JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. 78 (12) 1963–1973 (2013) UDC 547.828+544.022+542.913+544.4:51–3
JSCS–4543 *Original scientific paper*

Structure–reactivity correlation for the kinetics of the formation reaction of 4-(substituted phenyl)-1,4-dihydropyridines•

JOVICA V. UROŠEVIĆ[1]**, SAŠA Ž. DRMANIĆ[1#], JASMINA B. NIKOLIĆ[1#],
IVAN O. JURANIĆ[2#] and BRATISLAV Ž. JOVANOVIĆ[1*#]

[1]*Department of Organic Chemistry, Faculty of Technology and Metallurgy, University of Belgrade, Karnegijeva 4, 11120 Belgrade, Serbia and* [2]*Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia*

(Received 20 November, revised 28 November 2013)

Abstract: Quantitative structure–reactivity correlations for the kinetics of the Hantzsch synthesis of 4-(substituted phenyl)-1,4-dihydropyridines in the reaction between ethyl *m*- and *p*-substituted 2-benzylideneacetoacetate and the enamine (ethyl 3-aminocrotonate) was studied. The reaction kinetics was followed spectrophotometrically. It was found that the reaction correspond to second-order kinetics. Quantitative structure–reactivity correlations of log *k* were obtained with the corresponding substituent constants (σ, σ^+, σ_I and σ_R^+) using the Hammett and extended Hammett equation (dual substituent parameter, DSP, equation). They showed linear relationships with positive values of reaction constants (ρ). The obtained data were processed by linear regression analysis. It was confirmed that Michael addition of the enamine to benzylidene represented the slow step of the reaction with a high positive charge at the benzylidene molecule. MO calculations were performed and they were in agreement with the conclusions derived from the structure–reactivity correlations.

Keywords: 1,4-dihydropyridines; Hantzsch synthesis; Michael addition; Hammet equation; extended Hammett equation; MO calculations.

INTRODUCTION

The derivatives of 4-phenyl-1,4-dihydropyridine are often synthesized because of their importance due to their pharmaceutical properties (*e.g.*, the commercial drug nifedipine).[1,2] Derivatives of 1,4-dihydropyridines are used in the treatment

---

* Corresponding author. E-mail: bataj@tmf.bg.ac.rs
** Present address: School of Chemistry and Technology, "B. Đ. Kukar", Vlajkova 96, Leskovac, Serbia.
# Serbian Chemical Society member.

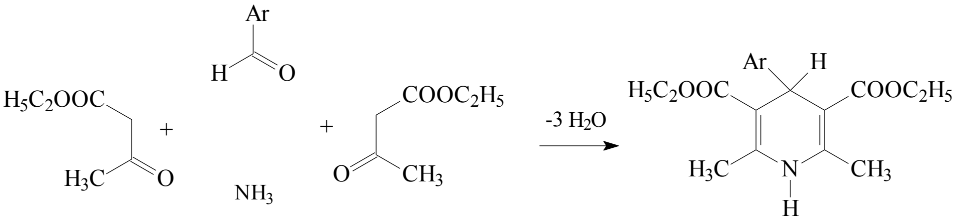
• Dedicated to Branislav Nikolić, a great scientist, a great professor, and above all, a great friend.

doi: 10.2298/JSC131120139U

of cardiac insufficiency, by increasing cardiac muscle contractions and decreasing blood pressure. Substituted 1,4-dihydropyridines are also known to be vasodilators, bronchodilators and anti-diabetic agents.[3]

The most common method for the synthesis of this group of compounds is the Hantzsch synthesis, which has often been studied in terms of the reactants, reaction conditions and the pharmacological effects of the products.[1,2]

The original Hantzsch synthesis starts from ethyl acetoacetate, ammonia and the appropriate aldehyde, depending on the required product (Scheme 1).[4,5]



Scheme 1. The Hantzsch synthesis.

