Spectral Properties of Novel 1,3-oxazol-5(4H)-ones With Substituted Benzylidene and Phenyl rings

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Abstract
In the present work, five novel (4Z)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-ones (azlactones) were investigated by the infra-red (IR) and nuclear magnetic resonance spectroscopy (NMR) of the ¹H and ¹³C nuclei. The spectral properties of the oxazolone ring were monitored with respect to the substituents at the benzylidene and phenyl rings. The compounds were prepared by the Erlenmeyer–Plöchl synthesis from the respective substituted aldehydes and hippuric acid. The IR absorption spectra, measured in chlorophorm, showed a clear splitting of the vibration band in the region characteristic for the carbonyl stretching vibration. This splitting was attributed to the Fermi resonance and the unperturbed wavenumbers of the carbonyl stretching bands were calculated. The chemical shifts of the carbons of the oxazolone ring were assigned. The influence of substituents on spectral properties was demonstrated and discussed. It was found that the oxazolone molecule constitutes an extended π-electron system, with an efficient transmission of electron effects.

Keywords: (Z)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one, substituent effect, C=O stretching vibration, Fermi resonance

1. Introduction

4-Benzylidene-2-phenyl-1,3-oxazol-5(4H)-ones (azlactones) are compounds with a significant synthetic potential and several biological and technological applications. The compounds can be, for example, used as inhibitors of the enzyme activity or as fluorescent sensors. In addition, the oxazolone molecule serves as a general template for the stereoselective syntheses of amino acids and heterocyclic scaffolds.

The structure of the compounds was investigated by several authors. It has been found that the stable conformation is cis (Z) with respect to the exocyclic C=C double bond. The absorption of the electromagnetic energy induces the transition to the trans (E) isomer. The E form, however, is metastable and the reverse transformation to the Z configuration occurs through the photoactivation. The compounds posses an extended π-conjugation system. Their properties are sensitive to substituent effects. The effect of substituents on the biological activity, the rate of ring-opening reactions, and spectral properties were demonstrated.

In solution, the hetero ring is unstable, opens easily and the respective fluorescence quantum yields are relatively low. In the solid state, however, the ring is stable and the quantum yields are enhanced. The significant photochemical and photophysical applications are, therefore, expected for the oxazolone molecules in the solid state, for instance, when embedded in a polymer matrix. The presence of weak van der Waals interactions and the lack of hydrogen bonds causes the molecules to pile up in the same direction and crystallize in noncentrosymmetric structures. The study of substituted 4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-ones showed that the second order harmonic generation (SHG) values of 4-benzoxazol-1,3-dioxol-5-ylmethylene-2-phenyloxazol-5(4H)-one were significantly higher compared to 4-(3,4-dimethoxybenzylidene)-2-phenyloxazol-5(4H)-one. This was attributed to a different way of piling up the molecular columns and to the resulting overlapping of the rings between the molecules in the π–π stacks. The relationship between the structure and the SHG efficiencies suggested that the dominant role was played by the expansion of the delocalized range of π-electrons by the electron donor group rather than the acceptor at the para position of the benzylidene ring. This observation has led to an intensive investigation of the oxazolones having electron donor...
substituents and especially the alkylxy and alkylamino substituted compounds have received a lot of consideration in recent years.\textsuperscript{18–20}

In the present work, we aim to investigate the spectral properties of five novel oxazolone molecules in order to shed further light on substituent effects. The structure of the compounds is given in Fig. 1. The spectral properties were studied for the compounds with the butoxy and isobutoxy electron donor groups located at the \textit{para} position of the phenyl ring. The effect of substitution was monitored by the change of substituents located at the benzyldiene ring.

![Diagram of compounds](image)

**Fig. 1**: The structure of the compounds investigated in the study. Ts stands for the tosyl group, i.e. \(4\)-Me\(\cdot\)C\(_6\)H\(_4\)\(-\)SO\(_2\).–.

