

Polarimetric Determination of Activation Heat Capacity (ΔC_p^\ddagger)

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The study of reaction mechanisms of solvolytic reactions involves the determination of various kinetic and thermodynamic parameters. To probe solute–solvent interactions, the heat capacity of activation (ΔC_p^\ddagger) is sometimes determined. This parameter is a measure of the deviation from linearity of a plot of $\log k$ versus $1/T$. Hence, the determination of ΔC_p^\ddagger requires very precise kinetic experiments. Most such kinetic experiments are based on conductimetric techniques, which in turn involves salt buffering of the solutions to get precise experimental results.

This study is aimed at determining whether salt buffering introduces a systematic bias in the heat capacity of activation.

Kinetic studies of solvolytic reactions aim at the determination of the reaction mechanism or, in current terminology, establishing the structure of the transition state. An important part of the knowledge about reaction mechanisms concerns the influence of the solvent. This knowledge is especially interesting when water is used as solvent since water is widely present and also has unique solvent properties. Investigations concerning the role of water in simple chemical reactions might therefore give insight in problem areas of basic importance.

Present knowledge about water is far from complete. Thus, for instance, several theories exist about the structure of pure water.^{1–5} In systems where water acts as solvent the degree of complexity increases even further. There are presently mainly qualitative rules developed of how water structure is influenced by the addition of solutes.^{6,7} Thus ionic species are said to break down existing water structure but nonpolar species, such as hydrocarbons, are said to have the opposite effect; the solvent structure is increased.

One way to approach the understanding of changes in solvent structure during a reaction is to

determine the activation parameters ΔH^\ddagger , ΔS^\ddagger and ΔC_p^\ddagger from the temperature dependence of the experimental rate constant. The parameter ΔC_p^\ddagger is considered to be related to how the structure of the system including the solvent changes from initial state to transition state (for a review, see Ref. 8).

A difficulty with the hydrolysis of organic molecules is that they in general are sparingly soluble in water. There are two ways to solve that problem. One is to choose a measuring method which works in very dilute solutions. Another is to modify the reactant so that the solubility increases. The first method usually means that conductometric measurements are performed. A comprehensive work of conductometric measurements of solvolytic reactions has been made by Robertson and coworkers.^{7,9–17} The method is well developed and the thermodynamic parameters can be determined with high reproducibility.

There is, however, an important objection against the conductometric method. In order to get good results, the experimental solution must be buffered with salt to give a salt concentration which is almost constant during the reaction. Otherwise, the conductivity will increase sharply in the beginning of the reaction, resulting in low precision in the kinetic measurements.

The buffering with salt might, however, change the structure of the solvent and thus introduce a systematic error in the estimation of the activation parameters. Hence, it is of interest to compare the results of the second approach, namely when the solubility of the reactant is increased so as to allow the kinetic study of a relatively undisturbed system.

Our primary interest has been to determine rate constants with high precision in order to obtain precise activation heat capacities (ΔC_p^\ddagger). We have not made any detailed mechanistic study of the present reactions but they have been assumed to

follow pseudo first order kinetics. To get information about whether salt buffering causes biased estimates of ΔC_p^\ddagger we have made two types of evaluations. In one we use a spline function to represent kinetic data and gives a local determination of the rate constants. In the other we use ordinary logarithmic linear representation to obtain a conventional determination of the rate constants.

From derived rate constants, activation heat capacities (ΔC_p^\ddagger) were evaluated in two ways. The results show that ΔC_p^\ddagger is very sensitive to the method of its determination. This constitutes a warning against using ΔC_p^\ddagger -values alone for the study of charges in solvent structure.

The steps in a ΔC_p^\ddagger determination. The determination of the activation heat capacity (ΔC_p^\ddagger) for a reaction involves two steps.

First a number of kinetic runs are made at different temperatures T_1, T_2, \dots, T_N (the temperature is constant within each kinetic run). The analysis of the resulting data gives values of the rate constant k at the different temperatures, say, k_1, k_2, \dots, k_N . Second, these resulting rate constants are, all together, analyzed by an extended Arrhenius model to provide estimates of the activation parameters ΔH^\ddagger , ΔS^\ddagger and ΔC_p^\ddagger at $T = T_0$.

$$\ln k = A + B(1/T - 1/T_0) + CF(T) + \varepsilon$$

$$\Delta H^\ddagger(T) = -BR - CR \cdot \frac{\partial F(T)}{\partial(1/T)} - RT$$

$$\Delta S^\ddagger(T) = AR - BR/T_0 +$$

$$CR \left\{ F(T) + T \frac{\partial F(T)}{\partial T} \right\} - R \ln \frac{ek_B T}{h}$$

$$\Delta C_p^\ddagger(T) = -CR \frac{\partial}{\partial T} \frac{\partial F(T)}{\partial(1/T)} - R$$

The function $F(T)$ can take different forms, the choice of which has no strong influence on the estimated activation parameters as long as T_0 is not too far outside the experimental temperature interval.^{8,13} We have used $F(T) = (1/T - 1/T_0)^2$ which is a numerically stable function.

