Investigation of the reaction mechanism of [4 + 2] cyclization of 2,3-dimethylbuta-1,3-diene to methyl acrylate using the Michaelis-Menten equation

Irina Kostiv

Department of Chemical Engineering, Lviv Polytechnic National University, st. Bandery 12, Lviv, 79013 Ukraine

e-mail: kostiv.irina@gmail.com

Keywords: *2,3-dimethylbuta-1,3-diene, methyl acrylate, methyl-3,4-dimethylcyclohex-3-ene-1-carboxylate, Michaelis–Menten equation, molecular complex.*

The cycloaddition reaction between 2,3-dimethylbuta-1,3-diene and methylacrylate proceeds by the second order kinetics. The rate constants increase with the increase in the excess of one of the reactants. The change in the effective rate constants is described by the Michaelis–Menten equation indicating that the reaction proceeds through the initial equilibrium stage of formation of a molecular complex stabilized by van der Waals interaction which then transforms into the product. The limiting stage of the reaction is established and its mechanism is suggested.

Introduction

Alkylcyclohexene carboxylates, as products of organic synthesis, belong to an inadequately studied class of substances. Published information on the methods of synthesis, chemical properties and areas of application are practically absent and relate mainly to saturated derivatives of cyclohexene carbonic acids. Besides, alkylcyclohexene compounds are raw materials for preparation of food flavors, perfumery compositions, plasticizers, comonomers, plant growth regulators, drugs and hydro-aromatic hydrocarbons.

Alkylcyclohexene compounds are increasingly being used as monomers in production of new polymeric materials. Alkylcyclohexenecarboxylates are the basis for

synthesis of polyfunctional polymers of diverse structures with a predefined set of physical-chemical characteristics [1-3].

Availability of homologous series creates a practical possibility of synthesis of secondary, tertiary and hydro-aromatic hydrocarbons and production of perfumery compositions [2]. Much of the esters of alkylcyclohexenecarbonic acids are structural fragments of vitamins, hormones and alkaloids.

Alkylcyclohexene carboxylates are starting materials for drugs, as well as modifiers, plasticizers, epoxyresins, and comonomers [1, 3]. They are used to create lotions, body emulsions, shampoos, day and night creams, perfumes, and food flavors [2]. In this work we studied the kinetics of interaction between 2,3-dimethylbuta-1,3-diene (DMB)

with methyl acrylate (MA) to optimize the process of producing methyl-3,4-dimethylcyclohex-3-ene-1-carboxylate (formula 1).

Experimental part

Kinetic studies were performed in temperature controlled sealed glass ampules according to the method described in [4], in the temperature range 403-433K. To the 10 cm³ ampules were charged methyl acrylate and 2,3-dimethylbuta-1,3-diene synthesized by us previously [5] in the molar ratios from 1:1 to 1:1.75 and some hydroquinone, the ampules were sealed and placed in a thermostat. At regular intervals, an ampule was removed from the thermostat, quickly cooled, opened, and the reaction mixture was analyzed by gas-liquid chromatography on a SELMI CHROM-1 apparatus. The quantitative analysis was performed with internal normalization. The accuracy of chromatographic analysis in multiple parallel determinations did not exceed 3% [6].

The investigated reaction proceeds according to the second-order kinetics. The values of effective rate constants are listed in Table 1. We found that the values of the effective second order constants increase with the increasing ratio 2,3-dimethylbuta-1,3-diene : methyl acrylate. The difference is more pronounced at higher temperatures. It was appropriate to examine in more detail the mechanism of this reaction. Note that the

mechanism of the [4 +2]-cycloaddition reaction today is still controversial [7].

The Diels-Alder reactions may actually take place according to a two-step mechanism [8–12]. Such a two-step mechanism with biradical intermediate takes place e.g. in the 2-chlorobuta-1,3-diene dimerization reaction [8]. On the other hand, reactions e.g. of 3-nitropyridine with 1-methoxy-3-trimethoxysilylbuta-1,3-diene [9], 4,6-dinitrobenzofuroxan with 1-trimethylsilyloxybuta-1,3-diene [10], aryl-substituted 1,2,4-triazines with 2-cyclopropylidene-1,3-dimethylimidazolidine [11] and 1,1,1-trifluor-3-nitroprop-2-ene derivatives with enamines [12] take place according to a two-step, zwitterionic mechanism.

