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pH-controlled release of auxin plant hormones from cucurbit[7]uril macrocycle

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Abstract

Background: The influence of pH on the formation of host-guest complexes between the cucurbit[7]uril (CB[7]) macrocyclic host and three auxin plant hormones, namely indole-3-acetic acid (IAA), 2-naphthalene acetic acid (2-NAA), and 2,4-dichlorophenoxyacetic acid (2,4-D), was studied by ¹H NMR and relaxation experiments.

Results: Only protonated auxins formed inclusion complexes with CB[7], exhibiting preferential encapsulation of the aromatic part inside the host cavity, and orientation of the carboxyl group towards the carbonyl-laced portals of CB[7]. At pH values above the auxin pK_a values, the guest molecules were negatively ionized and were no longer retained within the macrocyclic host, suggesting that a pH-controlled release of auxin guests from the CB[7] host is possible.

Conclusions: The development of a technology based on the use of cucurbit[n]urils for the pH-controlled release of auxin molecules in plant systems represents an opportunity to exploit these macrocyclic compounds in a variety of agricultural applications.

Keywords: Supramolecular chemistry; Host-guest systems; Cucurbiturils; Agrochemicals; NMR

Background

Food security is an incumbent social problem, exacerbated by an ever-increasing population, decreasing arable land, and ecological adversities such as soil erosion and climate change. Chemical and biochemical technologies to support crop production could therefore play a vital role towards food security in the coming years. In this context, a technology based on host-guest complexation of bioactive compounds by macrocyclic host molecules in aqueous media may represent a controlled release system that may achieve efficient and balanced regulation of plant growth and increase of crop yields [1]. Such an innovative technology may become important in sustainable agriculture to substitute inefficient application practices of agrochemicals resulting in their hazardous and expensive dissipation in the environment [2].

Auxin is the generic name for a class of plant hormones active in coordinating many growth processes in the life cycle of plants. Indole-3-acetic acid (IAA) is the most abundant and potent native auxin active in plants [3]. 2-Naphthalene acetic acid (2-NAA) is used as a

mimic for 1-naphthalene acetic acid synthetic auxin, which is commonly applied to stimulate the rooting potential of plant cuttings or to prevent fruit drop in orchards. The widely used 2,4-dichlorophenoxyacetic acid (2,4-D) is a synthetic plant growth regulator stimulating responses similar to those of natural auxins. Its auxin activity is mostly relevant at low concentrations (20 to 40 mg L⁻¹), while it becomes phytotoxic at relatively high concentrations [1].

Among many structurally and functionally different synthetic macrocycles, cucurbit[n]urils (CB[n]) are an interesting family of host molecules [4-9] consisting of a hydrophobic inner cavity with two identical carbonyl-laced portals. In addition to the hydrophobic interactions within the cavity, the polar carbonyl groups at the portals are capable of stabilizing host-guest complexes by forming hydrogen bonds and ion-dipole and dipole-dipole interactions with appropriate guests [4,5,10]. Research on the host-guest chemistry of CB[n] has attracted great attention on account of the potential application of these materials in the fields of biomedicine [11,12], photochemistry [13], materials science, and nanotechnology [4,5]. In particular, its higher water solubility (approximately 20 mM) [4,14] and intermediate cavity volume (210 Å³) [15] make CB[7] (Figure 1) an attractive host for complexation of guest molecules used in biology and medicine [5,6,16]. Such host-guest

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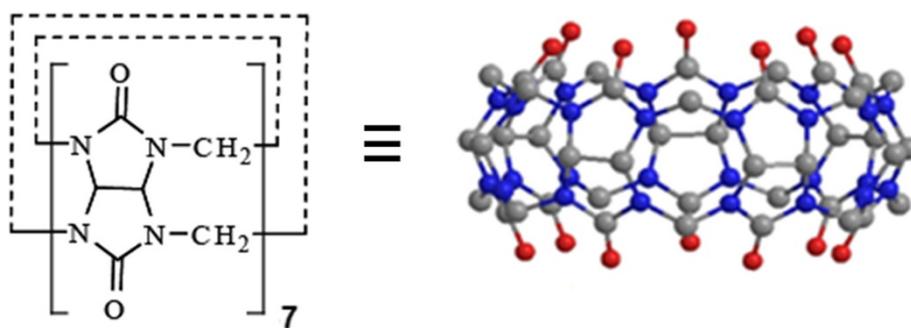


Figure 1 Structure of cucurbit[7]uril.

complexes have recently received considerable interest [17-20] as nontoxic drug delivery and controlled release systems. However, while a notable amount of literature reports are concerned with the interaction of neutral and cationic [21-25] guest molecules with cucurbit[*n*]urils, relatively little is known on the noncovalent complexation between weak organic acids and macrocyclic hosts.