### 2. Results and Discussion

#### 2.1. Stretching Frequencies of the C=O and C=N groups

1,3-Oxazol-5(4\(H\))-ones have multiple electrophilic reaction centres for an attack of the nucleophile. In most cases, they react at the carbonyl group.\textsuperscript{1,2,21} The nucleophilic attack often leads to a ring opening and the reaction products are, depending on the character of the nucleophilic

![Diagram of reaction](image)

**Fig. 2**: Ring opening of the hetero ring by a nucleophilic attack at the carbon of the carbonyl group.

Another important factor is the influence of substituents on the order of the chemical bond. Calculated bond orders of chemical bonds forming the 1,3-oxazol-5(4\(H\))-
ones 1a–1c and 2a,b are presented in Table 3. The bond orders are influenced by the electron withdrawing effect of the substituents. The m-NO$_2$ group at the benzylidene ring decreases the bond order of the C=N group. The influence of substituents, however, is evident also for the carbonyl group and not only for the chemical bonds forming the 5-membered heteronuclear ring. The strength of chemical bonds may be inferred from the force constant, which is proportional to the frequency of the critical vibration. We have, therefore, decided to study the stretching vibrations of the C=N and C=O groups in the liquid state.

The frequencies of the stretching vibrations were studied in CHCl$_3$ solutions. We have chosen the chloropromix as a solvent since the solubility of the compounds in this solvent was very good. The characteristic band of the C=N group was present at 1640–1680 cm$^{-1}$, in line with the literature. The absorption band had a high extinction coefficient and it had a simple shape with a clear, single peak maximum. The wavenumbers of the peak maximum together with the respective extinction coefficients for the compounds 1a–c, 2a,b are listed in Table 2. The intensity of the absorption band and the frequency of vibration are influenced by the character of the substituent at the benzylidene ring. Substituents with a strong electron withdrawing effect (m-NO$_2$) significantly decrease the intensity of the maxima (extinction coefficient).

The characteristic absorption band of the carbonyl group was found at 1770–1820 cm$^{-1}$. The shape of the absorption band, however, was not simple and consisted of a superposition of two or more overlapping single bands. We found two peak maxims – the more intense one at 1790 cm$^{-1}$ (A) and the less intense one at 1760 cm$^{-1}$ (B). A similar observation has also been found for other unsaturated lactones studied previously. The stronger band belongs to the fundamental C=O stretching vibration. The results are presented in Fig. 3.

![Fig. 3: The absorption bands of the compounds 1a–1c in the region characteristic for the stretching vibration of the carbonyl group.](image)

The complicated shape of the absorption band disables one to obtain the spectral characteristics precisely. Since the compounds have a characteristic deformation vibration of the C–H group $\omega$, present in the region of 880 cm$^{-1}$ (Table 2), it was anticipated that the complicated shape of the absorption band came out as a result of an interaction between the first overtone of this deformation vibration mode with the fundamental stretching vibration mode of the carbonyl group. This interaction is called Fermi resonance and causes shifting of the peak maxima. It is most often observed in the spectra of lactones and can be detected by the change of solvent. Based on the perturbation theory, we calculated the wavenumbers of the C=O

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Table 2: Wavenumbers (cm$^{-1}$) of the stretching vibration $\beta$ of the C=N group and of the out-of-plane C–H deformation vibration $\omega$ together with the corresponding extinction coefficients (dm$^3$ mol$^{-1}$ cm$^{-1}$).

<table>
<thead>
<tr>
<th></th>
<th>$\beta$(C=N)</th>
<th>$\omega$(C–H)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\nu$</td>
<td>$\epsilon$</td>
</tr>
<tr>
<td>1a</td>
<td>1659.2</td>
<td>642</td>
</tr>
<tr>
<td>1b</td>
<td>1656.0</td>
<td>699</td>
</tr>
<tr>
<td>1c</td>
<td>1654.4</td>
<td>796</td>
</tr>
<tr>
<td>2a</td>
<td>1659.6</td>
<td>588</td>
</tr>
<tr>
<td>2b</td>
<td>1656.0</td>
<td>699</td>
</tr>
</tbody>
</table>

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Table 3 IR absorption bands of oxazolones 1 and 2 in CHCl$_3$, $c$ = 12.0 mmol dm$^{-1}$, before and after the correction for Fermi resonance; $\nu$ – peak wavenumber (cm$^{-1}$), $A$ – absorbance at peak maximum, $\Delta\nu_{1/2}$ – half-peak width (cm$^{-1}$), $\epsilon$ – extinction coefficient (dm$^3$ mol$^{-1}$ cm$^{-1}$), $I$ – integrated intensity (dm$^3$ mol$^{-1}$ cm$^2$), $W$ – interaction coefficient

