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ORIGINAL ARTICLE

Inclusion complexes of Schiff bases as phytogrowth inhibitors

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Abstract This article details the preparation, characterization and phytotoxic evaluation of several Schiff base inclusion complexes obtained from β-cyclodextrin and *p*-sulfonic acid calix[6]arene. The inclusion complexes (1:1 molar ratio) were prepared by mixing a 5 mmol L^{-1} aqueous solution (containing 1 % DMSO) of Schiff bases (guests) with aqueous solution (containing 1 % DMSO) of 5 mmol L^{-1} of β-cyclodextrin or *p*-sulfonic acid calix[6]arene (hosts). The host–guest systems were characterized via a series of NMR experiments. The ability of the complexes to interfere with the radicle elongation of *Sorghum bicolor* (dicotyledonous species) and *Cucumis sativus* (monocotyledonous species) was evaluated. After 48 h, the inclusion complexes inhibited the radicle elongation of both species from 11 to 56 %. The formation of inclusion complexes was also investigated theoretically by molecular dynamics simulations in aqueous solution through implicit approach. Based on the experimental observation, the phytotoxic activity evaluated can be attributed to the formation of host–guest systems. This was supported by the theoretical findings based on stable interaction energy analyses for all the studied supramolecular systems.

Keywords Schiff base · Calix[*n*]arenes · Cyclodextrin · Phytotoxicity · Host–guest systems · Molecular dynamics

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Introduction

Cyclodextrins (CD) are oligosaccharides made up of six (α), seven (β), or eight (γ) *D*-glupyranoses linked by α-(1,4)-bonds [1–5]. In the pharmaceutical industry, these host molecules are widely used to enhance water solubility, chemical stability, bioavailability of insoluble or poorly soluble drugs, as well as to reduce toxicity and control the release rate of active compounds [6–9]. These effects are related to high molecular recognition ability of a variety of guest molecules including compounds of agrochemical interest [10–26]. Calix[*n*]arenes are another class of oligomer host molecules, constructed by linking phenol residues via methylene groups. Calix[*n*]arenes with various cavity sizes have been designed, each presenting conformation

isomers, with frequently modified phenolic hydroxy groups. As a result, calix[*n*]arenes have been used as platforms for the design and synthesis of biological active compounds [27–32].

Schiff bases are aldehyde- or ketone-like compounds in which the carbonyl group is replaced by an imine or azomethine group. They are widely used industrially, exhibiting a broad range of biological activities, such as antifungal, antibacterial, anti-malarial, anti-proliferative, anti-inflammatory, anti-viral, and anti-pyretic properties [33]. Despite the pharmacological properties of Schiff bases, only one study on their potential agrochemical properties has been reported. Huneck et al. [34] found that only a few Schiff bases inhibited wheat, rye, and barley seedlings. Although they presented varied biological activities, a limiting factor was insolubility or poor stability in water [35, 36].

Our group has studied compounds with phytotoxic activity and the host–guest chemistry of cyclodextrins and calix[*n*]arenes [37–43]. A natural extension of our study would be to evaluate the use of *β*-cyclodextrin and *p*-sulfonic acid calix[6]arene to increase the water solubility of Schiff bases as well as assess the phytotoxic activity of the resulting inclusion complexes. Thus, the aim of this study was to prepare and investigate the inclusion complex formed by *β*-cyclodextrin (**1**), *p*-sulfonic acid calix[6]arene (**2**) and Schiff bases **3**–**6** (Fig. 1). The phytotoxic effects of the host–guest systems on *Sorghum bicolor* and *Cucumis sativus* were investigated. In addition, theoretical investigation through molecular dynamics (MD) was carried out for all possible inclusion complexes to estimate relative stabilization energies and discuss host–guest formation.

Materials and methods

Chemicals and reagents

All reagents were of analytical grade. *β*-Cyclodextrin (99 %) and D_2O (99.75 %) were purchased from Aldrich; *p*-sulfonic acid calix[6]arene (**2**) was synthesized as previously described [44, 45].