Our aim was thus to study, by proton nuclear magnetic resonance (^1H NMR) spectroscopy, the binding that occurs in aqueous solution between the CB[7] macrocyclic host molecule and three weak organic acids of the auxin family, IAA, 2-NAA, and 2,4-D (Figure 2), and their response to changes in pH. To the best of our knowledge, this is the first report in which ^1H NMR relaxation measurements have been directly applied to evaluate auxin's binding properties to cucurbit[*n*]uril in aqueous solution.

Results and discussion

^1H NMR chemical shifts

IAA, 2-NAA, and 2,4-D are weak acids with only one dissociation constant in aqueous solution. Values of pK_a in

water for IAA and 2-NAA are 4.7 and 4.2, respectively, thus leaving these molecules fully protonated and uncharged at $\text{pH} \leq 2.0$ and as negatively charged anions only at $\text{pH} \geq 7.0$. Conversely, the pK_a value of 2.7 for 2,4-D renders the molecule totally ionized and negatively charged already at $\text{pH} \geq 5.0$.

Complexation with CB[7] is reported to shift the pK_a values of encapsulated guests [26,27]. Guests comprising suitable chromophores allow the direct spectrophotometric determination of complexation in the host through shifts in the pK_a values (i.e., the pK_a of guest before and after complexation) [28,29]. With the exception of the IAA-CB[7] complex at pH 1, the lack of distinct absorption maxima in the UV-vis region for complexes involving CB[7] and the other auxin guests prevented the determination of pK_a shifts, by UV-vis spectroscopy under pH changes. Therefore, the pK_a values of the carboxylic group of auxins, before and after CB[7] addition, were determined by a ^1H NMR study following the variation with pH of chemical shifts for protons in the alkyl groups next to the carboxylic moieties [30].

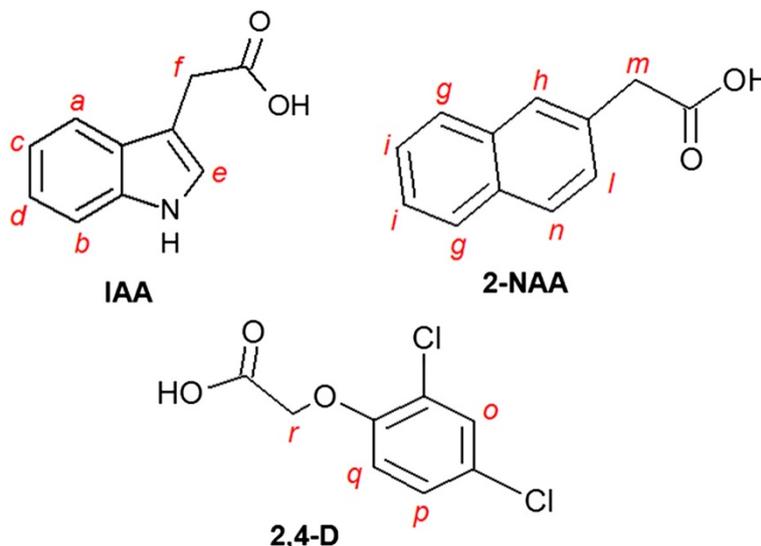


Figure 2 Chemical structure of the auxin guests used in this study.

No significant pK_a shifts were observed for the auxin guests upon addition of CB[7] (results not shown), most likely because the hormone carboxylic acid moieties, which are positioned outside the macrocyclic host, were not affected by changes in the electronic environment. Indeed, it is reported in the literature that when a similar position is adopted by carboxylic acid groups during the encapsulation of weak acids by CB[7], no pK_a shifts can be observed [31-33]. Conversely, an increase of the pK_a values, upon complexation with the CB[*n*] hosts, has been invariably reported at low pH values for guests holding protonated nitrogen-containing functional groups, [34-37] presumably due to stabilization of the protonated moieties by interaction with carbonyl portals in the CB[7] host. This interaction represents an additional binding strength over the hydrophobic forces which already keep the guest neutral forms inside the CB[7] even at higher pH.

