Molecular Encapsulation of Herbicide Terbuthylazine in Native and Modified $\beta$-Cyclodextrin

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The herbicide terbuthylazine (TBA) is widely used for preemergence or postemergence control of many grass and broadleaf weeds and has, besides other issues, a poor aqueous solubility profile that results in reduced bioavailability. Cyclodextrins and modified cyclodextrins were considered, among other substances, appropriate agents for improving pesticide water solubility. Therefore, the inclusion complex formation of terbuthylazine with $\beta$-cyclodextrin ($\beta$-CD) and hydroxypropyl-$\beta$-cyclodextrin (HP-$\beta$-CD) was studied to attain its aqueous solubility enhancement. Their characterization was accomplished with different analytical techniques, namely, by UV-Vis, DSC, FTIR, and $^1$H NMR. From the analysis of the complexation performance of the herbicide it was concluded that the interaction of terbuthylazine with CDs leads to the formation of inclusion complexes with a stoichiometry of 1:1. The association constants of the TBA/$\beta$-CD and TBA/HP-$\beta$-CD complexes were determined by UV. The mean values obtained for the stability constants are 460.4 ± 26.5 and 532.1 ± 27.6 to TBA/$\beta$-CD and TBA/HP-$\beta$-CD, respectively. $^1$H NMR data corroborate the formation of the TBA/$\beta$-CD and TBA/HP-$\beta$-CD complexes synthesized by the kneading method. A formulation incorporating TBA cyclodextrin complexes might lead to an improvement in terbuthylazine bioavailability. The development of TBA-CD formulations may be interesting since it would enable, through their inclusion into the hydrophobic cavity of CDs, enhancement of solubility, bioavailability, and stability of the herbicide.

1. Introduction

Pesticides are widely used worldwide in farming since they fight crop pests and reduce competition from weeds, thus improving agricultural yields and protecting the availability, quality, and price of produce to the benefit of farmers and consumers. However, their use does involve risk, because most have inherent properties that can endanger health and the environment if not used properly. Actually, there is now overwhelming evidence that some of these chemicals do pose a potential risk to humans arising from the exposure through environmental contamination or occupational use [1–3]. Yet, the beneficial outcome from use of pesticides provides evidence that pesticides will continue to be a vital tool in the diverse range of technologies that can maintain and improve living standards for the people of the world.

The impact on environment and human health by pesticides is associated with factors such as the amount of active ingredient in the pesticide formulation and/or the use of additives that are mixed with the active ingredient (wetting agents, diluents or solvents, preservatives, and emulsifiers) to improve the formulations performance, namely, their solubility and (photo)chemical and microbial stability. Although inert ingredients have no pesticidal activity, they may be biologically active and sometimes the most toxic component of a pesticide formulation [4].

Cyclodextrins (CDs) are natural cyclic oligosaccharides with 6, 7, or 8 glucose residues ($\alpha$-, $\beta$-, and $\gamma$-CD, resp.) linked by a (1–4) glycosidic bond. The $\beta$-form is the most
commonly employed for encapsulation purposes since it is the most accessible and the lowest-priced cyclodextrin [5]. Apart from these naturally occurring cyclodextrins, many other cyclodextrin derivatives have been synthesized. Each cyclodextrin has its own ability to form inclusion complexes with specific guests, an ability which depends on a proper fit of the guest molecule into the hydrophobic cyclodextrin cavity [6]. Actually, all derivatives have a changed hydrophobic cavity volume and also these modifications can improve solubility and stability against light or oxygen and help control the chemical activity of guest molecules [5]. 2-Hydroxypropyl-β-cyclodextrin (HP-β-CD) is an alternative to natural cyclodextrins, with enhanced water solubility and improved toxicological profile in comparison to its parent β-CD [7]. It has been shown that HP-β-CD is well tolerated in humans and by several animal species [7] and thus can be regarded as an interesting excipient for the development of safer and improved pesticide formulations.

