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Factors influencing the tautomeric form stabilization and spectral characteristics of 1-phenyl substituted pyrazol-5-ones

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The tautomerism of pyrazolone derivatives is a challenging field of study with importance for chemical and biological systems. Spectral analysis of different stabilized tautomeric forms of 1-phenyl-substituted pyrazolones and their photochemical behavior was conducted in different conditions. The experimental UV-spectral data in solvents have been compared with those after UV-light irradiation. The obtained results showed the presence of tahe photo isomerization process between the tautomeric forms of the compounds depending on the structure substituents at 3-and 4-position, polarity effect of the solvents, time of irradiation, temperature and concentration.

Keywords: 1-phenyl-substituted pyrazole-5-ones, spectral analysis, photoinduced tautomeric forms

INTRODUCTION

Pyrazoles and their derivatives are attractive compounds, because they have a wide variety of biological activities [1, 2] and different drugs possess a pyrazole ring as the key structural unit [3]. Some pyrazole derivatives have been proved to be cytotoxic on human cells lines [4-7] and at the same time, several drugs containing pyrazoles in their structure have been approved for the treatment of several types of cancer and amyotrophic lateral sclerosis (ALS) [8]. The phenyl-pyrazolone structural unit can be found in a large diversity of compounds with medicinal application [9]. On the other hand, the tautomerism of pyrazolone derivatives is a challenging field of study with importance for chemical and biological systems. The 1-phenyl substituted pyrazol-5-ones exist as three possible tautomeric forms: CH (a), OH (b) and NH (c) (Scheme 1), where relative proportions in the established equilibrium depends on the structure of the compounds, medium effects and possibilities for inter- and intramolecular interactions [10-13].

In the literature there are not enough data about the photochemical behavior of 1-substituted pyrazol-5-ones and especially for the compounds, which we studied. The UV-light influence is important from therapy point of view and initial research has been conducted already [14, 15]. After UV-irradiation the N-N bond is easier to break and photochemical cleavage of pyrazolone ring between nitrogen atoms in protic solvents is observed [16]. Under influence of light and atmospheric oxygen, the pyrazolone derivatives became yellow, possessing lower biological activity and higher toxicity [17, 18]. The kinetic investigations and photochemical rearrangement showed that their photostability depends in different factors and conditions [19].

In this work we continued our investigations on the photochemical behavior and the spectral elucidation of the possible tautomeric forms in different solvents of 3-methyl-1-phenyl pyrazole-5-one (MPhP), 1,3-diphenyl pyrazole-5-one (DPhP), 4-benzyl-3-methyl-1-phenyl pyrazole-5-one (4-BMPhP), 3,4-dimethyl pyrazole-5-one (3,4-di-MPhP) and 4,4'-methylidene-bis-(1,3-diphenyl pyrazole-5-one) (4,4'-MBDPhP) shown in Scheme 1.

Structural characterization of the CH-tautomers of two derivatives as MPhP and DPhP, has been carried out by IR-spectroscopic study using linear-dichroic (IR-LD) analysis [20, 22]. By reducing-difference procedure the NH-tautomeric form of DPhP was established in the polymer film after UV-light irradiation [23-25].

EXPERIMENTAL

The synthesis of the studied compounds is described elsewhere [26, 27]. The solvents used were Uvasol (Merck) products. The UV-absorption spectra in different solvents (1.10^{-4} mol/l solution, quartz cell of 1 cm) as isooctane, n-hexane, methanol, ethanol, acetonitrile and H_2O were recorded on an Agilent 8453 UV-VIS spectrometer with ± 3 nm resolution. The sample solution was irradiated from a distance of 15 cm using a medium pressure mercury vapor lamp and a system of liquid filters (310 nm). The irradiation intensity was $1.29.10^{16}$ quant $s^{-1}.cm^3$.

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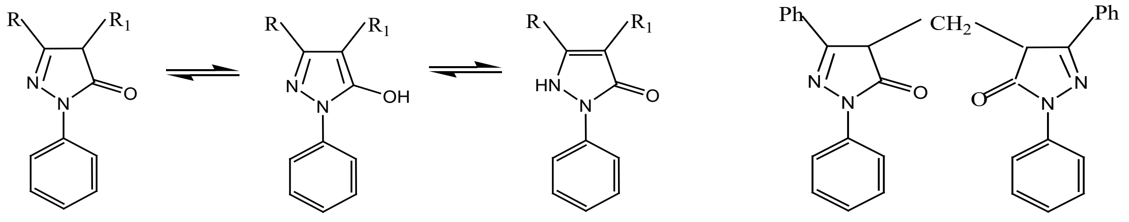