The pH titrations of IAA, 2-NAA, and 2,4-D by 1H NMR spectroscopy showed the influence of solution pH on binding interactions between both protonated and anionic forms of auxin molecules and CB[7]. 1H NMR spectra were used to determine the portion(s) of guest molecules located within the hydrophobic cavity, as opposed to those positioned adjacent to the polar carbonyl-laced portals of the cucurbit[*n*]urils [4,5,7]. An upfield shift of a guest proton resonance ($\Delta\delta_{lim} = \delta_{free} - \delta_{bound}$) indicates its average position within the shielding hydrophobic cavity, whereas a downfield shift suggests that the guest proton is near one of the deshielding carbonyl-laced portals [38].

The limiting chemical shift values, $\Delta\delta_{lim}$, for the auxin guests upon addition of one equivalent of CB[7], at selected pH values ranging from 1 to 12 are reported in Table 1. For the protonated IAA, all signals for indole protons exhibited an upfield shift and broadening (Figure 3, spectrum IV), thereby indicating a preferential encapsulation of the indole portion of IAA in the inner cucurbituril cavity. Conversely, the considerably smaller $\Delta\delta_{lim}$ value for the benzyl protons *f* next to the IAA carboxyl group suggested a proximity to the portal (Table 1). These CB[7]-induced shifts are highly suggestive of IAA-CB[7] complex formation, and that association/dissociation of the host-guest complex was fast on the NMR time scale since the observed chemical shifts were a time-weighted average of free and bound proton signals [38].

Since host-guest interactions are very sensitive to structural features, the negative charge produced on the guest molecule by deprotonation of the terminal auxin carboxyl group at high pH may disrupt the stability of the IAA-CB[7] complex. In fact, at high pH values, the IAA protons experienced negligible or downfield shifts (Figure 3, spectrum II) after addition of the macrocycle

Table 1 1H NMR limiting chemical shifts ($\Delta\delta_{lim}$) for protons in IAA, 2-NAA, and 2,4-D

$^1H^a$	pH					
	1.0	3.0	5.0	7.0	9.5	12.0
IAA						
a	0.0055	0.0049	-0.0003	-0.0012	0.0002	-0.0018
b	0.0056	0.0058	0.0024	0.0002	0.0035	0.0024
c	0.0042	0.0045	0.0012	0.0002	0.0012	0.0006
d	0.0054	0.0057	0.0021	0.0005	0.0024	0.0010
e	0.0026	0.0031	-0.0005	-0.0016	0.0000	-0.0009
f	0.0014	0.0021	0.0004	0.0004	0.0022	0.0010
2-NAA						
g	0.0182	0.0003	-0.0008	0.0015	0.0024	-0.0002
h	0.0136	-0.0014	-0.0014	0.0005	0.0010	-0.0096
i	0.0151	-0.0018	0.0000	0.0012	0.0025	-0.0002
l	0.0071	-0.0046	-0.0017	0.0002	0.0008	-0.0015
m	-0.0035	-0.0065	-0.0011	-0.0007	0.0000	-0.0014
n	ND	ND	ND	ND	ND	ND
2,4-D						
o	0.0036	0.0020	0.0007	0.0006	0.0011	0.0004
p	0.0073	0.0010	0.0005	0.0004	0.0006	0.0003
q	0.0039	0.0020	0.0004	0.0000	0.0007	-0.0004
r	ND	0.0008	0.0001	0.0002	0.0003	-0.0009

^aAuxin protons in IAA, 2-NAA and 2,4-D, upon addition of one equivalent of CB[7], and at different solution pH. Letters indicate positions of protons on auxins structure as reported in Figure 2. ND, not determined because it was masked by other signals. The $\Delta\delta_{lim}$ values were calculated as $\delta_{free\ guest} - \delta_{bound\ guest}$.

to the guest solution, thus suggesting that the auxin was outside of the CB[7] cavity and that no more intermolecular interactions occurred between the host and IAA. The absence of binding was likely due to the electrostatic repulsion between the IAA carboxylate negative charge and the carbonyl oxygens on the two electron-rich portals of CB[7], which overcomes any stabilization provided by the CB[7] hydrophobic cavity for the aromatic indole moiety.