<table>
<thead>
<tr>
<th></th>
<th>Branch A</th>
<th>Branch B</th>
<th>Corrected</th>
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<tbody>
<tr>
<td></td>
<td>$\nu$</td>
<td>$A$</td>
<td>$\Delta\nu_{1/2}$</td>
</tr>
<tr>
<td>1a</td>
<td>1799.2</td>
<td>0.597</td>
<td>27.3</td>
</tr>
<tr>
<td>1b</td>
<td>1794.8</td>
<td>0.632</td>
<td>26.9</td>
</tr>
<tr>
<td>1c</td>
<td>1793.9</td>
<td>0.723</td>
<td>21.2</td>
</tr>
<tr>
<td>2a</td>
<td>1799.6</td>
<td>0.532</td>
<td>29.6</td>
</tr>
<tr>
<td>2b</td>
<td>1794.6</td>
<td>0.666</td>
<td>26.4</td>
</tr>
</tbody>
</table>

$^a\Delta\nu = \nu_1^a - \nu_A$
before the interaction. We used the relations established by Nyquist et al.\textsuperscript{27} The results are presented in Table 3.

The shift of the peak maximum of the carbonyl absorption band due to Fermi resonance interaction ($\Delta \nu$) was $-3.7$ to $-5.9$ cm$^{-1}$ depending on the character of the substituent. In order to quantify the substituent effect on the carbonyl stretching frequencies we decided to use the Hammett equation. This equation is a representation of a so-called linear free energy relationship (LFER).\textsuperscript{28} The electron effect of the substituents was characterized by the Hammett ($\sigma$) constant.\textsuperscript{28} The Hammett plot of the unaltered wavenumbers of the carbonyl stretching vibration is presented in Fig. 4. The correlation was satisfactory (correlation coefficient $r = 0.9942$) and allowed us to unambiguously relate the effect on the frequency of the stretching vibration to the electron withdrawing effect of the substituents. Since the carbonyl group is not directly bound to the benzene ring, the successful correlation shows a significant transmission of electron effects in the oxazolone ring and suggests a presence of an extended $\pi$ electron system in the molecule. In order to confirm this suggestion, the transmission of the electron effects of the substituents was further investigated by the NMR spectroscopy.

![Fig. 4](image1.png)

**Fig. 4** The Hammett plot of the wavenumbers of the carbonyl stretching vibration.

### 2.2. Chemical Shifts of Carbons of the Oxazolone Ring

The NMR spectra of the $^1$H and $^{13}$C nuclei were measured for saturated chlorophorm solutions. The individual chemical shifts of carbons and protons were assigned using the advanced correlation techniques DQF $^1$H, $^1$H COSY, APT, DEPT and $^1$H--$^{13}$C HMQC.\textsuperscript{29} This procedure allowed for an unambiguous assignment of most chemical shifts. The individual chemical shifts of the carbons of the oxazolone ring are presented in Table 4.

![Fig. 5](image2.png)

**Fig. 5** The Hammett plot of the individual chemical shifts of the carbon $C_6$. For the numbering of atoms, see Table 1.

The chemical shifts of the hetero ring’s carbons ($C_2$ and $C_5$) could be correlated with the Hammett constants as well. The efficiency of the electron effect transmission, given by the slope, was smaller. The correlation between individual chemical shifts of the carbons of the oxazolone ring is given in Fig. 6. The chemical shifts of carbon $C_6$ literally influence the chemical shifts of the carbons of the hetero ring. From Fig. 6 it is also apparent that the transmission of the electron effects causes an increasing chemical shift of the carbon $C_5$ (carbon of the C=O group) and decreasing chemical shift of carbon $C_2$ (carbon of the C=N group). Since the chemical shift is related to the

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>$C_2$</th>
<th>$C_5$</th>
<th>$C_6$</th>
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<tr>
<td>1a</td>
<td>164.81</td>
<td>166.89</td>
<td>125.77</td>
</tr>
<tr>
<td>1b</td>
<td>163.84</td>
<td>167.43</td>
<td>127.79</td>
</tr>
<tr>
<td>1c</td>
<td>163.84</td>
<td>167.76</td>
<td>128.29</td>
</tr>
<tr>
<td>2a</td>
<td>164.68</td>
<td>166.69</td>
<td>125.79</td>
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<tr>
<td>2b</td>
<td>163.75</td>
<td>167.28</td>
<td>127.90</td>
</tr>
</tbody>
</table>

