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Temperature-rate profiles by polarimetric variable-temperature kinetic experiments to study racemization reactions

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Abstract

The racemization of (−)-adrenaline was followed by polarimetric variable-temperature kinetic experiments obtaining activation parameters and $k_{obs}(T)$ profile in one tenth of the time usually spent for traditional kinetic runs. A polarimeter connected to a computer for the acquisition and processing of the analytical data was used. The kinetic profiles were processed by both an integral method and a differential method. The results are in good agreement with each other and with those obtained by constant-temperature kinetics. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

The chemical structure of molecules of pharmaceutical interest is often characterised by the presence of stereogenic centres and, consequently, the existence of enantiomeric forms is possible. In these isomers there can be differences in pharmaceutical activity. Difference in therapeutical action, e.g. (−)-isoprenaline is a weak α-simpaticomimetic agonist while (+)-isomer is an antagonist; difference in the distribution of the drug in the organism, e.g. (−)-α-methyl L-dopa, after intravenous administration, reaches in several organs a higher concentration than the (+)-isomer; difference in metabolization, e.g. in the two antipodes of glutemide, or in the velocity of escretion like in (+)- and (−)-4-hydroxyanphetamine [1]. For this reason, in the last decades, a great research effort has been done both in stereoselective synthesis [2] and in chiral separation techniques [3] to obtain drugs in enantiopure forms. Moreover, in the study of chemical stability to degradation in solution much greater atten-

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tion than in the past has been devoted to the racemization processes [4].

The aim of this paper is to show a new way to study the stability of optical active compounds particularly those that racemize. It is based on the use of a modern polarimeter connected to a computer for the automatic collection of the analytical data and on the application of the variable-parameter kinetics (VPaK) [5].

VPaK enables to obtain the dependence of the rate constant on a physical parameter (T, P, C, etc.) in a single kinetic run by carrying out the experiment varying, in a controlled way, the value of the parameter [5]. The kinetic profile obtained in this way, under pseudo-first order conditions, is described by Eq. (1)

$$-\frac{dC}{dt} = \{k_{obs}[Par_i(t)]\}C \quad (1)$$

where C is the concentration of the monitored substrate, $Par_i(t)$ is the parameter i varying with time and $k_{obs}[Par_i(t)]$ is the specific rate depending on that parameter. The direct best fit of kinetic data to this equation leads to the optimised values of the terms regulating the dependence on the parameter. For example, in variable-temperature kinetics (VTK) the parameter changing with time is the temperature ($Par_i = T$); $k_{obs}(Par_i)$, the dependence function that links the k_{obs} to the parameter, is the Eyring equation; and the terms to optimise are the enthalpy and the entropy of activation. In generic variable-concentration kinetics (VCK), the parameter changing with time is the concentration of a species j that influences the reaction rate ($Par_i = C_j$), the dependence function is the rate law relative to the reaction mechanism, and the terms to optimise the rate constants of rate determining elementary steps. Kinetic data can be processed also by a differential method simply dividing the first derivative of the kinetic profile to the profile ($-(dC/dt)/C = k_{obs}[Par_i(t)]$).

Only the recent availability of fast computers for acquisition and processing of experimental data as well as computer aided devices for accurately varying the parameter inside the reaction vessel makes possible an easy and convenient application of this method and can explain why so far almost all the data given in the literature have been obtained by traditional constant-parameter kinetics.

Several applications have been made by the authors of VTK where $k_{obs}(T)$ profiles have been obtained with single kinetic runs using spectrophotometric and fluorimetric methods on organic [6], inorganic and organometallic [7,8] systems. VCK has been the subject of a communication where a single conductometric experiment carried out varying the concentration of thiourea yielded the dependence of k_{obs} on that concentration in a nucleophilic substitution reaction to a coordination compound [5]. Recently, a variable-pH kinetic experiment has been proposed where the entire pH-rate profile for the hydrolysis of aspirin has been obtained in a single kinetic run [9].

