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Simple and Rapid Determination of the Activation Parameters of Organic Reactions by Temperature-Dependent NMR Spectroscopy I. Application to Irreversible Reactions

Masahiro Satoh* **and Minoru Hirota**

Department of Synthetic Chemistry, Faculty of Engineering, Yokohama National University,
Hodogaya-ku, Yokohama 240

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A rapid and convenient method for the evaluation of activation enthalpies and entropies of reactions in solutions was contrived. This was realized by the stepwise elevation of the temperature of a reaction system using a variable temperature apparatus of NMR spectrometer. A repetition of rapid collection of FIDs (Free Inductive Decays) at every plateau part of temperature at regular intervals allows us to determine the time-conversion curve, from which the rates at various temperatures were obtained as the first derivatives. Several examples of applications are shown.

A general method to obtain activation energies and entropies of reactions is based on the Arrhenius plot, $\log k$ vs. $(1/T)$ plot, which is drawn by a repetition of the measurements of rates (k) as a function of temperature (T). This method is widely applied to various reactions of moderate rates. Since the rate is measured at a constant temperature in this conventional method, we hereafter call it the "isothermal" measurement.

However, the isothermal method needs several repetitions of the measurements at various temperatures in order to draw an Arrhenius plot. Thus the determination of activation parameters becomes difficult when the sample is very precious. In addition, repeated measurements at various temperatures need quite a long time to get activation parameters in the case of slow reactions.

In this situation, theoretical treatments on the kinetic analysis of a non-isothermal process under the programmed variation of temperature have been reported by several investigators.[1—6] However, the application of this "non-isothermal (NIT)" measurement is limited to the solid state process and a few very simple reactions because of the complexity of formulation and calculation. Further, we should not overlook the fact that the conformity of the NIT activation parameters with those from usual Arrhenius plots has never been proved.

In this paper, a general method for the analysis of non-isothermal reaction process was constructed and applied to the rate data measured under the stepwise elevation and depression of temperature. In the first place, the NIT method was tested on some irreversible organic reactions the activation quantities of which were determined previously by the conventional isothermal measurements. These results were compared with the activation quantities obtained from the conventional Arrhenius plots.

Theory and General Description of the Method

A rather general treatment of the NIT kinetic data has been reported by Kato and co-workers.[3] The method was applied to the reactions under the uniform rate of elevation of temperature, i.e. linearly programmed elevation of temperature.

To apply the NIT method to NMR samples whose temperature is controlled by a commercial variable temperature apparatus attached to a NMR spectrometer (hereafter we call this method "NIT-NMR method"), we contrived a modification of the Kato's method adaptable to such systems.

In NIT experiments, concentration (C) of the product, or reactant, after a reaction period (t) cannot be determined from the temperature (T) alone but is dependent on how the temperature changed as a function of time. Thus, even in the case of an irreversible first-order reaction, the concentration (C) expressed by Eq. 2 cannot be calculated without knowing the temperature as a function of time.

The rate should be formulated explicitly as a function of time in order to carry out the integration in Eq. 2.

$$-(\mathrm{d}C/\mathrm{d}t) = k(t)C, \tag{1}$$

$$C(t) = C_0 \ \exp(-\int k(t) \ \mathrm{d}t), \tag{2}$$

where C_0 is the initial concentration.

Similarly the concentration (Eq. 4) can be derived for an n-th order reaction from Eq. 3.

$$-(\mathrm{d}C/\mathrm{d}t) = k(t)C^n, \tag{3}$$

$$[C(t)]^{1-n} - (C_0)^{1-n} = (n-1) \ \exp(-\int k(t) \ \mathrm{d}t). \tag{4}$$

In principle, the integrations in (Eqs. 2 and 4) were accomplished in practice by a computer program for integration by replacing them by summation. In the NMR sample probe

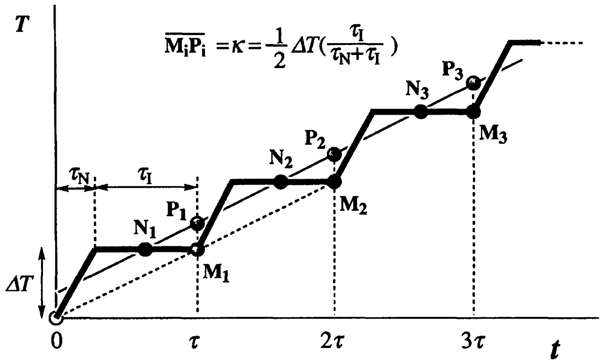


Fig. 1. Diagram of the stepwise non-isothermal (elevation temperature) curve and the derivation of a correction term.

of a usual variable temperature apparatus which is operated so as to raise a constant temperature at regular intervals (τ), the temperature is expected to vary stepwise as shown by the bold zigzag line in Fig. 1.

