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Influence of substituent on UV absorption and keto–enol tautomerism equilibrium of dibenzoylmethane derivatives

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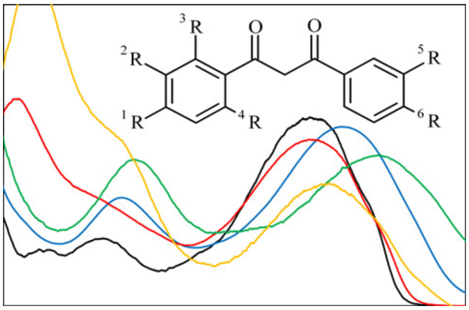
HIGHLIGHTS

- ▶ We have synthesized dibenzoylmethane and its 23 derivatives.
- ▶ We have researched the influence of substituent in aromatic ring of dibenzoylmethane derivative on UV absorption spectra.
- ▶ We have researched the influence of substituent in aromatic ring of dibenzoylmethane derivative on keto–enol tautomerism equilibrium.
- ▶ Our results revealed dissimilarity of substituent effects on absorption and keto–enol tautomerism of aromatic β-diketones.

GRAPHICAL ABSTRACT



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ABSTRACT

UV absorption spectra of dibenzoylmethane and its 23 derivatives with acetamide, *tert*-butyl, chloride, fluoride, hydroxyl, methyl, methoxy and nitro substituents in aromatic rings were collected. General influence of substituent on absorption maxima and absorption intensity was defined. Hyperchromic effects were observed for diketones with electron-donating groups in *para* postion. The keto–enol tautomerism equilibrium constant of obtained compounds was investigated with ^{1}H NMR spectroscopy. Significant changes of equilibrium were observed only for *ortho* substituted compounds. Results revealed dissimilarity of substituent effects on absorption and keto–enol tautomerism of aromatic β-diketones.

Introduction

Dibenzoylmethane (DBM) and its derivatives are known as aromatic β-diketones. They absorb UV-A radiation, and therefore are used as sunscreens in cosmetics. The most popular representative of these compounds is Avobenzone: 1-(4′-*tert*-butylphenyl)-3-(4″-methoxyphenyl)propane-1,3-dione. Nowadays, it is the only one UV-A sunscreen allowed to use in cosmetics in the USA [1]. However, Avobenozne has many disadvantages. It has low photostability [2] and can cause allergic reaction [3]. Therefore, new derivatives of DBM should be investigated for application of UV-A sunscreens.

β-diketones exist in two tautomeric forms: keto form and enol tautomer with intra-molecular hydrogen bonding. It is known, that latter tautomer is responsible for absorption of radiation in the UV-A range [4], so research on absorption of UV-radiation should be supported with research on keto–enol tautomerism equilibrium of these compounds.

Many derivatives of DBM have been synthesized so far, however, there is a lack of particular research on their spectroscopic properties. Such studies concerned mainly application of diketones to spectrophotometric determination of metal ions such as Ni^{2+} [5],

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Co^{2+} [6]. *Sager's* team researched UV absorption of mono and disubstituted derivatives of DBM with fluoride, nitro and methoxy substituents, however, investigation concerned mainly results of spectroscopy of tris(diketonate) complexes [7]. Detailed spectroscopic properties of diketones with mehoxy groups and halogen substituents were described in [8], but authors focused on photostability and omitted keto–enol tautomerism. Reasearch of UV absorption and keto–enol tautomerism of diketones was done by Hammond et al. [9], however, direct relation between these phenomena was not defined. Later works on keto–enol tautomerism of diketones are available mainly in Russian [10] or Chinese language journals [11,12]. Therefore, we present research, in which an influence of substituent on UV absorption of dibenzoylmethane derivatives is supported with keto–enol tautomerism equilibrium studies.

Results

We have synthesized DBM and its 23 derivatives. All of compounds except nitro derivatives were obtained in crossed Claisen condenstation of proper ester and ketone. Diketones with nitro groups were synthesized *via* chalcone or by acylation of vinyl acetate with nitrobenzoyl chlorides. Structures of synthesized compounds is given on the Fig. 1. Yields and substituents are given in Table 1.

In our former work [13], we have proved that influence of solvent on absorption of UV radiation is insignificant, therefore we present only spectra collected in ethanol. Aromatic diketones have main absorption band in the UV-A region $\lambda_1 = 280–400$ nm. Apart from that, two other weaker bands can be identified: $\lambda_2 = 230–280$ nm and $\lambda_3 = 200–230$ nm. The absorption maxima and the molar extinction of compounds **1–24** are given in Table 2. UV spectra of synthesized compounds are given on Figs. 2–5.