In the case of the other two auxin molecules (2-NAA and 2,4-D), the 1H NMR spectroscopic experiments showed similar trends in chemical shift changes upon addition of CB[7] in aqueous solution. Addition of the host to an acidic solution of either 2-NAA or 2,4-D caused the upfield shifts, signal broadening of the guest aromatic protons, and concomitant downfield or negligible shifts of signals for protons near the auxin carboxylic acid group (Figure 4 (spectrum IV) and Figure 5 (spectrum IV)). These observations are consistent with the formation of a complex in which the aromatic core of the guest is accommodated in the hydrophobic cavity of the cucurbit[*n*]uril host, leaving the carboxylic acid near the carbonyl portals of CB[7]. Furthermore, as

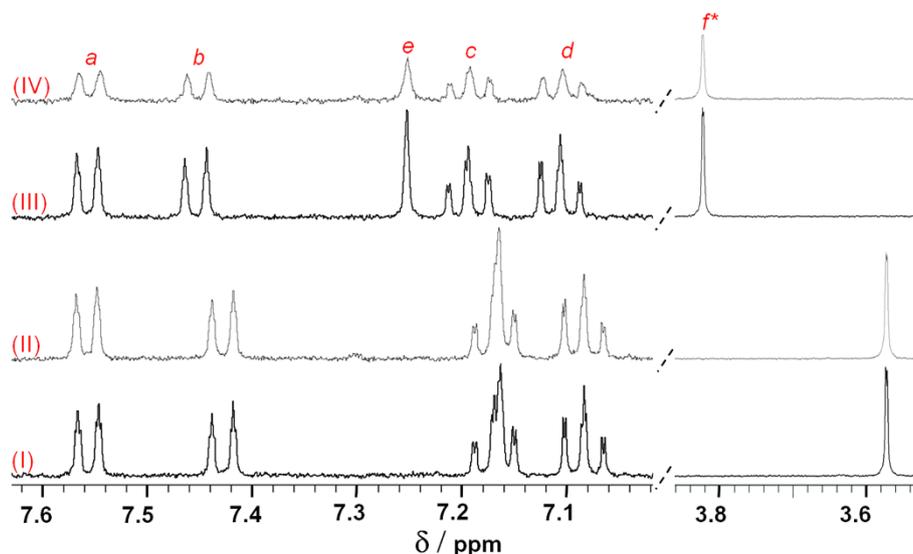


Figure 3 ^1H NMR spectra of 0.4 mM IAA without and with 1.0 equivalent of CB[7]. They were recorded at pH 12.0 (spectra I and II) and pH 1.0 (spectra III and IV). The intensity of the signal marked by the asterisk is four-fold higher than that of the other signals.

reported above for IAA, the deprotonation of the carboxylic acid on 2-NAA and 2,4-D significantly affects the affinity of these molecules toward CB[7]. Indeed, anionic carboxylates are repelled by the negatively polarized carbonyl portals of the macrocycle, leading to complex dissociation (Table 1 and Figure 4 (spectrum II) and Figure 5 (spectrum II)).

The association/dissociation behavior of auxin complexes with CB[7] as a function of pH is in line with the supramolecular chemistry of cucurbit[*n*]urils previously reported [4,5,10]. The adducts of the protonated auxins

with CB[7] are likely stabilized by hydrogen bonds between the host carbonyl portals and the auxins' protonated carboxyl groups. Moreover, the hydrophobic effect that directed the aromatic part of auxins into the hydrophobic cavity of CB[7] was also an important supramolecular driving force for binding in aqueous solution. However, the high pH deprotonation of the carboxylic acid led to an electrostatic repulsion that overcame the hydrophobic affinity of auxins to CB[7]. These findings revealed a completely reversible and pH-switchable binding between important auxin guest molecules and CB[7].