The line consists of a repetition of isothermal and linearly elevated (or fallen) parts at regular intervals. Integration to obtain the concentration changes in isothermal parts can be practiced easily, giving the concentration by Eq. 5. The "linearly elevated" parts can also be integrated by the method (Eq. 6) reported by Amasaki and co-workers.[2]

Isothermal parts;

$$C(t) = C_j \exp[-k_j(t - j\tau - \tau_N)], \text{ where } (j+1)\tau > t \geq j\tau. \quad (5)$$

Linearly varied parts;

$$C(t) = C_i \exp[k_0/\xi(1+\gamma)]\ \{(1+\xi t)^{\gamma+1} - (1+i\xi\tau)^{\gamma+1}\}, \quad (6)$$
$$\text{where } (i+1)\tau > t \geq i\tau,$$

where $\gamma = \eta E_a/R$, η is the speed of elevation of temperature, and ξ is a parameter to conform the linearity. If the integration is carried out stepwise, the time-conversion curve (abbreviated to *C–t* curve) will be obtained. However, this procedure is tedious and time-consuming.

In this situation, we tried to contrive an equivalent but more easily manageable method for the calculation of activation parameters. This was achieved with a very good approximation by replacing the stepwise *T–t* curve by a *T–t* line for a uniform temperature-elevation process. The assumed equivalent *T–t* line passes the centers (N_1, N_2, $\cdots$ N_i) of the plateau (isothermal) parts (Fig. 1). However the samplings at the centers of the plateau periods waste the time of the isothermal parts after the collections of FIDs; viz. the time interval between the data acquisition and the onset of the next temperature raise is not used. Sampling at the end of the every plateau (M_1, M_2, $\cdots$ M_i) on the stepwise *T–t* diagram should be more effective. This was done by calculating the vertical temperature deviation (M_iP_i) on the equivalent *T–t* line from the point M_i on the stepwise *T–t* line. The corrected temperature (T_{s_i}) are given by Eq. 7, where $\varkappa$ is the correction term and τ_N and τ_I are the durations of non-isothermal and isothermal periods, respectively.

$$T_{s_i} = T_i + \varkappa, \quad (7)$$
$$\varkappa = +\Delta T/2[\tau_I/(\tau_I + \tau_N)] \text{ for stepwise elevation of } T,$$
$$\varkappa = -\Delta T/2[\tau_I/(\tau_I + \tau_N)] \text{ for stepwise depression of } T.$$

Equation 7 includes the approximation that the rate is linearly dependent on temperature within a relatively small variation of temperature (Fig. 1). This approximation was tested by our experiments which showed the effectiveness of this approximation.

The calculations can further be facilitated by expanding the concentration ($C(t)$ in Eq. 6) to a power series of t.

$$C(t) = a_0 + \Sigma a_m t^m, \quad (8)$$

$$\mathrm{d}C(t)/\mathrm{d}t = \Sigma m a_m t^{m-1}, \quad (9)$$

where $C(t)$ can be the concentration of either the reactant or the product and a_0 and a_m are regression factors. Actually the summation up to $m=4$ gives sufficiently accurate results. Thus, the rate constant at any temperature can be obtained from Eq. 9 derived as the first derivative of Eq. 8 and the T_{s_i} values can be obtained from Eq. 7. These calculations can easily be carried out numerically.

The NIT experiments were generally carried out in the order itemized below.

1) Two (or more) reactants were kept separately at the initial temperature (preferably either of the reactants must be kept in an NMR sample tube), and mixed quickly when the experiment starts (at $t=0$).

2) The FIDs of the reaction system were collected (accumulated 4 times) after τ_m. The temperature of the system was raised (or lowered) immediately after the acquisition of the data.

3) The operation 2) was repeated at $t = \tau_m + (n-1)\tau$ ($\tau = \tau_I + \tau_N$, $n = 1,2,3\cdots$).

4) The conversions of the reactants were calculated from the NMR data (from FIDs) and apparent time conversion (*C–t*) curve is drawn (numerical data of conversion as a function of time were obtained).

5) The NIT-NMR analysis gave the activation parameters.

Usually FID data were collected at more than six different temperatures in order for the least squares determination of a_0 and a_m in Eqs. 8 and 9. Rate data necessary for the estimation of activation parameters were calculated at every point of FID collection except for the last point. The first derivative (slope) at the data point of the highest conversion-end of the curve should contain larger error because we cannot interpolate the curvature by the two neighboring data points. Thus, the last (end) point was ignored in order to obtain reliable gradients ($\mathrm{d}C/\mathrm{d}t$).