Preparation of inclusion complexes

Inclusion complexes **1/3–6** or **2/3–6** in a 1:1 molar ratio were obtained by mixing a 5 mmol L^{-1} aqueous solution (containing 1% DMSO) of compounds **3**, **4**, **5**, or **6** with aqueous solution (containing 1 % DMSO) of 5 mmol L^{-1} of host **1** or **2**. Solutions with the following guest–host ratios were prepared: 15:0; 12:3; 10.5:4.5; 9:6; 7.5:7.5; 6:9; 4.5:10.5 and 3:12. In these solutions, the total number of moles of the species was kept constant while the mole fraction of each species varied. Each system was stirred for 24 h at room temperature. The ideal mixing time to equilibrium was determined for each system (data not presented). For each solution, NMR spectra were recorded as described in the NMR spectroscopy section.

NMR spectroscopy

All experiments were performed at 298 K in D_2O containing 1 % DMSO-d_6. Routine 1D ^1H spectra were acquired in a MERCURY-300 Varian spectrometer operating at 300.069 MHz for ^1H (64 k data points, 30° excitation pulse duration of 2.2 μs, spectral width of 6 kHz,

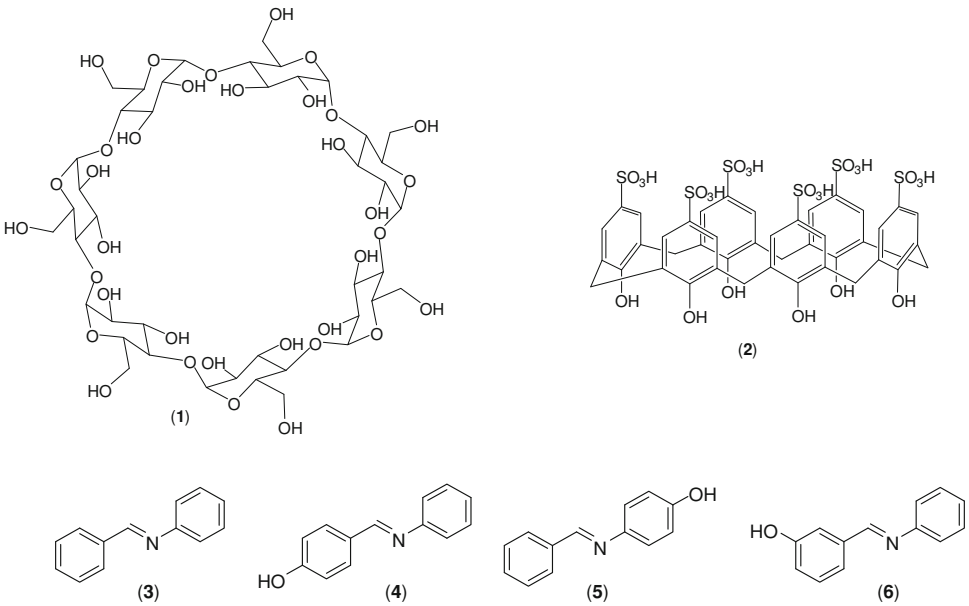


Fig. 1 Structures of *β*-cyclodextrin (**1**), *p*-sulfonic acid calix[6]arene (**2**) and the Schiff bases: *N*-benzylideneaniline (**3**), 4-(phenylimino)methyl)phenol (**4**), 4-(benzylideneamino) phenol (**5**) and 3-(phenylimino)-methyl)phenol (**6**)