Data analysis. ΔC_p^\ddagger has usually been estimated on the basis of kinetic data measured in the temperature region 0–100 °C. In this investigation the kinetics were carried out at three different temperatures (50, 60 and 70 °C). At each temperature three runs were made with pure and three with salt buffered water, respectively. The

Table 1. Temperatures, rate constants (the average of three runs) and activation parameters for the local determination (with spline function) in pure water.

| °C | $1/T \times 10^3$ K ⁻¹ | $k_0 \times 10^4$ s ⁻¹ | $-\ln k_0$ | ΔH^\ddagger cal mol ⁻¹ | $-\Delta C_p^\ddagger$ cal mol ⁻¹ K ⁻¹ |
|--------|--------------------------------------|--------------------------------------|------------|--|---|
| 50.016 | 3.0943 | 1.4440 | 8.8429 | | |
| 55.015 | | | | 27069 | |
| 60.015 | 3.0015 | 5.2768 | 7.5470 | | 53 ± 30 |
| 65.015 | | | | 26540 | |
| 70.016 | 2.9140 | 17.4828 | 6.3488 | | |

Table 2. Temperatures, rate constants (the average of three runs) and activation parameters for the local determination (with spline function) in 0.2 mol l⁻¹ sodium bromide solution.

| °C | $1/T \times 10^3$ K ⁻¹ | $k_0 \times 10^4$ s ⁻¹ | $-\ln k_0$ | ΔH^\ddagger cal mol ⁻¹ | $-\Delta C_p^\ddagger$ cal mol ⁻¹ K ⁻¹ |
|--------|--------------------------------------|--------------------------------------|------------|--|---|
| 50.016 | 3.0943 | 1.5741 | 8.7557 | | |
| 55.015 | | | | 26968 | |
| 60.014 | 3.0015 | 5.7231 | 7.4658 | | 37 ± 30 |
| 65.020 | | | | 26597 | |
| 70.026 | 2.9139 | 19.0410 | 6.2637 | | |

initial concentrations of substrate varied between 0.19 and 0.23 mol l⁻¹. The initial rate constants, k_0 , were determined by extrapolation from the derived rate constants between 11 and 16 min (Tables 1 and 2).

Determination of the rate constant at constant temperature. 1. Local determination of rate constants. To avoid systematic deviations introduced by ion buffering or other procedures to keep the medium constant, one can try to run the kinetic experiment as cleanly as possible and instead estimate the rate constant early in the reaction. This method has been used in the present investigation. Half of the kinetic experiments have been carried out without salt buffering, *i.e.*, using a measuring method which disturbs the system as little as possible. We compare the results with the results obtained by conventional treatment.

The kinetic data analysis has been made by fitting a spline function to the experimental data.¹⁴⁻¹⁶ These consist of the observed rotation of polarized light which decreases with time when the optical active reactant goes over into products. First order kinetics give the theoretical equation for the change of the rotation of polarized light (α) with time (t), eqn. (1), and in integrated form, eqn. (2).

$$d\alpha/dt = -k(\alpha - \alpha_\infty) \quad (1)$$

$$\alpha = (\alpha_0 - \alpha_\infty)e^{-kt} + \alpha_\infty \quad (2)$$

The rate constant k can be estimated by fitting either of the two equations to the experimental data. In practise, eqn. (1) is usually used, but eqn. (2) is preferable because of its better statistical properties.¹⁰ Both equations can mask rather big deviations from first order kinetics due to the collinearity between the parameters α_0 and k . The problem is avoided by fitting the measured data (α_i, t_i) to a spline function $S(t_i)$, eqn. (3). In each point i one can define a local first order rate constant, eqn. (4). The derivative $dS(t)/dt$ is calculated from the fitted spline function and α_∞ is taken from the measured infinity value (after 10 half lives). The initial rate constant, k_0 , can then be calculated from an extrapolation of k_1 versus time (Fig. 1).

