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Kinetic study of the indomethacin synthesis and thermal decomposition reactions

Mariana Rusu [a], Maria Olea [a,*], D. Rusu [b]

[a] *Faculty of Chemistry and Chemical Engineering, 'Babes-Bolyai' University, 11 Arany Janos, 3400 Cluj-Napoca, Romania*
[b] *Faculty of Pharmacy, 'Iuliu Hatieganu' University, 12 Ion Creanga, 3400 Cluj-Napoca, Romania*

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Abstract

The kinetics of indomethacin synthesis (achieved through a new method) was studied at 80°C. The reaction proceeds in four steps. In the first step, by the condensation of levulinic acid with *p*-chlorobenzoyl-*p*-methoxy-phenyl-hydrazine in homogeneous acidic catalysis an intermediate is formed. In the second step, by the isomerisation of this intermediate a hydrazo compound is formed. In the third step, the isomerisation is followed by the *o*-benzydinic transposition of the reaction product mentioned above. In the fourth step, indomethacin is formed through a cyclization reaction. The rate constant of the indomethacin synthesis reaction was determined assuming that the cyclization reaction constitutes the rate-determining step. Spectrophotometric methods were used both in order to investigate the kinetics of the synthesis reaction and to verify the proposed mechanism. Then, a thermogravimetric study was performed on the purpose of finding out the temperature range in which indomethacin is stable. From the thermogravimetric curve kinetic parameters have been derived, using different calculation techniques.

Keywords: Kinetics; Spectrophotometric and thermal analysis; Indomethacin

1. Introduction

Indomethacin (1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1-H-indole-3-acetic acid) is a member of a class of drugs called NSAIDS (non-steroidal anti-inflammatory drugs). This drug has anti-inflammatory, analgesic and antipyretic properties [1] and as such, it has a very wide variety of applications. NSAIDS work by binding and inactivating the enzyme cyclooxygenase, a critical enzyme in prostaglandin biosynthesis [2].

Indomethacin synthesis has been reported for the first time by Shen et al. in 1963 [3]. At that time, of some 350 indole derivatives studied, only indomethacin has demonstrated a high degree of anti-inflammatory activity. Nowadays, it is not necessary to study such a large number of compounds, because new tools, as QSAR (Quantitative Structure-Activity Relationships) and Neural Networks, can be used in drug design [4,5].

* Corresponding author. Present address: The University of Tokyo, Graduate School of Science, Department of Chemistry, 7-3-1 Hongo, Bunkyo-Ku, Tokyo 113-0033, Japan.

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Nowadays, the elucidation of reaction mechanism and the optimization of process conditions in organic syntheses by kinetics studies are more important.

In a general way a kinetic study of reaction mechanism includes these four components [6]:

1. Experimental kinetics.
2. Determination of the rate equation(s).
3. Writing the kinetic scheme.
4. Proposal of transition-state structures, stereochemistries, and energetics.

In particular, steps 2 and 3 may be strongly interdependent. Our present concern is with these steps. A mechanism may be defined as a sequence of elementary steps, which gives an accounting of the entire kinetic behavior of a reaction.

The kinetic study for the indomethacin synthesis process as well as the kinetic study for its thermal decomposition were not yet reported in the literature.

2. Experimental

2.1. Spectroscopy

The UV spectra were recorded on 10^{-5} methanolic solutions using a Specol-UV–VIS-spectrophotometer. Samples, with a 2 ml volume, were diluted for 3500 times.

2.2. Thermal analysis

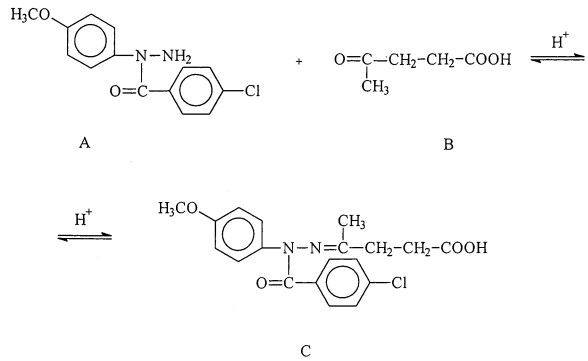
The thermal measurements were carried out with a OD-102 type Paulik-Erdey derivatograpf (MOM), sample weight 100 mg, constant heating rate 20°C/min.