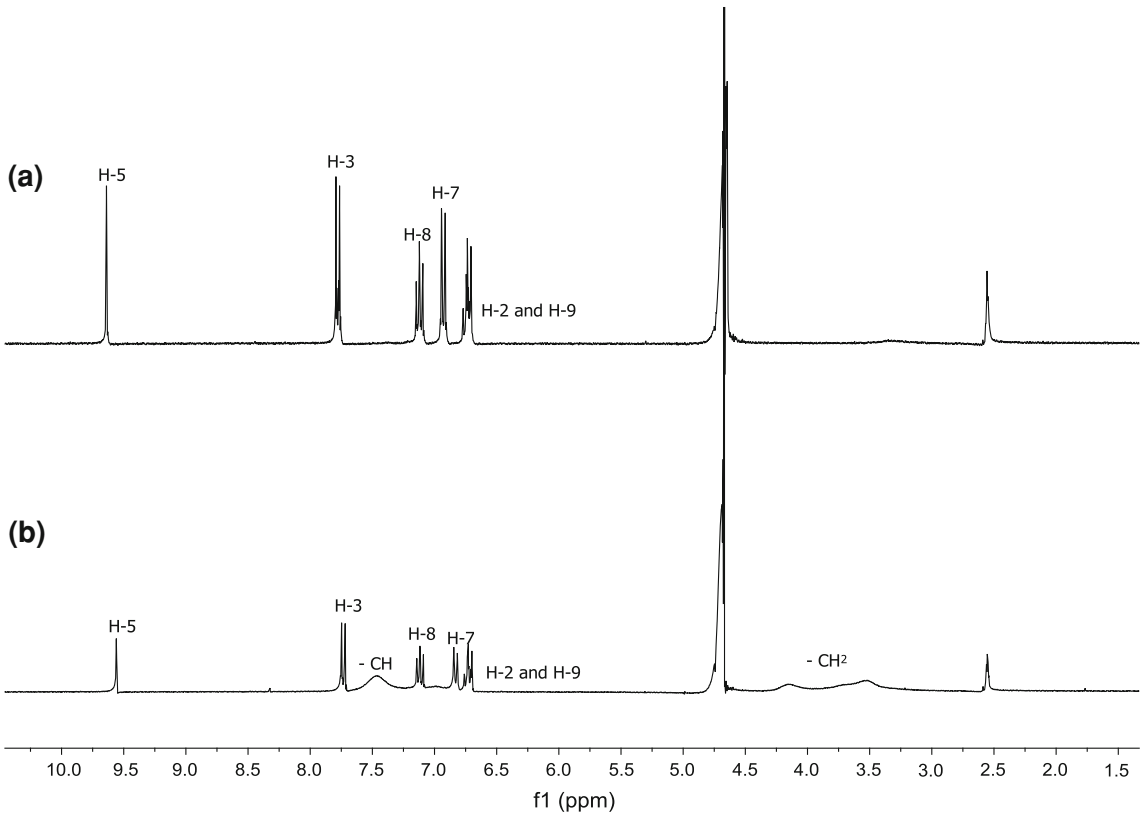


Fig. 2 ^{1}H NMR spectra (300.069 MHz; D_2O containing 1 % DMSO-d_6;δ_{HDO} 4.67; 298 K, 5 mmol L^{-1} each) of the pure compound **4** (**a**) and **2/4** complex (**b**)

acquisition time of 3.3 s and relaxation delay of 10 ms) in a 5 mm probe with inverse detection mode at room temperature, unless stated otherwise. The chemical shifts were calibrated considering the δ_{HDO} signal (4.67) as reference.

Determination of complexation stoichiometry

Job plots were prepared with 5 mmol L^{1-} stock solutions of compounds (**1**), (**2**), (**3**), (**4**), (**5**), and (**6**) [46].

Synthesis of Schiff bases

Schiff bases **3**–**6** were prepared by the condensation of the appropriate amines with benzaldehydes in toluene using a Dean Stark apparatus as previously described [35]. The solvent was evaporated, and the compounds purified by crystallization.