The aldehyde could be aliphatic, heteroaromatic or aromatic. 1,3-Diketones could be used as the active methylene compound instead of ethylacetoacetate, whereby the corresponding 3,5-diacyl-1,4-dihydropyridines are formed.[6,7] Ammonium salts, formamide or hexamethylenetetramine are often applied as the source of nitrogen instead of ammonia.[8,9]

One modification of this synthesis can be realized by the use of a specific enamine (ethyl 3-aminocrotonate) instead of ethyl acetoacetate[10,11] in the presence of various aldehydes.

The second possible modification consists of the reaction of the enamine with aldehydes and esters (or nitriles) or β-keto carboxylic acids, which enable the synthesis of asymmetric 1,4-dihydropyridines.[12]

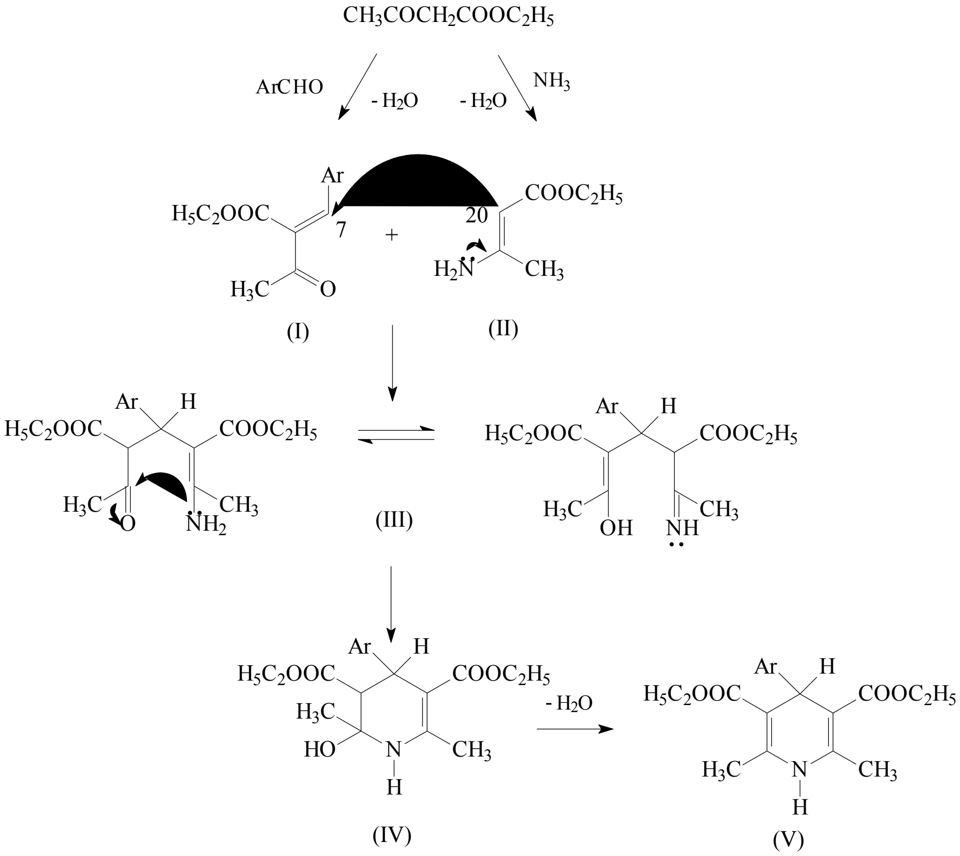
A significant modification of the Hantzsch synthesis is also the reaction of the enamine and ethyl arylideneacetoacetate,[6,11,13] the kinetics of which are discussed in this paper.

The influence of the properties and positions of the substituents on the benzaldehyde ring on the product yield in the examined reaction showed that electron-accepting substituents considerably increase the yield. The yield is the lowest for *o*-substituted benzaldehydes because of steric hindrance to the reaction. In the case of *m*-substituted benzaldehydes, it was registered that the yields were somewhat higher than those for the corresponding *p*-substituted benzaldehydes.[14]

The mechanism of the Hantzsch synthesis[5] is given in Scheme 2.