$$\alpha_i = S(t_i) + \epsilon_i \quad (3)$$

$$k_i = - \left\{ \frac{dS(t)}{dt} \right\}_{t=t_i} / (\alpha_i - \alpha_\infty) \quad (4)$$

As can be seen from the plot the kinetics have stabilized at about 11 min after initial mixing. Since the medium is unbuffered, this kinetic behaviour is normal. In principle, extrapolation for determining the initial rate constant should be avoided not to introduce unwarranted imprecision. From Fig. 1 we

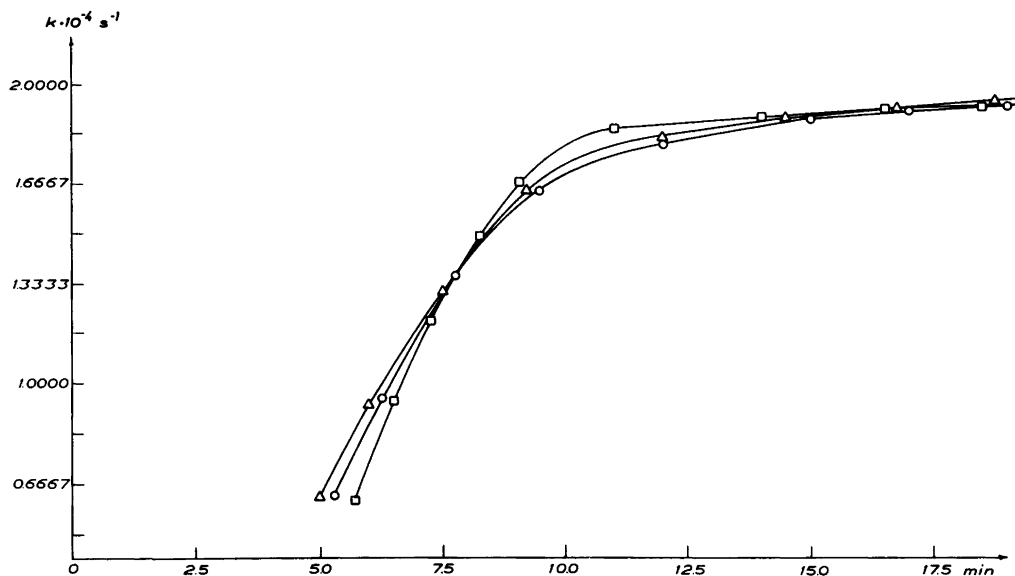


Fig. 1. Plot of derived rate constants at 50 °C versus time. The different curves correspond to different initial concentrations.

see that for three runs at the same temperature, but with different initial concentrations, the three curves cut each other at about 7.5 min. Using this cut as a value of the initial rate constant, we got a value of ΔC_p^\ddagger around $-650 \text{ cal mol}^{-1} \text{ K}^{-1}$ for the solvolysis of *R*(+)-2-methanesulfonyloxy-1-propanol in water (we use calories instead of joules in this paper as that the comparison with older results will be easier).^{*} Such large values have never been reported for water solvolysis (but for *t*-butyl alcohol solvolysis¹³), so we regarded these values as dubious. The average of three runs (at the same temperature) in the time interval 11–16 min were then used for the extrapolation to time zero. The

^{*} 1 cal = 4.184 J.

resulting ΔC_p^\ddagger value was then more normal, about $50 \text{ cal mol}^{-1} \text{ K}^{-1}$.

However, the calculated k_0 -values have rather low precision. This implies that the activation heat capacity cannot be determined with as high precision as desirable. To allow precise determinations of ΔC_p^\ddagger the uncertainty in the determined rate constant (k_i) should not be greater than 0.5%.

The ΔC_p^\ddagger values determined by Robertson *et al.* were originally claimed to be accurate to about $\pm 3 \text{ cal mol}^{-1} \text{ K}^{-1}$, but recently larger confidence intervals of about $\pm 15 \text{ cal mol}^{-1} \text{ K}^{-1}$ have been published¹⁷ for the same data. If we treat our data in the same way as done by Robertson *et al.* (see next section), *i.e.* eqn. (1) above and (2) estimating ΔC_p^\ddagger