3. Kinetics

3.1. Kinetics of the indomethacin synthesis reaction

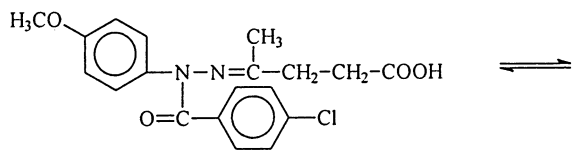
Based on a new method of indomethacin synthesis [7] we have assumed the following mechanism of the reaction:

1. The condensation of levulinic acid with *p*-chlorobenzoyl-*p*-methoxy-phenylhydrazine, in acidic catalysis (H_3PO_4):



A B C

2. The isomerisation of product C with the formation of a hydrazo compound:



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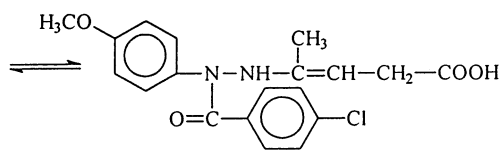
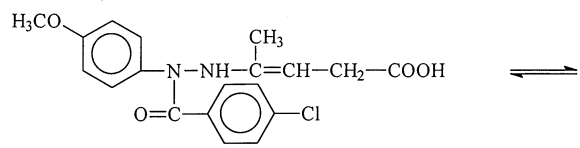


D

3. The *o*-benzydinic transposition of the reaction product mentioned above (R. Robinson, 1918):



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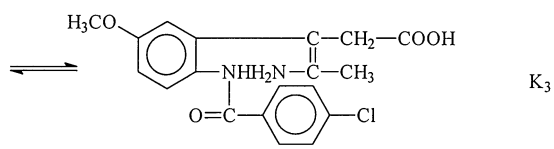
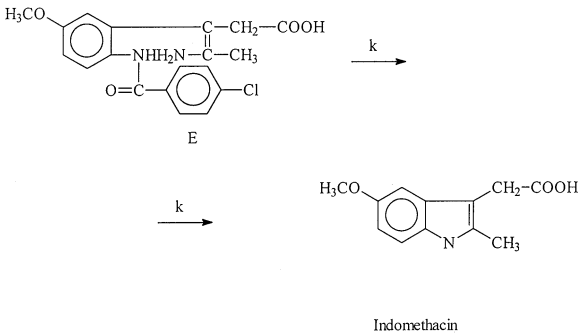


E

4. The cyclization:



According to the results of a complete UV-spectrophotometric study of the process [8] we have considered the cyclization reaction as rate determined step (rds) and the reaction rate can be written as

$$R = k[\mathrm{E}]. \quad (1)$$

Subsequent to successive application of the pre-equilibrium approximation we can write

$$K_3 = [\mathrm{E}]/[\mathrm{D}] \quad (2)$$

from where

$$[\mathrm{E}] = K_3[\mathrm{D}]. \quad (3)$$

Then,

$$K_2 = [\mathrm{D}]/[\mathrm{C}] \quad (4)$$

and

$$[\mathrm{D}] = K_2[\mathrm{C}]. \quad (5)$$

But

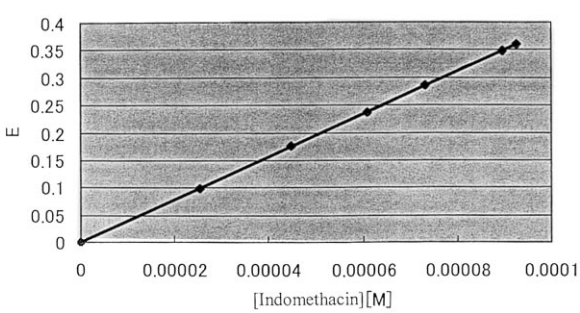


Fig. 1. The standard curve.

$$K_1 = [\mathrm{C}]/([\mathrm{A}][\mathrm{B}]) \quad (6)$$

and

$$[\mathrm{C}] = K_1[\mathrm{A}][\mathrm{B}]. \quad (7)$$

Now, the reaction rate is expressed with respect to only of the easily measurable reactant concentrations:

$$R = kK_1K_2K_3[\mathrm{A}][\mathrm{B}] \quad (8)$$

or

$$R = k_{\mathrm{obs}}[\mathrm{A}][\mathrm{B}], \quad (9)$$

where

$$k_{\mathrm{obs}} = kK_1K_2K_3. \quad (10)$$

As Eq. (9) shows we have supposed that the process was of second order (which means of first order with respect of each reactant).