Here a polarimetric VTK experiment is proposed. In this case, the optical rotation α is followed, instead of the concentration C, going from the initial value α_0 to a final value that can be α_∞ for a generic reaction or zero for a racemization process. For a modulating function $T(t) = T_0 + \gamma t$ the mathematical model assumes the form of Eq. (2)

$$\frac{1}{(\alpha-\alpha_\infty)}\frac{d\alpha}{dt} = \frac{k_B(T_0+\gamma t)}{h}\exp\left[\frac{\Delta S^\ddagger}{R}\right]\exp\left[-\frac{\Delta H^\ddagger}{R(T_0+\gamma t)}\right] \quad (2)$$

or, in the integrated version, the form of Eq. (3).

$$\alpha = (\alpha_0-\alpha_\infty)\exp\left\{-\frac{k}{h}\exp\left[\frac{\Delta S^\ddagger}{R}\right]\int_0^t (T_0+\gamma t)\exp\left[-\frac{\Delta H^\ddagger}{R(T_0+\gamma t)}\right]dt\right\} + \alpha_\infty \quad (3)$$

The reaction studied is the racemization of adrenaline, one of the most representative optically active drug. Adrenaline is an active principle in the medulla of the adrenal gland which is used in a direct acting simpaticomimetic. Major effects of adrenaline include increased speed and force of cardiac contraction and increasing blood flow of skeletal muscle. In therapy (−)-adrenaline has an important role in the management of acute aller-

gic reactions and can be life saving in patients with anaphylactic shock [10]. It is obvious that racemization of adrenaline may have dramatic effects on patient's health because (+)-adrenaline is less active than the (−)-antipode.

2. Experimental

2.1. Material

(−)-Adrenaline was purchased from Sigma. No further purification was necessary.

2.2. Solutions

The hydrogen ion concentration was obtained by using a 1 M solution of HCl.

2.3. Kinetic measurements

The kinetics of the racemization of adrenaline were followed polarimetrically by both VTK runs and traditional constant-temperature kinetic (CTK) runs, to have some direct comparative data.

2.3.1. Constant-temperature kinetics

The experiments were carried out inside a 1 dm thermostated polarimetric tube with a temperature accuracy of ± 0.05 K. The rate constants k_{obs} (s^{-1}) were obtained from a non-linear least squares fit of the experimental data to $\alpha = \alpha_\infty + (\alpha_0 - \alpha_\infty)\exp(-k_{obs}t)$ with α_0, α_∞, and k_{obs} as the parameters to be optimised (α = optical rotation during the reaction, α_0 = optical rotation at the start of the reaction, α_∞ = optical rotation at completion of reaction).

2.3.2. Variable-temperature kinetics

Kinetic runs were carried out using a Perkin-Elmer Polarimeter 341 connected to a Pentium II 800 MHz computer and equipped with a 1 dm polarimetric tube thermostated by a HAAKE C 25 thermostating bath which allows a controlled change of the temperature with time with an accuracy of ± 0.05 K. The temperature was checked by a platinum resistor directly inserted into the polarimetric tube and connected to the computer (readout resolution 0.01 K). The optical rotation-temperature-time data were automatically acquired by using a Visual Basic program. The acquisition speed was 10 samples min^{-1}, sufficient to have a good fit to the mathematical model and a good density of points for an accurate evaluation of the first derivative in the range of k_{obs} studied.

Due to the relatively short range of temperature used in VTK experiments (< 30 K), small effects (i) on the optical rotation, (ii) on the concentration of the optical active species caused by thermal expansion of the solvent, and (iii) on the pH value were not considered, because they were negligible.

2.4. Data processing

Processing [11] of stored data was done using the Jandel Scientific Table Curve 2D.