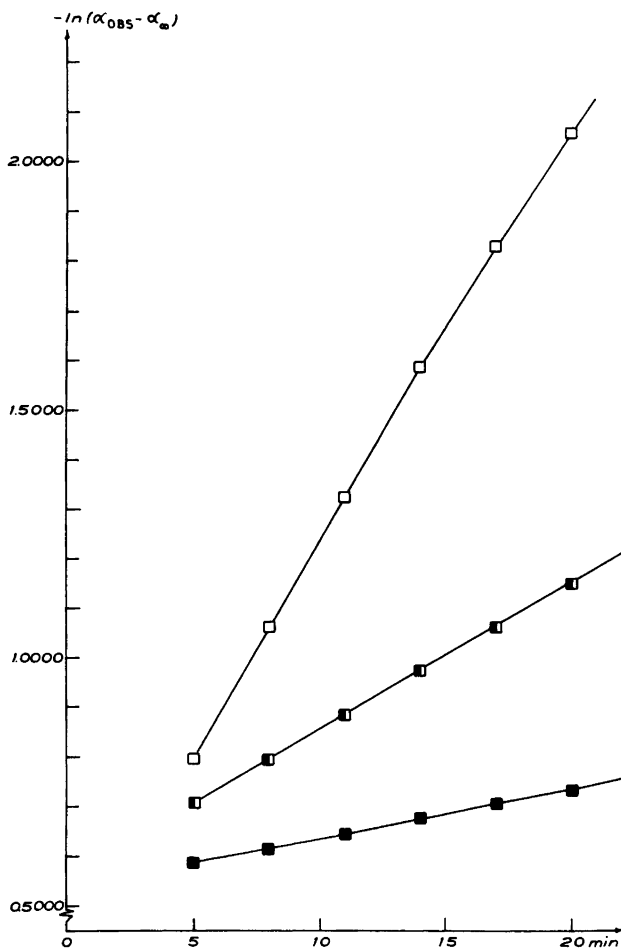


Fig. 2. Logarithmic representation of rotation data in pure water (\square 70°C, \blacksquare 60°C, \blacksquare 50°C).

from the Valentiner equation¹⁷

$$\ln k = A/T + B \ln T + C$$

we get an estimated precision which is comparable to that of Robertson,⁷ i.e. a precision in k of 0.5%.

Thus we conclude that the reported precision of k and hence of ΔC_p^\ddagger is grossly misleading due to the masking of error of measurement in the kinetic data analysis.

2. *Conventional method.* To determine a rate constant for a reaction at a given temperature, experimental data are usually fitted to a postulated kinetic equation, by least squares.^{10,11} In solvolysis reactions the kinetic model generally adopted is the simple first order model where observed variables

proportional to reactant concentrations vary exponentially with time (eqn. 1). Thus a straight line is fitted to the logarithmic measurements values. The deviations which usually are greatest in the beginning and towards the end of the reaction are given less significance or completely neglected.

In our case we made logarithmic plots of the rotation data $[\ln(\alpha_{\text{obs}} - \alpha_\infty)]$. A straight line was fitted to the different kinetic experiments by least squares and initial rate constants, k'_0 , were evaluated (Figs. 2 and 3, Tables 3 and 4). ΔH^\ddagger and ΔC_p^\ddagger from these rate constants at different temperatures were calculated from a plot of $\ln k$ versus $1/T$. The results are represented in Tables 1–4.

The conventional method of rate constant determination works well as long as no systematic

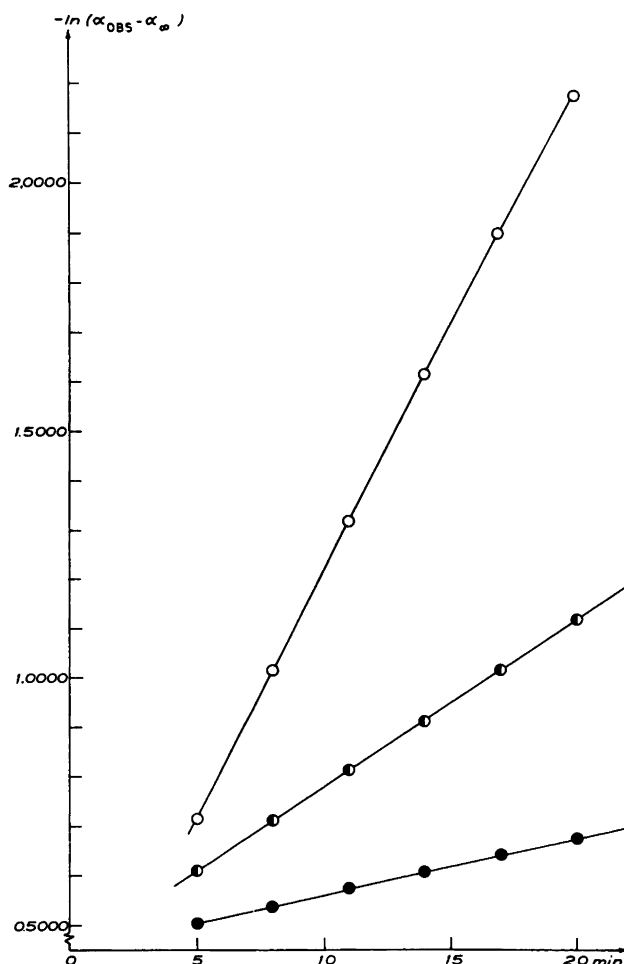


Fig. 3. Logarithmic representation of rotation data in 0.2 M NaBr-solution (○ 70°C, ◐ 60°C, ● 50°C).