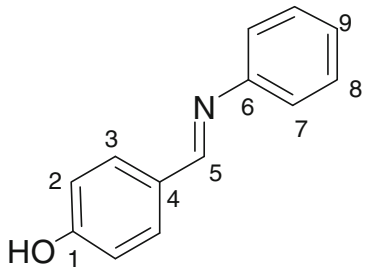
Phytotoxic evaluation: radicle elongation assay on sand with *S. bicolor* and *C.* seeds

Sorghum bicolor and *C. sativus* seeds were placed on germination paper imbibed with distilled water in a germination chamber with a saturated relative humidity, at 301 ± 1 K for 24 h. Solutions containing 5×10^{-4} mol L^{-1} of compounds **1** or **2**, or inclusion complexes **1/3**–**6** and **2/3**–**6** (molar ratio 1:1) were prepared as previously described to adsorb acid-washed sand (0.125 mL g^{-1}) in Petri dishes (id = 9 cm and height = 3 cm). Groups of seven germinated *S. bicolor* or *C. sativus* seeds were placed on each plate. The Petri dishes were sealed with parafilm® and incubated at 301 ± 1 K, in the dark at 75° inclination. After 24 h and 48 h, root length was measured to the nearest millimeter. All treatments were replicated four times in a completely randomized design. The percentage of radicle growth inhibition or stimulation was calculated in relation to the radicle length of the control, treated with distilled water containing 1 % DMSO. The results were analyzed by ANOVA and Scott–Knott's multiple-range tests at $P \leq 0.05$ by using the software GENES (Genetics and Statistical Analysis. Version 2007.0.0—Universidade Federal de Viçosa, Viçosa—MG, Brazil).

Theoretical calculations

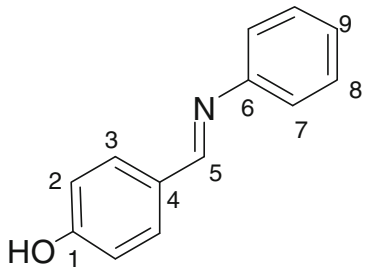
Molecular dynamics (MD) simulations in aqueous media were carried out for the Schiff bases and all possibly host–guest systems using the GAFF (Generalized AMBER force field) as implemented in the AMBER 10 package [47]. Cutoff radii for van der Waals and Coulombic electrostatic interactions were 8 and 20 Å, respectively. All C–H and

Table 1 ^{1}H NMR chemical shifts (δ) and chemical shift differences ($\Delta\delta = \delta_{\mathbf{4}\ \text{free}} - \delta_{\mathbf{4}\ \text{complex}}$) of the pure compound **4** and its complexes with β-cyclodextrin **1/4** (5 mmol L^{-1} samples, 298 K)



Hydrogens	4 δ	1/4 δ	1/4 $\Delta\delta = \delta_{free} - \delta_{complex}$
H-**2** and H-**9**	6.74	6.78	−0.04
H-**7**	6.93	6.94	−0.01
H-**8**	7.12	7.16	−0.04
H-**3**	7.78	7.80	−0.02
H-**5**	9.64	9.56	0.08

Table 2 ^{1}H NMR chemical shifts (δ) and chemical shift differences ($\Delta\delta = \delta_{\mathbf{4}free} - \delta_{\mathbf{4}complex}$) of the pure compound **4** and its complexes with *p*-sulfonic acid calix[6]arene **2/4** (5 mmol L^{-1} samples, 298 K)



Hydrogens	4 δ	2/4 δ	2/4 $\Delta\delta = \delta_{free} - \delta_{complex}$
H-**2** and H-**9**	6.74	6.78	−0.04
H-**7**	6.93	6.83	0.10
H-**8**	7.12	7.12	0.00
H-**3**	7.78	7.74	0.04
H-**5**	9.64	9.56	0.09