The data presented in Table 4 show that substituents affected the individual chemical shifts of all carbons listed. The effect was most pronounced for carbon $C_6$ which was directly bound to the benzene ring bearing the variable substituent and led to an increase of the chemical shift by the $m$-NO$_2$ group. The effect of substituents was characterized by the $\sigma$ constant and the individual chemical shifts could be given in a Hammett plot. The Hammett plot is presented in Fig. 5. The correlation was very good (correlation coefficient 0.9990). It can be, therefore, concluded that the chemical shifts were controlled by the electron withdrawing effect of the substituents. A very high magnitude of the slope of the Hammett plot given in Fig. 5 ($\rho = -5.32$) corresponds to a very efficient transmission of the electron effects.
electron density around a nucleus, the transmission of the
electron effects may, in turn, influence the relative reactivity
of the C=O and C=N groups towards a nucleophilic
attack. It will be a task for a future study to investigate the
attack of the electrophilic centre of the compounds in the
ring opening reactions.

3. Conclusion

In the present study, we have investigated five novel
substituted (4Z)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-ones by IR and NMR spectroscopy in chlorophorm
solutions in order to demonstrate and understand the sub-
stituent effect on spectral properties. The absorption
bands of the carbonyl stretching vibration showed a clear
splitting. This effect was attributed to a Fermi resonance
interaction between the first overtone of a deformation vi-
bration of the C–H group and a fundamental stretching
mode of the C=O group. The unperturbed frequencies we-
re calculated based on the relations resulting from the per-
turbation theory.

The frequencies of the stretching vibrations of the
C=N and C=O group were found to be significantly inf-
luenced by substituent effects. A successful correlation
between the wavenumbers of the carbonyl group and the
Hammett substituent constants was found. This result
shows the control of spectral properties by the electron
withdrawing/donating effect of the substituents. The tran-
smission of the electron effects in the oxazolone ring was
further investigated by the 13C NMR spectroscopy. Suc-
cessful Hammett plots were found for the chemical shifts
of the carbon directly bound to the benzene ring bearing
the variable substituent and also for the carbons of the he-
tero ring. These results suggest a presence of an extended
π electron system in the oxazolone molecule. The electron
withdrawing groups were found to have an opposite effect
on the individual chemical shifts of the carbons C2 and C5
of the oxazolone ring. It can be suggested that the relative
reactivity of the electrophilic centres of the C=N and C=O
groups towards an attack of a nucleophile shall be diffe-
rent for different substituents. It will be a task for a future
study to investigate the rate and mechanism of the ring
opening reactions of the substituted compounds.

4. Experimental

(4Z)-4-(Substituted benzylidene)-2-(substituted phenyl)-1,3-oxazol-5(4H)-ones were prepared by the
cyclodehydration–condensation of the appropriate al-
dehyde and hippuric acid in dry acetic anhydride cataly-
sed by acetate anion (Erlenmeyer–Plöchl synthesis, Fig.
7). Details of the experimental procedure can be found el-
sewhere.11,17 The purity of the compounds was monitored
by the IR and the NMR spectroscopy. The melting points
found are listed in Table 5. The UV-VIS absorption bands
in the 70% (v/v) aqueous dioxane were not single peaks
but had a vibrational structure. The peak maxima are pre-
sented in Table 5.

Table 5 Melting points of the compounds, recrystallization sol-
vents and wavelengths (in nm) of the peak maximum in 70% aque-
ous dioxane for compounds 1 and 2.

<table>
<thead>
<tr>
<th>Cmpd.</th>
<th>m.p./°C</th>
<th>Recrystal. Solvent</th>
<th>λmax</th>
</tr>
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<tbody>
<tr>
<td>1a</td>
<td>147–150</td>
<td>Ethanol</td>
<td>377</td>
</tr>
<tr>
<td>1b</td>
<td>140–143</td>
<td>Ethanol</td>
<td>378</td>
</tr>
<tr>
<td>1c</td>
<td>141–143</td>
<td>Ethanol</td>
<td>379</td>
</tr>
<tr>
<td>2a</td>
<td>124–127</td>
<td>Ethanol</td>
<td>377</td>
</tr>
<tr>
<td>2b</td>
<td>129–132</td>
<td>Ethanol</td>
<td>379</td>
</tr>
</tbody>
</table>

The IR spectra were recorded for the chlorophorm
solutions of the compounds 1 and 2 on a Zeiss Specord
M-80 spectrometer at room temperature using NaCl cells
of 0.1 cm thickness. The concentration of the compounds
was 12.0 × 10⁻³ mol dm⁻³. The CHCl₃ was of spectrosco-
pic purity (Merck). The peak positions were referenced to
the standard spectrum of polystyrene.