In order to determine the rate constant and to prove the reaction order, the indolisation reaction was surveyed by means of spectrophotometric methods.

We have measured the extinction for $\lambda = 320$ nm (where indomethacin UV-absorption was maximum) at several time intervals, subsequent to obtaining the standard curve. As Fig. 1 shows, that curve is an almost perfect straight line (its equation is $\mathrm{E} = 3.89 \times 10^3$ [Indomethacin], the correlation coefficient being $R^2 = 0.99994$).

Experimentally, the molar ratio was A:B = 1:1.2. Thus the rate equation could be written as

$$R = k_{\mathrm{obs}}[\mathrm{A}]\{[\mathrm{B}_0] - [\mathrm{A}_0] + [\mathrm{A}]\}, \quad (11)$$

where 0 refers to the initial concentrations.

A more simple equation was obtained when the conversion, X_A, was used instead of concentrations and when we introduced the excess ratio, γ, as follows:

$$\gamma = [\mathrm{B}_0]/[\mathrm{A}_0]. \quad (12)$$

Consequently,

$$R = k_{\mathrm{obs}}[\mathrm{A}_0]^2(1 - X_\mathrm{A})(\gamma - X_\mathrm{A}). \quad (13)$$

The conversion has been calculated from its relation with the concentration of the reaction product i.e. indomethacin:

$$[\text{Indomethacin}] = [\mathrm{A}_0]\ X_\mathrm{A}. \quad (14)$$

Table 1
Kinetic data for the indolization reaction

No.	T (min)	E	$[\text{Indomethacin}]_{\text{uv-sample}}$[M]	$[\text{Indomethacin}]_{\text{reaction}}$[M]	X_A	[A]	[B]
1	0	0	0	0	0	0.63	0.756
2	15	0.099	2.54×10^{-5}	0.0889	0.141	0.541	0.667
3	30	0.175	4.49×10^{-5}	0.157	0.249	0.473	0.599
4	45	0.237	6.09×10^{-5}	0.213	0.338	0.417	0.543
5	60	0.285	7.32×10^{-5}	0.256	0.406	0.374	0.500
6	75	0.349	8.97×10^{-5}	0.314	0.498	0.316	0.442
7	90	0.360	9.25×10^{-5}	0.324	0.514	0.306	0.432

3.2. Kinetics of the thermal decomposition process

The thermogravimetric data have been employed in order to find out the kinetic parameters. The data were obtained both under isotherm conditions and under dynamic conditions of temperature. Thermogravimetrics in dynamic conditions has a double advantage. On the one hand it allows for the estimation of the kinetic parameters from a single thermogram and on the other, the kinetic study can be performed in a large temperature range. Consequently, we could obtain complete information about the thermal properties of the sample. Our main concern was the temperature limits within our substance is stable as this led to the finding out of the temperature interval suitable for the synthesis process [9].

From the recorded derivatograms the following magnitudes have been derived: the temperature ranges in which sample weight losses/increases were more significant (TG curve), the temperature of maximum rate in weight loss (DTG peak temperatures), the domain in which the physical and chemical changes are exo- or endothermic (DTA peak temperatures).

4. Results and discussions

Table 1 presents both the measured (at 80°C) and calculated data, for the synthesis reaction of indomethacin. The initial concentrations were $[A_0] = 0.63$ M and $[B_0] = 0.756$ M, respectively.

The derivatogram is shown in Fig. 2. Our substance i.e. indomethacin, is stable up to 248°C. The DTA curve shows that the melting of our substance brings about an endothermic peak, at 162°C. Between 248 and 420°C a decomposition reaction occurs (see the exothermic peak at 370°C). In this interval the weight loss is about 25% caused by elimination of the groups: $-OCH_3$ and $-H_2C-COOH$.

Between 420 and 720°C a second decomposition process takes place (an exothermic peak at 640°C or a maximum value on the DTG curve).

The sample weight attains a minimum value at about 740°C only when the burning process is over.

The results are presented in Table 2.

In order to determine k_{obs}, we have integrated the rate equation and we have obtained

$$k_{obs}[A_0]t = 1/(\gamma-1)\ln(\gamma - X_A)/\{\lambda(1-X_A)\}, \quad (15)$$

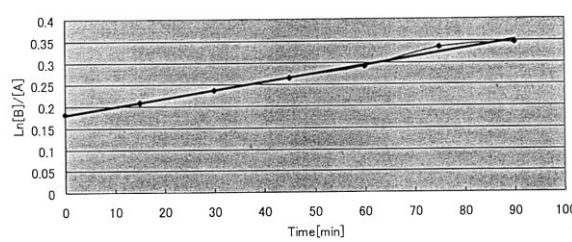


Fig. 2. Test for the bimolecular reaction.