The active methylene compound (ethyl acetoacetate) reacts with the aldehyde to give the corresponding ethyl arylideneacetoacetate (**I**), while with ammonia, it gives the enamine (**II**). In the subsequent step, **I** and **II** react by a so-called

Michael addition to yield the tautomeric keto–enamine (**III**), which is converted by cyclization to hydroxytetrahydropyridine (**IV**). The 1,4-dihydropyridine (**V**) is formed from (**IV**) by elimination of water.



Scheme 2. The mechanism of the Hantzsch synthesis.

The aim of this study was to analyze the kinetics of this reaction using *m*- and *p*-substituted derivatives of ethyl benzylideneacetoacetate (Scheme 2, Ar = *m*- and *p*-substituted benzaldehydes, where the substituents (X) were: H (**Ia**); *p*-NO_2 (**Ib**), *p*-Cl (**Ic**), *m*-OCH_3 (**Id**), *p*-OCH_3 (**Ie**) and the enamine (ethyl 3-aminocrotonate) (**II**) in ethanol as solvent. The described kinetic data have not hitherto been mentioned in the literature.

The analysis of the obtained kinetic data was realized by correlation with the Hammet equation and the extended Hammett equation (dual substituent parameter, DSP, equation) in order to explain the reaction mechanism.[15]

EXPERIMENTAL

Synthesis

All substituted 4-phenyl-1,4-dihydropridines (Scheme 2: ***Va*****–*****Ve****).* All compounds were obtained by mixing equimolar amounts (0.05 mol) of 25 % ammonia and the required benzaldehyde, 0.1 mol of ethyl acetoacetate and 25 cm^3 of methanol. The reaction mixture was mixed, refluxed for 6 h at 65 °C and then cooled in to crystallize the products. The raw crystals were drained and recrystallized from methanol. The following compounds were synthesized: diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**Va**); diethyl 2,6-dimethyl-4-*p*-nitrophenyl-1,4-dihydropyridine-3,5-dicarboxylate (**Vb**); diethyl 2,6-dimethyl-4-*p*-chlorophenyl-1,4-dihydropyridine-3,5-dicarboxylate (**Vc**); diethyl 2,6-dimethyl-4-*m*-methoxyphenyl-1,4-dihydropyridine-3,5-dicarboxylate (**Vd**); diethyl 2,6-dimethyl-4-*p*-methoxyphenyl-1,4-dihydropyridine-3,5-dicarboxylate (**Ve**). The melting points of the obtained compounds were in agreement with literature data.[6,16,17]

Enamine (ethyl 3-aminocrotonate) (Scheme 2: ***II****).* A current of ammonia was passed through 250 cm^3 of ethyl acetoacetate at 35 °C for 5 h. The reaction mixture divided into two layers: the top layer (water and ammonia) was removed and the bottom layer extracted with diethyl ether, then dried and the solvent was evaporated and the enamine distilled under vacuum.[18]

Substituted ethyl benzylideneacetoacetates (Scheme 2: ***Ia*****–*****Ie****).* Equimolar quantities of ethyl acetoacetate and the required benzaldehyde were mixed at –5 °C with piperidine in ethanol (1:2). The reaction mixture was left in a freezer for a few days, until crystals of the raw ester were formed. Subsequently, they were recrystallized from diethyl ether. The following compounds were synthesized: ethyl 2-benzylideneacetoacetate (**Ia**); ethyl 2-(*p*-nitrobenzylidene)acetoacetate (**Ib**); ethyl 2-(*p*-chlorobenzylidene)acetoacetate (**Ic**); ethyl 2-(*m*-methoxybenzylidene)acetoacetate (**Id**) and ethyl 2(*p*-methoxybenzylidene)acetoacetate (**Ie**). The melting points of the obtained compounds were in agreement with the literature data.[19]

All the employed chemicals were of *p.a.* quality (Fluka, Subsidiary of the Sigma–Aldrich Company, St. Louis, MO, USA).

The structures of all compounds were confirmed by their UV and FTIR spectra (Shimadzu 1700A and Bomem MB-Series, respectively).