3. Results and discussion

Fig. 1 shows the change in optical rotation during the racemization of (−)-adrenaline in aqueous solution containing HCl (1 M), at 321.0 K. Processing these data using the traditional exponential equation gave the optimised value of

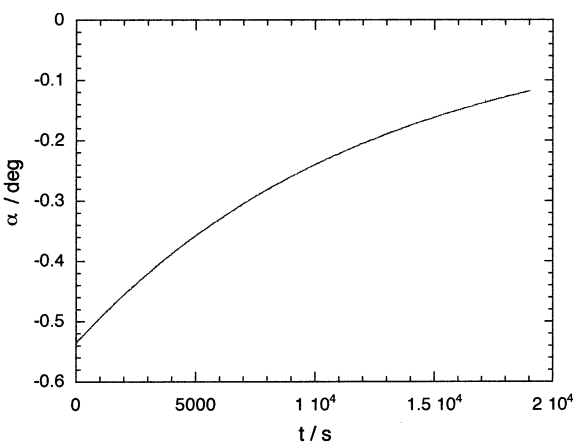

Fig. 1. Change in optical rotation, at 321.0 K, during the racemization of (−)-adrenaline in water 1 M in HCl.

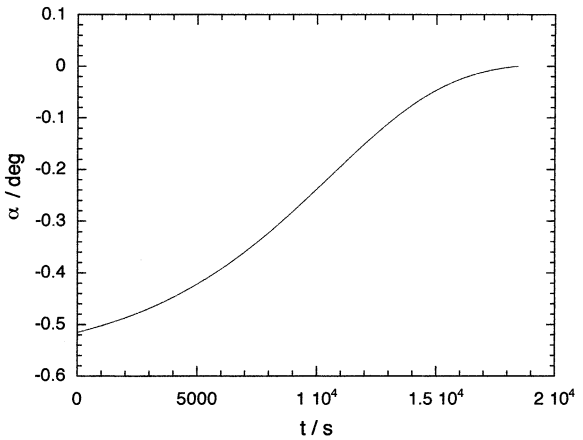

Fig. 2. Change in optical rotation during the racemization of (−)-adrenaline in water 1 M in HCl at the variable-temperature T (K) $= 309.6 + 16.94 \times 10^{-4} t$ (s).

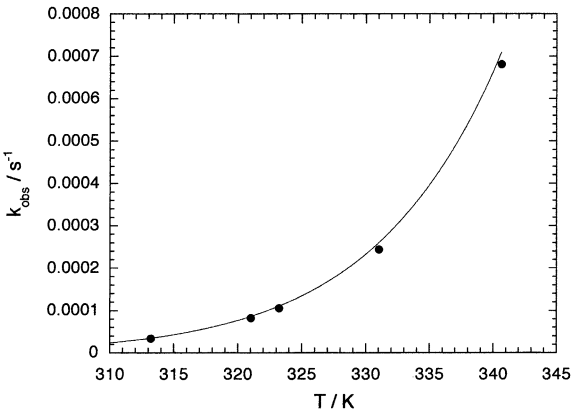

Fig. 3. $k_{obs}(T)$ profile of the racemization of adrenaline in water (1 M in HCl) built using the activation parameters obtained by a single VTK run (solid line). Plane circles refer to traditional CTK runs carried out under the same conditions.

the rate constant at this temperature, $k_{obs} = 8.21 \times 10^{-5}$ s^{-1}. Fig. 2 shows the kinetic profile obtained, polarimetrically, for the same reaction, in a VTK experiment at a linearly increasing temperature $T = T_0 + \gamma t$ with $T_0 = 309.6$ K and $\gamma = 0.001694$ K s^{-1}. It has a typical sigmoidal shape due to the acceleration caused by the increase of the temperature. The fit of this profile to Eq. (3), with α_0, α_∞, $\Delta S^{\neq}$ and $\Delta H^{\neq}$ as the parameters to be optimised, gave the activation parameters ($\Delta S^{\neq} = -27 \pm 1$ J K^{-1} mol^{-1}, $\Delta H^{\neq} = 95 \pm 1$ kJ mol^{-1}, $R^2 = 0.99999$). Thousands of analytical points acquired in real time by the computer ensured a very good description of the experiment so that the excellent values of standard deviation and correlation coefficient underline a perfect adherence to the mathematical model (theoretical curve in Fig. 2 is not reported because graphically coincident with the experimental one), the goodness of the method as well as its right performance. $\Delta S^{\neq}$ and $\Delta H^{\neq}$ where then used to build the $k(T)$ profile (Fig. 3) containing the rate constants for the entire range studied. The values obtained by the traditional method are in accordance with this result but required at least ten times the time spent for the VTK run as can be seen by the ratio of the sum of the CTK reaction times by the VTK reaction time. This can be very useful particularly in studies concerning a series of compounds to be analysed and/or a series of environmental conditions to be taken into account. A tenfold factor can signify a lot of experimental time to save. Another kinetic run was carried out at a linear increasing temperature $T = T_0 + \gamma t$ with $T_0 = 320.7$ K and $\gamma = 0.001694$ K s^{-1}. Activation parameters and $k(T)$ profile were the same, within the experimental error ($\Delta S^{\neq} = -27 \pm 1$ J K^{-1} mol^{-1}, $\Delta H^{\neq} = 95 \pm 1$ kJ mol^{-1}, $R^2 = 0.99999$). This confirms the validity of the method and underlines the reproducibility of the results.