Table 2
The results of the deritographic study

Compound	n	E_a (kcal/mol)	A
Indomethacin	1.14	7.285	14.14
	0.79	11.695	222.38

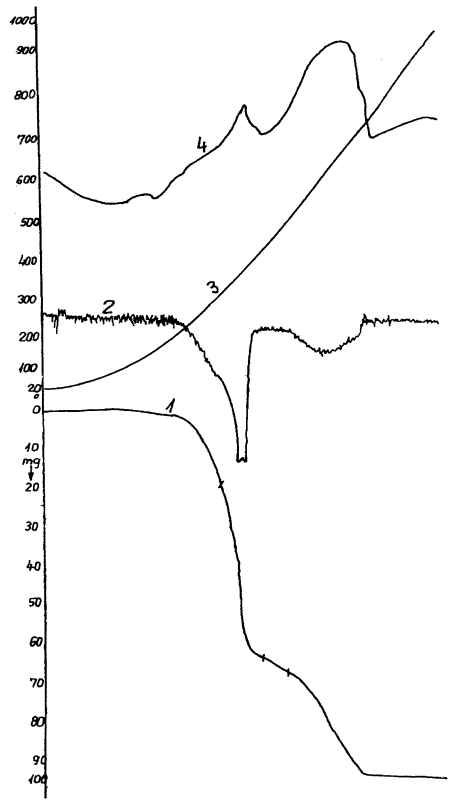


Fig. 3. The derivatogram: (1) TG curve; (2) DTG curve; (3) $T=f(t)$; (4) Data curve.

which has allowed us to calculate the k_{obs} value for each moment of time. The calculated values were: 1.422×10^{-2}; 1.422×10^{-2}; 1.440×10^{-2}; 1.427×10^{-2}; 1.619×10^{-2}; 1.431×10^{-2} M^{-1} min^{-1}, respectively. As values are almost similar an average value, $k_{obs} = 1.46 \times 10^{-2}$ M^{-1} min^{-1}, has been accepted for k_{obs}.

The constancy in the calculated k_{obs} values means that the supposed reaction order is correct. An alternative to this way for verifying the reaction order is to plot the integrated rate equation versus time Eq. (10). From Eq. (15),

$$\ln[B]/[A] = \ln \gamma + \{[B_0] - [A_0]\} k_{obs} t. \quad (16)$$

As Fig. 3 shows, the plotted function is linear over the entire time of reaction. As expected, its equation is $\ln[A]/[B] = 0.182 + 0.00189*t$, $R^2 = 0.9899$ and $k_{obs} = 1.496 \times 10^{-2}$ M^{-1} min^{-1} (the error from the calculated value is 2.46%). Therefore, the reaction is second order, as we have supposed.

The kinetic parameters for the two thermal decomposition processes have been calculated by using the Freeman–Caroll method. We can write the rate equation as follows

$$dw_t/dT = A/a \ \exp(-E_a/(RT)) W_r^n, \quad (17)$$

where $a = dT/dt$, and then, by applying the logarithmic form for the successive measurements

$$(\Delta \log(dw_t/dT))$$

$$/((\Delta \log(W_r))$$

$$= n - (E_a/(2.303R)\Delta(1/T))/(\Delta \log(W_r)), \quad (18)$$

where $P = (\Delta \log(dw_t/\ dT))/((\Delta \log(w_r))$ and $Q = 10^3\ (\Delta T^{-1})/(\Delta \log(w_r))$. we could find out the activation energy and the reaction order. In Eq. (17), the parameters have the following significance: w_t = the weight loss at t; w_r = the residual quantity; w_∞ = the complete loss; T = temperature (in Kelvin degrees).

5. Conclusions

In conclusion we can say that the Indomethacin synthesis process is a complex one and includes some elementary steps, the last of them being the rds. The reaction order is two and the twice mediated value for k_{obs} is 1.478×10^{-2} M^{-1} min^{-1}.

The kinetic study for the synthesis process as well as the kinetic study for the thermal decomposition of indomethacin were performed for the first time. The kinetic parameters have been estimated by means relatively simple, although of high precision, spectrophotometric and thermal methods.

The mechanism suggested for the synthesis process has been confirmed by the experimental data.

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