On the basis of UV spectra of derivatives with fluoride (**3**–**6**, Fig. 2) and chloride atoms (**7–10**, Fig. 3), typical influence of substituent position can be seen. Only *para* substituted derivatives (**3**, **6**, **7**, **10**) have shown hyperchromic effects and strong bathochromic shifts in the λ_1 band. Similar effects can be found in the λ_2 band for compounds with chloride atom in *para* position (**3**, **6**). Attendance of substituent in *ortho* position causes hypochromic effect, much weaker for fluoride (**9**) than for chloride (**5**). Both of these derivatives have also shown hypsochromic effect exclusively. In the spectra of compounds with halogen substituent in the *meta* position, the differences between chloride and fluoride come out. Chloride derivative's (**4**) spectrum does not differs from DBM (**1**) spectrum considerably except bathochromic shift, however, *meta* fluoride substituted derivative (**8**) shown small bathochromic effect and hypochromic effects in all bands comparable to its *ortho* isomer (**9**). Disparities between UV spectra of *meta* halogen substituted derivatives (**4** and **8**) arise probably from different inductive effects of these substituents. Curiously enough, the hyperchromic effects of derivatives with two *para* substituents are not cumulative, as they were in the case of methoxy derivatives [13], however, bathochromic effects are cumulative, so the red shifts of di-substituted derivatives are respectively higher than those of mono-substituted derivatives.

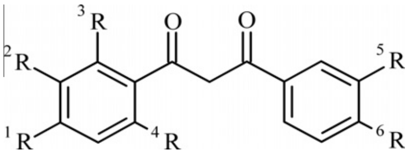

Fig. 1. Structure of synthesized diketones.

Table 1
Substituents and yields of synthesized compounds.

Diketone	^{1}R	^{2}R	^{3}R	^{4}R	^{5}R	^{6}R	Yield
1	H	H	H	H	H	H	80%
2	H	H	OCH_3	OCH_3	H	H	69%
3	Cl	H	H	H	H	H	76%
4	H	Cl	H	H	H	H	68%
5	H	H	Cl	H	H	H	87%
6	Cl	H	H	H	H	Cl	81%
7	F	H	H	H	H	H	73%
8	H	F	H	H	H	H	65%
9	H	H	F	H	H	H	66%
10	F	H	H	H	H	F	75%
11	NHAc	H	H	H	H	H	54%
12	Br	H	H	H	H	H	60%
13	Br	H	H	H	H	Br	69%
14	CH_3	H	H	H	H	H	73%
15	CH_3	H	H	H	H	CH_3	79%
16	$C(CH_3)_3$	H	H	H	H	H	77%
17	$C(CH_3)_3$	H	H	H	H	$C(CH_3)_3$	82%
18	OH	H	H	H	H	H	59%
19	NO_2	H	H	H	H	H	94%
20	H	NO_2	H	H	H	H	63%
21	NO_2	H	H	H	H	NO_2	42%
22	H	NO_2	H	H	NO_2	H	48%
23	$C(CH_3)_3$	H	H	H	H	OCH_3	75%
24	OCH_3	H	H	H	H	H	75%

Influence of nitro substituent (**19**–**22**) emphasizes very clearly both in the λ_1 and λ_2 range (Fig. 5). In the long wave range hypochromic effects can be observed for *meta* and *para* isomers, however, for *meta*-nitro substituted compounds the effect is stronger. The influence of substituent in this position on β-dicarbonyl chromophore is connected mainly with substituent inductive effect, so it can be concluded, that worsening of diketone's absorption is caused by electron-withdrawing substituent. Strong bathochromic effects can be observed in the range λ_1 as well as in the range λ_2 for *para* substituted compounds, what is related to conjugation of substituent in that position with β-dicarbonyl moiety. Value of mono and di-substituted nitro derivatives' bathochromic shifts are respectively $\Delta\lambda_{mono} = 14.2$ nm and $\Delta\lambda_{di} = 30.6$ nm (in the range $\lambda_1 = 280–400$ nm) and respectively $\Delta\lambda_{mono} = 8.6$ nm and $\Delta\lambda_{di} = 13.4$ nm (in the range $\lambda_2 = 235–280$ nm), what shows the cumulative character of these groups in this position. The most interesting effect caused by nitro group in *para* position is increase in absorption intensity in the range $\lambda_2 = 235–280$ nm, which is unusually strong among researched derivatives. Study on keto–enol tautomerism equilibrium of these compounds revealed that they exist mainly in enol form, therefore we can state that changes in UV absorption do not originate from change in keto–enol tautomerism equilibrium. In the case of *meta* substituted nitro derivatives, absorption bands in the λ_2 range were covered or strongly shifted to the range $\lambda_3 = 210–235$ nm.