The ¹H and ¹³C NMR spectra of the 1a–c, 2a,b were
recorded for saturated CDCl₃ solutions at 300 K with a
Bruker Avance DPX spectrometer working at 200.13
MHz for proton and 50.32 MHz for ¹³C, respectively. The
chemical shifts were referenced to the signal of TMS. The
individual chemical shifts (in ppm) and results of elemen-

![Fig. 6: The correlation of individual chemical shifts of carbons C2
and C5 of the oxazolone ring. For the numbering of atoms, see Tab-
le 1.](image)

![Fig. 7: Erlenmeyer–Plöchl synthesis.](image)
(4Z)-2-(4-Butoxyphenyl)-4-(3-nitrobenzylidene)-1,3-oxazol-5(4H)-one (1a): 
1H NMR δ 1.10 (t, 3H, CH3CH2CH2CH2O); 1.75 (sx, 2H, CH2CH2CH2CH2O); 1.96 (p, 2H, CH2CH2CH2CH2O); 4.24 (t, 2H, CH2CH2CH2CH2O); 7.06–7.41 (m, 3H); 7.78 (t, 1H, Ar-H); 8.20–8.55 (m, 4H, Ar-H). 13C NMR δ 14.18, 19.53, 31.39, 68.41, 115.15, 116.81, 124.53, 125.77, 126.29, 129.68, 130.87, 135.28, 135.88, 137.21, 148.50, 164.06, 164.81, 166.89. Anal. Calcd for C20H18N2O5: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.88; H, 4.61; N, 7.52.

4-[(Z)-2-(4-Butoxyphenyl)-5-oxo-1,3-oxazol-4(5H)-ylidene]methylphenyl 4-methylbenzenesulfonate (1b): 
1H NMR δ 1.17 (t, 3H, CH3CH2CH2CH2O); 1.70 (m, 2H, CH2CH2CH2CH2O); 1.98 (m, 2H, CH2CH2CH2CH2O); 2.62 (s, 3H, CH3-Ar); 4.21 (t, 2H, CH2CH2CH2CH2O); 7.12–7.25 (m, 5H); 7.48 (d, 2H, Ar-H); 7.88 (d, 2H, Ar-H); 8.16–8.30 (m, 4H, Ar-H). 13C NMR δ 14.17, 19.51, 22.06, 31.38, 68.32, 115.02, 117.19, 122.77, 127.79, 128.50, 129.90, 130.21, 130.32, 120.37, 133.46, 134.07, 145.61, 150.78, 163.67, 163.84, 167.43. Anal. Calcd for C20H18N2O5S: C, 65.97; H, 5.13; N, 2.85. Found: C, 66.34; H, 5.31; N, 2.69.

5. References
Povzetek

Članek predstavlja pet novih (4Z)-4-benziliden-2-fenil-1,3-oksazol-5(4H)-onov (azlaktonov), raziskanih s pomočjo infrardeče (IR) ter jedrske magnetne resonančne spektroskopije (NMR) jeder 1H in 13C. Spektroskopske lastnosti oksazolonskega obroča smo spremljali glede na substituente na benzilidenskem oz. fenilnem obroču. Spojine smo pripravili z Erlenmeyer–Plöchlov sintezo iz ustrezno substituiranih aldehidov in hipurne kisline. IR absorpcijski spektri, izmerjeni v kloroformu, so pokazali jasen razcep vibracijskih trakov v območju, ki je značilno za karbonilne raztezne (stretching) vibracije. Ta razcep se lahko pripiše Fermijevi resonanci; izračunali smo tudi valovna tevila karbonilnih stretching trakov v neperturbiranih sistemih. Asignirali smo tudi kemijske premike ogljikov oksazolonskega obroča. Vpliv substituentov na spektralne lastnosti je bil raziskan in razložen. Ugotovljeno je bilo tudi, da oksazolonska molekula vsebuje razpotegnjen π-elektronski sistem, po katerem se elektronski vplivi učinkovito prenašajo.