium chloride (M') salts<sup>11</sup>. Chromatogram peaks are identified and resolved (see Figs. 2–5). Areas for reactant, added inert standard, and product formed in the void section can all be measured for subsequent kinetic analysis.

### Reaction samples and solvents

The reaction sample solution contained 0.0004 *M* of TCTPCl<sub>2</sub> reactant, 0.25 *M* of tetrahydrofuran with 0.017 *M* of 1-phenyloctane inert standard in methanol in all of our experiments. The initial peak ratio of reactant to inert standard measured at 0.9 ml/min methanol was 1.58  $\pm$  0.03. The flow-rate of the mobile phase was varied in a random fashion at 0.1, 0.2, 0.3, 0.6, and 0.9 ml/min. At least four replicate runs were conducted for each flow-rate to provide good experimental data structure for regression analysis. The mobile-phase solvent contained 0.25 *M* tetrahydrofuran in methanol, the base catalyst concentration being varied as follows:

- (1) 4-picoline 0.00615 *M* at 25°C;
- (2) 4-picoline 0.00615 *M* at 35°C;
- (3) pyridine 0.00745 *M* at 25°C;
- (4) pyridine 0.00745 *M* at 35°C.

An experimental design, incorporating features of the four series of experiments above was performed; each containing three separate void-column features: (a) without void (a typical LC reactor), (b) with void column 100 ft. × 0.01 in. I.D. ( $V_{\text{void}} = 1.7 \pm 0.1$  ml), and (c) with void column 50 ft. × 0.02 in. I.D. ( $V_{\text{void}} = 3.7 \pm 0.1$  ml).

#### REACTION KINETIC DATA ANALYSIS

The kinetic analysis for the void-column LC reactor was performed using measured peak areas for reactant, inert standard, and product formed in the void column. Both, linearized and non-linear, rate expressions were used to determine reaction kinetics in both the stationary and mobile phases simultaneously; the rate constants evaluated from these different rate expressions can be cross-checked to insure accurate determination of rate constants in each phase.

##### *Linearized rate expression*

For any designated void column, connected between two packed chromatographic columns, the ratio of  $(t_m + t_{\text{void}})/t_s$  is invariant, where subscripts "m" and "s" for time (*t*) indicate reactant residence periods in the mobile and stationary phases, respectively;  $t_{\text{void}}$  is time in the void column. This experimental feature can be incorporated into a generalized LC reactor treatment, where the total mobile-phase retention time then is  $t_m + t_{\text{void}}$ . The chromatographic area ratio of reactant to inert standard,  $A_R/A_I$ , is equal to (see ref. 1 for detailed derivation)

$$\ln \left( \frac{A_R}{A_I} \right) = \ln \left( \frac{A_R}{A_I} \right)_{t=0} - k_{\text{app}} t_R \quad (1)$$

where the apparent reaction rate constant,  $k_{\text{app}}$ , applies to the total reactant retention time in the system,  $t_R$  (eqn. 2). By employing different void column sizes in LC reactor arrays,  $(t_m + t_{\text{void}})/t_s$  ratios can be varied to provide independent measurement of rate constants in both phases. Then

$$k_{\text{app}} = k_s \left( \frac{t_s}{t_R} \right) + k_m \left( \frac{t_m + t_v}{t_R} \right) \quad (2)$$

or

$$k_{\text{app}} = k_s \left( \frac{t_s}{t_R} \right) + k_m \left( \frac{t_m}{t_R} \right) \left( \frac{t_m + t_v}{t_m} \right) \quad (3)$$

where  $t_m$  or mobile volume can be determined separately, *e.g.* by use of the homologous series method<sup>2,12</sup>. By plotting  $k_{app}$  against the total retention time ratio,  $(t_m + t_v)/t_R$  or  $(t_m + t_v)/t_m$ , following eqns. 2 and 3, the rate constants in the mobile and the stationary phases,  $k_m$  and  $k_s$ , can be obtained directly from the slope and the intercept of the linear plot. This linearized method is advantageous, because it can provide direct visual display on the trend of kinetic measurements. If a first-order reaction is involved, the plot should be linear, and any poor fit of experimental data can be reviewed. This treatment also is free of any need for nonlinear regression software in a computer. Nevertheless, the rate constant measurement is of limited accuracy, since the best-fit straight line with limited data points (*i.e.*, LC reactor, 100 ft.  $\times$  0.01 in. I.D., and 50 ft.  $\times$  0.02 in. I.D. each give a single value in the plot, as illustrated in Fig. 8 below) is subject to errors. The error structure for the original experimental data is also changed upon linearization<sup>13,14</sup>.

#### Non-linear rate expressions

For first-order reactions in the void-columns LC reactor, the output reactant peak area follows an exponential decay<sup>1,3</sup>:

$$\frac{A_R}{A_I} = \left( \frac{A_R}{A_I} \right)_{t=0} \exp(-k_{m,v}t_v - k_{m,c}t_m - k_s t_s) \quad (4)$$

where  $k_{m,v}$  and  $k_{m,c}$  represent the mobile phase rate constant in the void and packed sections, respectively. A discrimination between these two parameters is important because it is desirable to examine the effects of flow pattern or velocity profile on the rate constant measurement.

The first order rate constant in the void section,  $k_{m,v}$ , can be evaluated separately from the area ratio of void peak to inert standard peak,  $A_v/A_I$ :

$$\frac{A_v}{A_I} = \left( \frac{S_R}{S_P} \right) \left( \frac{A_R}{A_I} \right)_{t=0} [1 - \exp(-k_{m,v}t_v)] \quad (5)$$

where  $S_R/S_P$  is the ratio of the detector sensitivity factor for reactant and product.