(a)
CH-form

(b)
OH-form

(c)
NH-form

(d)

Scheme 1. Tautomeric forms of 1-phenyl-3, 4-substituted pyrazole-5-ones: R = $-CH_3$, R_1= H (MPhP); R = $-C_6H_5$, R_1= H (DPhP); R = $-CH_3$, R_1 = $-CH_2C_6H_5$(4-BMPhP); R = $-CH_3$, R_1 = $-CH_3$ (3,4-di-MPhP); R = Ph, R_1 = $-CH_2$-DPhP) - 4,4'-methyliden-bis-(1,3-diphenyl pyrazole-5-ones), (4,4'-MBDPhP) (d)

Table 1. UV-spectral data in different solvents for studied compounds

Compound	Solvent, λ [nm]					
	n-Hexane	Isooctane	EtOH	MeOH	H2O	CH3CN
MPhP*	246, 270-330sh	248	244	246	240, 275sh	243, 270 sh
DPhP*	264, 322	265, 325	268	270	264	266
3,4-di-MPhP	236	246	243	251, 286sh	262	254
4-BMPhP	245	248	250, 278sh	248, 270sh	248, 270	247, 272sh
4,4'-MBDPhP	265, 325	252, 315	263	258	**256**	267

* According to [20, 24, 25]

RESULTS AND DISCUSSION

Although the application of UV-spectroscopy is complicated by overlapping of the broad absorption maxima [10, 11], we studied the compounds mentioned above and the corresponding tautomeric forms in solution for spectral elucidation and explanation of photochemical relations. The obtained results could be used for establishing of some correlations connected to compounds structure influence, medium effect, UV-light irradiation, as well as and other factors concerning spectral characteristics and stabilization of the corresponding tautomeric forms.

UV-spectral analysis

The UV-spectral data of the investigated compounds in different solvents before irradiation are presented in Table 1. According to previous results in some nonpolar solvents (chloroform) DPhP and MPhP stabilized the CH-form [23]. In solvents as n-hexane, isooctane, DPhP stabilized the CH-form too, with charge transfer (CT) origin of the band at longer wavelengths [23, 27, 28], while MPhP preferred the HO-tautomeric form [24, 25]. The latter is in contradiction with literature data for nonpolar solvents [11, 12]. For the other compounds, some results in the used solvents are similar to those of MPhP (4- BMPhP, 3,4-di-MPhP in isooctane and n-hexane) stabilizing the HO-form and DPhP (4,4'-MBDPhP in n-hexane) stabilizing CH-form) (see Table 1).

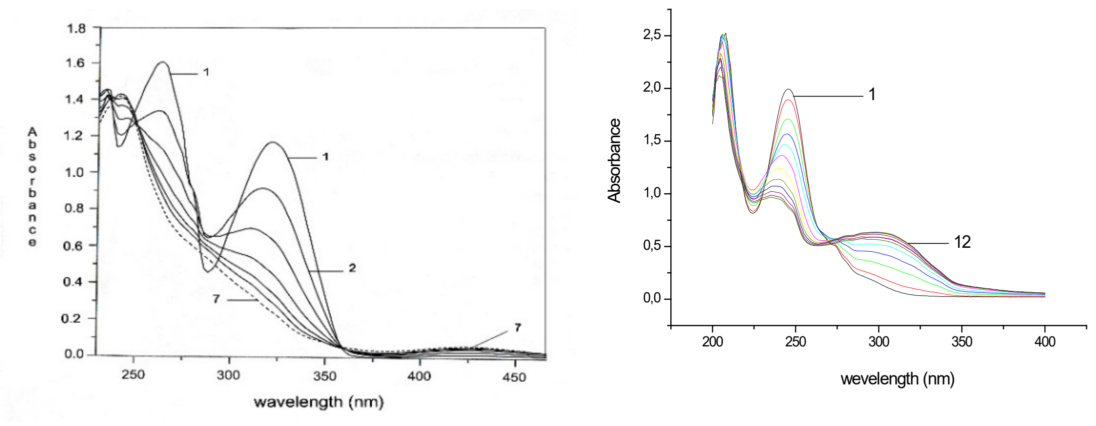
In polar solvents (MeOH, EtOH) MPhP and DPhP stabilized the OH-tautomer [8, 21, 23, 27]. But for 4-BMPhP and MPhP in water and acetonitrile, the bands are at 240-250 nm (OH-form) with a shoulder at 270-280 nm (Table 1). The second maximum should be considered as a characteristic of a third NH-tautomeric form, i.e., in these solvents a mixture between the two OH- and NH-forms is available. Similar bands have been observed for 2,3-dimethyl-1-phenyl pyrazol-5-one (which is a model compound for NH-form) in different solvents [24]. The experimental results for 4,4'-MBDPhP suggest a domination of HO-tautomer, confirming its stabilization in polar solvents. The observed differences in the spectral characteristics can be additionally explained in different degree by compounds structure influence, polarity effects of solvents and specific interactions between solvent and dissolved molecules.