O–H bond lengths were fixed using the SHAKE algorithm. Based on our previous work [48] all MD runs were initiated at 5 K and warmed up to 50 K during 10 ps and equilibrated for 100 ps. Subsequently, five similar consecutive MD steps were executed. In each step, the structures were warmed up to 50 K along 10 ps and equilibrated during 100 ps. All MD simulations with length of 1,000 ps had a time step of 1.5 fs and were performed at 298.15 K. The solvent effect was included within the Born solvation model, as currently implemented in AMBER 10 package [49]. β-Cyclodextrin starting geometry was obtained from crystallographic data from which hydration water molecules were removed, prior to MD simulations [50]. Other starting geometries were constructed using appropriate molecular modeling software. The aqueous MD interaction energy (ΔE) of each host–guest system formed with β-cyclodextrin (**1**) or *p*-sulfonic acid calix[6]arene (**2**) was evaluated from the differences in the average total potential energy of the complexes and isolate host and guest molecules. For all studied host–guest systems, two distinct guest orientations were investigated.

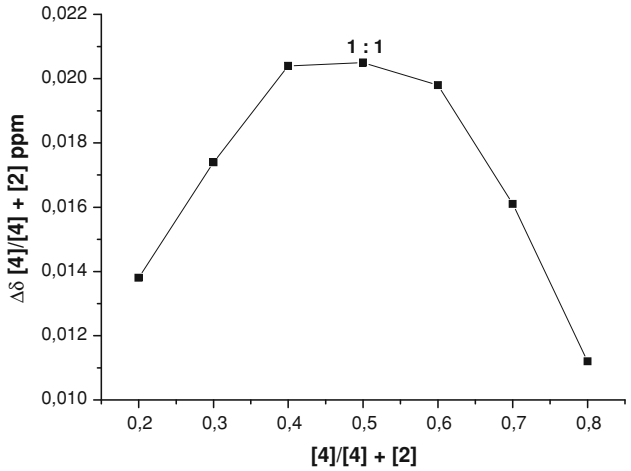


Fig. 3 Job plots for the complex formed between Schiff base **4** and *p*-sulfonic acid calix[6]arene (**2**)

Results and discussion

The Schiff bases **3–6** were prepared by condensing appropriate amines with benzaldehydes in toluene using a Dean Stark apparatus according to our previous publication [35]. The synthesized compounds were fully characterized by IR and NMR spectroscopy and elemental analysis.

The inclusion complexes between β-cyclodextrin (**1**), *p*-sulfonic acid calix[6]arene (**2**) and the Schiff bases **3–6** were prepared by stirring appropriate amounts of the host compounds and the Schiff bases in aqueous solution containing 1 % DMSO for 24 h. Clear solutions were obtained in all cases. The degree of complexation between β-cyclodextrin (**1**) or *p*-sulfonic acid calix[6]arene (**2**) and Schiff bases **3–6** was determined by NMR in aqueous solutions.

We started our investigation by analyzing the complexation-induced hydrogen chemical shifts ($\Delta\delta$), in the **2/4** complex and comparing these values with those for the free Schiff base **4** (Fig. 2). The host hydrogens were observed as a single resonance due to the fast exchange between a free guest and a complexed one on the NMR time scale.

Table 3 Effect of *β*-ciclodextrin (**1**), *p*-sulfonic acid calix[6]arene (**2**) and Schiff base inclusion complexes **1/3–6** and **2/3–6** on radicle growth of *Sorghum bicolor* seedlings after 24 and 48 h

Compound/complex 0.125 mL g^{-1}	*S. bicolor*			
	24 h		48 h	
	Radicle length (cm)a	Inhibition (%)	Radicle length (cm)a	Inhibition (%)
1	1.76a	9	5.83a	No inhibition
2	1.55b	20	4.81b	11
1/3	2.00a	No inhibition	5.03b	7
1/4	1.17d	39	2.41e	56
1/5	1.07d	45	4.82b	11
1/6	1.85a	4	5.61a	No inhibition
2/3	1.43c	26	4.34c	20
2/4	1.61b	17	4.49c	17
2/5	1.12d	42	3.22d	41
2/6	1.55b	20	4.24c	22
Control	1.93a	0	5.43a	0