By obtaining  $A_R/A_I$  ratios with varying retention times,  $t_v$ ,  $t_m$ , and  $t_s$ , through altering void column size and eluent flow-rate (0.1–0.9 ml/min), the initial reactant/inert peak area ratio ( $t = 0$ ) and the rate constant in each phase ( $k_{m,v}$ ,  $k_{m,c}$  and  $k_s$ ) can be estimated using nonlinear regression with eqn. 4 (a four-parameter model). Other simplified (three-parameter) models are available when any known value of these parameters is introduced into the equation. The error structure assumed to be independently distributed<sup>15</sup> is not changed, and more accurate estimates can be obtained with a total of more than 100 data points regressed simultaneously.

A complementary model based on the total product area formed at the system outlet (including the void peak),  $A_p + A_v$ , is also available for analysis<sup>16</sup>:

$$\frac{A_p + A_v}{A_I} = C_1 - C_2 \exp(-k_{m,v}t_v - k_{m,c}t_m - k_s t_s) \quad (6)$$

where  $C_1$  and  $C_2$  are empirical constants, as discussed elsewhere<sup>17</sup>. However, since the reaction chromatogram for base-catalyzed reaction of TCTPCl<sub>2</sub> does not show a resolved pyridinium or 4-picolinium chloride product peak for interpretation because of void-peak formation confounded with other side-products, this rate expression is not recommended for use in evaluating kinetic parameters.

## RESULTS AND DISCUSSION

### Pyridine (0.00745 M) at 35°C

Three series of reaction chromatograms at various flow-rates are shown: Fig. 2 for an LC reactor without the void column, Fig. 3 for the void-column LC reactor with a 100 ft. × 0.01 in. I.D. void column, and Fig. 4 for the LC reactor with 50 ft. × 0.02 in. I.D. void column. In these chromatograms, the decrease of the reactant peak with the increase of the void volume and the retention time can be easily perceived. The chromatogram can be divided into three parts: void, product, and reactant using the procedures described earlier<sup>3,16,18</sup>. A typical chromatogram interpretation with a 100 ft. × 0.01 in. I.D. void column is illustrated in Fig. 5. All peak areas were measured using a planimeter as well as area counts from the data processing unit. The reactant/inert peak area ratios were plotted against the total reactant retention times on a semi-logarithmic scale for both the 100 ft. × 0.01 in. I.D. void-column LC reactor (Fig. 6) and the 50 ft. × 0.02 in. I.D. void-column LC reactor (Fig. 7). Good linearity was observed for both chromatographic reactor systems (correlation coefficient  $r = 0.965$  and  $0.990$ ) with good estimates of the initial reactant/inert standard area ratio (1.47 to 1.58). The  $k_{app}$  values were obtained from the slopes estimated by linear regression; they were then plotted against two different

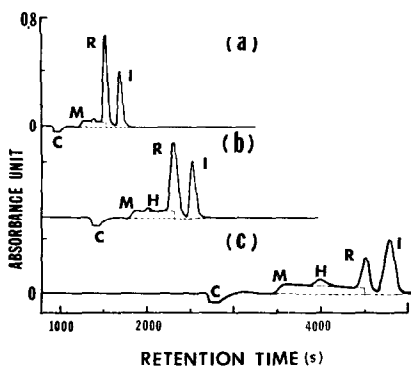


Fig. 2. Typical set of reaction chromatograms for the LC reactor without the void column. Mobile phase: 0.0075 M pyridine–0.123 M THF in methanol at 35°C. R = Reactant (TCTPCl<sub>2</sub>), I = inert standard (1-phenylheptane), M = product (pyridinium, Cl-TCTP), H = Half methyl ester (methyl, Cl-TCTP), C = catalyst (pyridine) vacancy peak. (See text for formulae.) Flow-rate: (a) 0.32 ml/min; (b) 0.21 ml/min; (c) 0.11 ml/min. (See ref. 11 for reactions.)

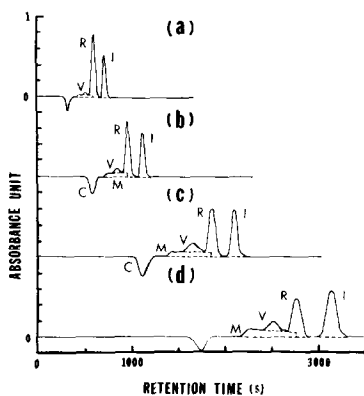


Fig. 3. Typical set of chromatograms for the LC reactor with 100 ft. × 0.01 in. I.D. void column. Mobile phase: 0.0075 M pyridine–0.123 M THF in methanol at 35°C. R = Reactant (TCTPCl<sub>2</sub>), I = inert standard (1-phenylheptane), M = product (pyridinium, Cl-TCTP), C = catalyst (pyridine) vacancy peak, V = product (pyridinium, Cl-TCTP) formed in the void volume. Flow-rate: (a) 0.95 ml/min; (b) 0.63 ml/min; (c) 0.32 ml/min; (d) 0.21 ml/min.

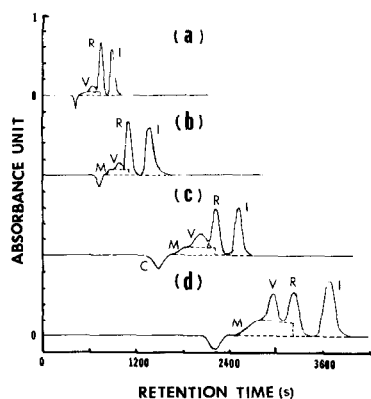


Fig. 4. Typical set of chromatograms for the LC reactor with 50 ft.  $\times$  0.02 in. I.D. void column. Mobile phase: 0.0075 *M* pyridine–0.123 *M* THF in methanol at 35°C. R = Reactant (TCTPCl<sub>2</sub>), I = Inert standard (1-phenyloctane), M = product (pyridinium, Cl-TCTP), V = product (pyridinium salt) formed in the void section, C = catalyst (pyridine) vacancy peak. Flow-rate: (a) 0.95 ml/min; (b) 0.63 ml/min; (c) 0.32 ml/min; (d) 0.21 ml/min.