Kinetic measurements

Reaction rates of the modified Hantzsch syntheses (Scheme 2) between enamine (**II**) and the ethyl *m*- and *p*-substituted benzylideneacetoacetates (**Ia**–**Ie**) were followed by UV spectrophotometry. The UV spectra of the examined compounds were recorded using a Shimadzu 1700A spectrophotometer.

The kinetic experiments were realized at a concentration of 0.03 M for both reactants in absolute ethanol at temperature 78 °C, with mixing for 6 h. Aliquots of 0.1 cm^3 were taken every hour, diluted to 25 cm^3 with absolute ethanol and their absorbances at the specific wavelength were measured.

The increases in the absorbance of the synthesized 4-phenyl-1,4-dihydropyridines were followed at wavelengths of about 355 nm (marked by arrow in Fig. 1), which originates from the 1,4-dihydropyridine ring. The wavelengths used in kinetics measurements are given in Table I. The concentrations of reaction products were determined from the recorded absorbances using a calibration diagram according the Lambert–Beer law ($A = slope \times c$, where A is the measured absorbance and c is the concentration of the reaction product).

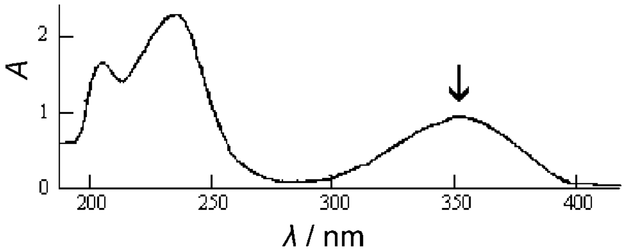


Fig. 1. The UV spectra of 4-phenyl-1,4-dihydropyridine.

TABLE I. The wavelengths used for the kinetic measurements

Compd.	Substituent	λ / nm
1	H	355.0
2	p-NO_2	355.0
3	p-Cl	355.6
4	m-OCH_3	354.6
5	p-OCH_3	354.2

The corresponding linear dependences of the concentrations of the reaction products on time confirmed the assumption that the reaction obeyed second order kinetics ($kt = (c_0 - x)^{-1} - c_0^{-1}$, where k is reaction rate constant, t is time, c_0 is initial reactant concentration and x reaction variable). Using linear regression analysis, k values were calculated.

RESULTS AND DISCUSSION

A typical absorbance spectrum of 4-phenyl-1,4-dihydropyridine is shown in Fig. 1. The absorbance spectra of the reactants, as well as the FTIR spectra of the investigated compounds are in accordance with literature data.[20]

The obtained values of the rate constants for the reaction between the ethyl *m*- and *p*-substituted benzylideneacetoacetates (**Ia**–**Ie**) and the enamine (**II**) in ethanol under reflux (78 °C), shown in Scheme 2, are given in Table II.

TABLE II. The calculated reaction rate constants for the examined Hantzsch syntheses in ethanol at 78 °C and the corresponding Hammett substituent constants σ and the Brown electrophilic σ^+ constants[21]

Compd.	Substituent	k / 10^{-6} dm^3 mol^{-1} s^{-1}	log (k / dm^3 mol^{-1} s^{-1})	$\sigma_{m/p}$	$\sigma^+_{m/p}$
1	H	2.96	–5.53	0	0
2	p-NO_2	13.8	–4.86	0.81	0.79
3	p-Cl	2.42	–5.62	0.24	0.11
4	m-OCH_3	1.64	–5.78	0.10	0.05
5	p -OCH_3	0.347	–6.46	–0.28	–0.78

The basic form of the Hammett equation, the classic Hammett equation, is:

$$\log k = \rho\sigma + \log k_0 \qquad (1)$$

where the logarithm of the reaction rate constant, *k*, represented as a function of the electronic effects of substituents (expressed by the substituent constant, σ) and the parameter ρ (reaction constant), displays the sensitivity of the reaction rate constant of the unsubstituted compound to substituent effects. It is a well-known and reliable method to determine quantitatively a structure–reactivity relationship.[15]

The established Hammett correlation with the data given in Table II is as follows:

$$\log k = (1.32 \pm 0.13)\ \sigma_{m/p} - (5.88 \pm 0.11) \tag{2}$$

$$r = 0.931,\ s = 0.24,\ F = 20,\ n = 5$$

where, r – correlation coefficient, s – standard deviation, F – Fisher's test, n – number of points included in the correlation.