[a] Means followed by same letter in the columns do not differ by the Scott–Knott's test at $P \leq 0.05$

Table 4 Effects of *β*-cyclodextrin (**1**), *p*-sulfonic acid calix[6]arene (**2**) and Schiff base inclusion complexes **1/3–6** and **2/3–6** on radicle growth of *Cucumis sativum* seedlings after 24 and 48 h

Compound/complex 0.125 mL g^{-1}	*C. sativum*			
	24 h		48 h	
	Radicle length (cm)[a]	Inhibition (%)	Radicle length (cm)[a]	Inhibition (%)
1	2.16b	24	4.89a	16
2	2.39b	16	5.70a	2
1/3	1.85c	35	4.33b	26
1/4	2.26b	20	5.28a	10
1/5	2.19b	23	5.18a	11
1/6	2.15b	24	4.98a	15
2/3	1.92c	32	4.13b	29
2/4	2.22b	22	5.23a	10
2/5	1.77c	37	4.17b	29
2/6	2.19b	23	4.57b	22
Control	2.83a	0	5.84a	0

[a] Means followed by same letter in the columns do not differ by the Scott–Knott's test at $P \leq 0.05$

Table 5 Interaction energies evaluated for all host–guest systems formed with the Schiff base guests **3**, **4**, **5,** or **6** and *β*-cyclodextrin (**1**) or *p*-sulfonic acid calix[6]arene (**2**) hosts

Host–guest complex	Interaction energy (ΔE^a) in kcal mol^{-1}
1/3	-17 ± 9
1/4	-15 ± 9
1/5	-16 ± 9
1/6	-16 ± 9
2/3	-16 ± 8
2/4	-16 ± 8
2/5	-14 ± 8
2/6	-15 ± 8

[a] Average data evaluated from 1,000 ps MD simulation at 298.15 K within the Born solvation model

The analysis of chemical shifts revealed that the hydrogens of Schiff base **4** presented a small variation of chemical shifts in the presence of *p*-sulfonic acid calix[6]arene (≤0.1 ppm), as well as in the presence of *β*-cyclodextrin (≤0.08 ppm), as it can be seen in Tables 1 and 2.

The stoichiometries for the **1/4** and **2/4** complexes were found to be 1:1, determined by Job plot's method. Figure 3 shows a Job's plot for the complex **2/4**.

The trends described above concerning complexes **1/4** and **2/4** were similar to the other inclusion complexes.

The biological effects of the host compounds **1** and **2**, as well as the complexes (**1/3–6**) and **2/3–6** screened for phytotoxicity are summarized in Tables 3 and 4.

Based on the data, dicotyledonous *S. bicolor* species presented a slight radicle reduction when treated with host