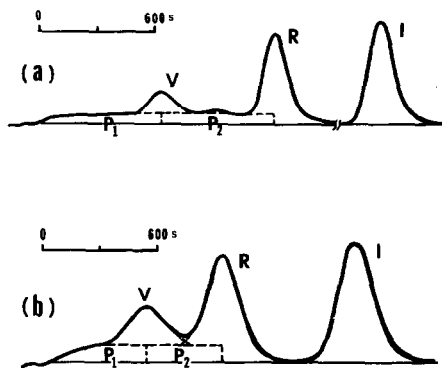


Fig. 5. Reaction chromatogram interpretation for the single void-column LC reactor. (a) with 100 ft.  $\times$  0.01 in. I.D. void column at 0.21 ml/min; (b) with 50 ft.  $\times$  0.02 in. I.D. void column at 0.32 ml/min. Mobile phase: 0.0075 *M* pyridine–0.123 *M* THF in methanol at 35°C. V = Product (pyridinium, Cl-TCTP) peak formed in the void section, P<sub>1</sub>, P<sub>2</sub> = product M (pyridinium, Cl-TCTP) formed in the first and second packed columns, respectively. R = Reactant (TCTPCl<sub>2</sub>), I = inert standard (1-phenylheptane).

retention ratios,  $(t_m + t_v/t_R$  and  $(t_m + t_v)/t_m$ , on the basis of reactant retention volumes at 8.4 ml (Fig. 8a and b). The rate constants with one standard deviation,  $k_m$  and  $k_s$ , were also estimated using linear least-squares in the MINITAB statistical package<sup>19</sup>. Excellent linearity ( $t = 0.997$  and  $0.998$ ) was found for both methods, indicating that simple first-order reaction kinetics are followed in the void-column chromatographic system. The agreement of rate estimates using different retention

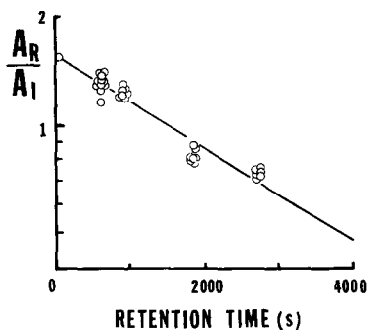


Fig. 6. Inert standard method plot of area ratio  $A_R/A_I$  versus reactant retention time,  $t_R$ , for the void-column LC reactor with 50 ft.  $\times$  0.02 in. I.D. void column at 35°C. Catalyst: 0.0075 *M* pyridine in methanol.  $A_R/A_I = \ln(1.581 \pm 0.058) - (0.0003058 \pm 0.00001185)t_R$  by linear regression, using eqn. 1.

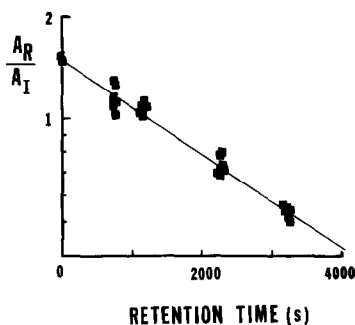


Fig. 7. Inert standard method plot of area ratio  $A_R/A_I$  versus reactant retention time  $t_R$  for the void-column LC reactor with 50 ft.  $\times$  0.02 in. I.D. void column at 35°C. Catalyst: 0.0075 *M* pyridine in methanol.  $A_R/A_I = \ln(1.467 \pm 0.053) - (0.0003105 \pm 0.0000078)t_R$  by linear regression, using eqn. 1.



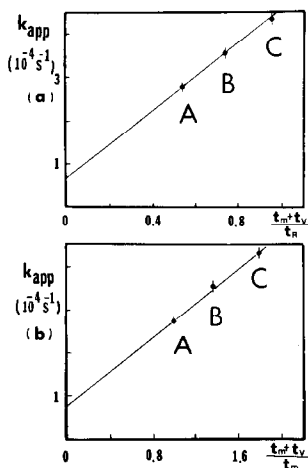


Fig. 8. Linear plot of apparent rate constant,  $k_{app}$ , versus retention time ratio (a)  $(t_m + t_v)/t_R$  and (b)  $(t_m + t_v)/t_m$  for the void-column LC reactor. Reaction: the first-step of 0.0075 *M* pyridine-catalyzed esterification of TCTPCl<sub>2</sub> at 35°C (reaction a). Here, points A, B and C correspond to the apparent rate constant values, obtained from the LC reactor without the void column, the void-column LC reactor with 100 ft.  $\times$  0.01 in. I.D. void column (Fig. 6), and the reactor with 50 ft.  $\times$  0.02 in. I.D. void column (Fig. 7), respectively. (See eqns. 2 and 3.)

ratios (see eqns. 2 and 3) suggests little effect from retention data measurements. The mobile phase rate constants [ $k_m = (3.83 \pm 0.23) \cdot 10^{-4}$  or  $(3.74 \pm 0.28) \cdot 10^{-4} \text{ s}^{-1}$ ] were quite comparable to data obtained from a complete mixed batch reactor [ $(3.80 \pm 0.15) \cdot 10^{-4} \text{ s}^{-1}$ ]. This supports the earlier assumption that the mobile-phase composition is homogeneous. The axial dispersion effect, which might be significant in LC columns<sup>2,20</sup>, apparently does not affect the kinetic measurements for first-order reactions. Furthermore, it validates the LC reactor approach for evaluation reaction kinetics in the mobile phase solvent.