UV-spectral analysis of irradiated compounds in solution

As was stated above, there are not enough data in the literature about the photochemical behavior of 1-substituted pyrazolones. We investigated our compounds after irradiation with UV-light (λ=310 nm) in different solvents and the experimental results are presented below.

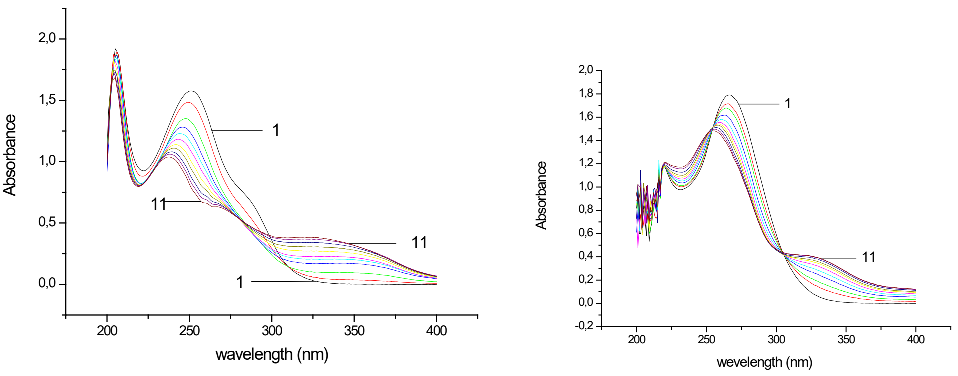
Irradiation in non-polar solvents

The data for DPhP in nonpolar solvents indicate stabilization of the CH-tautomer [17, 19]. However, the irradiation in other solvents, such as n-hexane leads to disappearance of the band at 325 nm and appearance of a new one at 245-250 nm, which is a hypsochromic shift (Fig.1(1)). The latter single band characterizes the HO-form [21, 24] and the available isosbestic points (260 and 350 nm) in the spectrum assume a photo-transformation process between the tautomeric forms, i.e. CH→OH photo-isomerization is realized. The data for MPhP in nonpolar solvents are discussed in [25] showing OH→CH photo isomerization only in isooctane.



(1) (2)

Fig. 1. UV-spectra of DPhP (1) and 4-BMPhP (2) in n-hexane: 1- before irradiation. 2 - 7, 12- after irradiation for 30 sec.



(1) (2)

Fig. 2. UV-spectra of 3,4-di-MPhP in MeOH (1) and 4,4-BMDPhP in CH_3CN (2): 1-before irradiation; 9-11 after irradiation for 30 sec.

A similar result we obtained also for 4-BMPhP in n-hexane (Fig. 1(2) and isooctane, where irradiation leads to the same spectral changes and photo transformation. For the compound 4,4'-BMDPhP after irradiation only decreasing intensity of the absorption bands is observed, i.e. no photo isomerization is realized, which means that the used solvents are not appropriate for photochemical isomerization, which depends on their polarity and specific inter- and intramolecular interaction. Moreover, the obtained experimental results reveal a different photochemical behavior of the compounds at the identical spectral and experimental conditions. The observed reversible OH$\rightleftarrows$CH isomerization after irradiation of some of compounds is analogous to the keto-enol tautomerism of β-dicarbonyl compounds after irradiation [29-31].

Irradiation in polar solvents

Experimental results for MPhP and DPhP in polar solvents are already discussed [17, 19-21], where the HO-form is stabilized with a single absorption maximum in the UV-spectrum.

However, after irradiation of MPhP in these solvents the spectra are practically not changed, which means more stability and different behavior toward UV-light irradiation. The experimentally observed data for the other compounds after irradiation correlate well with some established above dependences.