Terbuthylazine (N2-tert-butyl-6-chloro-N4-ethyl-1,3,5-triazine-2,4-diamine, Figure 1) is an herbicide used for foliar spraying on maize and sorghum against annual and perennial monocotyledonous and dicotyledonous weeds [8]. Although terbuthylazine is widely used within the EU, its frequent detection in surface and groundwater, together with its medium to high persistence in soil and intrinsic toxicological properties, may pose a risk both for human and environmental health [8, 9]. These concerns become even more relevant as the production of maize is increasing globally, a trend that is expected to continue in the future even more relevant as the production of maize is increasing

without additional purification. De-ionised water (conductivity < 0.1 µS cm⁻¹) was used throughout all the experiments.

2.2. Phase Solubility Studies. The stoichiometry of pesticide-cyclodextrin complexes and their stability or binding constants are frequently obtained from the phase solubility diagrams. These phase solubility studies were performed by the method reported by Higuchi and Connors [19]. Excess amount of terbuthylazine (20 mg) was added to 25 mL aqueous solutions containing increasing amounts of β-CD (0, 1, 3, 6, and 9 mmol L⁻¹) and HP-β-CD (0, 5, 10, 15, 20, 25, and 30 mmol L⁻¹). The suspensions were shaken on a rotary shaker (IKA KS 4000i, Germany) at 25 ± 2°C for 48 h until reaching the equilibrium. All suspensions were filtered through a 0.45 µm membrane filter (Millipore) and properly diluted and the concentration of terbuthylazine was determined by spectrophotometry (Shimadzu UV-Vis Spectrophotometer, UV-1700, Japan) at 222 nm. The UV absorption of β-CD and HP-β-CD was negligible at the assay wavelength.

The phase solubility diagrams were obtained plotting the equilibrium concentrations of terbuthylazine against the concentration of the respective CD. The apparent stability constants, KS, were calculated from the straight line of the phase solubility diagrams, assuming a 1:1 stoichiometry, using

\[ K_S = \frac{\text{slope}}{S_0 (1 - \text{slope})} \]

where S₀ represents the intrinsic solubility of terbuthylazine.

Each experiment was performed in triplicate, with the mean (±SD) being reported.

2.3. Preparation of Solid Binary Systems

2.3.1. Inclusion Complexes. The preparation of terbuthylazine/β-CD and terbuthylazine/HP-β-CD inclusion complexes was performed using the kneading method. An equimolar amount of terbuthylazine and each of the CD under study were accurately weighed and transferred to a mortar. The mixture was then triturated in the mortar with a small volume of methanol until a homogenous paste was formed. The paste was kneaded for 30 min and then dried overnight, at room temperature, in a desiccator under vacuum. The dried complex was ground using a mortar, sieved (60 mesh), and kept in a closed container protected from light.

Figure 1: Chemical structure of the herbicide terbuthylazine.

2. Experimental

2.1. Chemicals. Terbuthylazine (TBA), β-cyclodextrin (β-CD), and (2-Hydroxypropyl)-β-cyclodextrin (HP-β-CD) were purchased from Sigma-Aldrich Química S.A. (Sintra, Portugal). Deuterated solvents and tetramethylsilane (TMS) were obtained from Merck (Lisbon, Portugal). All other reagents and solvents were proanalysis grade and used
2.3.2. Physical Mixtures. Physical mixtures of terbuthylazine and cyclodextrins (β-CD and HP-β-CD) in 1:1 molar ratio were prepared by blending the individual components, previously sieved (60 mesh), in a mortar for 15 minutes. The mixtures obtained were kept in a closed container protected from light.

2.4. UV/Visible Spectroscopy. Spectrophotometric measurements were performed to quantify terbuthylazine in its free and CD-complexed form. Given the poor water solubility of terbuthylazine standard curves were prepared in water/methanol (v/v = 4:1). Spectrophotometric scans were performed between 190 and 340 nm to monitor the UV spectra of terbuthylazine. The absorbance maximum of 222 nm was used to quantify terbuthylazine concentration.

2.5. Differential Scanning Calorimetry (DSC). DSC measurements were performed with a Netzsch DSC 204 calorimeter (Netzsch, Germany). The accurately weighed sample was placed in an aluminum pan. An empty aluminum pan was used as reference. The experiments were carried out in nitrogen atmosphere (flow rate 70 ml min⁻¹) at a scanning rate of 10°C/min in the range of 25–400°C.