A separate nonlinear least-squares analysis with 134 data points was conducted, using eqn. 4, and the results are summarized in Table I. The nonlinear regression routine LS which used a modified Newton–Gauss method was employed for parameter estimation<sup>21</sup>. Examination of the results showed that rate estimates in both mobile and the stationary phases were quite comparable to the predicted or experimental values, the correlation between  $k_m$  and  $k_s$  was decoupled (coefficient =  $-0.88316$ ), and the residuals were randomly distributed around the model-predicted values. If we assume that the rate constant in the packed section is known ( $3.8 \cdot 10^{-4} \text{ s}^{-1}$ ), the rate estimate in the void column [ $k_{m,v} = (4.10 \pm 0.66) \cdot 10^{-4} \text{ s}^{-1}$ ] was in fair agreement with the batch reactor value [ $k_{m,c} = (3.80 \pm 0.15) \cdot 10^{-4} \text{ s}^{-1}$ ]. The discrepancy might arise from the effect of velocity profiles in the void section. It has been established that for first-order reactions conversion is smaller in a laminar-flow reactor than in a plug-flow (packed-bed) reactor<sup>22</sup>. For the flow-rates (0.1–0.9 ml/min) used here, a laminar flow is developed in the void column; thus, it is reasonable to obtain an overestimated rate constant ( $k_{m,v}$ ) in the void section, assuming the same conversion.

Although relatively large errors were associated with the estimates, it is per-

TABLE I

COMPARISON OF METHANOL-THF MOBILE PHASE RATE CONSTANTS IN THE VOID AND THE PACKED COLUMNS OF THE LC REACTOR FOR THE 0.0075 M PYRIDINE-CATALYZED REACTION OF TCTPCl<sub>2</sub> AT 35°C

RSS = residual sum of squares.

$A_{R0}/A_I^*$	$k_m(\text{void})^{**}$ ( $10^{-4} \text{ s}^{-1}$ )	$k_m(\text{packed})^{**}$ ( $10^{-4} \text{ s}^{-1}$ )	$k_s(\text{column})^{***}$ ( $10^{-4} \text{ s}^{-1}$ )	Corr. matrix	RSS
1.524 ± 0.032 <sup>§</sup>		4.021 ± 0.587	1.209 ± 0.833	$\begin{vmatrix} 1 & & & \\ 0.35033 & 1 & & \\ 0.01285 & -0.90038 & 1 & \\ & & & \end{vmatrix}$	0.64238
1.524 ± 0.032 <sup>§§</sup>		3.975 ± 0.536	1.254 ± 0.757	$\begin{vmatrix} 1 & & & \\ 0.36392 & 1 & & \\ 0.02936 & -0.88316 & 1 & \\ & & & \end{vmatrix}$	0.63314
1.526 ± 0.033 <sup>§§§</sup>	4.096 ± 0.659	3.80	1.473 ± 0.357	$\begin{vmatrix} 1 & & & \\ 0.39234 & 1 & & \\ 0.70313 & -0.08850 & 1 & \\ & & & \end{vmatrix}$	0.64118
1.58 <sup>†</sup>	3.709 ± 0.157	—	—	—	0.5180

\* Experimental measurement is 1.58 ± 1.62.

\*\* From completely mixing batch reactor study,  $k_m = (3.80 \pm 0.15) \cdot 10^{-4} \text{ s}^{-1}$ .

\*\*\* Predicted rate constants for stationary phase models I and II are  $(2.38 \pm 0.43) \cdot 10^{-4} \text{ s}^{-1}$  and  $(0.75 \pm 0.24) \cdot 10^{-4} \text{ s}^{-1}$  respectively; see ref. 1 for detailed calculations and discussion.

§ Estimated with  $V_m + V_{\text{void}} = 8.1 \text{ ml}$  using  $A_R/A_I$  measurements (eqn. 4).

§§ Estimated with  $V_m + V_{\text{void}} = 8.3 \text{ ml}$  using  $A_R/A_I$  measurements (eqn. 4).

§§§ Substituted with a "known" value of the mobile phase constant to decouple  $k_s$  and  $k_{m,\text{void}}$  (eqn. 4).

† Estimated using  $A_R/A_I$  measurements (eqn. 5).

TABLE II  
COMPARISON OF METHANOL-THE MOBILE PHASE RATE CONSTANTS IN THE VOID AND THE PACKED COLUMNS OF THE LC REACTOR  
FOR THE 0.0075 M PYRIDINE-CATALYZED REACTION OF TCTPCl<sub>2</sub> AT 25°C

$A_{\text{rel}}/A_I^*$	$k_m(\text{void})^{**}$ ( $10^{-4} \text{ s}^{-1}$ )	$k_m(\text{packed})^{**}$ ( $10^{-4} \text{ s}^{-1}$ )	$k_p(\text{column})^{***}$ ( $10^{-4} \text{ s}^{-1}$ )	Corr. matrix	RSS
1.510 ± 0.027 <sup>§</sup>		2.194 ± 0.387	0.316 ± 0.495	$\begin{vmatrix} 1 & & & & \\ 0.47641 & 1 & & & \\ -0.14754 & -0.91193 & 1 & & \\ & & & & \\ & & & & \end{vmatrix}$	0.36349
1.509 ± 0.026 <sup>§§</sup>		2.110 ± 0.355	0.460 ± 0.437	$\begin{vmatrix} 1 & & & & \\ 0.48530 & 1 & & & \\ -0.11817 & -0.89098 & 1 & & \\ & & & & \\ & & & & \end{vmatrix}$	0.36516
1.512 ± 0.029 <sup>§§§</sup>	2.194 ± 0.624	1.853 ± 3.963	0.752 ± 4.528	$\begin{vmatrix} 1 & & & & \\ 0.54277 & 1 & & & \\ -0.28323 & -0.74855 & 1 & & \\ 0.31298 & 0.75008 & -0.99904 & 1 & \\ & & & & \end{vmatrix}$	0.36230
1.511 ± 0.027 <sup>†</sup>	2.159 ± 0.412	2.15	0.414 ± 0.198	$\begin{vmatrix} 1 & & & & \\ 0.51993 & 1 & & & \\ 0.71389 & 0.07745 & 1 & & \\ & & & & \\ & & & & \end{vmatrix}$	0.36237
1.511 ± 0.025 <sup>†</sup>	2.15	2.035 ± 2.615	0.545 ± 2.981	$\begin{vmatrix} 1 & & & & \\ 0.21833 & 1 & & & \\ -0.16678 & -0.99781 & 1 & & \\ & & & & \\ & & & & \end{vmatrix}$	0.36237

