NH-acidities and Hammett correlation of 3-para substituted phenyl-1,2,4-oxadiazol-5(4H)-ones and 1,2 λ4 3,5-oxathiadiazole 2-oxides in nonaqueous media

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Abstract: NH acidities of some 3-(p-substitutedphenyl)-1,2,4-oxadiazol-5(4H)-ones and 4-(p-substitutedphenyl)-1,2 λ4 3,5-oxathiadiazole 2-oxides were determined in methanol by means of potentiometric titration with sodium methoxide. pKₐ values of the title compounds calculated from the potentiometric data were interpreted on the basis of structural effects caused by para-substituted groups on the phenyl ring by plotting pKₐ values versus Hammett σ⁺ constants, which gave excellent linear correlations.

Key words: Potentiometry, oxadiazol-5(4H)-one, oxathiadiazol 2-oxide, linear Hammett correlation

1. Introduction

1,2,4-Oxadiazol-5(4H)-ones and 1,2λ4 3,5-oxathiadiazole 2-oxides are typical acidic heterocycles that are classically used by medicinal chemists as carboxylic acid bioisosters.¹ In particular, heterocyclic scaffold 1,2,4-oxadiazol-5(4H)-ones are found in AT1 antagonists, COX inhibitors, PLA2 inhibitors, and modulators of GluR,²⁻⁵ and they serve as precursors and protecting groups for amidines, which are utilized as an important class with biological functionality and as antihypertensive drugs.⁶⁻¹⁰ Moreover, 3H-1,2λ4 3,5-oxathiadiazole 2-oxides have been reported to be used to control hyperglycemia associated with type 2 (noninsulin dependent) diabetes mellitus, and they were clinically found to have advantages over 4 divergent classes of drugs that are in use.¹¹

Potentiometric titration in nonaqueous media is a standard method for the determination of the basicity and acidity of various heterocyclic compounds, particularly in pharmaceutical analyses since many organic compounds of pharmaceutical importance do not dissolve in water thoroughly. Furthermore, due to the amphotericity of water, only a very limited range of acid and base strengths can be determined in this solvent and in trying to compare the protonation and deprotonation tendencies of such heterocycles in alternant solvents,¹²⁻¹⁵

In continuation of our studies on the acid-base equilibria of amidoximes and related heterocyclic compounds,¹⁶⁻¹⁸ we report herein acidity measurements and Hammett correlations of a series of 3-(para-substituted phenyl-1,2,4-oxadiazol-5(4H)-ones and 4-(para-substituted phenyl)-3H-1,2λ4 3,5-oxathiadiazole 2-oxides (Scheme 1) in methanol as nonaqueous medium.

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2. Experimental

1,2,4-Oxadiazol-5(4H)-ones (2a–l) and 1,2λ4,3,5-oxathiaziazol-2-oxides (3a–l) were prepared according to the procedures described previously.19–24

2.1. Potentiometric titrations

Titrations were performed in a 50-mL glass vessel designed for this work and equipped with a combined pH electrode (Ingold), argon inlet and outlet tubes, a magnetic stirrer, and an inlet for titrant (sodium methoxide) addition. A microburette with 0.01-mL graduations was used to add titrant. A Thermo Scientific Orion 4 Star pH/ISE meter equipped with a modified electrode (saturated KCl solution in anhydrous methanol instead of aqueous KCl solution) was used to read out the cell EMF.

The concentrations of the oxadiazolones and oxathiaziazole 2-oxides were maintained as 10^{-3} M in dry methanol. Potentiometric measurements were conducted with constant stirring of 30 mL of sample solution (magnetic stir-bar) at 25.0 ± 0.1 °C. Titration curves were constructed by plotting the potential change (from the initial baseline value) versus the concentration of the titrant solution added. In order to calculate the end points the Kolthoff method was utilized. The half neutralization potentials (HNP) were then determined by using fine sigmoidal curves. In calculations of the pK_a values, mV value of a standard buffer solution and HNP values from the sigmoidal curves of the samples were used, and 59 mV was taken as corresponding to 1 pH unit.

3. Results and discussion

3-Aryl-substituted 1,2,4-oxadiazol-5(4H)-ones 2a–l were synthesized following the literature procedure25,26 by reacting monoamidoximes with 1,1'-carbonyldimidazole (CDI) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 3-aryl substituted 1,2λ4,3,5-oxathiaziazole 2-oxides 3a–l were prepared similarly to the procedure27 described by the condensation of mono amidoximes 1a–l with thionyl chloride along with pyridine (Schemes 1 and 2).