2.6. Fourier Transform Infrared Spectroscopy (FTIR). Infrared spectra were obtained using a Thermo Scientific Nicolet 6700 FTIR spectrometer (Thermo Fisher Scientific, USA) using KBr disks. The samples were ground and mixed thoroughly with KBr and the disks were prepared by compressing the powder. The scanning range was kept from 4000 to 400 cm⁻¹.

2.7. ¹H NMR Analysis. ¹H NMR spectra were performed at room temperature and recorded on a Bruker Avance III operating at 400 MHz. According to the overall solubility of terbuthylazine, β-CD, HP-β-CD, and the respective inclusion complexes, NMR spectra were accomplished in deuterated dimethyl sulfoxide (DMSO-d₆) for β-CD complexes experiments and in an 8:1 (v:v) mixture of deuterated methanol and chloroform (CD₃OD : CDCl₃) for HP-β-CD experiments. The same final concentration (about 50 mM) of all the solutions and volume of solvent was used throughout all the experiments in order to accurately correlate the chemical shifts of the different spectra. Chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane (TMS) as internal reference. Chemical shifts changes (Δδ) were calculated according to the formula Δδ = δ(complex) − δ(free).

3. Results and Discussion

3.1. Phase Solubility Studies. One of the most useful and widely applied analytical approaches for measuring equilibrium solubility is based on the phase solubility technique proposed by Higuchi and Connors [19]. Phase solubility analysis involves an examination of the effect of cyclodextrin on the substrate, that is, the herbicide. Thus, the evaluated equilibrium concentrations of terbuthylazine were plotted against the concentration of the respective CDs and in this way the phase solubility diagrams were constructed.

![Figure 2: Phase solubility diagrams of terbuthylazine with (■, — blue) β-CD and (▲, — red) HP-β-CD, in aqueous solution at 25 ± 2°C. Values are mean ± SD (n = 3).](image)

Table 1: Stability constants (Ks) of terbuthylazine inclusion complexes with the studied cyclodextrins.

<table>
<thead>
<tr>
<th></th>
<th>S₀ ± SD (10⁻⁵ M)</th>
<th>a ± SD</th>
<th>Kₛ ± SD (M⁻¹)</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-CD</td>
<td>0.0439 ± 0.0005</td>
<td>0.0198</td>
<td>460.4 ± 26.5</td>
<td>0.999</td>
</tr>
<tr>
<td>HP-β-CD</td>
<td>0.0388 ± 0.0070</td>
<td>0.0201</td>
<td>532.1 ± 27.6</td>
<td>0.992</td>
</tr>
</tbody>
</table>

(Figure 2). In both cases, the aqueous solubility of the herbicide increased linearly as a function of CD.

This linear relationship is a feature of a A₂ phase solubility profile [20]. As the slope of the plots is less than unity, a 1:1 molecular complex is formed for the two β-CDs [20]. The stability constant (Kₛ) is a useful index to estimate the binding strength of host-guest and the changes in the physicochemical properties of the guest in the complex. The Kₛ values of the complexation were calculated from the phase solubility diagrams according to (1) (see experimental). Stability constants, Kₛ, calculated for terbuthylazine/β-CD and terbuthylazine/HP-β-CD inclusion complexes, were 460.4 ± 26.5 and 532.1 ± 27.6 M⁻¹, respectively (Table 1). The results found showed that the hydroxypropyl substitution in β-CD enhances both cyclodextrin solubility and its complexation ability, expressed by the highest Kₛ value (Table 1).

3.2. Inclusion Complexes Characterization. The assessment of the formation of an inclusion complex and its full characterization often requires the use of different analytical methods, whose results have to be combined and examined together, since each method explores a particular feature of the inclusion complex. The concomitant use of different techniques can allow a better and more in-depth understanding of host-guest interactions and help in selection of the most appropriate CD for a given guest molecule [21].

3.2.1. UV/Visible Spectroscopy. UV-Vis spectroscopy is a simple and useful technique to study the formation of host-guest complexes in solution. Modifications of the UV spectrum of
Absorbance (a.u.)