Although the correlation coefficient is not optimal ($r < 0.95$), the positive value of the reaction constant ($\rho = 1.32$) points to the conclusion that the electron-acceptor substituents are accelerating the reaction, which could be confirmed by the values of the reaction rate constants. The Hammett equation gives a less reliable correlation of log k and the σ^- values (nucleophilic substituent constants) with an unsatisfactory correlation coefficient ($r < 0.90$).

On the other hand, when the Hammett correlation with the corresponding electrophilic Brown constants was determined, Eq. (3) was obtained:

$$\log k = (1.01 \pm 0.11)\sigma^+_{m,p} - (5.68 \pm 0.06) \tag{3}$$

$$r = 0.981,\ s = 0.13,\ F = 76,\ n = 5$$

More successful correlation with electrophilic (σ^+) constants, as well as the observed fact that the electron-accepting substituents increased the reaction rate, suggests that the kinetic data should be treated by the Taft equation[22] of the dual substituent parameter (DSP), which belongs to the extended Hammett equations. It is of the form:

$$\log k = \rho_I \sigma_I + \rho_R \sigma_R + \log k_0 \tag{4}$$

By application of Eq. (4), the electronic substituent effects can be divided into inductive (σ_I) and resonance (σ_R). The corresponding reaction constants are ρ_I and ρ_R.

The inductive substituent constants and the various scales of the resonance substituent constants are given in Table III.

The different scales for the σ_R substituent constants describe the different ranges of the interactions of the present substituents and the reaction center, which enables a better insight into reaction mechanism. The unreliable correlations of DSP equation with σ_I and σ_R^- indicates to the conclusion that no negative charge develops at the reaction center, which would be delocalized by electron-accepting groups.

TABLE III. Inductive (σ_I) and various resonance (σ_R) subsitutent constants[23]

Substituent	σ_I	$\sigma_{R\ (BA)}$	σ_R^+	σ_R^-
H	0	0	0	0
p-NO_2	0.65	0.16	0.16	0.47
p-Cl	0.46	–0.23	–0.36	–0.23
m-OCH_3[a]	0.27	–0.214	–0.357	–0.157
p-OCH_3	0.27	–0.61	–1.02	–0.45

[a]The values were obtained from the expression $0.35\sigma_R$ for p-OCH_3

An excellent DSP correlation was obtained with the σ_R^+ and σ_I values:

$$\log k = (0.75 \pm 0.08)\sigma_I + (1.12 \pm 0.04)\sigma_R^+ - (5.54 \pm 0.04) \tag{5}$$

$$r = 0.999,\ s = 0.04,\ F = 406,\ n = 5$$

From Eq. (5), the conclusion could be drawn that the reaction center is a strong electron-acceptor with a high positive charge, which can be stabilized by electron-donating groups.

In order to explain the given structure–reactivity correlation analysis (LFER), MO calculations of this reaction were undertaken.

The calculation was realized by MOPAC semi-empirical quantum-chemical program package, using the PM6 Hamiltonian.[24] The geometric variable that was used to mimic the reaction coordinates was the distance between atoms (7) and (20), which are connected by an arrow in Scheme 2. The distance between these atoms was systematically diminished without any other geometric constraint. A shallow energy minimum, Fig. 2, was found at 3.2 Å (the structure is shown in Fig. 3). Further approach of reactants goes through a transition state (Fig. 2) at 2.006 Å (the structure is shown in Fig. 4). This structure was confirmed by vibration analysis, showing only one negative vibration. Further approach is accompanied by a lowering of the potential energy.