In the case of interaction between methyl acrylate and 2,3-dimethylbuta-1,3-diene, the reaction can take place in two ways (Scheme 1): with the primary interaction of the atoms C (1) and C (7) (the way T11-I1-T12) or with the primary interaction of the atoms C (2) and C (10) T21-I2-T22) (Scheme 1). In the first way, the T11-I1-T12 reaction passes through the transition state T11 while the interaction of the atom C (1) AMA and C (13) DMB occurs with the overcoming of the energy barrier Ea (T11).

The formation of the metastable intermediate I1 and the transition state T12 followed by the interaction of the C (4) MA and C (8) DMB atoms also passes concertedly and leads to the target product Peq, in which the carboxylate group is in equatorial position to the cyclohexene ring. The formation of a cycle occurs at the exit from the second transition state T12 with dysrotatory rotation of the boundary orbitals of the atoms a C (4) MA and C (8) DMB.

In the second way, T21-I2-T22, the reaction passes through the transition state T21 to overcome the energy barrier E_a (T21) in the case of the preparation of methyl-3,4-dimethylcyclohex-3-ene-1-carboxylate and the subsequent formation of intermediate I2 through the transition state T22 to the product Pax.

Scheme 1 Interaction between DMB and MA

The Arrhenius equation described satisfactorily the dependence of the effective rate constants on temperature for different ratios (**Figure 1**), which allowed us the calculation of the formal activation energy and other activation parameters of the overall process (Table 1).

Table 1 Effective rate constants and activation parameters of the cycloaddition reaction between 2,3-dimethylbuta-1,3-diene and methyl acrylate

AMA : DMB	$(k_{\text{eff}} \pm \Delta k) \times 10^6, \text{ l mol}^{-1} \text{ s}^{-1}$				$E_{\text{eff}}, \text{ kJ mol}^{-1}$	$\Delta H_{\text{eff}}, \text{ kJ mol}^{-1}$	$\Delta S_{\text{eff}}, \text{ J mol}^{-1}$
	403K	413K	423K	433K			
1 : 1	2.6 ± 0.2	6.2 ± 0.2	9.9 ± 0.3	11.9 ± 0.5	72.5	56.4	-160.2
1 : 1.25	3.5 ± 0.2	7.1 ± 0.3	11.2 ± 0.4	16.7 ± 0.5	73.6	64.3	-155.1
1 : 1.4	4.0 ± 0.2	8.5 ± 0.3	13.4 ± 0.4	19.3 ± 0.5	74.8	68.2	-152.5
1 : 1.5	4.9 ± 0.2	10.3 ± 0.3	16.9 ± 0.5	23.9 ± 0.7	75.9	74.6	-148.2
1 : 1.6	5.8 ± 0.2	12.3 ± 0.3	19.6 ± 0.5	28.9 ± 0.7	76.4	78.5	-145.6
1 : 1.75	7.2 ± 0.2	14.4 ± 0.3	25.5 ± 0.5	36.0 ± 0.7	78.1	87.2	-139.9

The correlation coefficient was satisfactory in all cases ($R^2 > 0.95$). The analysis of the parameters made it possible to establish that upon increase in

the 2,3-dimethylbuta-1,3-diene excess and the accompanying increase in the values of k_{eff} a systematic increase was observed in the effective energy (ΔE_{eff}) and the effective activation enthalpy (ΔH_{eff}). Simultaneously, the value of the effective activation entropy ($-\Delta S_{\text{eff}}$) also increased.

For all ratios of reagents an isokinetic relationship was observed with a high degree of correlation ($R^2 = 0.99$) between the effective entropy and enthalpy of reaction, which allowed the calculation of the isokinetic temperature $T_{\text{iso}} = 287 \text{ K}$ (Figure 2) that was far from the investigated temperature range.