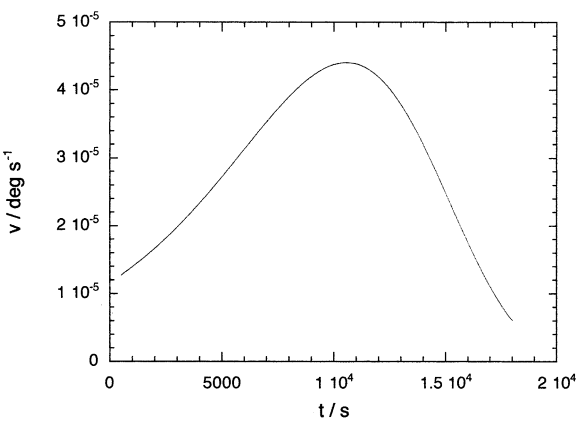

Fig. 4. Trend of the reaction rate during the variable-temperature experiment as obtained by the first derivative of the kinetic profile reported in Fig. 1.

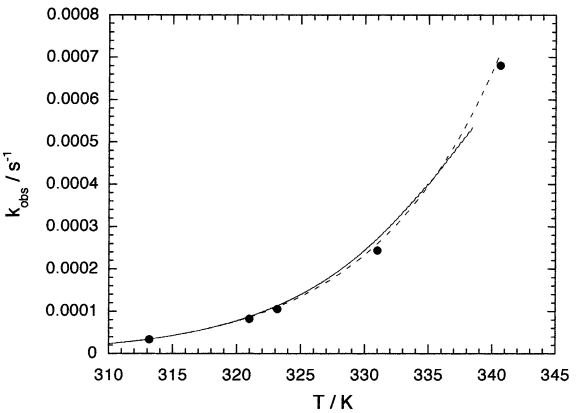

Fig. 5. Dependence of the pseudo-first order rate constant of the racemization of adrenaline in water (1 M in HCl) as obtained by dividing the first derivative of the kinetic profile reported in Fig. 1 to $(\alpha - \alpha_{\infty})$ (solid line). Dashed line refers to the $k_{obs}(T)$ profile obtained by the direct fit, plane circles refer to traditional CTK runs.

VTK profiles were also processed by the differential method. Fig. 4 shows the first derivative of the profile reported in Fig. 1 obtained by the Savitzky–Golay method [12]. It shows the trend of the reaction rate during the process, increasing in the first part and then decreasing in the second part for the decrease in concentration of the reactant. The ratio of this derivative to the profile itself, according to Eq. (2), gave the whole dependence of the rate constant on the parameter temperature. The $k(T)$ profile obtained in this way is identical to that obtained by the direct fit (Fig. 5).

4. Conclusions

By using VPaK, the k(Par) profile of a reacting species can be determined just from a single kinetic run. VTK can even be used polarimetrically, extending this new way of collecting kinetic data to reactions involving optically active compounds which are often difficult to follow otherwise. Using standard instruments and easily available software, time and chemicals can be saved obtaining the same accuracy in the results.

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