This approach does not go smoothly. At a distance of 2.58 Å, a hydrogen atom transfer occurs from the amine nitrogen to the acetyl oxygen of other moiety. At 1.549 Å, the structure of the primary product is achieved (Fig. 5).

Simple reasoning suggests that the electron density shifts from the enamine to the benzylic moiety during the reaction. The partial atomic charges were calculated according to the Mulliken method and their variation on the atoms involved in the formation of a new C–C bond are presented in Fig. 6. Upper line shows the variation of electronic charge on the benzylic carbon as the function of distance. It shows a continuously increasing positive charge until the transition state is achieved. Then, at shorter distances, the electron density from the enamine goes to form new C–C bond.

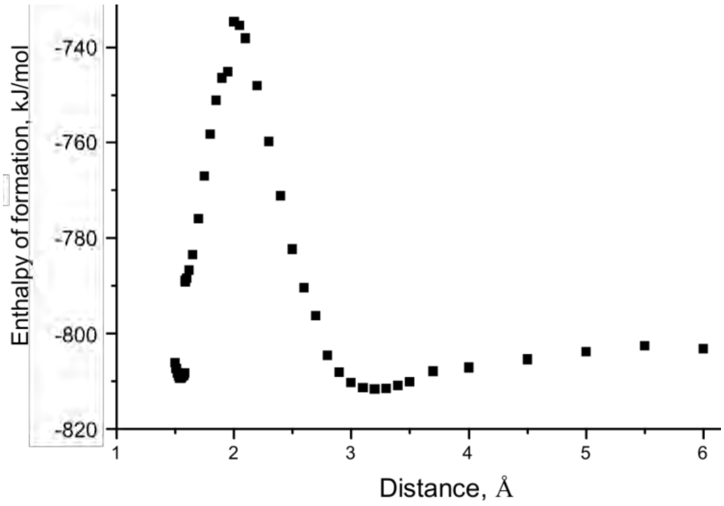


Fig. 2. Energy profile along the reaction coordinate.

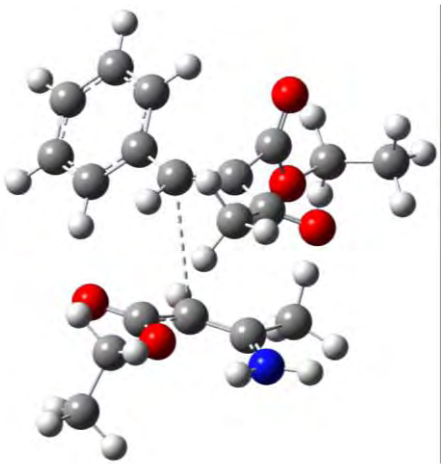


Fig. 3. (Meta)stable arrangement of reactants at distance 3.2 Å.

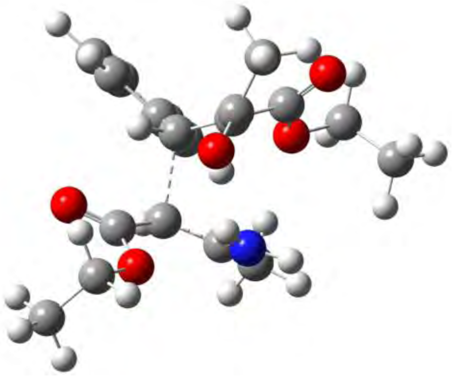


Fig. 4. Transition state for the reaction outlined in Scheme 2.

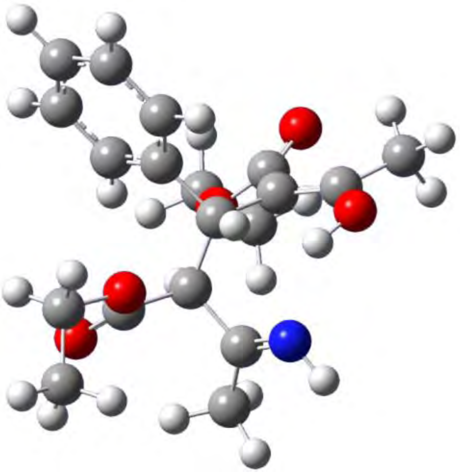


Fig. 5. Structure of the adduct at 1.549 Å.