**Scheme 1.** Synthesis of 3-<i>p</i>-substituted phenyl-1,2,4-oxadiazol-5(4H)<i></i>-ones (2a–l).
Scheme 2. Synthesis of 3-\(p\)-substituted phenyl-3\(H\)-1,2,4-\(\Lambda^4\),3,5-oxathiadiazole 2-oxides (3a−l).

\[ \text{SOCl}_2, \text{pyridine} \]
\[ \text{THF} \]
\[ \text{Room temp.} \]
\[ 1 \text{ h} \]

<table>
<thead>
<tr>
<th>R</th>
<th>3a</th>
<th>H</th>
<th>3g</th>
<th>MeO</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b</td>
<td>Me</td>
<td>3h</td>
<td>MeS</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>F</td>
<td>3i</td>
<td>CF(_3)</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td>Cl</td>
<td>3j</td>
<td>CN</td>
<td></td>
</tr>
<tr>
<td>3e</td>
<td>Br</td>
<td>3k</td>
<td>NO(_2)</td>
<td></td>
</tr>
<tr>
<td>3f</td>
<td>I</td>
<td>3l</td>
<td>NMe(_2)</td>
<td></td>
</tr>
</tbody>
</table>

\(\text{p}K_a\) values of aromatic heterocyclic compounds bearing oxygen and nitrogen in the same ring, namely oxadiazolones and oxathiadiazole 2-oxides, were determined potentiometrically in nonaqueous medium, anhydrous methanol, by using sodium methoxide as titrant. Overall results are compiled in Table 1, indicating the \(\sigma^+\) constants for each substituent encountered, and typical titration curves for each series of the compounds are shown in Figures 1 and 2.

**Figure 1.** Representative titration curve of mL titrant vs. \(\Delta\text{mV}\) of 4-\(p\)-nitrophenyl-1,2,4-oxadiazol-5(4\(H\))−one (2k).

**Figure 2.** Representative titration curve of mL titrant vs. \(\Delta\text{mV}\) of 3-\(p\)-nitro 3\(H\)-1,2 \(\Lambda^4\),3,4,5-oxathiadiazole 2-oxide (3k).
Table 1. Experimental pKₐ values of oxadiazolones (2a–l) and oxathiadiazole 2-oxides (3a–l) in methanol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>pKₐ (oxadiazolone)</th>
<th>σ⁺</th>
<th>Entry</th>
<th>R</th>
<th>pKₐ (oxathiadiazole 2-oxide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>H</td>
<td>6.35 ± 0.02</td>
<td>0.00</td>
<td>3a</td>
<td>H</td>
<td>6.12 ± 0.01</td>
</tr>
<tr>
<td>2b</td>
<td>CH₃</td>
<td>6.80 ± 0.04</td>
<td>-0.31</td>
<td>3b</td>
<td>CH₃</td>
<td>6.40 ± 0.04</td>
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<tr>
<td>2c</td>
<td>4-F</td>
<td>6.50 ± 0.01</td>
<td>-0.07</td>
<td>3c</td>
<td>4-F</td>
<td>6.17 ± 0.05</td>
</tr>
<tr>
<td>2d</td>
<td>4-Cl</td>
<td>6.30 ± 0.02</td>
<td>0.11</td>
<td>3d</td>
<td>4-Cl</td>
<td>6.05 ± 0.07</td>
</tr>
<tr>
<td>2e</td>
<td>4-Br</td>
<td>6.18 ± 0.05</td>
<td>0.15</td>
<td>3e</td>
<td>4-Br</td>
<td>5.76 ± 0.01</td>
</tr>
<tr>
<td>2f</td>
<td>4-I</td>
<td>6.28 ± 0.03</td>
<td>0.14</td>
<td>3f</td>
<td>4-I</td>
<td>5.90 ± 0.03</td>
</tr>
<tr>
<td>2g</td>
<td>4-CH₃O</td>
<td>7.24 ± 0.06</td>
<td>-0.78</td>
<td>3g</td>
<td>4-CH₃O</td>
<td>7.00 ± 0.08</td>
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<tr>
<td>2h</td>
<td>4-CH₃S</td>
<td>7.10 ± 0.06</td>
<td>-0.60</td>
<td>3h</td>
<td>4-CH₃S</td>
<td>6.80 ± 0.02</td>
</tr>
<tr>
<td>2i</td>
<td>4-CF₃</td>
<td>5.69 ± 0.13</td>
<td>0.61</td>
<td>3i</td>
<td>4-CF₃</td>
<td>5.45 ± 0.06</td>
</tr>
<tr>
<td>2j</td>
<td>4-CN</td>
<td>5.60 ± 0.01</td>
<td>0.66</td>
<td>3j</td>
<td>4-CN</td>
<td>5.36 ± 0.07</td>
</tr>
<tr>
<td>2k</td>
<td>4-NO₂</td>
<td>5.44 ± 0.10</td>
<td>0.79</td>
<td>3k</td>
<td>4-NO₂</td>
<td>5.07 ± 0.12</td>
</tr>
<tr>
<td>2l</td>
<td>4-N(CH₃)₂</td>
<td>8.30 ± 0.16</td>
<td>-1.70</td>
<td>3l</td>
<td>4-N(CH₃)₂</td>
<td>8.04 ± 0.15</td>
</tr>
</tbody>
</table>