From the rate data thus obtained, activation quantities were calculated by Eq. 10, where n is the reaction-order of the reactant (usually $n \geq 1$).

$$\ln[-(1/C^n)(\mathrm{d}C/\mathrm{d}t)] = \ln A - E/RT_s, \quad (10)$$

where A is a pre-exponential factor, E is the activation energy, and R is the gas constant.

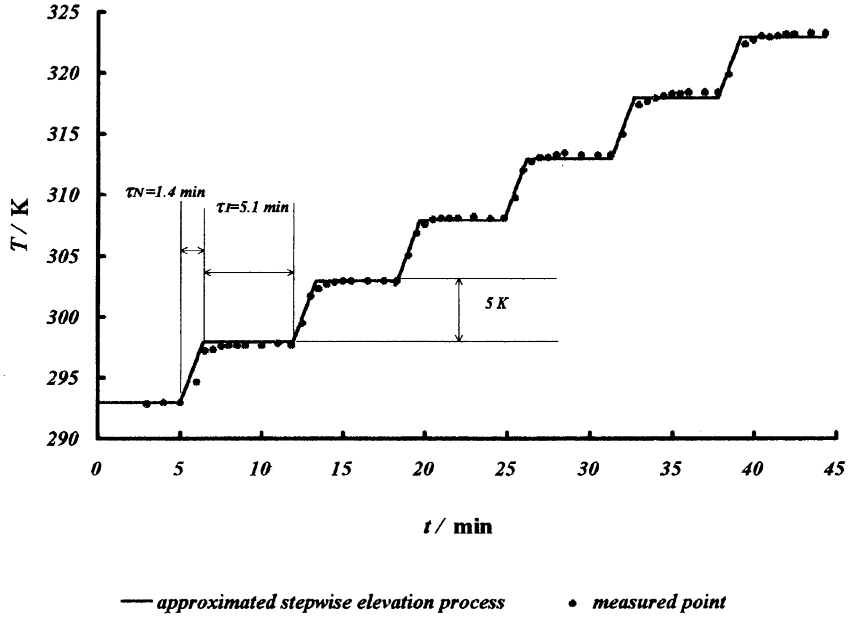


Fig. 2. The real stepwise elevation process of the apparatus used (EVTS 3).

Experimental

General Procedures. All of the compounds used in the kinetic measurements are known. They were either prepared by the reported methods[17,18] or purchased commercially. The deuterium-labelled solvents are also commercially available. Variable temperature ^{1}H NMR spectra were obtained on a JEOL-EX270 NMR spectrometer equipped with a JEOL EVTS-3 variable temperature apparatus.

Determination of τ_N of the Variable Temperature Apparatus. The τ_N value is inherent in the employed variable temperature apparatus. It depends in a complicated manner on the performance of the apparatus. So we determined it by measuring the temperature of the reaction system as a function of time under the conditions of the operation of temperature elevation. The observed T–t curve (Fig. 2) gives 1.40 min as the τ_N for the temperature variation of 5 °C in our apparatus (JEOL EVTS-3). Hereafter, our routine measurements were carried out under the conditions: ΔT=+5.0 °C, τ_I=5.10 min, and τ_N=1.40 min.

Measurements. The procedure can be illustrated by the example of the methylation of pyridine by iodomethane. A 5 mmϕ sample tube containing 0.10 mmol of iodomethane (14.2 mg) and 0.60 ml (0.752 g) of nitrobenzene-d_5 (as a solvent) was kept in the NMR sample probe maintained at 20 °C for more than 5 min. Then, an equimolar amount (0.10 mmol, 7.9 mg) of pyridine (the less volatile reactant) was added quickly and the sample tube was returned to the probe instantly. This could be done within 5 s. and the time started at this moment (t=0).

The shim of the magnet was adjusted within two minutes, and then the FID was accumulated 4 times under the following con-

Table 2. Time, Concentration of Product, and T_s for the Reaction of Pyridine with Iodomethane

Selected time	Conversion	Concentration of product[a)]	$T_s - 273.15$
		mM	°C
0'00"	0.00	0.00	21.76
5'50"	1.67×10^{-2}	2.69	21.76
12'20"	3.63×10^{-2}	5.92	26.76
18'50"	6.49×10^{-2}	10.6	31.76
25'20"	1.04×10^{-1}	17.0	36.76
31'50"	1.59×10^{-1}	25.9	41.76
38'20"	2.32×10^{-1}	37.8	46.76
44'50"	3.09×10^{-1}	50.2	51.76

a) The concentration of product can be calculated by $C_{\rm pr}=(C^0_{\rm react})/(1+I_{\rm react}/I_{\rm pr})$, where $C^0_{\rm react}$ is the initial concentration of a reactant.