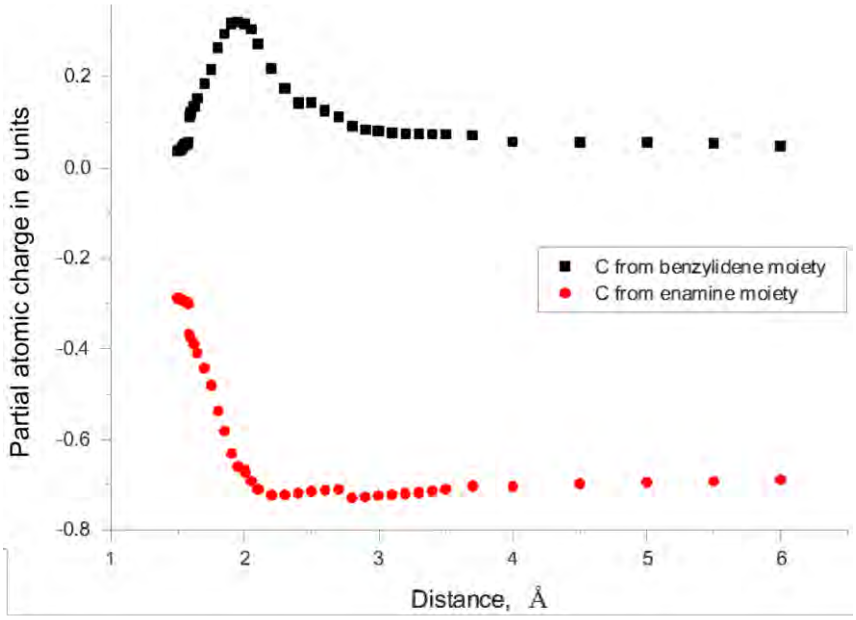


Fig. 6. Partial atomic charges on carbons directly involved in metathesis.

Therefore, the increasing electron demand at the benzylic reaction center is stabilized by electron-donor substituents on the aromatic ring, which should correlate with the σ^+ substituent constants (as was found by LFER analysis).

CONCLUSIONS

The study of the kinetics of the Hantzsch synthesis of substituted 1,4-dihydropyridines, with the *m*- and *p*-substituted benzylideneacetoacetates and an enamine as reactants was presented. It was established that this reaction follows second order kinetics.

The reaction rate constants were analyzed by the Hammett equation and an extended Hammett equation (the DSP equation) using various substituent constants. It was concluded that a nucleophilic attack of the enamine on benzylideneacetoacetate causes an increase in the positive charge on the benzylic atom of benzylidene in the transition state, which enabled the stabilization by the electron-donating substituents. This conclusion established by the structure–reactivity relationships was explained and confirmed by MO calculations.

Acknowledgement. Our gratitude goes to the Ministry Education, Science and Technological Development of the Republic of Serbia (Grants 172013 and 172035) for financial support.

ИЗВОД

КОРЕЛАЦИЈЕ СТРУКТУРЕ И РЕАКТИВНОСТИ ЗА КИНЕТИКУ РЕАКЦИЈЕ СИНТЕЗЕ СУПСТИТУИСАНИХ 4-ФЕНИЛ-1,4-ДИХИДРОПИРИДИНА

ЈОВИЦА В. УРОШЕВИЋ[1], САША Ж. ДРМАНИЋ[1], ЈАСМИНА Б. НИКОЛИЋ[1], ИВАН О. ЈУРАНИЋ[2]
и БРАТИСЛАВ Ж. ЈОВАНОВИЋ[1]

[1]*Катедра за органску хемију, Технолошко–металуршки факултет, Универзитета у Београду, Карнегијева 4, 11120 Београд и* [2]*Институт за хемију, технологију и металургију Универзитета у Београду, Његошева 12, 11000 Београд*