Deprotonation of the oxadiazolones 2a–l by methoxide will take place on the sp³-hybridized 4-amino nitrogen. The resulting heterocyclic anion, oxadiazol-5-olate, is now stabilized due to the delocalization of negative charge through exocyclic oxygen, thus producing an aromatic oxadiazole structure (Scheme 3).

Electron-withdrawing and electron-releasing substituents (R groups) existing on the para position of the phenyl ring in the case of oxadiazolones will have a remarkable impact on the acidities of these heterocycles. In this regard, electron-donating substituents like dimethylamino, methoxy, and thiomethoxy cause an increase in pKₐ values as much as 8.30, 7.24, and 7.10, respectively, while electron-withdrawing ones, such as NO₂, CN, and CF₃, give rise to much lower pKₐ values of 5.44, 5.60, and 5.69, respectively, which are in accord with the decreasing values of Hammett sigma para constants.

In a similar manner, we can illustrate the deprotonation of oxathiadiazole 2-oxides, which further gives 4-aryl-1,2,4-oxadiazol-5(4H)-ones with aromatic stability (Scheme 4).

Again we can observe the higher acidities of the oxathiadiazole 2-oxides compared to oxadiazolones in the case of electron-withdrawing substituents and this tendency can be attributed to the higher polarization of S=O bond than C=O bond, causing easier deprotonation of NH hydrogens of oxathiadiazole 2-oxides.
pK\textsubscript{a} values obtained for the title compounds were correlated with Hammett $\sigma_p^+$ constants,\textsuperscript{28} which have also been used for para substituents interacting with the aromatic ring through resonance delocalization of the lone pairs.\textsuperscript{29,30} In Figure 3, it can be clearly perceived that electron-releasing groups (ERGs), i.e. dimethylamino, methoxy, and thiomethoxy, which have lower Hammett $\sigma_p^+$ values with higher pK\textsubscript{a} values, appeared on one end of the line (right lower end), and electron-withdrawing (EWG) substituents, i.e. NO\textsubscript{2}, CN and CF\textsubscript{3}, which have higher Hammett $\sigma_p^+$ constants with lower pK\textsubscript{a} values, appeared on the other end of the graph (left upper end). In general, the acidities measured experimentally in nonaqueous solvents such as methanol, dimethyl sulfoxide, dimethoxyethane, and acetonitrile are expected to be lower than those obtained in water due to the higher stabilization of the ionic species in water.\textsuperscript{31–35}

A similar observation was made for oxathiadiazol-2-oxides (Figure 4).

**Figure 3.** Hammett plot indicating linear correlation between electronic parameter of the substituents on the oxadiazol-5(4\textsubscript{H})-ones (2a–l) and pK\textsubscript{a} values obtained in anhydrous methanol.

**Figure 4.** Hammett plot indicating linear correlation between electronic parameter of the substituents on the oxathiadiazol-2-oxides (3a–l) and pK\textsubscript{a} values obtained in anhydrous methanol.

These results are in good accordance with the expected behavior of these groups predicated on the proticity of amino hydrogen of oxadiazolones. In this regard, when there are electron-releasing groups present
on the phenyl ring there will be an increase in electron density, which may result in resonance delocalization of the lone pairs on the N, O, and S atoms (N(CH$_3$)$_2$, CH$_3$O, CH$_3$S) through the aromatic ring, thus reducing their acidity to a remarkable extent. In the presence of electron-withdrawing groups (NO$_2$, CN, CF$_3$) on the phenyl ring, a reverse effect on $pK_a$ values is observed due to the substantial decrease in the electron density of the amino nitrogen atom of the oxadiazolones mesomerically, thus causing an increase in the proticity of amino hydrogens.

4. Conclusions

In this work, we clearly demonstrated the acidity measurements (pK$_a$) of a series of oxadiazolones and 1,2,4,5-oxathiadiazol-2-oxides potentiometrically in anhydrous methanol. In addition, excellent linear correlations between pK$_a$ values and Hammett $\sigma_p^+$ constants were established and the results were interpreted by taking account of the electronic–mesomeric nature of the existing groups on the phenyl ring at the 3-position of the title oxygen, nitrogen containing 5-membered heterocycles.

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References