Table 1. Examples of NIT-NMR Measurements for the Reaction of Pyridine with Iodomethane

Time for elevation temperature	Shim adjustment	Acquisition of FIDs	$I_{\rm react}/I_{\rm pr}$ [a)]	Temp
				°C
0'00"	4'45"	4'45"—5'50"	59.61	19.8
6'00"—9'15"	9'15"—11'15"	11'15"—12'20"	27.17	24.8
12'30"—15'45"	15'45"—17'45"	17'45"—18'50"	14.41	29.8
19'00"—22'15"	22'15"—24'15"	24'15"—25'20"	8.593	34.8
25'30"—28'45"	28'45"—30'45"	30'45"—31'50"	5.286	39.8
32'00"—35'15"	35'15"—37'15"	37'15"—38'20"	3.302	44.8
38'30"—41'45"	41'45"—43'45"	43'45"—44'50"	2.241	49.8

a) $I_{\rm react}$ and $I_{\rm pr}$ are the integral intensities of the reactant and product, respectively.

ditions: acquisition time, 3.031 s; pulse delay, 3.969 s; repetition time, 7.0 s; pulse width 6.0 μs and 32876 data points. The collected data were stored on a hard disk for the calculation of the rates and the activation parameters. All these operations were completed within τ_I (This actually needed 3.25 min, in this case, which is shorter than τ_I, while τ_I=5.10 min). Then, the temperature of the system was raised to 25 °C (when ΔT=5.0 °C). After an elapse of time longer than τ_N (5.10 min, in this case), exactly the same operations were repeated. After seven repetitions, the temperature reached 50 °C, when the measurement was stopped after the final collection of FIDs.

An example of the timings all through a run of measurements is given in Table 1. As determined previously, real τ_N is 1.40 min for the elevation of 5 ° of temperature (ΔT=5.0°) up to 60 °C. Using τ_N=1.40 min, τ_I=5.10 min, ΔT=5.0 °C and Eq. 8a gave the value of 1.96 °C; thus $T_s=T_{obs}+1.96$. The time-conversion data in Table 2 were fitted to the polynomial equation (Eq. 8) by the least squares calculation with Multi-regression analysis program.[19] The best-fit equation and its first derivative are given by Eqs. 8a and 9a, respectively, where t is measured in minutes.

$$C_{pr} = (2.5 \times 10^{-4}) + (2.80 \times 10^{-4})t + (1.18 \times 10^{-5})t^2 + (1.57 \times 10^{-7})t^3, \quad (8a)$$

$$dC_{pr}/dt = (2.80 \times 10^{-4}) + (2.36 \times 10^{-5})t + (4.71 \times 10^{-7})t^2 \quad (9a)$$

On the other hand, the reaction rate (dC_{pr}/dt) should be expressed by Eq. 11 at any temperature, where k is a rate constant under non-isothermal conditions. By using the time–T_s correlation in Table 2 and Eq. 11, the rate constant at every T_s could be evaluated. In Eq. 11, C_{pr}, C_{MeI} and C_{py} refer, respectively, to the concentrations of the product (*N*-methylpyridinium iodide), iodomethane, and pyridine.

$$dC_{pr}/dt = kC_{MeI}C_{py} \quad (11)$$

From the reason given in the last paragraph of the Method section, the last point of set of an experimental values was excluded from the calculation of activation quantities.

Thus obtained sets of k and T_s will give the activation quantities by applying the Arrhenius equation. Activation enthalpies and entropies were calculated from E_a (kJ mol^{-1}) and A (min^{-1} for the first-order reaction or 1 mol^{-1} min^{-1} for the second-order reaction) values by the following equations where k is Bolzman's constant and h is Planck's constant.

$$\Delta H^{\ddagger} = E - RT \quad (12)$$

$$\Delta S^{\ddagger} = R\ [\ln (Ah/60ekT)] \quad (13)$$

The magnitude of temperature elevation (or depression) ΔT is usually constant throughout an experiment, even though the data can be analyzed with much labor in the case of a regularly varied temperature gap.

Results and Discussion

In order to examine the validity of our NIT-NMR method, we determined the activation parameters for several organic reactions whose activation parameters were previously determined by well established conventional methods. These test reactions were carefully selected on the basis of the following criteria: (1) the reactants concerned do not induce any other sidereactions under the experimental conditions, (2) the mechanism (and the order) of reaction is well-known and shown to be unchanged under the experimental conditions, and (3) the reaction system does not contain any species capable of changing the reaction rate. The rates and activation parameters of the test reactions were determined by our NIT-NMR method described above.

The *C–t* curve was obtained by the least squares calculations including all data points. The first derivatives of the *C–t* curve at the data points which were also calculated numerically could by used as the rate data for the calculation of activation quantities $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. From the reason given above, the calculation was carried out excluding the one datum at the highest conversion.