Concerning 3,4-diMPhP and 4,4-BMDPhP in MeOH and CH_3CN solutions, new bands (240-252, 320-330 nm) appeared and the presence of isosbestic points at 245 and 320 nm assumes OH → CH photoisomerization (Fig. 2). In EtOH and CH_3CN, 4-BMPhP stabilize the NH-tautomer and UV-irradiation leads to disappearance of the second maximum at 270 nm and shift to 250 nm, furthermore a new band at 320 nm appears (Fig. 3). The latter two bands belong to the CH-tautomer, which corresponds to tautomeric transition from the NH, OH into the CH form, i.e. a process of photoisomerization NH, OH → CH form. Such kind of photo transformation in solution is not established till now in our investigations of 1-phenyl substituted pyrazol-5-ones.

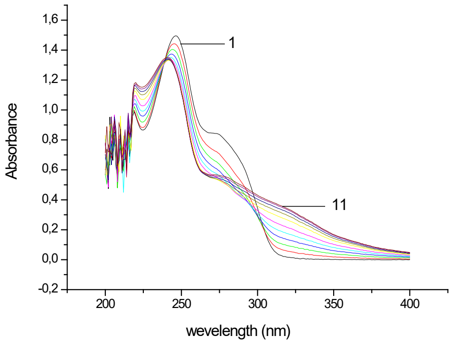
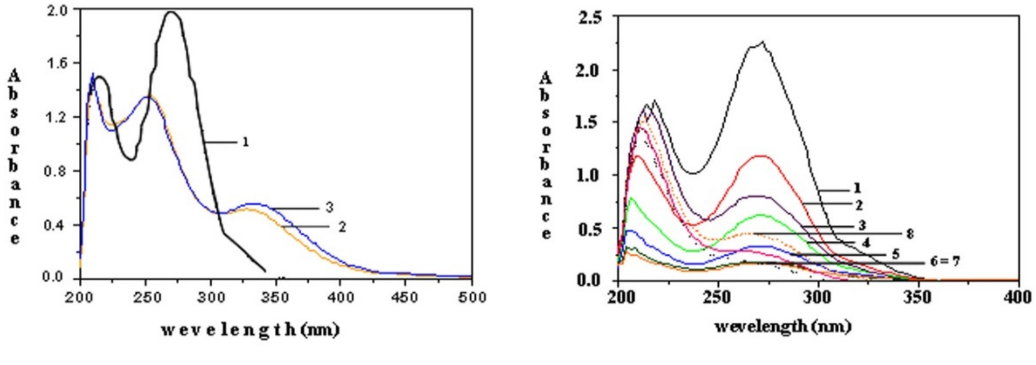


Fig. 3. UV-spectra of 4-BMPhP (1) in CH_3CN:1-before irradiation; 9-11 after irradiation for 30 sec.

These results show the significant influence of the substituents' structure at 3-and 4-position on the spectral characteristics and photochemical behavior of the compounds. Another explanation of these facts probably consists in the different steric disposition of the substituents at 1,3 and 4- position toward pyrazolone ring plane in the corresponding tautomeric forms [19, 21]. We have studied the influence of other factors such as temperature, concentration, and UV-light irradiation on the spectra, but only for DPhP in EtOH. The obtained results showed insignificant temperature and concentration dependence of the spectral characteristics (Figs. 4(1) and 4(2)) for the investigated compound. From the obtained experimental data the following could be said: i) a structure influence of the substituents in the pyrazole ring (3- and 4-position) on the spectral characteristics and photochemical behavior of the investigated compounds is established, which can be explained with specific disposition of the different substituents at 3-position toward the pyrazole ring plane in the tautomeric forms, as well as the substituents structure at 4-position; ii) some of the solvents (mainly polar) are more appropriate for transformation or photochemical isomerization; iii) the influence of other factors as temperature and concentration is insignificant.

CONCLUSION

The obtained results revealed that the specific spectral and photochemical behavior of the investigated compounds depends on their structure, kind of solvent, and irradiation with UV-light. Furthermore, DPhP showed a higher activity and lower stability in solution than MPhP, while for 4BMPhP another kind of photo transformation was established.



(1) (2)

Fig. 4. UV spectra of DPhP: (1) in ETOH: 1-at room temperature; 2-at room temperature after 12 min irradiation; 3-at 60° after 12 min irradiation; (2) in EtOH at different concentrations; 1- 1×10^{-4}M; 3 - 2.5×10^{-5}M; 6 - 6.25×10^{-6} M.

In the other cases the photoisomerization is very specific. No correlations for the investigated compounds were established between structure, spectral characteristics, stability of tautomeric forms and their photo transformation, because of the very specific behavior of the compounds.

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