\* Experimental measurement in 1.58–1.60.

\*\* From completely mixing batch reactor study,  $k_m = (2.15 \pm 0.09) \cdot 10^{-4} \text{ s}^{-1}$ .

\*\*\* Predicted rate constants for stationary phase models I and II are  $(1.54 \pm 0.28) \cdot 10^{-4} \text{ s}^{-1}$  and  $(0.43 \pm 0.15) \cdot 10^{-4} \text{ s}^{-1}$  respectively.

§ Estimated with the column dead volume,  $V_m = 4.5 \text{ ml}$ , using a three-parameter model (eqn. 4).

§§ Estimated with the column dead volume,  $V_m = 4.6 \text{ ml}$ , using a three-parameter model (eqn. 4).

§§§ Obtained from the  $A_{\text{rel}}/A_I$  measurements (eqn. 4) with a four-parameter model.

† Substituted with a "known" value of the mobile-phase rate constant,  $k_m$ .

inent to find that  $k_s$  and  $k_{m, \text{void}}$  were completely decoupled (coefficient =  $-0.0885$ ). A separate estimation, using the  $A_v/A_1$  data (eqn. 5), also showed good consistency for the rate constant in the void section [ $(3.71 \pm 0.16) \cdot 10^{-4} \text{ s}^{-1}$ ]. The independently determined rate estimates in the stationary phase [ $k_s = (1.21 \pm 0.83) \cdot 10^{-4}$  or  $(1.25 \pm 0.76) \cdot 10^{-4} \text{ s}^{-1}$ ] support the concept of a composite stationary phase, operative between models I and II but favoring model II, as discussed in a previous paper<sup>1</sup>. Here model I refers to the stationary phase model, proposed by Knox and Pryde<sup>2,3</sup>, where solute molecules interact with the associated methanol pseudo-layer only, while model II refers to a generalized stationary phase model, composed of methanol molecules associated with octadecylsilane ligands, as proposed by Yonker *et al.*<sup>2,4</sup>.

#### *Pyridine (0.00745 M) at 25°C*

The linear plots of  $A_R/A_1$  versus  $t_R$  for the first step of the TCTPCl<sub>2</sub> reaction with 0.00745 M pyridine catalyst in tetrahydrofuran (THF)–methanol (2:98) at 25°C were obtained in a similar manner for the single void-column LC reactor with both a 100 ft.  $\times$  0.01 in. void column and a 50 ft.  $\times$  0.02 in. I.D. void column. These plots manifest good linearity and agreement with initial experimental values. The calculated apparent rate constants, obtained from eqn. 1, were then plotted against two retention time ratios,  $(t_m + t_v)/t_R$  and  $(t_m + t_v)/t_m$ , to evaluate the rate constants  $k_m$  and  $k_s$ , respectively, using eqns. 2 and 3. Relatively large errors were associated with the stationary phase estimates [ $k_s = (0.76 \pm 1.38) \cdot 10^{-4}$  or  $(0.78 \pm 1.41) \cdot 10^{-4} \text{ s}^{-1}$ ] because of the more scattered  $k_{\text{app}}$  values associated with the low conversion for this slow reaction. Nevertheless, the estimates still show fair agreement with the predicted value from the idealized dispersion [ $k_{s, \text{II}} = (0.43 \pm 0.15) \cdot 10^{-4} \text{ s}^{-1}$ ] compared with that of Knox and Pryde [ $k_{s, \text{I}} = (1.54 \pm 0.28) \cdot 10^{-4} \text{ s}^{-1}$ ]. Since the mobile phase rate values [ $k_m = (2.07 \pm 0.88) \cdot 10^{-4}$  or  $(2.06 \pm 0.90) \cdot 10^{-4} \text{ s}^{-1}$ ] are comparable with the value obtained from a well-mixed batch reactor [ $(2.15 \pm 0.09) \cdot 10^{-4} \text{ s}^{-1}$ ], it appears that there are little or no external (diffusion from the bulk liquid in the interstices to the particle surface) or internal (pore diffusion) mass transfer limitations. This is because the reaction rates studied here are relatively slow, so that the effect of reactant diffusion is not significant in the measurement<sup>2</sup>.