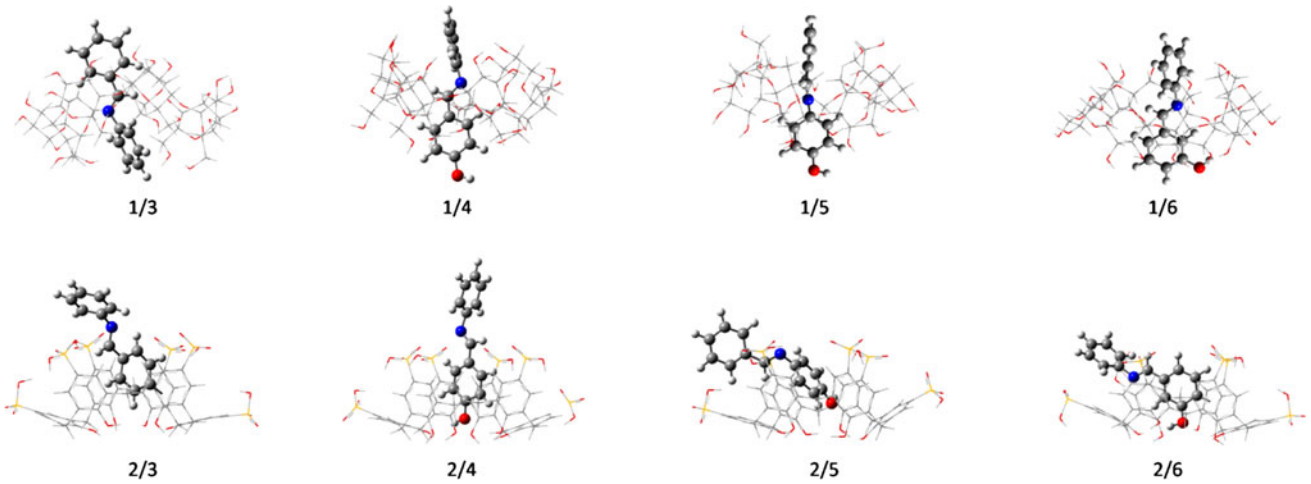


Fig. 4 Final MD geometries obtained after 1,000 ps of simulation at 298.15 K. The solvent effect has been included within the Born solvation model, as currently implemented in AMBER 10 package

compound **2**, while no effect was observed with compound **1**. Radicle growth of monocotyledonous *C. sativus* species was initially (24 h) affected by both compounds **1** and **2**, but this effect was no longer noticeable after 48 h. Therefore, these compounds can be considered good candidates for active carrier systems in herbicide formulations. It should be mentioned that such studies are very important for both pharmaceutical and agrochemical applications [51].

Focusing on the host–guest systems, complex **1/4** promoted the highest radicle reduction in *S. bicolor* (56 % inhibition after 48 h), followed by complex **2/5** (about 41 % inhibition) (Table 3). According to Table 4, the species *C. sativus* was more affected by the complexes **1/3**, **2/3** and **2/5** (about 30 % inhibition).

The data in Tables 3 and 4 suggest that complex **2/5** can be an unspecific phytotoxic combination, acting indiscriminately in *S. bicolor* and *C. sativus*. The complexes containing compound **3** (**1/3** and **2/3**) appear to be more selective to *C. sativus,* whereas complex **1/4** was more selective to *S. bicolor*. The complexes containing compound **6** showed the lowest activities (about 20 %). In general, all the treatments were less effective on *C. sativus*.

To support the experimental evidence on the formation of host–guest systems, all possible inclusion compounds were theoretically investigated. Two distinct guest orientations were tested and no significant differences were found concerning guest orientation within the MD approach. The simulation data has been summarized in Table 5.

In light of the approximations of the model used, it can be stated, based on Table 5 data, that all the associations studied form stable host–guest systems. In addition, according to the average values, no host–guest system can be identified as the most stable one.

Bearing in mind that the β-cyclodextrin host (**1**) or *p*-sulfonic acid calix[6]arene (**2**) do not possess significant phytotoxic activities (see Tables 3, 4), it can be stated that the active compounds correspond to the host–guest systems depicted in Fig. 4. Furthermore, it must be mentioned that, in the study by Huneck and co-workers, the Schiff bases **3**, **4** and **5** were inactive against wheat, rye, and barley [34]. Although the plant species used in this study to evaluate the phytotoxicity of the inclusion complexes were different, improved biological activity of the Schiff bases was demonstrated.

Conclusion

In this paper, we have investigated the formation of inclusion complexes between β-cyclodextrin (**1**), *p*-sulfonic acid calix[6]arene (**2**) and Schiff bases **3**–**6**. Due to the low activity of compounds **1** and **2** and very low solubility of the Schiff bases studied, the observed phytotoxic activity was ascribed to host–guest systems formed between the aldimines and host molecules **1** and **2**. This is supported by theoretical investigation identifying favorable interaction energies for all the studied host–guest systems through MD simulations. This inclusion complexation should be regarded as an important step in the design of novel formulations of Schiff bases for agrochemical purposes.

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