Table 3. Temperatures, rate constants (the average of three runs) and activation parameters for the logarithmic determination in pure water.

| °C | $1/T \times 10^3$ K ⁻¹ | $k'_0 \times 10^4$ s ⁻¹ | $-\ln k'_0$ | ΔH^\ddagger cal mol ⁻¹ | $-\Delta C_p^\ddagger$ cal mol ⁻¹ K ⁻¹ |
|--------|--------------------------------------|---------------------------------------|-------------|--|---|
| 50.016 | 3.0943 | 1.6895 | 8.6859 | | |
| 55.015 | | | | 22457 | |
| 60.015 | 3.0015 | 5.0370 | 7.5936 | | 89 ± 15 |
| 65.015 | | | | 21825 | |
| 70.016 | 2.9140 | 13.5627 | 6.6030 | | |

Table 4. Temperatures, rate constants (the average of three runs) and activation parameters for the logarithmic determination in 0.2 mol l⁻¹ sodium bromide solution.

| °C | $1/T \times 10^3$ K ⁻¹ | $k'_0 \times 10^4$ s ⁻¹ | $-\ln k'_0$ | ΔH^\ddagger cal mol ⁻¹ | $-\Delta C_p^\ddagger$ cal mol ⁻¹ K ⁻¹ |
|--------|--------------------------------------|---------------------------------------|-------------|--|---|
| 50.016 | 3.0943 | 1.9261 | 8.5548 | | |
| 55.015 | | | | 22457 | |
| 60.014 | 3.0015 | 5.6675 | 7.4756 | | 16 ± 15 |
| 65.020 | | | | 22296 | |
| 70.026 | 2.9139 | 15.6003 | 6.4631 | | |

deviations occur between data and kinetic equation. Unfortunately such systematic deviations are common, due to several reasons. The environment of the reaction can change during the reaction, usually most rapidly in the beginning. Secondly, the phenomenological rate constant is often a more or less complicated combination of mechanistic rate constants and the reaction is then "first order" only at a steady state.

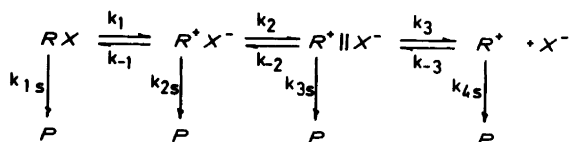
In studies of solvolytic reactions it is helpful to consider the general solvolytic scheme (Scheme 1).¹² By this scheme the whole spectrum of reactions, from S_N1 to S_N2, can be described. Regardless of what type of reaction we have according to the scheme, it is clear that the first order kinetic model contains simplifications.

DISCUSSION

Comparing the two sets of parameters evaluated by the local and traditional methods, the values of k_0

and k'_0 differ very much. They give activation heat capacities which differ numerically but lie in the expected region (-100 to 0 cal mol⁻¹ K⁻¹). In the local determination, the extrapolation technique gives a low precision in k_0 : larger than 1%. Therefore ΔH^\ddagger has such a large imprecision that small differences (less than 30 cal mol⁻¹ K⁻¹) in ΔC_p^\ddagger between pure and salt buffered solutions cannot be seen. In the other case using logarithmic rate data to determine k'_0 , the plots show straight line behaviour in the initial kinetic region. Here the apparent error in k'_0 is 0.5% and the corresponding error in ΔC_p^\ddagger becomes smaller, leading to a significant difference between ΔC_p^\ddagger in pure and salt buffered water, respectively.

The reason for the nonacceptable uncertainty in the determination of rate constants is probably not the experimental method. The temperature control and the polarimetric registration of the velocity should guarantee very precise measurements. The discrepancies between local and traditional



Scheme 1.

determination of rate constants occur because the traditional method evidently is capable of masking systematic errors. We note that the reaction medium indeed changes during the reaction due to production of methanesulfonic acid. Therefore, the results of the local analyses are the only ones which, in principle, are consistent with the present chemical view of the reaction mechanism.