<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>220</th>
<th>240</th>
<th>260</th>
<th>280</th>
<th>300</th>
<th>320</th>
<th>340</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mM</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5 mM</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10 mM</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20 mM</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 3: UV-Vis spectral changes in terbuthylazine upon addition of different concentrations of HP-β-CD at 25 ± 2°C: (— light gray) 0 mM; (— gray) 5 mM; (— dark gray) 10 mM; and (— black) 20 mM.

Upon addition of increasing concentrations of the cyclodextrins (β-CD and HP-β-CD), the absorption maximum of terbuthylazine at 222 nm increases in intensity which can be a consequence of the inclusion complex formation. The results obtained for terbuthylazine in the absence and presence of HP-β-CD are shown in Figure 3.

3.2.2. Differential Scanning Calorimetry (DSC). DSC is the most largely used thermal method for the investigation of solid-state interactions between guest molecules and CDs. The DSC profiles of pure components (terbuthylazine, HP-β-CD) and binary systems (physical mixture and inclusion complex) are shown in Figure 4. The thermal curve obtained for terbuthylazine is typical of a crystalline anhydrous substance with a sharp fusion endotherm at 177.2°C, corresponding to the melting point of the herbicide, followed by a liquid-gas-phase transition process at 273.2°C[22]. The first endotherm peak observed around 100°C for HP-β-CD corresponds to dehydration process, followed by an irreversible solid-solid phase transition at 260°C and, finally, to a degradation process, which took place at around 330°C. The thermal curve of the physical mixture is the sum of the curves of the pure components, presenting the CD dehydration band and the terbuthylazine melting peak. The thermal curve obtained for the solid inclusion complex of terbuthylazine with the cyclodextrins, obtained by kneading method, does not show the herbicide endothermic peak at 177.2°C (Figure 4). The same pattern was observed for terbuthylazine/β-CD complex. The complete disappearance of the crystalline melting peak of terbuthylazine in the DSC curve of the complexes can be assumed as an evidence of the insertion of the herbicide molecule inside the CDs cavity.

3.2.3. Fourier Transform Infrared Spectroscopy (FTIR). FTIR is widely used in the study of guest-CD solid complexes since the occurrence of changes in the characteristic bands of the guest molecule spectrum (broadening, variations in peak intensity, and/or shifts in their wavenumber) can be an indication of complex formation. Figure 5 illustrates the FTIR spectra of β-CD, HP-β-CD, terbuthylazine, and the inclusion complexes. IR spectra of β-CD and HP-β-CD both showed characteristic bands belonging to oligosaccharides: 3401 cm⁻¹ (O–H stretching vibration), 2930 cm⁻¹ (C–H stretching vibration), 1640 cm⁻¹ (O–H bending vibration), and 1157 cm⁻¹ (C–O stretching vibration). Terbuthylazine is characterized by the appearance of bands at 3261 cm⁻¹ (N–H stretching), 3116 cm⁻¹ (NH····N combination band), 1618 cm⁻¹ (triazine ring vibration), 1545 cm⁻¹ (N–H deformation), 1398 cm⁻¹ (C–C aliphatic, C(CH₃)₃), and 1224 cm⁻¹ (C–C aliphatic).

The spectra of physical mixtures of terbuthylazine with native and modified β-cyclodextrin were almost the sum of pure components spectra, and no significant variations of the drug FTIR bands were observed. On the contrary, changes in the FTIR spectra were observed after the inclusion complexes of terbuthylazine and cyclodextrins were formed (Figure 5). In both cases, the band at 1545 cm⁻¹ assigned to N–H deformation shifted to 1552 cm⁻¹ and its intensity significantly decreased in the inclusion complex. Although all other peaks decrease in their intensity, they showed insignificant shifts, considering the spectral resolution used. This data seems to show that the inclusion of TBA in the cyclodextrins occurs through the N-ethyl side chain, which makes the interaction more evident for the N–H deformation band. These results are consistent with the data from NMR studies (see next section). The changes that occurred in IR spectra of samples indicated the formation of inclusion complexes in solid state.