Figure 1. Dependence of the effective rate constant of cycloaddition between 2,3-dimethylbuta-1,3-diene and methyl acrylate on temperature for different ratios of reactants: 2,3-dimethylbuta-1,3-diene : methyl acrylate

The increase in E_{eff} and ΔH_{eff} with increasing excess of 2,3-dimethylbuta-1,3-diene and a simultaneous increase in ΔS_{eff} indicate the

increasing steric hindrances in the reaction course. This finding suggests also that the reaction mechanism is unique in the studied range of the reagents ratio. Such a systematic change in the rate constants with an increase in excess of one of the reactants is typical of the reactions that include the formation of the molecular complex stabilized by van der Waals interaction [13, 14]. A similar reaction course has been proved also for several cases [13, 14], where the formation of molecular complex stabilised by van der Waals interaction was confirmed by the methods of quantum-chemical modeling.

Figure 2. Dependence of the effective activation entropy on the effective activation enthalpy of the cycloaddition between 2,3-dimethylbuta-1,3-diene and methyl acrylate.

For these reactions the effective second-order rate constant does not remain constant at the change in the reagent ratio, and the kinetics of the process is described by the Michaelis–Menten equation:

$$(2) \quad 403\text{K}: 1/k_{\text{eff}} = -331500C_A + 708910, (R^2=0.990) \quad (4)$$

$$413\text{K}: 1/k_{\text{eff}} = -131591C_A + 297689, (R^2=0.976) \quad (5)$$

$$423\text{K}: 1/k_{\text{eff}} = -87327C_A + 192769, (R^2=0.971) \quad (6)$$

$$433\text{K}: 1/k_{\text{eff}} = -75758C_A + 157315, (R^2=0.986) \quad (7)$$

where k_{eff} is experimentally determined

effective second order rate constant ($\text{l mol}^{-1} \text{s}^{-1}$)

for each reagent ratio,

K_{eq} is the equilibrium constant (l mol^{-1}) for the

molecular complex formation,

k_{conv} is the rate constant (s^{-1}) of the intermediate

complex conversion into the reaction product,

C_A is the molar concentration (M) of the substance taken in excess.

Results and discussion

In our case, the change in the effective rate constants of the 2,3-dimethylbuta-1,3-diene cycloaddition to methyl acrylate as a dependence on the ratio of reactants is also satisfactorily described by the Michaelis–Menten equation (2). This fact suggests that the cycloaddition reaction between 2,3-dimethylbuta-1,3-diene and methyl acrylate proceeds through a stage of equilibrium with the formation of a molecular complex stabilized by van der Waals interaction [13, 14] followed by its conversion into the reaction product [Eq. (3)].

From the dependences shown in **Figure 3** for four temperatures, we obtained the following linear equations:

Figure 3. Dependence of the effective rate constant of cycloaddition between 2,3-dimethylbuta-1,3-diene and methyl acrylate on the molar ratio of reagents in the temperature range 403–433K.

The slope of the obtained straight lines gives the rate constants of the conversion of the molecular complex stabilized by van der Waals interaction in the reaction product (k_{conv}). The values of the intercepts on the ordinate axis give the equilibrium constants of the complex formation (Table 2) according to the expression $K_{\text{eq}} = 1/(k_{\text{eff}} k_{\text{conv}})$.

The dependence of the equilibrium constant (K_{eq}) of the molecular complex formation is described by the isobar (**Figure 4**, $R^2 = 0.993$). The dependence of the rate

constants of conversion (k_{conv}) on temperature is described by the Arrhenius equation (**Figure 5**, $R^2 = 0.999$), which allows the calculation of the activation parameters of the molecular complex conversion in the reaction product (Table 2).

Figure 4. Dependence of the equilibrium constant of the formation of intermediate complex on the temperature.