During research on influence of alkyl substituents (**14–17**, Fig. 4), some regularities were found. In the range $\lambda_1 = 280–400$ nm, existence of alkyl substituents in *para* position induces bathochromic shifts and slight hyperchromic effects, which result from electro-donating character of these substituents. Both influence on absorption maxima and its intensity seem to be cumulative. Bathochromic and hyperchromic effects of di-substituted derivatives are respectively stronger. Influence of substituent in the range $\lambda_2 = 235–280$ nm is similar. Both for methyl (**14**, **15**) and *tert*-butyl (**16**, **17**) substituents bathochromic and hyperchromic effects can be observed, respectively stronger for di-substituted derivatives, however, influence on absorption intensity is irregular.

In the case of derivatives with various substituents in *ortho* position (**2**, **5**, **9**), besides resonance and inductive effects, we deal with third effect – steric. Steric hindrance, which is formed by

Table 2
Molar absorption coefficients and absorption maxima of the synthesized diketones.

Diketone	λ_1 = 280–400 nm			λ_2 = 235–280 nm		λ_3 = 210–235 nm	
	λ_{max}	$\Delta\lambda^{(a)}$	ε_{max}	λ_{max}	ε_{max}	λ_{max}	ε_{max}
2	328.2	−14.2	17438	250.4	6219	<210.0	–
3	347.8	5.4	28901	257.6	10299	<210.0	–
4	345.6	3.2	24865	251.8	9304	<210.0	–
5	340.0	−2.4	19239	252.6	7220	<210.0	–
6	351.8	9.4	28932	261.0	11045	<210.0	–
7	353.4	11.0	28289	<235	–	<210.0	–
8	345.0	2.6	22450	252.0	9564	217.8	55140
9	339.8	−2.6	22536	250.8	8174	217.8	50845
10	356.6	14.2	27735	235.4	7193	<210.0	–
11	360.0	17.6	34835	<235	–	228.0	10770
12	347.8	5.4	27909	260.8	9706	<210.0	–
13	350.8	8.4	30299	265.8	11189	<210.0	–
14	347.6	5.2	26877	257.0	8274	<210.0	–
15	352.4	10.0	29448	262.4	9373	<210.0	–
16	349.2	6.8	27005	258.6	8033	231.2	6266
17	354.2	11.8	27822	263.8	9974	232.0	7083
18	357.4	15.0	27282	242.8	8261	<210.0	–
19	356.6	14.2	23754	261.6	14358	<210.0	–
20	342.4	0.0	22079	<235	–	216.8	27491
21	373.0	30.6	20007	266.4	19451	<210.0	–
22	350.6	8.2	16260	<235	–	224.8	44906
23	359.8	17.4	33756	<235	–	218.0	169846
24	354.0	11.6	33973	<235	–	<210.0	–

(a) Difference between derivative absorption maximum and DBM absorption maximum.

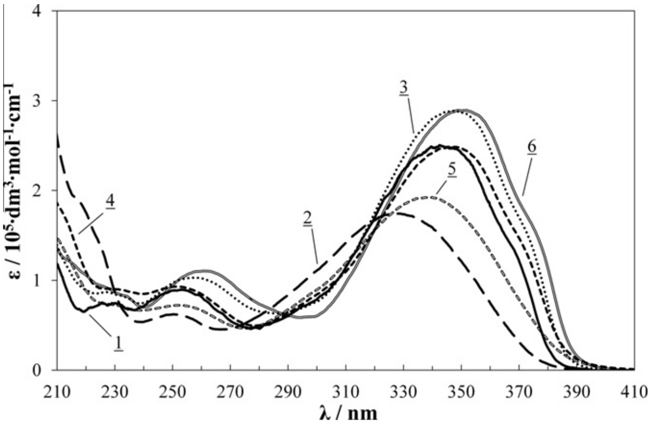

Fig. 2. Absorption spectra of compounds **1**–**6** in ethanol. C = 50 μmol/dm³.