The results from the nonlinear regression analysis are summarized in Table II. The calculated rate constants in both phases agree with the expected values but less error is associated with the stationary phase estimate. This is because a total of 110 data from three void-column experiments were regressed simultaneously to decouple as well as estimate the rate parameters in the two-phase chromatographic system. The effect of a variation of dead volume measurement,  $V_m$ , on the kinetic studies was also tested; while an error of 0.1 ml in  $V_m = 4.5 \text{ ml}$  produces only a *ca.* 4% error in the mobile phase rate constant, it can cause about 30% uncertainty in the stationary phase value. When the decoupling role of the void column was removed by using a "known" value ( $2.15 \cdot 10^{-4} \text{ s}^{-1}$ ) for  $k_{m, \text{void}}$ , highly correlated but less accurate rate estimates were obtained (coefficient =  $-0.99781$ ); when the mobile phase rate constant from a batch study ( $k_{m, \text{c}} = 2.15 \cdot 10^{-4} \text{ s}^{-1}$ ) was directly substituted into the treatment based on eqn. 4, the estimates of  $k_{m, \text{void}}$  and  $k_s$  were completely decoupled (coefficient =  $0.07745$ ). This demonstrates the realization of the original objective of decoupling rate constants with the introduction of an independently varied void-column size.

## 4-Picoline (0.00615 M) at 35°C

The apparent rate constants obtained from the linear plots of  $\ln(A_R/A_I)$  versus  $t_R$  (Figs. 9 and 10) were again plotted against two retention time ratios to evaluate rate constants in both phases (Fig. 11a and b). Linearity ( $r = 1.000$ ) was observed for both cases. It is worth noting again that the dead-volume estimate does have a significant effect on the rate-constant measurements. For the 50 ft.  $\times$  0.02 in. I.D. void-column LC reactor in both figures, the dashed and solid lines represent the linear plots with  $V_m + V_{\text{void}} = 8.3$  and 8.1 ml, respectively. An error of 0.2 ml can change the mobile phase estimates from  $(7.77 \pm 0.06) \cdot 10^{-4}$  or  $(7.74 \pm 0.20) \cdot 10^{-4}$  to  $(8.13 \pm 0.14) \cdot 10^{-4}$  or  $(8.14 \pm 0.01) \cdot 10^{-4} \text{ s}^{-1}$ , and the stationary phase values from  $(1.61 \pm 0.10) \cdot 10^{-4}$  or  $(1.71 \pm 0.35) \cdot 10^{-4}$  to  $(1.12 \pm 0.24) \cdot 10^{-4}$  or  $1.16 \pm 0.01) \cdot 10^{-4} \text{ s}^{-1}$ . Thus, kinetic studies utilizing the LC reactor require not only accurate area measurements but also accurate determination of reactant retention data and dead-volume.

As before, a nonlinear regression with 120  $A_R/A_I$  data was conducted using eqn. 4. The estimated rate parameters in the mobile phase were comparable with the batch reactor values (Table III), while the stationary-phase rates were in agreement with those predicted from the modified model of Burke *et al.*<sup>24</sup> rather than that of Knox and Pryde<sup>23</sup>. This discrimination between the stationary phase models is achieved through the measurements. To check for any possible systematic errors during experiments, the reproducibility of the apparent rate constant was further examined. The  $k_{\text{app}}$  value without the void column, obtained from this work  $[(4.99 \pm 0.07) \cdot 10^{-4} \text{ s}^{-1}]$ , was compared with that measured by Bolme and Langer<sup>25</sup>  $[(4.95 \pm 0.24) \cdot 10^{-4} \text{ s}^{-1}]$ , who used a different sample preparation procedure, different initial ratio of reactant to inert standard, and a different data analysis method [to correct for large accumulation of undesired (4-methoxycarbonyl-2,3,5,6-tetrachloro-

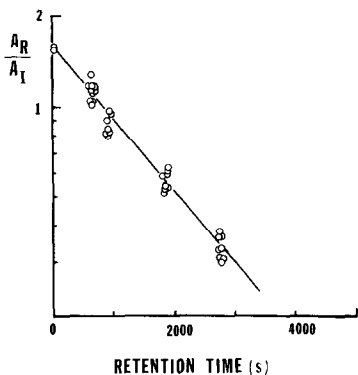


Fig. 9. Inert standard method plot of area ratio  $A_R/A_I$  versus reactant retention time,  $t_R$ , for the void-column LC reactor with 100 ft.  $\times$  0.01 in. I.D. void column at 35°C. Catalyst: 0.00615 M 4-picoline in methanol.  $A_R/A_I = \ln(1.551 \pm 0.054) - (0.000556 \pm 0.0000098)t_R$  by linear regression, using eqn. 1.

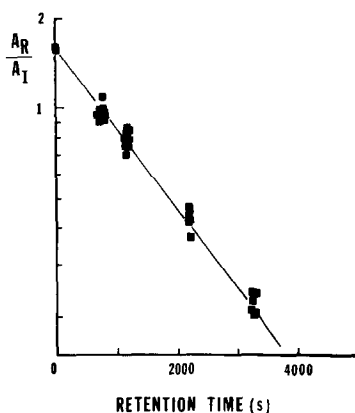


Fig. 10. Inert standard method plot of area ratio  $A_R/A_I$  versus reactant retention time,  $t_R$ , for the void-column LC reactor with 50 ft.  $\times$  0.02 in. I.D. void column at 35°C. Catalyst: 0.00615 M 4-picoline in methanol.  $A_R/A_I = \ln(1.518 \pm 0.051) - (0.000600 \pm 0.0000088)t_R$  by linear regression, using eqn. 1.