3.2.4. Nuclear Magnetic Resonance (NMR) Analysis. NMR is a technique that is often used in the study of cyclodextrin...
inclusion complexes since it can provide information about the presence of guest-host interactions and the stoichiometry of the inclusion process [23–26]. H3’ and H5’ protons of glucose (or modified glucose) units of cyclodextrins are facing the interior of the CD cavity whereas H6’ protons are located in its rim. All the other protons (H1’, H2’, and H4’) are located outside the cavity [27, 28]. The guest-host inclusion process will produce variable changes in the chemical shifts (δ) of some hydrogens belonging either to the ligand or the CD. In fact, if the chemical environment is affected by the inclusion of a compound in CD, the chemical shifts of the hydrogens of the internal surface of the CDs cavities (H3’ and H5’) will change significantly, whereas the external surface hydrogens (H1’, H2’, and H4’) will remain mainly unaffected.

Accordingly, additional data supporting the inclusion of terbutylazine (TBA) in the cavity of CDs was obtained by proton nuclear magnetic resonance spectroscopy (1H-NMR). The formation of TBA/CDs complexes can be established by determining the chemical shift displacements (Δδ) of the proton signals of the guest (TBA) and the hosts (CDs) after complexation. When TBA is incorporated in CD, the hydrogen atoms located inside the cavity (H3’ and H5’) should experience significant changes in their chemical shift (δ) values when compared to the hydrogens outside the cavity. Simultaneously, hydrogens of TBA that interact more closely with the cavity should also be the ones that experience more noteworthy displacements.

In summary, the formation of an inclusion complex can be established from the comparison of the chemical shifts of the guest before and after interaction with CDs. The complete

Table 2: 1H NMR chemical shift (δ) data of TBA, β-CD, and TBA/β-CD complex (see Scheme 1).

<table>
<thead>
<tr>
<th>H assignment</th>
<th>δ TBA (DMSO)</th>
<th>δ β-CD (DMSO)</th>
<th>δ TBA/β-CD (DMSO)</th>
<th>Δδ</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH3</td>
<td>3.244</td>
<td>—</td>
<td>3.370</td>
<td>0.126</td>
</tr>
<tr>
<td>CH3’</td>
<td>1.100</td>
<td>—</td>
<td>1.067</td>
<td>−0.033</td>
</tr>
<tr>
<td>H1’</td>
<td>—</td>
<td>5.708</td>
<td>5.708</td>
<td>0.000</td>
</tr>
<tr>
<td>H3’</td>
<td>—</td>
<td>5.661</td>
<td>5.654</td>
<td>−0.007</td>
</tr>
<tr>
<td>H5’</td>
<td>—</td>
<td>4.828</td>
<td>4.854</td>
<td>0.026</td>
</tr>
<tr>
<td>H6’</td>
<td>—</td>
<td>4.434</td>
<td>4.432</td>
<td>−0.002</td>
</tr>
<tr>
<td>H2’</td>
<td>—</td>
<td>3.642</td>
<td>3.640</td>
<td>−0.002</td>
</tr>
<tr>
<td>H4’</td>
<td>—</td>
<td>3.566</td>
<td>3.568</td>
<td>0.002</td>
</tr>
</tbody>
</table>

NMR proton assignment for β-CD and HP-β-CD has already been reported, and the data obtained during this work are in good agreement with previous reported results [29, 30].

1H NMR spectra of TBA, β-CD, and the inclusion complex of TBA with β-CD in DMSO-d6 are shown in Figure 6. The chemical shift (δ) data of TBA and β-CD before and after the formation of inclusion complex were listed in Table 2. A positive Δδ result is an evidence of downfield displacements while a negative one supports upfield displacements. The significant chemical shift displacements found in the spectra of TBA/β-CD sample, when comparing with free β-CD (host) (Table 2), point out the occurrence of a complexation process.
From the data analysis one can conclude that CH$_3$ protons from TBA undergo upfield displacements in the presence of cyclodextrin while CH$_2$ protons experience downfield displacements. These findings are due to host-guest interactions, which cause anisotropic effects, occurring in the CD cavity [31, 32]. In fact, the most important changes were observed for N-ethyl side chain, namely, with CH$_2$ and CH$_3$ protons, indicating that this part of TBA is deeply included in the CD. The previous assumptions are also sustained by the downfield displacements observed for H$_5$ protons of β-CD cavity and upfield displacements for H$_3$. These shielding and deshielding effects on these particular hydrogens on the
cavity, along with no significant changes on the protons of the external surface of CD, are consistent with host-guest interaction.