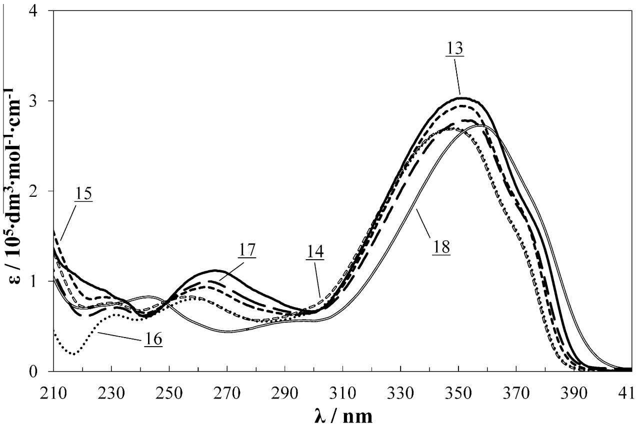

Fig. 4. Absorption spectra of compounds **13**–**18** in ethanol. C = 50 μmol/dm³.

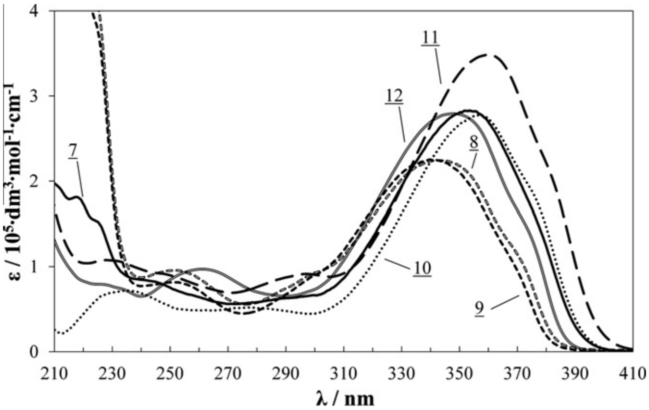

Fig. 3. Absorption spectra of compounds **7**–**12** in ethanol. C = 50 μmol/dm³.

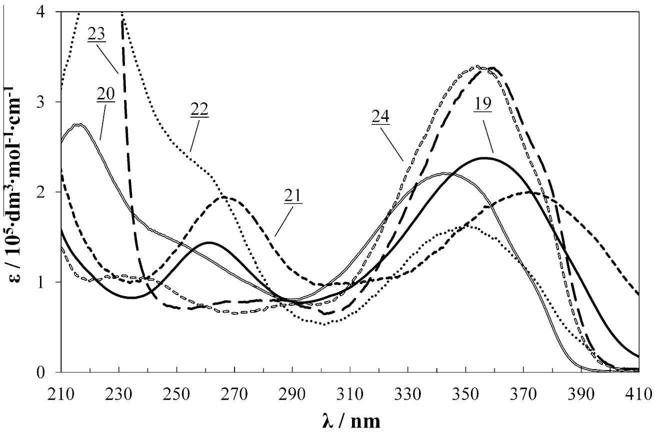

Fig. 5. Absorption spectra of compounds **19**–**24** in ethanol. C = 50 μmol/dm³.

substituent in *ortho* position has essential impact on absorption of UV radiation. It causes rotation of benzene ring, and therefore, disturbs the conjugation of aromatic ring with β-diketone moiety.

Regardless of researched *ortho* substituent (fluoride, chloride, methoxyl group), in the λ_1 = 280–400 nm range, hypochromic

Table 3
The enol percentages and keto–enol tautomerism equilibrium constant (K_T) of DBM and its derivatives in various solvents.