Проучаван је квантитативан однос структуре и реактивности за кинетику Ханчове синтезе супституисаних 4-фенил-1,4-дихидропиридина у реакцији етил-*m*- и *p*-супституисаних 2-бензилиден-ацетоацетата и енамина. Кинетика испитиване реакције је праћена спектрофотометријским методом. Запажено је да је реч о реакцији другог реда. Квантитативне корелације структуре и реактивности које изражавају логаритам одређене константе брзине реакције (log k) у зависности од одговарајућих константи супституената (σ, σ^{+},σ_{I} и σ_{R}^{+}) одређене су за Хаметову (Hammett) и проширену Хаметову једначину (DSP-једначину). Показале су линеарну зависност са позитивним вредностима нагиба, односно реакционе константе (ρ). Тиме је потврђено да Мајклова (Michael) адиција енамина на бензилиден представља спори ступањ у реакцији са израженим позитивним наелектрисањем на молекулу бензилидена. МО прорачуни су такође урађени и њихови резултати су били у складу са закључцима изведеним из корелација структуре и реактивности.

(Примљено 20. новембра, ревидирано 28. новембра 2013)

REFERENCES

1. H. R. Roodsari, A. M Sadeghipour, Z. N. Harat, P. Daneshgar, M. Vosooghi, A. Shafiee, *J. App. Sci.* **8** (2008) 158
2. S. Patra, *Int. J. Pharm., Chem. Biol. Sci.* **2** (2012) 482
3. H. Lullman. K. Mohr, A. Ziegler, D. Bieger, *Color Atlas of Pharmacology*, Thieme Verlag, New York, 2000, p. 118
4. A. Hantzsch, *Liebigs Ann.* **215** (1882) 1
5. U. Eisner, J. Kuthan, *Chem. Rev.* **72** (1972) 1
6. J. A. Berson, E. Brown, *J. Am. Chem. Soc* **77** (1955) 444

7. C. A. C. Hailey, P. Maitland, *J. Chem. Soc.* (1951) 3155
8. N. Sugimoto, *J. Pharm. Soc. Jpn.* **64** (1944) 192
9. M. Jonescu, V. N. Georgescu, *Bull. Soc. Chim. Fr.* **41** (1927) 627
10. A. H. Cook, I. M. Heilbronn, L. J. Steger, *J. Chem. Soc.* (1943) 413
11. A. P. Phillips, *J. Am. Chem. Soc.* **72** (1950) 2780
12. H. J. Kahn, V. Petrow, R. Rewald, B. Sturgeon, *J. Chem. Soc.* (1949) 2128
13. A. Courts, V. Petrow, *J. Chem. Soc.* (1952) 1
14. *Pyridine and Its Derivatives,* Part I, E. Klinsberg, Ed., Interscience, New York, 1961, p. 66
15. L. P. Hammett, *J. Am. Chem. Soc.* **59** (1937) 96
16. L. E. Hinkel, E. E. Ayling, W. H. Morgan, *J. Chem. Soc.* (1931) 1835
17. A. R. Katritzky, D. L. Osterkamp, T. I. Yousaf, *Tetrahedron* **42** (1986) 5729
18. A. Gomez-Sanchez, A. M. Walle, J. Bellanato, *J. Chem. Soc., B* (1971) 2330
19. P. D. Gardner, R. L. Brandon, *J. Org. Chem.* **22** (1957) 1704
20. J. V. Uroševic, *MS Thesis*, Faculty of Technology and Metallurgy, Belgrade, 2009 (in Serbian), and references therein
21. M. B. Smith, J. March, *Advanced Organic Chemistry,* 6th ed. Wiley, New York, 2007, p. 404
22. R. W. Taft, *J. Am. Chem. Soc.* **79** (1957) 1045
23. R. A. Y. Jones, *Physical and Mechanistic Organic Chemistry,* Cambridge University Press, Cambridge, UK, 1979, p. 56
24. J. P. Stewart, *J. Mol. Model.* **13** (2007) 1173.