TABLE III  
ESTIMATION OF METHANOL-THE MOBILE PHASE RATE CONSTANTS IN THE VOID AND THE PACKED COLUMNS OF THE LC REACTOR FOR THE 0.00615 M 4-PICOLINE-CATALYZED REACTION OF TCTPCl<sub>2</sub> AT 35°C

$A_{\text{sol}}/A_I^*$	$k_m(\text{void})^{**}$ ( $10^{-4} \text{ s}^{-1}$ )	$k_m(\text{packed})^{**}$ ( $10^{-4} \text{ s}^{-1}$ )	$k_s(\text{column})^{***}$ ( $10^{-4} \text{ s}^{-1}$ )	Corr. matrix	RSS
1.496 ± 0.032 <sup>§</sup>		7.706 ± 0.616	1.215 ± 1.047	$\begin{vmatrix} 1 & & & \\ 0.17889 & 1 & & \\ 0.27002 & -0.86633 & 1 & \\ & & & \end{vmatrix}$	0.25504
1.496 ± 0.033 <sup>§§</sup>		8.080 ± 0.677	0.720 ± 1.135	$\begin{vmatrix} 1 & & & \\ 0.13837 & 1 & & \\ 0.26826 & -0.89015 & 1 & \\ & & & \end{vmatrix}$	0.24966
1.496 ± 0.033	7.812 ± 0.700	7.26	1.713 ± 0.553	$\begin{vmatrix} 1 & & & \\ 0.22034 & 1 & & \\ 0.75560 & -0.26608 & 1 & \\ & & & \end{vmatrix}$	0.26025
1.489 ± 0.034	7.26	8.028 ± 5.330	0.884 ± 6.912	$\begin{vmatrix} 1 & & & \\ -0.33680 & 1 & & \\ 0.39957 & -0.99694 & 1 & \\ & & & \end{vmatrix}$	0.26565

\* Experimental measurement is 1.58-1.67.

\*\* From completely mixing batch reactor study,  $k_m = (7.26 \pm 0.06) \cdot 10^{-4} \text{ s}^{-1}$ .

\*\*\* Predicted rate constants for stationary phase models I and II are  $(3.97 \pm 0.45) \cdot 10^{-4} \text{ s}^{-1}$  and  $(1.25 \pm 0.25) \cdot 10^{-4} \text{ s}^{-1}$  respectively.

§ With  $V_m + V_{\text{void}} = 8.1 \text{ ml}$  from  $A_R/A_I$  measurements (eqn. 4).

§§ With  $V_m + V_{\text{void}} = 8.3 \text{ ml}$  from  $A_R/A_I$  measurements (eqn. 4).

TABLE IV  
ESTIMATION OF METHANOL-THE MOBILE PHASE RATE CONSTANTS IN THE VOID AND THE PACKED COLUMNS OF THE LC REACTOR FOR THE 0.00615 M 4-PICOLINE-CATALYZED REACTION OF TCPCl<sub>2</sub> AT 25°C

$A_{\text{rel}}/A_I^*$	$k_m(\text{void})^{**}$ ( $10^{-4} \text{ s}^{-1}$ )	$k_m(\text{packed})^{**}$ ( $10^{-4} \text{ s}^{-1}$ )	$k_s(\text{column})^{***}$ ( $10^{-4} \text{ s}^{-1}$ )	Corr. matrix	RRS
$1.401 \pm 0.264^{\S}$		$3.670 \pm 0.777$	$1.442 \pm 1.095$	$\begin{vmatrix} 1 & & & \\ 0.3108 & 1 & & \\ -0.0477 & 0.9069 & 1 & \\ & & & \end{vmatrix}$	0.29020
$1.400 \pm 0.0372^{\S}$	4.00	$3.677 \pm 0.758$	$1.057 \pm 0.469$	$\begin{vmatrix} 1 & & & \\ 0.3644 & 1 & & \\ 0.6903 & -0.1763 & 1 & \\ & & & \end{vmatrix}$	0.29016
$1.40^{\S}$	4.00	$3.675 \pm 0.701$	$1.055 \pm 0.338$	$\begin{vmatrix} 1 & & & \\ -0.6350 & 1 & & \\ & & & \end{vmatrix}$	0.29016
$1.590 \pm 2.388^{\S\S}$	$3.386 \pm 5.594$	—	—	$\begin{vmatrix} 1 & & & \\ & & & \\ -0.99950 & 1 & & \\ & & & \end{vmatrix}$	0.00976
$1.40^{\S\S}$	$3.898 \pm 0.204$	—	—	$\begin{vmatrix} 1 & & & \\ & & & \\ & & & \\ & & & \end{vmatrix}$	0.00978

\* Experimental measurement is  $1.45 \pm 0.05$ .

\*\* From completely mixing batch reactor study,  $k_m = (4.03 \pm 0.06) \cdot 10^{-4} \text{ s}^{-1}$ .

\*\*\* Predicted rate constants for stationary phase models I and II are  $(3.24 \pm 0.52) \cdot 10^{-4} \text{ s}^{-1}$  and  $(0.90 \pm 0.27) \cdot 10^{-4} \text{ s}^{-1}$  respectively.

§ Values obtained from the  $A_R/A_I$  measurements (eqn. 4).

§§ Values from the  $A_S/A_I$  measurements (eqn. 5).

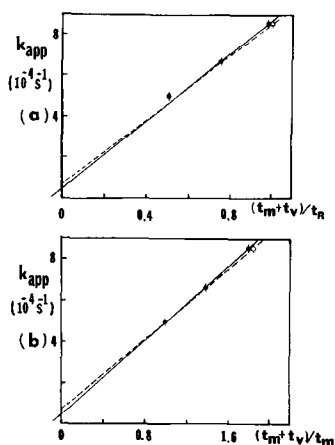


Fig. 11. Linear plot of apparent rate constant,  $k_{app}$ , versus retention time ratio (a)  $(t_m + t_v)/t_R$  and (b)  $(t_m + t_v)/t_m$  for the void-column LC reactor. Reaction: the first-step of 0.00615 *M* 4-picoline-catalyzed esterification of TCTPCl<sub>2</sub> at 35°C. The dashed and solid lines represent the linear plots with  $V_m + V_{void} = 8.3$  and 8.1 ml, respectively. (See text for detailed discussion.)

benzoyl chloride) half ester intermediate]. The agreement between these two values, measured three years apart, reflects the consistency and reproducibility of the LC reactor experimental results under carefully controlled conditions.