Diketone	Enol percentage				K_T			
	DMSO-d_6	Acetone-d_6	$CDCl_3$	Benzene-d_6	DMSO-d_6	Acetone-d_6	$CDCl_3$	Benzene-d_6
1	94.0	97.7	97.8	99.9	15.7	42.5	44.5	999.0
2	81.9	92.0	97.4	94.9	4.5	11.5	37.5	18.6
3	94.5	98.3	97.8	98.5	17.2	57.8	44.5	65.7
4	95.1	–[a]	98.9	98.4	19.4	–[a]	89.9	61.5
5	93.8	98.2	98.4	99.8	15.1	54.6	61.5	499.0
6	92.5	97.9	98.1	98.6	12.3	46.6	51.6	70.4
7	–[a]	–[a]	97.7	>99.9	–[a]	–[a]	42.5	>999
8	94.5	98.3	98.2	99.2	17.2	57.8	54.6	124.0
9	86.9	96.4	98.7	>99.9	6.6	26.8	75.9	>999
10	91.4	97.0	99.6	97.9	10.6	32.3	249.0	46.6
11	93.0	96.6	97.4	>99.9	13.3	28.4	37.5	>999
12	94.3	97.3	97.5	98.6	16.5	36.0	39.0	70.4
13	94.4	96.4	97.9	98.7	16.9	26.8	46.6	75.9
14	92.9	96.8	96.1	98.1	13.1	30.3	24.6	51.6
15	92.4	95.4	95.2	97.7	12.2	20.7	19.8	42.5
16	92.8	96.9	96.0	97.8	12.9	31.3	24.0	44.5
17	92.0	98.4	95.2	99.8	11.5	61.5	19.8	499.0
18	91.0	96.1	94.8	96.8	10.1	24.6	18.2	30.3
19	96.1	98.0	99.2	99.0	24.6	49.0	124.0	99.0
20	95.7	99.2	98.2	98.8	22.3	124.0	54.6	82.3
21	99.9	97.4	–[b]	–[b]	999.0	37.5	–[b]	–[b]
22	91.9	90.9	–[b]	–[b]	11.3	10.0	–[b]	–[b]
23	90.9	97.9	99.0	97.7	10.0	46.6	99.0	42.5
24	93.7	97.3	95.7	99.7	14.9	36.0	22.3	332.3

[a] Characteristic signal of enol tautomer's protone was covered, and enol content was not determined.
[b] Enol content not determined because of low solubility of compound.

effect was always observed. This effect is certainly caused by steric hindrance, as the strength of this effect rises with increasing Van der Waals radius. Influence on position of absorption maxima is different. From our former work [13] it is known, that methoxyl group causes strong bathochromic effect ($\Delta\lambda$ = 12.2 nm), and now we proved, that fluoride and chloride atoms in *ortho* position cause slight hypsochromic shifts (respectively $\Delta\lambda_{\mathbf{9}} = -2.6$ nm and $\Delta\lambda_{\mathbf{5}} = -2.4$ nm). These differences may come from distinct character of these substituents – methoxyl group is typical electron-donating group, and fluoride and chloride atoms, are electron-withdrawing substituents. Differences in absorption of radiation in the range λ_2 = 235–280 nm are insignificant, however, slight hypsochromic shifts were always observed.

Interesting results were found in the case of derivative with two methoxyl groups in *ortho* position in the same benzene ring (**2**). Appreciable hypochromic and hypsochromic ($\Delta\lambda_{\mathbf{2}} = -14.2$ nm), effects can be found in the range λ_1 = 280–400 nm, what is rather surprising as the former research proved, that derivative with methoxyl groups in *ortho* position in different benzene rings had quite strong bathochromic effect [13]. Such differences can arise from fact, that existence of methoxyl group in different rings causes rotation of both benzene rings, and in the case of two methoxyl groups in one ring, only one ring is rotated, but to a higher degree.

Influence of substituents in *meta* position (**4**, **8**, **20**) on absorption of radiation in the range λ_1 = 280–400 nm is slight, however, hypochromic effect can be always observed. Effect on position of absorption maxima is also insignificant and values of shifts related to DBM are about 0–3 nm. Greater differences can be seen in the range λ_3 = 210–235 nm, where high absorption band appears, especially strong for nitro-derivative.

Research on UV absorption of *para*-substituted derivatives revealed, that all investigated substituents indicate bathochromic shift and almost all of them cause hyperchromic effect. The exception was nitro substituent – the one with the most electron-withdrawing character amongst researched substituents. The strongest hyperchromic effects were observed for compounds with hydroxyl or acetamide group – groups with the most electron-donating character amongst researched substituents. However, the molar absorption coefficient is smaller than that of derivative with methoxyl group in the *para* position. So it could be assumed, that influence of substituent in *para* position on the UV absorption depends directly on electron withdrawing/donating character of the substituent. We made an attempt to correlate the absorption intensity and Hammet substituent constant, which determine electron withdrawing/donating character of the substituent. It turned out, that absorption intensity cannot be correlated with Hammet substituent constants, what means, that influence of substituent doesn't come directly from electron characteristic of the substituent, but is more complicated. Consequently, it is impossible to predict which derivative of DBM will give the best results.