It is difficult to get a good estimate of ΔC_p^\ddagger for the solvolysis reactions due to difficulties in estimating unbiased rate constants. Hence our conclusion is that ΔC_p^\ddagger is not a good indicator for solvent structure, since it is so sensitive to the method of its determination.

With the present methodology, either the medium must be salt buffered to allow conductrimetric methods to be used or the reactant concentration must be increased to allow the use of spectroscopic or polarimetric measurements. In the former case the medium changes during the reaction leading to an imprecision in the determined rate constants. In the latter case one gets a biased ΔC_p^\ddagger value.

To repeat, there is a risk with the "constant medium" approach in the determination of activation heat capacities. This parameter is intimately connected with phenomena such as solvent structure, solute-solvent interactions *etc.*, and the medium buffering might disturb these phenomena significantly.

EXPERIMENTAL

Choice of compound. The choice of compound for the solvolytic reactions had to fulfil three criteria.

1. The substance should be optically active and be sufficiently pure.

2. The substance ought to have a suitable reactivity to make the half life between 7 and 80 min.

3. The substance should at least be slightly soluble in water.

A hydroxy group was included in the substrate to increase the solubility in water. At first *R*(+)-2-chloro-1-propanol and *R*(+)-2-bromo-1-propanol were synthesized from *L*-alanine but their reactivity was too low, forcing the kinetic experiments to be run at 70, 80 and 90 °C.¹⁸⁻²¹ However, at 90 °C small bubbles were formed in the reaction cell, despite use of thoroughly degassed water, and this rendered the polarimetric method unstable.

To increase the substrate reactivity, the leaving group was changed from halide to sulfonate. A series of such esters were synthesized (mesyl-, tosyl-, brosyl and nosyl-). The starting material used was ethyl *R*(+)-lactate. All these compounds fulfilled the

criteria 1 and 2 above but only the methanesulfonate (mesyl-) had a suitable water solubility.

Data analysis. 1. Spline function fitting. We use the program system, SPLINFIT, developed in our laboratory. A spline function is defined as a piecewise polynomial function of degree *P* (in SPLINFIT *P*=2 or 3). The polynomials join each other in the knots (ξ_i , *i*=1 to *M*), and are subjected to continuity conditions on the functions and the first *P*-1 derivatives in these knots. Use of SPLINFIT is recommended for empirical representation of the data (y_i, x_i) when no rigid mathematical model like $y_i = e^{-kx_i}$ or $y_i = \sin(ax_i)$ *etc.* can be found to fit the data within the errors of measurements. The fitting is either pure least square or pseudo least square resulting in a functional description of y_i as a spline function of x_i , $y_i = S(x_i) + \varepsilon_i$. This gives in our case the local rate constant $k_{loc} = \{dS/dt\}/(\alpha - \alpha_\infty)$ (Fig. 1).

2. The Guggenheim method. To check the traditional method of fitting kinetic data of a determined infinity value we also fitted the kinetic data to the Guggenheim equation.²² That method is used for evaluating the rate constant of a first order reaction which does not require a knowledge of the magnitude of the initial or final concentration of the reacting species. No significant difference between the use of the Guggenheim method and the use of an ordinary logarithmic fit (involving an infinity value) could be found.

Temperature control. Careful measurement of the reaction velocity demands a good temperature stability, better than 0.01 K. This is easy to fulfil with modern proportionally regulated thermostats if the reaction vessel can be immersed in the thermostat. This is common procedure with calorimetric or conductimetric measurements.

When kinetic experiments are carried out with instruments having an optical beam (IR, UV, polarimeter *etc.*), the temperature control becomes more difficult, because the thermostated liquid must pass through tubes to a separate compartment. To achieve a high temperature stability in the sample cell the system of three thermostats shown in Fig. 4 has been used. All tubing is thoroughly isolated from the environment.

Temperature measurement. A well proven method for temperature measurement is to use Pt-resistance thermometers. The advantage is good resolution and, after calibration, a good determination of the absolute temperature. A major disadvantage is the time-consuming procedure of calibration. Another disadvantage is that a complete set up of instruments for doing the calibration is costly.