In order to examine the reliability of the method, the quarternization of *N*,*N*-dimethylaniline by iodomethane in methanol-d_4 (the Menchutkin reaction) was chosen as the test reaction.[7] The amounts of the reactant (A) and the product (B) were determined from the integrated intensities of the "key band" signals H_A and H_B, respectively (see Table 5). The rate of this reaction was measured at various rates of temperature elevation and depression and at various timings. The agreement of kinetic data from different measurements was examined. Thus obtained NIT kinetic data were simultaneously compared with those from well-established Arrhenius plots.

(14)

The activation enthalpy and entropy of the reaction under exactly the same conditions but using non-deuteriated methanol as the solvent was reported by Evans[7] to be $\Delta H^{\ddagger}$=61.7±1.0 kJ mol^{-1} and $\Delta S^{\ddagger}$=−120±3.2 J mol^{-1} K^{-1},

Table 3. The Enthalpies and Entropies of Activation (at 300 K) for the Quarternization of *N*,*N*-Dimethylaniline by Iodomethane Determined by the NIT-NMR Method

Entry	ΔT	τ_I	τ_N	NIT activation quantities		Deviation from the reference	
	K	min	min	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	$\Delta\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
1	10.0	5.10	1.40	62.1 ± 0.7	−118 ± 3.2	+0.4	+2
2	5.0	5.10	1.40	60.8 ± 0.3	−112 ± 0.8	−0.9	−2
3	2.5	5.10	1.40	63.0 ± 0.1	−112 ± 0.4	+1.3	+8
4	5.0	11.6	1.40	61.4 ± 2.0	−120 ± 6.5	−0.3	0
5	−5.0	5.10	1.40	63.8 ± 2.9	−117 ± 9.6	+2.1	+3
Ref.(Arrhenius plot)[7]				61.7 ± 1.0	−120 ± 3.2		

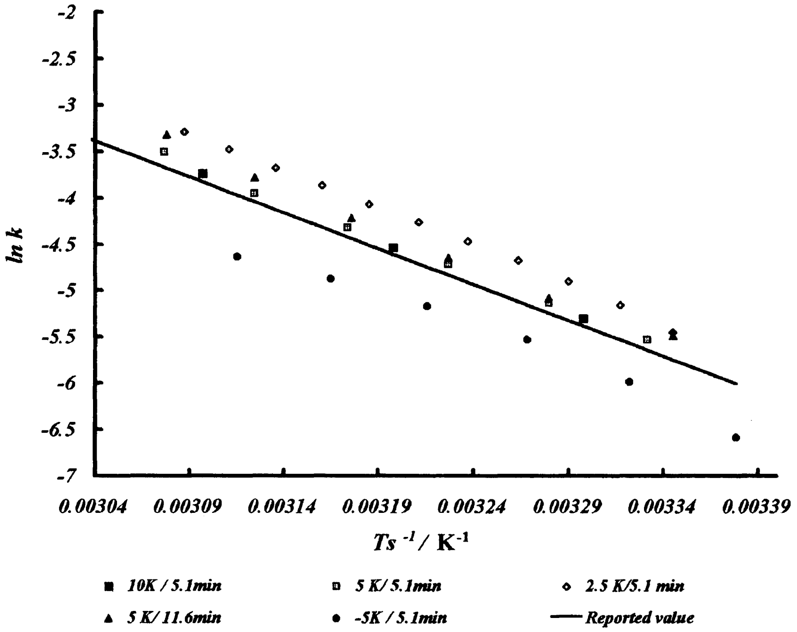


Fig. 3. The $\ln k$ vs. $T_s{}^{-1}$ plot for the reaction of Eq. 14.

respectively. As the solvent deuterium effect is expected to be negligibly small, the activation parameters by our NIT-NMR method were compared with these values. The activation quantities obtained by us are given in Table 3 together with the deviations ($\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$) from the reported values with the conventional isothermal method.[7] The rates (k) from various runs of experiments should comprise a straight line in the $\log k$ vs. $(1/T_s)$ plot (Fig. 3). Actually the rate data come within a relatively narrow band in the $\log k$ vs. $(1/T_s)$ plot due to the errors accompanying the measurements. This can be a proof for the accuracy and the reproducibility of the NIT-NMR experiment. However, the data points (filled circles) for the measurement under decreasing temperature lie out of the band area, this should be improved further.

Even in a run (Entry 5) during the lowering of temperature, the activation enthalpy and entropy were determined by analyzing the C–t curve. The activation parameters thus obtained again agree with the reported values fairly well. Judging from the experimental errors, we expect that the temperature depression measurement will be considerably less precise than the temperature elevation measurement. This comes largely from the difficulty in adjusting the initial temperature of sample uniformly. As the initial velocity of the reaction is high, this causes a larger error all through the measurement. From this consideration, the temperature depression measurement must be useful as well in the cases of fast reactions which start from the ambient (or lower) temperature and proceed at moderate rates below this temperature.