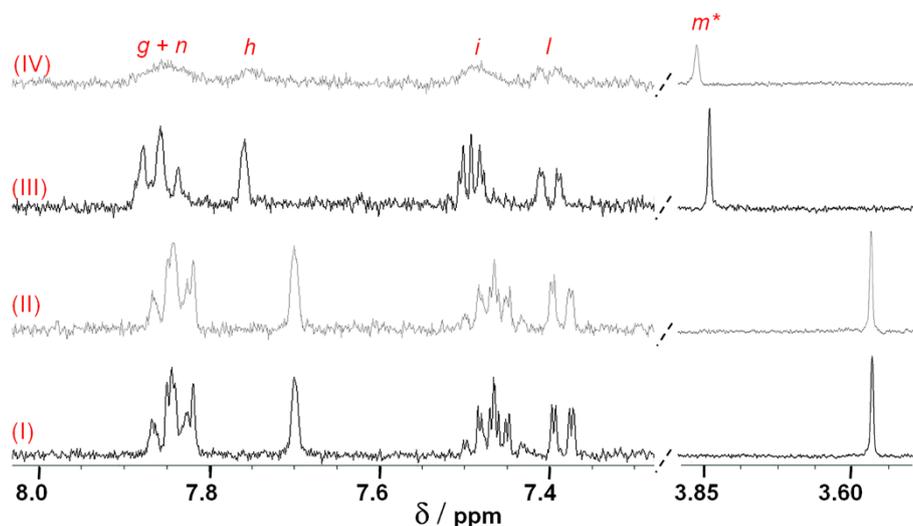


Figure 4 ^1H NMR spectra of 0.4 mM 2-NAA without and with 1.0 equivalent of CB[7]. They were recorded at pH 12.0 (spectra I and II) and pH 1.0 (spectra III and IV). The intensity of the signal marked by the asterisk is four-fold higher than that of the other signals.

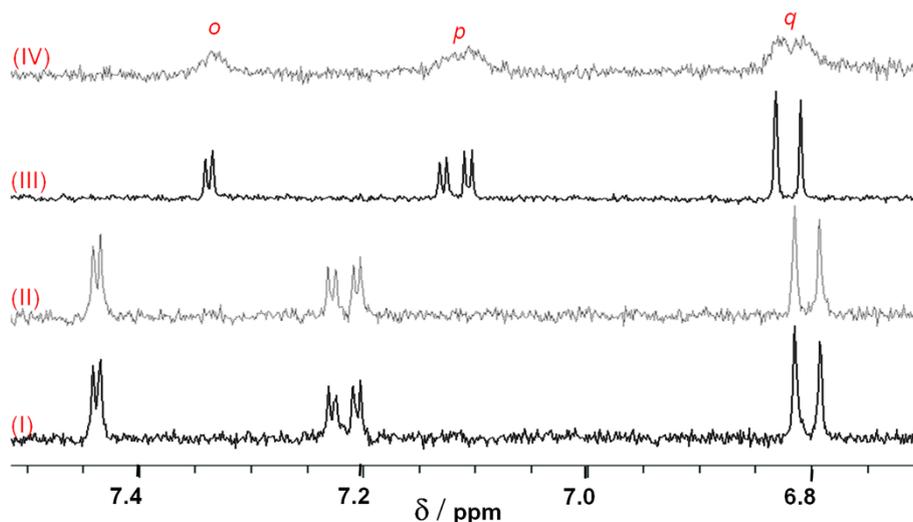


Figure 5 ^1H NMR spectra of 0.4 mM 2,4-D without and with 1.0 equivalent of CB[7]. They were recorded at pH 12.0 (spectra I and II) and pH 1.0 (spectra III and IV). The signal of r proton is not visible in the spectrum because it is overlying the water signal.

^1H NMR relaxation times

Relaxation experiments agreed with results of chemical shift changes observed in ^1H NMR spectra upon pH titrations. The ^1H spin-lattice (T_1) and spin-spin (T_2) relaxation times measured for IAA, 2-NAA, and 2,4-D, in

the absence and presence of CB[7] at pH 1 and 12, are given in Table 2. At pH 1, the addition of 1.0 equivalent of CB[7] caused a considerable decrease in T_1 values of 2,4-D. A significant decrease was also observed for T_2 values of aromatic protons of IAA, 2-NAA, and 2,4-D in