The same $^1$H NMR spectroscopy study was also performed for TBA/HP-β-CD inclusion complex (Figure 7). The chemical shift data ($\delta$) of free TBA, HP-β-CD, and TBA/HP-β-CD complex are presented in Table 3. The observed chemical shift displacements present in the TBA/HP-β-CD complex spectra, when compared to that found in free TBA and HP-β-CD, suggest the occurrence of interactions between TBA and cyclodextrin. The variation of the chemical shifts of the hydrogen atoms (H3' and H5') of the CD in the complex is a clear indicative of the inclusion of TBA inside of HP-β-CD cavity. The upfield chemical shift of these hydrogens is coherent with the increase in electron density inside the cavity. TBA inclusion is also highlighted by the neglectable displacement effects on chemical shifts of the hydrogen atoms located outside of the cavity of HP-β-CD. In the presence of cyclodextrin the TBA protons exhibit significant upfield and downfield shifts that are more evident for the N-ethyl side chain of TBA. The data support the hypothesis that the protons of this group are placed inside the HP-β-CD cavity.

4. Conclusions

The inclusion process of terbuthylazine, an herbicide with limited solubility, with native and a modified β-cyclodextrin was investigated in both solid state and aqueous solution. Phase solubility studies indicate that the solubility of terbuthylazine is significantly increased in the presence of both cyclodextrins, β-CD, and HP-β-CD. Information obtained using different analytical techniques showed that solid terbuthylazine/β-CD and terbuthylazine/HP-β-CD
### Table 3: \(^1\)H NMR chemical shift (\(\delta\)) data of TBA, HP-\(\beta\)-CD, and TBA/HP-\(\beta\)-CD complex (see Scheme 2).

<table>
<thead>
<tr>
<th>H assignment</th>
<th>(\delta) TBA ((\text{CD}_3\text{OD}/\text{CDCl}_3))</th>
<th>(\delta) HP-(\beta)-CD ((\text{CD}_3\text{OD}/\text{CDCl}_3))</th>
<th>(\delta) TBA/HP-(\beta)-CD ((\text{CD}_3\text{OD}/\text{CDCl}_3))</th>
<th>(\Delta\delta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_2)</td>
<td>3.400</td>
<td>—</td>
<td>3.445</td>
<td>0.045</td>
</tr>
<tr>
<td>t-Butyl</td>
<td>1.426</td>
<td>—</td>
<td>1.430</td>
<td>0.004</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>1.192</td>
<td>—</td>
<td>1.150</td>
<td>-0.042</td>
</tr>
<tr>
<td>H1'</td>
<td>—</td>
<td>5.099</td>
<td>5.097</td>
<td>-0.002</td>
</tr>
<tr>
<td>H3'</td>
<td>—</td>
<td>3.974</td>
<td>3.963</td>
<td>-0.011</td>
</tr>
<tr>
<td>H5'</td>
<td>—</td>
<td>3.830</td>
<td>3.821</td>
<td>-0.009</td>
</tr>
<tr>
<td>H6'</td>
<td>—</td>
<td>3.757</td>
<td>3.757</td>
<td>0.000</td>
</tr>
<tr>
<td>H2'</td>
<td>—</td>
<td>3.520</td>
<td>3.521</td>
<td>0.001</td>
</tr>
<tr>
<td>H4'</td>
<td>—</td>
<td>3.416</td>
<td>3.416</td>
<td>0.000</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>—</td>
<td>1.126</td>
<td>1.126</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**Scheme 2**

inclusion complexes can be prepared at a 1:1 molar ratio by kneading method. NMR data confirm the formation of the TBA/HP-\(\beta\)-CD and TBA/HP-\(\beta\)-CD complexes, synthesized by the kneading method.

The data presented here may be used for the development of novel TBA formulations as CDs have been shown to be effective in increase of the solubility of the herbicide. Therefore, terbuthylazine complexes can contribute to an improvement of the effectiveness of herbicide, namely, its bioavailability, by providing the same effect using a lower dose.

### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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### References