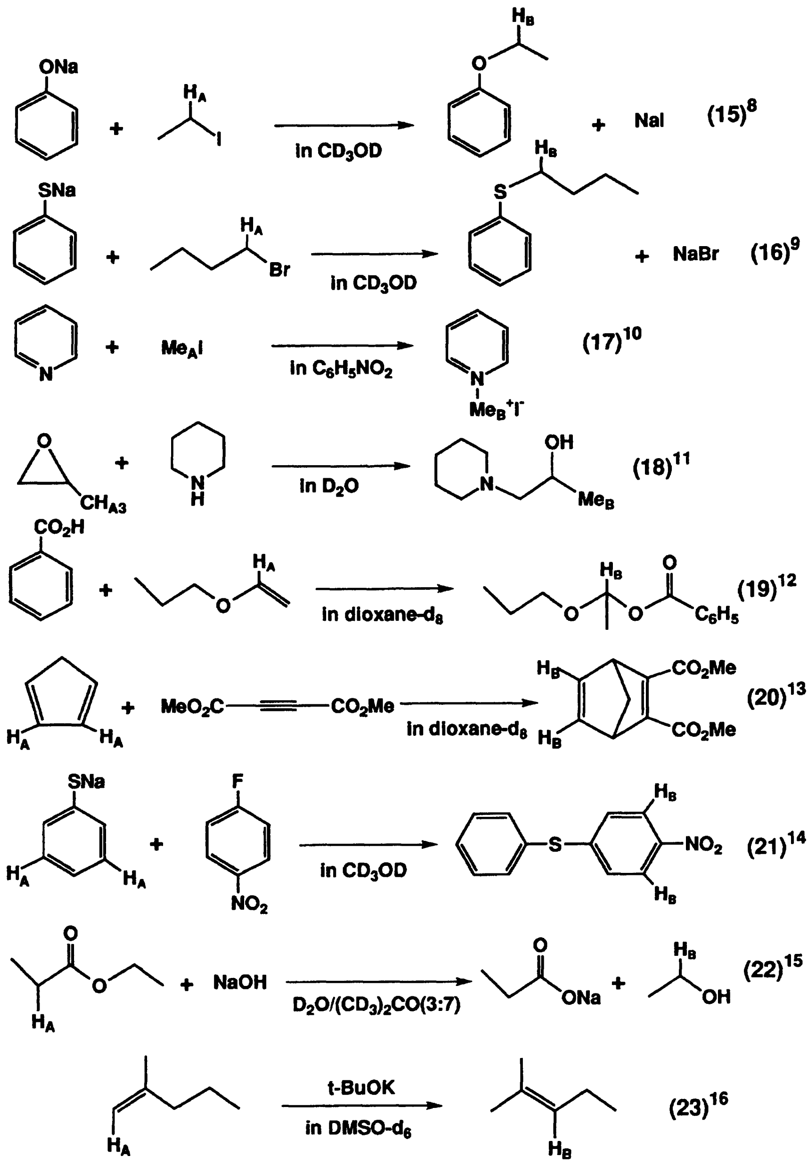
For the five runs (Entry1—5) in Table 3, the standard deviations for the difference ($\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$) of NIT and isothermal values are 1.1 kJ mol^{-1} and 3.3 J mol^{-1} K^{-1}, respectively. The deviation is equal to the experimental errors of the isothermal data i.e., 1.0 kJ mol^{-1} and 3.2 J mol^{-1} K^{-1}. Significance test assuming the significance level of 1% showed that there is no significant difference between the deviation and the experimental errors.

This will lead us further into a consideration of the rate constants (k-values). Table 4 shows the k-values and these average relative errors (Δk) obtained from the activation quantities of the NIT and isothermal method described above. Statistical treatment of the average relative errors gives the standard deviation SD(Δk)=0.27. Though this value is a lit-

Table 4. The Comparison of Rate Constants (10^3 M^{-1} min^{-1}) by the NIT and Isothermal Method for the Reaction in Eq. 14

Entry	ΔT	τ_I	τ_N	Temperature/°C						Average
	K	min	min	24.8	29.8	34.8	39.8	44.8	49.8	relative error[a)]
1	10.0	5.10	1.40	3.2	4.9	7.4	11	16	24	−0.03
2	5.0	5.10	1.40	3.3	5.1	7.6	11	17	24	−0.00
3	2.5	5.10	1.40	4.5	6.9	11	16	24	35	+0.40
4	5.0	11.6	1.40	3.6	5.5	8.4	12	18	27	+0.10
5	−5.0	5.10	1.40	1.8	2.8	4.3	6.5	9.7	14	−0.43
Ref.				3.3	5.0	7.6	11	17	24	0.00

a) Average relative error (Δk) is the average to the number of data of relative errors (Δk) calculated by $(k_{\mathrm{NIT}}-k_{\mathrm{IT}})/k_{\mathrm{NIT}}$, where k_{NIT} is rate constant by NIT-NMR method and k_{IT} is rate constant by the isothermal method.