Table 2. Equilibrium constants (k_{eq}) and thermodynamic parameters of formation of the intermediate complex, the rate constants (k_{conv}) and activation parameters of its transformation into a product of the reaction

Constants	403K	413K	423K	433K	ΔH_{eq} , kJ mol ⁻¹	ΔS_{eq} , J mol ⁻¹ K ⁻¹	ΔG_{eq} , kJ mol ⁻¹
$K_{\text{eq}} \cdot 10^1$	4.67	4.42	4.54	4.77	8.4	-228.5	98.2

					E_{conv} , kJ mol ⁻¹	$\Delta H_{\text{conv}}^{\#}$, kJ mol ⁻¹	$\Delta S_{\text{conv}}^{\#}$, J mol ⁻¹ K ⁻¹
$k_{\text{conv}} \cdot 10^6$, s ⁻¹	1.41	3.36	5.19	6.36	72.3	44.5	-168.1

Figure 5. Dependence of the rate constants of conversion of the intermediate complex in the reaction product on the temperature.

The found positive ΔG_{eq} and negative ΔS_{eq} values indicate the energy advantage of the molecular complex formation. At the same time a relatively fast decomposition of the molecular complex suggests that its formation is the limiting stage of the process. Thus, we established for the first time that the kinetics of the investigated process obeyed Michaelis–Menten equation, which was valid in the case of the reaction course through the stage of the associative equilibrium. It is an argument in favor of this reaction to proceed by the mechanism of concerted cycloaddition. However, the nature of the interaction of the components should be studied in more detail.

It is known that the addition of a diene molecule to the dienophile double bond originates from a certain deficiency of the electron density on this double bond due to its interactions with the other active groups, and the stronger conjugation with them, the easier the diene addition. Indeed, when k_{eff} of 2,3-dimethylbuta-1,3-diene interaction with methyl acrylate at 353K is $0.74 \times 10^{-6} \text{ mol l}^{-1} \text{ s}^{-1}$ (determined graphically), the k_{eff} for the interaction of 2,3-dimethylbuta-1,3-diene with 1,4-naphthoquinone, where the π -bond interacts with two C=O groups, is $0.14 \times 10^{-5} \text{ mol l}^{-1} \text{ s}^{-1}$ (in hexane) [15], and with its 5-substituted derivatives it is even two orders of magnitude higher, $1.5 \times 10^{-3} \text{ mol l}^{-1} \text{ s}^{-1}$ [16]. The accelerating effect of electronegative substituents, like cyano group or halogen, on the cycloaddition reaction is even more pronounced. Thus, in the interaction of cyclopentadiene with methyl acrylate at 303K in dioxane k_{eff} is $2.8 \times 10^{-5} \text{ mol l}^{-1} \text{ s}^{-1}$, with fumaric acid dinitrile, $155 \times 10^{-5} \text{ mol l}^{-1} \text{ s}^{-1}$, and with tetracyanoethylene, $10200 \times 10^{-5} \text{ mol l}^{-1} \text{ s}^{-1}$. In such cases it is reasonable to assume that a relatively strong donor–acceptor bond arises between the reagents [17].

Conclusions

The results of the study of kinetic regularities in the process of synthesis of methyl-3,4-dimethylcyclohexa-3-ene-1-carboxylate and the study of the mechanism of

this reaction showing its correspondence to the Michaelis–Menten equation confirm the formation of a molecular complex between the reagents, 2,3-dimethylbuta-1,3-diene and methylacrylate. The study of thermodynamic parameters of formation of the molecular complex suggests that the limiting stage is the slow formation of a molecular complex, the activation parameters of the transformation of the molecular complex in the product indicates that the conversion of the molecular complex in the product occurs rapidly and spontaneously.