#### 4-Picoline (0.00615 *M*) at 25°C

The linearized method (eqn. 1) was used again to evaluate the apparent rate constants for both the 100 ft.  $\times$  0.01 in. I.D. void-column LC reactor and the 50 ft.  $\times$  0.02 in. I.D. void-column LC reactor. Despite data scattering for the large void column at low flow-rates because of dispersion effects, good linearity was still observed for both cases ( $r = 0.987$  and 0.985). This is because the first-order rate constant would be independent of reactant concentration variation due to moderate flow dispersion (dilution) along the chromatographic column. The rate constants in both phases were measured from the linear plots to estimate reaction kinetics in both phases. Use of two different retention ratios assures consistent rate estimates, free of measurement error, in retention data. The estimated mobile phase kinetics [ $k_m = (3.66 \pm 0.33) \cdot 10^{-4}$  or  $(3.61 \pm 0.38) \cdot 10^{-4} \text{ s}^{-1}$ ] agree within the experimental error with the batch reactor value [ $(4.03 \pm 0.06) \cdot 10^{-4} \text{ s}^{-1}$ ], while those in the stationary phase suggest a generalized model involving both the methanol pseudo-layer and the octadecylsilanes [ $k_{s,II} = (0.90 \pm 0.27) \cdot 10^{-4} \text{ s}^{-1}$ ]. Results from the nonlinear models of eqns. 4 and 5 with 80 data points all drew the same conclusions regarding the "homogeneous continuum" assumption in the mobile phase and the generalized-partition stationary phase mechanism (Table IV).

Generally speaking, the single void-column LC reactor appears to be a suitable method for studying the on-line two-phase reaction kinetics simultaneously. By simply varying the void-column size and the eluent flow-rate, reactant residence times in two phases can be changed because of the incorporation of retention variation in the void column of the void-column LC reactor array; thus, rate constants in each phase can be measured independently.



The reaction technique illustrated here can be utilized as a diagnostic method for detecting any void zone in chromatographic columns<sup>26</sup>; from the shape of the reaction product curve in the chromatograms substantial information can be obtained about the homogeneity of the column packing. Knowledge of the first-order mobile and stationary phase rate constants and a detectable void peak also make it possible to estimate void-zone volumes<sup>3</sup>.

## APPENDIX

*Temperature inhomogeneity effect on reaction kinetic measurement in LC reactors*

For the analytical-scale chromatographic reactor with small pulsed injection of reactant solution, isothermal conditions have been assumed for the whole reactor system. For GC reactors, this temperature homogeneity assumption is valid, except for extremely exothermic or endothermic reactions. However, LC columns of moderate lengths are usually operated at pressure drops up to several thousand pounds per square inch to obtain reasonable flow-rates through the 5–10  $\mu\text{m}$  microparticle-packed columns. Under such conditions, internal heat generation, due to irreversible viscous dissipation, can result in non-uniform temperature distribution in the column<sup>27,28</sup>.

For our LC reactor, where the radial dependence of temperature ( $T$ ) is not of major concern, it would be of interest to know the magnitude of a maximum possible temperature increase due to the viscous dissipation<sup>29–31</sup>. For methanol flow-rates ranging from 0.1 to 0.9 ml/min,

(a) At 0.9 ml/min methanol with pressure drop ( $\Delta p$ ) about 2000 p.s.i.,

$$\Delta T_{\max} = \frac{u_0(\Delta p/L)R^2}{4k_c} = \frac{F}{\pi} \frac{(\Delta p/L)}{4k_c}, \quad k_{c,\text{methanol}} = 0.0004 \text{ cal/cm s } ^\circ\text{C} \quad (\text{A1})$$

where  $u_0$  is the linear velocity of the mobile phase solvent,  $L$  is the column length,  $R$  is the column internal radius and  $F$  is the mobile phase flow-rate; therefore

$$\begin{aligned} \Delta T_{\max} &= \frac{0.90 \text{ ml/min} \left( \frac{2000 \text{ p.s.i.}}{14.7 \text{ p.s.i.}} \cdot 1033.3 \text{ gr cm/50 cm} \right)}{\pi \cdot 4 \cdot 0.0004 \cdot 60 \text{ cal/cm min } ^\circ\text{C}} \\ &= 0.084 \cdot 10^5 \text{ gr cm } \frac{^\circ\text{C}}{\text{cal}} \\ &= 0.084 \text{ kg}_f \text{ m} \cdot 23.44 \frac{\text{cal}}{\text{kg}_f \text{ m cal}} \frac{^\circ\text{C}}{\text{cal}} \simeq 2^\circ\text{C} \end{aligned} \quad (\text{A2})$$

The average temperature increase will be around  $1^\circ\text{C}$ . For activation energies of base-catalyzed reactions studied here,  $E_a = 10\,500 \text{ cal/mol}$ , thus only 6% error in rate constant measurements will be incurred due to viscous heat generation at 0.9 ml/min flow-rate.

(b) At 0.1 ml/min methanol with pressure drop about 500 p.s.i., the same

treatment can be applied to obtain  $\Delta T_{\max} = 0.08^{\circ}\text{C}$  or  $\Delta T_{\text{average}} = 0.04^{\circ}\text{C}$ . Thus, only 0.25% error will be introduced into rate-constant estimates.

The calculation above shows that the influence of the viscous heat effect should not be significant, since the flow-rate range here is limited to below 0.9 ml/min to achieve appreciable residence time for the relatively slow reactions. Therefore, for the analytical physicochemical application purpose, the chromatographic system can be assumed to be isothermal, as outlined in the ideal chromatographic reactor treatment<sup>3,2</sup>. However, precautions would be appropriate when high flow-rates with small particle sizes are employed.

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