Scheme 1. Selected irreversible organic reactions.

Table 5. The Key Band NMR Signals used for the Determination of the Reactants and the Products in the Kinetic Studies

Reaction Eq. No.	δ (H_A)	δ (H_B)
14	2.13 (3H, s)	3.60 (3H, s)
15	4.01 (2H, q, J=7.9 Hz)	3.18 (2H, q, J=7.6 Hz)
16	3.43 (2H, t, J=8.8 Hz)	2.91 (2H, q, J=7.3 Hz)
17	1.51 (3H, s)	4.88 (3H, s)
18	1.31 (3H, d, J=5.3 Hz)	1.15 (3H, d, J=6.3 Hz)
19	6.40 (1H, q, J=6.9 Hz)	6.13 (1H, q, J=4.1 Hz)
20	8.30 (2H, q, J=4.6 Hz)	8.08 (2H, d, J=9.2 Hz)
21	3.62 (2H, q, J=7.3 Hz)	2.43 (2H, q, J=7.6 Hz)
22	6.48 (4H, dd)	6.90 (2H, s)
23	4.90 (2H, d, J=8.6 Hz)	5.33 (1H, tt, J=7.1 Hz)

tle larger as a experimental error, the agreement is excellent if we consider the ease of the measurement.

Next we applied the method to the determination of the rates of a variety of reactions (given in Scheme 1) which are shown to be practically irreversible. The amounts of the reactant (A) and the product (B) were determined again from the integrated intensities of the "key band" signals H_A and H_B, respectively. These hydrogen atoms are depicted in Scheme 1; their chemical shifts are given in Table 5. The rates of these reactions had previously been determined by the isothermal method and were readily available for comparison. The results are given in Table 6 together with the corresponding reported values from conventional Arrhenius plots.

For the ten runs excluding entries 15, 19, and 23 in Table 6, the experimental errors for the NIT activation parameters [SD($\Delta H^{\ddagger}$)=1.4 and SD($\Delta S^{\ddagger}$)=4.3] were almost equal to these for the isothermal method [SD($\Delta H^{\ddagger}$)=1.2 and SD($\Delta S^{\ddagger}$)=3.9]. Added to this, since the standard deviations for the difference ($\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$) of NIT and isothermal values are 1.2

Table 6. The Comparison of the NIT and the Isothermal Activation Quantities for Various Reactions

Reaction	NIT (Present work)		Isothermal (Literature)[8—16)]		Difference	
Eq. No.	$\Delta H^\ddagger$/kJ mol^{-1}	$\Delta S^\ddagger$/J mol^{-1} K^{-1}	$\Delta H^\ddagger$/kJ mol^{-1}	$\Delta S^\ddagger$/J mol^{-1} K^{-1}	$\Delta\Delta H^\ddagger$	$\Delta\Delta S^\ddagger$
14	60.8±0.3	−122±0.8	61.7±1.0	−120±3.2	−0.9	−2
15	87.1±3.5	−34.1±11	86.8±0.2	−40.2±0.6	+0.3	+6.1
15′			[88.4±5.0	−30.3±16	−1.3	−3.8][a)]
16	70.5±2.6	−51.1±8.5	69.6±3.8	−56.8±12	+0.9	+5.7
17	54.9±1.2	−126±3.7	55.7±0.3	−124±1.1	−0.8	−2
18	50.2±0.5	−121±1.6	50.4±1.2	−125±4.1	−0.2	+4
19	64.5±1.9	−125±5.7	65.0±0.8	−143±2.5	−0.5	+18
19′			[63.0±11	−131±32	+1.5	+6][a)]
20	53.9±1.7	−127±5.3	55.2	−123	−1.3	−4
21	81.6±1.4	−45.6±4.3	80.3±0.0	−47.7±0.1	+1.3	+2.1
22	41.8±5.0	−138±16	42.3±0.9	−135±2.9	−0.5	−3
23	89.4±2.1	−51.2±6.3	92.8±3.0	−38.9±9.0	−3.4	−12
23′			[87.4±8.9	−50.3±28	+2.0	−0.9][a)]

a) The activation parameters determined by isothermal method in this work are given in brackets.

kJ mol^{-1} and 4.3 J mol^{-1} K^{-1}, the deviation is almost equal to the experimental errors of isothermal data just mentioned above. Therefore it seems reasonable to suppose that the NIT activation parameters are nearly as accurate as those from Arrhenius plots.