Table 2 T_1 and T_2 relaxation time values for protons of IAA, 2-NAA, and 2,4-D

$^1\text{H}^a$	T_1 (s)				T_2 (s)			
	pH 1.0		pH 12.0		pH 1.0		pH 12.0	
	-CB[7]	+CB[7]	-CB[7]	+CB[7]	-CB[7]	+CB[7]	-CB[7]	+CB[7]
IAA								
a	5.184	5.067	5.342	4.727	3.157	0.384	2.559	2.500
b	7.427	6.766	7.531	6.533	4.690	0.466	2.677	2.547
c	4.512	4.337	6.236	5.765	1.372	0.496	2.535	2.240
d	4.071	3.714	4.014	3.645	1.276	0.402	2.425	2.279
e	9.158	8.244	8.911	7.945	1.986	0.350	3.025	3.025
f	1.681	1.643	1.642	1.617	0.678	0.414	1.398	1.364
2-NAA								
g	3.415	2.063	4.042	2.625	2.351	0.079	2.063	0.803
h	3.114	2.758	4.172	2.405	1.410	0.098	2.483	1.257
i	3.876	2.629	4.252	3.413	1.629	0.078	2.399	1.099
l	4.531	3.075	3.879	3.119	2.108	0.103	2.420	1.852
m	1.447	1.401	3.656	1.853	1.130	0.693	1.266	1.130
n	ND	ND	ND	ND	ND	ND	ND	ND
2,4-D								
o	8.030	3.557	6.659	5.832	4.521	0.447	1.290	1.319
p	4.465	2.471	3.440	3.252	3.435	0.152	0.993	1.104
q	3.294	1.642	2.031	2.514	3.122	0.104	1.120	0.981
r	ND	ND	ND	ND	ND	ND	ND	ND

^aAuxin protons in IAA, 2-NAA and 2,4-D, in the absence and presence of CB[7], at pH 1.0 and 12.0. Letters indicate positions of protons on auxins structure as reported in Figure 2. ND, not determined.

complexes with CB[7] under acidic conditions (Table 2). Only auxin protons near the carboxyl group remained nearly unaltered. On the contrary, at pH 12 and with CB[7], the shortening of T_2 values was negligible for all protons on the three auxin molecules. These results suggest an overall reduction in auxin molecular mobility in acidic solution due to formation of noncovalent host-guest complexes between the protonated auxin molecules and the host. Again, dissociation of the carboxylic acid groups at high pH caused the release of auxins from CB[7].

Experimental

Materials

Cucurbit[7]uril was prepared as documented previously [39]. IAA, 2-NAA, and 2,4-D were used as received (Sigma-Aldrich Corporation, St. Louis, MO, USA). The auxin molecules were dissolved separately to reach 0.4 mM in solutions containing 10% (v/v) of deuterated water (99.8% D_2O/H_2O ; Armar Chemicals, Döttingen, Switzerland) and buffers to ensure the following pH values of 1 (hydrochloric acid/sodium chloride (0.05 M)), 3 (citric acid/sodium citrate (0.05 M)), 5 (sodium acetate/acetic acid (0.05 M)), 7 (sodium dihydrogen phosphate/disodium hydrogen phosphate (0.05 M)), 9.5 (ammonia/ammonium chloride (0.05 M)), and 12 (sodium hydroxide (0.05 M)). Then, CB[7] was added to its final concentration of 0.4 mM, to form auxin-CB[7] complexes. All samples were incubated for 48 h to reach complexation equilibrium. Samples were transferred into 5-mm NMR tubes, and the solutions were degassed gently by N_2 flux for 5 min before NMR analysis.

Methods

A 400-MHz Bruker Avance (Rheinstetten, Germany) spectrometer, equipped with a 5-mm Bruker broadband observe (BBO) probe, working at 1H frequency of 400.13 MHz, was employed to conduct all liquid-state NMR measurements at a temperature of 298 ± 1 K. 1H NMR spectra were acquired for all samples with 22 s of thermal equilibrium delay, 90° pulse length ranging between 13.05 and 14.35 μs , 32,768 time domain points, and 64 transients.

The 1H longitudinal (spin-lattice) relaxation time constants (T_1) of auxin proton signals were measured at pH 1 and 12 by applying an inversion recovery pulse sequence, with 16 increments and variable delays from 0.5 to 25 s. The transverse (spin-spin) relaxation time constants (T_2) were obtained using a Carr-Purcell-Meiboom-Gill (CPMG) pulse sequence with 16 increments and 2 (2 ms) to 2,000 (5,000 ms) spin-echo repetitions, with a constant 0.5-ms spin-echo delay. A time domain of 32,768 points and 22 s of thermal equilibrium delay were set for all relaxation experiments.

The 1H spectral width had a range of 16 ppm (6,410.5 Hz), and the residual water signal was removed from 1H NMR spectra by pre-saturation technique. All spectra were baseline-corrected and processed by Bruker Topspin Software (v.2.1). No zero filling, as well as 0.2- and 0.5-Hz line broadenings, was adopted to Fourier transform the free induction decays (FID) of spectra deriving from conventional 1D proton acquisitions and relaxation experiments, respectively. Relaxation times of auxin molecules were calculated using MestReC NMR Processing (v. 4.9.9.9) and Origin (v.6.1) software.