Quantitative influence of methoxyl (**24**) and *tert*-butyl (**16**) group on increase of absorption intensity are respectively 36% and 8%. The compound with both this groups – Avobenzone (**23**) – showed hyperchromic effect about 35%. It means that *tert*-butyl group in structure of Avobenzone affects only on position on absorption maxima, and does not affect on absorption intensity.

Keto–enol tautomerism

Keto–enol tautomerism equilibrium was researched with ^{1}H NMR technique in four solvents: benzene-d_6, $CDCl_3$, acetone-d_6 and DMSO-d_6. The enol percentages (x_E) of DBM and its derivatives were calculated from intensities of characteristic proton's peaks, and are shown in the Table 3. Keto–enol equilibrium constant was calculated with formula: $K_T = (x_E)/(1-x_E)$.

These results exhibit general influence of solvent on keto–enol tautomerism equilibrium. In all investigated solvents, researched compounds exist mainly as enol tautomers, however, tendency to shift equilibrium toward the keto tautomer witch increasing solvent polarity is noticeable. It is so, because intra-molecular hydrogen bond in enol form has a structure of a pseudo-cyclic system, which is more favorable in non-polar solvents.

Research on keto–enol tautomerism equilibrium of various derivatives of DBM proved, that existence of *ortho* substituent always shifts the equilibrium towards the keto-form. This effect is a consequence of steric hindrance, however, its quantity is not related directly with Van der Waals radius. It suggests, that influence of *ortho* substituent on keto–enol tautomerism equilibrium is connected also with other substituent characteristic apart from Van der Waals radius. One should keep in mind, that number of researched *ortho* substituents is too small to draw reliable conclusions.

The largest shift to keto-form can be observed in compound having two methoxy group in *ortho* position in one ring (**2**). Enol percentages are from 81.9% (DMSO-d_6) to 97.4% ($CDCl_3$), what means, that shift is smaller, than shift in the case of derivative with methoxyl group in *ortho* position in each benzene ring [13].

Influence of various substituents in *meta* position on keto–enol tautomerism is insignificant. Most of investigated derivatives have similar enol percentages as DBM. Somewhat increased percentage was observed for compound with nitro groups in *para* postion (**22**), however, due to very low solubility of this compound, keto–enol tautomerism was studied only in acetone-d_6 and DMSO-d_6.

The enol percentages results of *para* substituted derivatives of DBM are surprising. All researched *para* substituted compounds gave similar results as DBM. Again, compound with two nitro groups showed some deviation, but the results are only in acetone-d_6 and DMSO-d_6.

Conclusions

Derivatives with substituents in *ortho* position showed significant hypochromic effects, which was related to Van der Waals radius of the substituent. It confirms the thesis, that hypochromic effect is caused by rotation of benzene ring which decreases molecule coplanarity and disturbs the conjugation. Influence of substituents in *meta* position is slight, however, in the range $\lambda_1 = 280–400$ nm hypochromic effects were always indicated. More differences could be seen in the range $\lambda_3 = 210–235$ nm, where strong absorption band appeared. Research on compounds with substituents in *para* position proved, that all substituents induce bathochromic effect, which is a result of conjugation through benzene ring. Hyperchromic effects were observed for derivatives with electron-donating substituent, however, it is impossible to predict by simple correlation, which substituent will gave the best results. Among investigated, the strongest increase in absorption intensity was observed for methoxyl, *N*-acetamide and hydroxyl substituent.

Results from research on ^{1}H NMR spectra of synthesized compounds gave general conclusions about influence of solvent and substituent on keto–enol tautomerism equilibrium. In all investigated solvents, synthesized β-diketones exist mainly as enol tautomer. Increase of solvent polarity, shifts gently an equilibrium towards the keto tautomer. It is caused by formation of intramolecular hydrogen bond in the enol form, which has pseudo-cyclic structure and therefore is less polar. Influence of substituents on tautomerism equilibrium is rather different that on UV absorption. The most appreciable changes in keto–enol tautomerism can be observed for *ortho*-substituted compounds. All researched substituents in *ortho* position shifts the equilibrium towards the keto form .The source of this impact is the disturbance of conjugation caused by steric hindrance. Influence of substituents in *meta* and *para* positions on keto–enol tautomerism is insignificant.

These results clearly indicate, that although keto–enol tautomerism equilibrium and UV absorption are strictly related to each other, the influence of diketone's substituent on these phenomena is quite different.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.saa.2012.07.109.

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