References

- [1] Anisimova NA, Kuzhaeva AA, Berkova GA, Berestovitskaya V.M. Synthesis and Structure of Nitrocyclohexenylcarboxylates. Russian Journal of General Chemistry 2011;81(9):1845–1852
- [2] Monnier-Benoit P, Jabin I, Jaubert JN. Synthesis of 2,4-dimethyl-cyclohex-3-ene carboxaldehyde derivatives with olfactory properties. C. R. Chimie 2007;10(3):259-267
- [3] Farina V, Reeves JT, Senanayake CH, Song JJ. Asymmetric Synthesis of Active Pharmaceutical Ingredients. Chem. Rev. 2006;106(7):2734–2793
- [4] Polyova I, Marshalok G, Yatchyshyn J, Polyuzhin I. Kinetics of allyl-1,3,4-trimethylcyclo-hex-3-encarboxylate obtaining. Chemistry & Chemical Technology 2012;6(2):119-122
- [5] Polevaya IS, Fedevich MD, Polyuzhin IP, Marshalok OI. Optimization of synthesis conditions of 2,3-dimethylbutadiene. Russian Journal of Applied Chemistry 2011;84(2):261-265
- [6] Marshalok H, Kostiv I, Polyuzhin I, Marshalok O, Vytrykush N. Optymalizacja procesu otrzymywania 1,3,4-trimetylocykloheks-3-eno-1-karboksylanu metylu. Przemysl Chemiczny 2016;95(4):1000-1005

- [7] Jasinski R. A reexamination of the molecular mechanism of the Diels–Alder reaction between tetrafluoroethene and cyclopentadiene. *Reaction Kinetics, Mechanisms and Catalysis* 2016;(119):49–57
- [8] Firestone RA. Volume of Concert and Heavy Atom Effects in Diels-Alder Reaction Mechanisms. *Tetrahedron* 1996;(52):14459–14468
- [9] Ormachea CM, Mancini PME, Kneeteman MN, Domingo LR Understanding the participation of 3-nitropyridine in polar Diels–Alder reactions. A DFT study. *Computational and Theoretical Chemistry* 2015;(1072):37–42
- [10] Lakhdar S, Terrier F, Vichard D, Berionni G, El-Guesmi N, Goumont R, Boubaker T. The Diels–Alder Reaction of 4,6-Dinitrobenzofuroxan with 1-Trimethylsilyloxybuta-1,3-diene: A Case Example of a Stepwise Cycloaddition Chemistry: A European Journal 2010;(16):5681–5690
- [11] Kessler S, Neuburger M, Wegner H. Domino Inverse Electron-Demand Diels–Alder Cyclopropanation Reaction of Diazines Catalyzed by a Bidentate Lewis Acid. *Journal of the American Chemical Society* 2012;134(43):17885–17888
- [12] Korotayev VYu, Barkov AYu, Slepukhin PA, Kodess MI, Sosnovskikh VYa. Diastereoselective reactions of 1,1,1-trichloro(trifluoro)-3-nitrobut-2-enes with 2-morpholinoalk-1-enes. *Mendeleev Communications* 2011;(21):112–114
- [13] Plevaya IS, Makitra GG, Marshalok GA, Kovalskyi YaP. Effect of the reactants molar ratio on the kinetics of cycloaddition of 2,3-dimethylbuta-1,3-diene to allyl methacrylate. *Russian Journal of General Chemistry* 2012;82(12):1970-1974
- [14] Kostiv I, Marshalok O, Marshalok G, Pyrig I. Effect of the reactants molar ratio on the kinetics of the reaction to obtain 2-hydroxyethyl-1,3,4 trimethyl-cyclohex-3-encarboxylate. *Chemistry and Chemical Technology* 2015;9(3):277-280
- [15]. Corsico CA, Desimoni G, Ferrari E, Righetti P, Tacconi G. Solvent effect as the result of frontier molecular orbital interaction-1 : The diels-alder reaction between 1,4-naphthoquinone and 2,3-dimethylbutadiene. *Tetrahedron* 1984;40(9):1611-1615.
- [16] Desimoni G, Faita G, Righetti P, Tacconi G. DielsAlder Reactions in Micellar Media. *J. Chem. Soc.* 1989;2(3):437-441
- [17] Blankenburg B, Fiedler H, Hampelm M, Hauthal H, Just G, Kahlert K. Über die Anwendung linearer Freier-Energie-Beziehungen auf Diels–Alder-Reaktionen. *J. Prakt. Chem.* 1974;316(5):804-816