If the demands in the determination of the absolute temperature, are relaxed, it is much easier to deal with high precision temperature measurements. Thus temperature differences can still be measured very precisely, while absolute

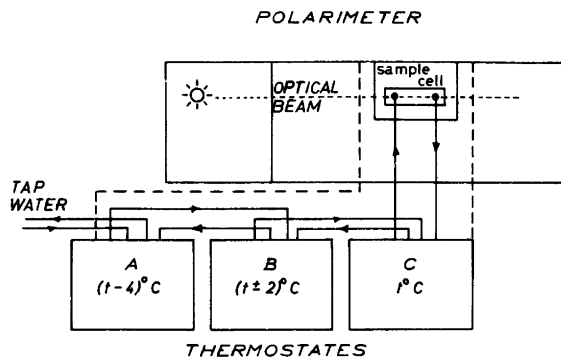


Fig. 4. A schematic picture from above over the instrument and the thermostats (A, B and C). The area between the dashed lines is isolated from the environment by polystyrene. Thermostat A is connected to the ordinary tap water ($+7^{\circ}\text{C}$) and is set *ca.* 4°C lower than C. Thermostat B which is proportionally regulated. This is used for the fine adjustment of the performance of C. B is set $0-2^{\circ}\text{C}$ below C for $t\ 35^{\circ}\text{C}$ and $0-2^{\circ}\text{C}$ above C for $t\ 35^{\circ}\text{C}$. The temperature variation in the sample cell at 25°C is better than $0.001\ \text{K}$ and at 70°C $0.005\ \text{K}$.

temperatures are measured with somewhat lower precision. Since only the temperature differences between the different runs are essential for precise ΔC_p^{\ddagger} values, this is the route taken here. An error of the absolute temperature of $1\ \text{K}$ results in a systematic error of about 0.0003% , far below the imprecision of about 0.1% in the rate constants due to random temperature variation of $0.003\ \text{K}$. Today thermistors and resistance bridges are available which are easy to handle. In our experiments we have used a KNAUER resistance bridge and as a temperature probe CUPROSWEM[®]. The latter is a copper based thermistor with a linear temperature characteristic, a temperature coefficient of 0.43% and a temperature region of -50 to $+200^{\circ}\text{C}$. The absolute temperature can be determined within $0.01\ \text{K}$ by using calibrated mercury thermometers. The temperature measurement itself is performed by using two precision decades which are coupled to the arms of a Wheatstone bridge. The resolution then becomes $0.003\ \text{K}$. With other thermistors it is

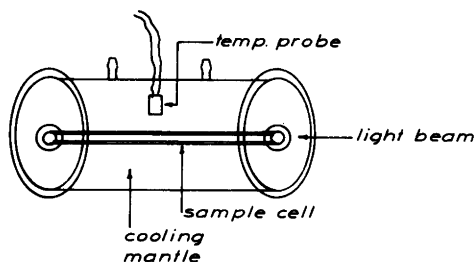


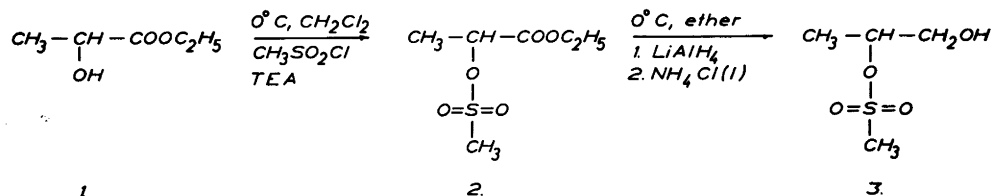
Fig. 5. Polarimeter cell showing the localization of the temperature probe.

possible to achieve a higher resolution but our experience is that they do not have good long-time stability.

As we have used a polarimeter we cannot place the temperature probe directly into the reaction cell. The probe would interfere with the polarized light. Instead we are forced to place it in the cooling mantle which surrounds the cell (Fig. 5). The temperature stability inside the reaction cell has been measured with a small thermistor (YSI) and the fluctuation at 25°C is smaller than $0.001\ \text{K}$. The intervals given are therefore slightly larger than the actual ones. The output from the bridge is connected to a recorder. In that way it is possible to follow the temperature variation during a kinetic run.

In conclusion, the described experimental set-up for the kinetic study of solvolysis reactions has the following performance. For temperature control in the kinetic cell see Fig. 2. Relative temperature difference measurements $0.03\ \text{K}$. Precision of the measurement of polarized light 0.001° . The apparent precision of conventional first order rate constant is about 0.5% (see above). Precision of local rate constant is about 1% . Every kinetic run consists of 100 measured points, recorded at a speed of four points per minute. The temperature difference between different kinetic runs is $10\ \text{K}$ (50 , 60 and 70°C). The apparent precision of the resulting ΔC_p^{\ddagger} values are when using local rate constants $\pm 30\ \text{cal mol}^{-1}\ \text{K}^{-1}$ and when using conventional determined rate constants $\pm 15\ \text{cal mol}^{-1}\ \text{K}^{-1}$ (under the assumption that the kinetic model is correct).