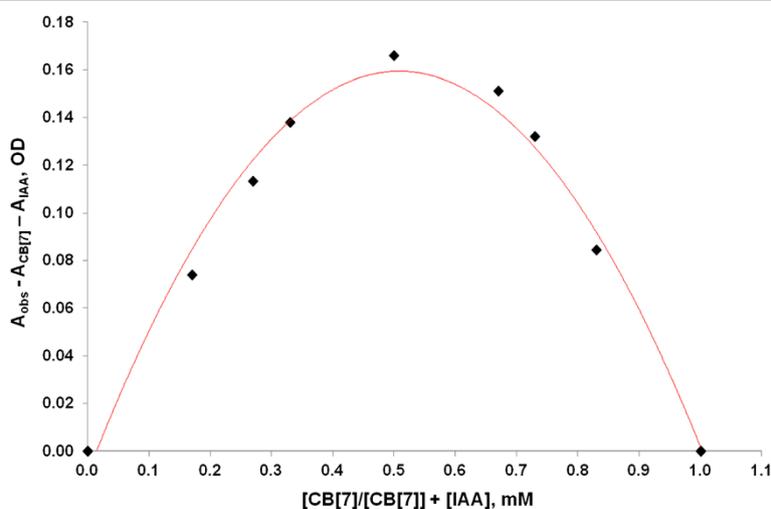


Figure 6 Plot of absorbance changes at 525 nm as a function of $[CB[7]]/[CB[7]] + [IAA]$. Line shows best fit of the experimental data to the 1:1 binding model. Aobs, absorbance observed; ACB[7], absorbance CB[7]; AIAA, absorbance IAA.

Assignment of proton signals was achieved through two-dimensional (2D) experiments: homonuclear ^1H - ^1H correlation spectroscopy (COSY), total correlation spectroscopy (TOCSY), nuclear Overhauser enhancement spectroscopy (NOESY), and heteronuclear ^1H - ^{13}C heteronuclear single-quantum correlation (HSQC), and heteronuclear multiple bond coherence (HMBC). Homonuclear and heteronuclear 2D experiments were acquired with 48 and 80 scans, respectively, 16 dummy scans, a time domain of two k points (F2), and 256 experiments (F1). In detail, TOCSY and NOESY experiments were conducted with a mixing time of 80 and 900 ms, respectively, while HSQC and HMBC experiments were optimized for 145-Hz short-range and 8.5-Hz long-range J_{CH} couplings. All 2D experiments were gradient-enhanced, except for TOCSY.

The host-guest binding constant and stoichiometry for the IAA-CB[7] complex were determined by means of UV-visible (vis) spectroscopy (PerkinElmer Lambda 25, Branford, CT, USA) at $\lambda_{\text{max}} = 525$ nm. In order to reduce uncertainties due to concomitant presence of both the IAA protonated and dissociated forms, a CB[7] titration of IAA was conducted at pH 1.0, where only protonated species are present. The derived Job plot (Figure 6) indicated that a host-guest complex between CB[7] and the protonated IAA was formed in a 1:1 stoichiometry, while calculation of the binding constant [40] provided a value of $9.6 (\pm 0.8) \times 10^2 \text{ M}^{-1}$.

Conclusions

We report for the first time the supramolecular host-guest interactions of the macrocycle CB[7] with bioactive auxin molecules IAA, 2-NAA, and 2,4-D. NMR spectroscopy showed that, for auxins dissolved in acidic aqueous solutions, the addition of CB[7] led to changes in both the shape and chemical shifts of auxin resonances and to a decrease of relaxation times. Conversely, when auxins were negatively charged (i.e., deprotonated), the presence of CB[7] did not induce any significant changes in chemical shifts and relaxation times. We conclude that cucurbit[7]uril is capable of hosting the protonated forms of the investigated plant growth molecules within its hydrophobic cavity, whereas the anionic forms of the auxins are released from the macrocycle, thereby suggesting pH control over the sequestration and release of auxin molecules within CB[7]. Such a system has the advantage of being readily triggered at any desirable time by simply and reproducibly adjusting the soil medium pH, a parameter that is easily controlled. These findings may provide a new approach to the host-guest chemistry of cucurbit[n]urils for the development of a controlled release technology of weakly acidic agrochemicals to plant systems.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors have contributed substantially to the work. They read and approved the final manuscript.

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