A few runs (Entry 15, 19, 23) in Table 6 showed a considerably large disagreement between the isothermal (reported) and the NIT activation quantities. The redetermination by isothermal-NMR methods was carried out on their runs and the results are given in the brackets of Table 6. Our new data on the whole agreed better than the old reported values. What has to be noticed is that NIT-NMR experimental errors are smaller than these in our isothermal NMR method. This may come from a larger temperature error of isothermal method than one of NIT method at higher temperature than the ambient temperature.

Table 7. The Comparison of Rate Constants (10^3 M^{-1} min^{-1}) by the NIT and Isothermal Method for the Reactions in Scheme 1 (1 M=1 mol dm^{-3})

Reaction Eq. No.	Temperature/°C						Average relative error[a)]
	24.8	29.8	34.8	39.8	44.8	49.8	
14	3.3	5.1	7.6	11	17	24	−0.00
Ref.	*3.3*	*5.0*	*7.6*	*11*	*17*	*24*	
15	3.3	6.0	11	19	32	54	+0.82
Ref.	*1.8*	*3.3*	*5.8*	*10*	*17*	*29*	
15′	3.1	5.7	10	18	31	53	(+0.04)[b)]
16	3.6×10^2	5.8×10^2	9.2×10^2	1.5×10^3	2.3×10^3	3.5×10^3	+0.44
Ref.	2.5×10^2	4.1×10^2	6.5×10^2	1.0×10^3	1.6×10^3	2.4×10^3	
17	23	34	50	71	1.0×10^2	1.4×10^2	+0.13
Ref.	*16*	*22*	*31*	*43*	*60*	*82*	
18	2.7×10^2	3.9×10^2	5.5×10^2	7.6×10^2	1.0×10^3	1.4×10^3	+0.75
Ref.	1.6×10^2	2.2×10^2	3.1×10^2	4.4×10^2	6.0×10^2	8.2×10^2	
19	0.56	0.87	1.3	2.0	3.0	4.5	+9.74
Ref.	*0.051*	*0.080*	*0.12*	*0.19*	*0.30*	*0.42*	
19′	0.49	0.75	1.1	1.7	2.6	3.8	(+0.17)[b)]
20	30	44	63	90	1.3×10^2	1.8×10^2	−0.01
Ref.	*30*	*44*	*64*	*91*	1.2×10^2	1.8×10^2	
21	7.5	13	23	38	64	1.0×10^2	−0.22
Ref.	*9.9*	*17*	*29*	*49*	*81*	1.3×10^2	
22	1.1×10^3	1.5×10^3	1.9×10^3	2.5×10^3	3.3×10^3	4.3×10^3	−0.19
Ref.	1.3×10^3	1.8×10^3	2.4×10^3	3.2×10^3	4.1×10^3	5.4×10^3	
23	0.17	0.31	0.55	0.98	1.7	2.9	−0.16
Ref.	*0.19*	*0.35*	*0.65*	*1.1*	*2.1*	*3.7*	
23′	0.42	0.77	1.4	2.4	4.1	7.0	(−0.59)[b)]

a) Average relative error (Δk) is the average to the number of data of relative errors (Δk) calculated by $(k_{\mathrm{NIT}}-k_{\mathrm{IT}})/k_{\mathrm{NIT}}$, where k_{NIT} is rate constant by NIT-NMR method and k_{IT} is rate constant by the isothermal method. b) Average relative errors in reference to our isothermal NMR method are given in parentheses.

Statistical treatment for the difference of the NIT and the isothermal activation parameters gives the following confidence intervals of standard deviation at 99% confidence level, namely $\mathrm{SD}(\Delta\Delta H^{\ddagger},99\%)=0.80$—$2.3\ \mathrm{kJ\,mol^{-1}}$ and $\mathrm{SD}(\Delta\Delta S^{\ddagger},99\%)=2.6$—$7.5\ \mathrm{kJ\,mol^{-1}\,K^{-1}}$. Significance test (the test for equality between two means or variances) assuming the significance level of 1% showed that there is no significant difference between the activation parameters from the two methods.

In the same way as we said in Table 4, the k values and these average relative errors (Δk) obtained from the activation parameters of the NIT and isothermal method are given in Table 7. Expect for Entries 15, 19, 23, the confidence intervals of standard deviation values at 99% confidence level are $\mathrm{SD}(\Delta k)=0.23$—$0.65$. The significance test (the test for equality between two means or variances) assuming the significance level of 1% showed that there is no significant difference between the k-values from the two methods. The results mentioned above guarantee the validity of our NIT-NMR experiments.

In conclusion, the NIT-NMR method applied on variable temperature NMR data is very convenient and time-economizing in determining activation parameters of reactions. Only a time-programmed variable temperature measurement gives the activation parameters in nearly the same accuracy as the conventional isothermal method. Before this determination, however, the order of the reaction needs to be determined preliminarily.

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