Product study. In order to identify the products of



Scheme 2.

the solvolysis reaction we used an HPLC equipment (Laboratory Control Constametric II pump, a Spectromonitor III UV-detector, a Rheodyne 7010 injection valve with a 20 μl loop and a dichrosorbCN 100 \times 4 mm column) in combination with high resolution NMR (Bruker WH-250).

The chromatogram from the HPLC showed 3 peaks, which were collected separately. After extraction with dichloromethane and evaporation, the residues (about 1 mg) were dissolved in CDCl_3 . The NMR spectra of the 3 fractions showed that the major products of the reaction were 1,2-propanediol and methanesulfonic acid.

Preparation of starting material. Scheme 2 shows the synthesis of the sulfonate exemplified by the methanesulfonate. The first step is a well known procedure.^{2,3} In the second step reducing the carboxylic ester moiety in presence of the sulfonic ester imposed a problem. Slow addition of an LiAlH_4 -suspension was found to give good yield. Keeping the reducing agent at a low concentration favoured the formation of a complex with the carboxylic ester.

All 2-sulfonyloxy-1-propanols made were obtained as oils. Their thermal instability excluded purification by distillation or gas chromatography. Partition chromatography on SEPHADEX LH-20 with 1,2-dichloroethane as eluent gave pure 3. The kinetics were followed in a modified (extern start and stop) PERKINELMER 141 polarimeter equipped with a LEINE & LINDE shaft angle digitiser and a ELESTA bidirectional counter. Temperature-control and -measurement were performed as described earlier. Quartz distilled and degassed water was used.

Preparation of 2.^{2,3} An amount of 11.81 g (0.1 mol) of R(\pm)-ethyl lactate (Fluka, reagent grade, $[\alpha]_{\text{D}}^{25} +11.20$ (neat)) was dissolved in 150 ml of dichloromethane. To this solution was added 15.29 g (0.15 mol) of triethylamine, TEA. The solution was cooled with an ice bath and 15.4 g (0.11 mol) of methanesulfonyl chloride dissolved in 50 ml dichloromethane was added during 15 min. The precipitated hydrochloride was filtered off and the reaction mixture was extracted with 25 ml portions of 15% hydrochloric acid to remove excess TEA.

The organic layer was washed with saturated sodium hydrogen carbonate solution followed by water and dried with sodium sulfate. Removal of solvent afforded 18.6 g (95%), $[\alpha]_{\text{D}}^{25} -63.06$ (neat), $^1\text{H NMR}$ (60 MHz, CDCl_3): 1.33 (3 H, t), 1.58 (3 H, d), 3.08 (3 H, s), 4.23 (2 H, q), 5.03 (1 H, q).

Preparation of 3. An amount of 58.87 g (0.3 mol) of R(-)-ethyl 2-methanesulfonyloxypropionate (2) was dissolved in 250 ml of dry diethyl ether. A suspension of 6.08 g (0.16 mol) LiAlH_4 in 100 ml of dry diethyl ether was added slowly under helium atmosphere to the solution at 0 $^\circ\text{C}$. The temperature was not allowed to exceed 10 $^\circ\text{C}$. The formation of complex sometimes occurred giving a gluey mass in the reaction vessel and therefore it was necessary to use an efficient mechanical stirrer. The complex was hydrolyzed by the addition of saturated ammonium chloride solution. Usual aqueous work-up afforded 9.5 g (82%) of crude product, containing 60% of 3 (NMR).

Purification of 3. The crude product was purified by column chromatography. A column 30 (id) \times 310 mm packed with SEPHADEX LH-20 and 1,2-dichloroethane as eluent was used. An LKB 2089 UVICORD III at a wavelength of 254 nm was used for detection. Elution velocity was 0.7–0.9 ml min^{-1} . The retention time for 3 was about 7 h. Using this method it was possible to get 3 in very high purity. $[\alpha]_{\text{D}}^{25} +15.49$ (c=10.435, CH_2Cl_2), $^1\text{H NMR}$ (60 MHz, CDCl_3): 1.37 (3 H, d), 3.1 (3 H, s), 3.42 (1 H, s), 3.66 (2 H, c), 4.78 (1 H, c), $^{13}\text{C NMR}$ (15 MHz, CDCl_3): 17.34, 38.44, 65.36, 81.02.

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