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A superior and accessible cavitand receptor for the binding of monoterpenes and sesquiterpenes in water†

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A water-soluble receptor based on resorcin[4]arene featuring 8 solubilising carboxylate units (**BC4**) has been obtained in a straightforward manner without chromatographic purifications. **BC4** is soluble in water in a wide range of pH, and is able to accommodate guests of different sizes and shapes, including monoterpenes and sesquiterpenes, providing enhanced binding capabilities with respect to previously reported analogues. The molecular recognition events within **BC4** are sensitive to subtle changes in guest shape and size, as illustrated by disparate exchange kinetics observed among the guests tested.

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Introduction

Water soluble synthetic receptors are the quintessential example of bioinspired hosts and have great potential in the development of bioinspired catalysis or sensing devices for analyte detection in biological media.^{1,2} The binding of organic molecules in aqueous media benefits from the hydrophobic effect, resulting in better binding abilities for a given water soluble host in relation to lipophilic analogues operating in organic media, where competitive binding by solvent molecules is significant. Cavitand receptors based on resorcin[4]arenes and featuring benzimidazole panels were first introduced by Rebek and co-workers and constitute a particularly interesting subset of hosts for studies in aqueous media (Fig. 1).³ The benzimidazole units are placed at the appropriate distance and orientation to establish hydrogen bonds with bridging water molecules, stabilizing the binding competent closed form of the cavitand (the so-called *vase* conformation) by means of an uninterrupted hydrogen bond network. In contrast, the *vase* form is typically disrupted by protic solvents in other cavitand scaffolds, making them less appealing for applications in water.⁴ Benzimidazole-type cavitands (**BC**) are ren-

dered water-soluble by addition of solubilizing groups at either the upper rim^{5–8} or the feet of the resorcin[4]arene core.^{9–11} Of the two approaches, the former is the most straightforward from a synthetic point of view, allowing the preparation of sizable amounts of cavitands without chromatographic purifications in five steps from resorcinol (Fig. 1a). This accessibility has popularized such receptors for a range of applications specially in sensing,^{12–19} but also in catalysis²⁰ and *trans*-membrane transport.²¹ The use of arrays of **BC** receptors as highly sensitive and selective sensory systems has proved particularly useful.^{12–14,16–18} Despite this demonstrated utility, only a reduced set of water-soluble upper rim functionalized **BCs** has been developed (**BC1–3**, Fig. 1b), all suffering from a limited operative range of pH (either basic or acidic). With these limitations in mind and given our interest in developing containers for binding biologically relevant molecules,²² we set out to develop an improved **BC** host with a deeper hydrophobic pocket and an enhanced solubility profile. We report here the synthesis of this new receptor **BC4** and its binding capabilities against a set of terpenes and alkaloids (Fig. 1c).

Results and discussion

While **BC**-type receptors can be easily synthesized from octanetro precursor **1** (Scheme 1), the diversification of the structure is not trivial given the impossibility to purify the (highly polar) reaction intermediates by chromatography, and the reduced number of functional imidate precursors available. As a result, only four different benzimidazole cavitands with functional groups suitable for further elaboration have been described.^{5–8,23} We envisaged that imidate **3** would be accessi-

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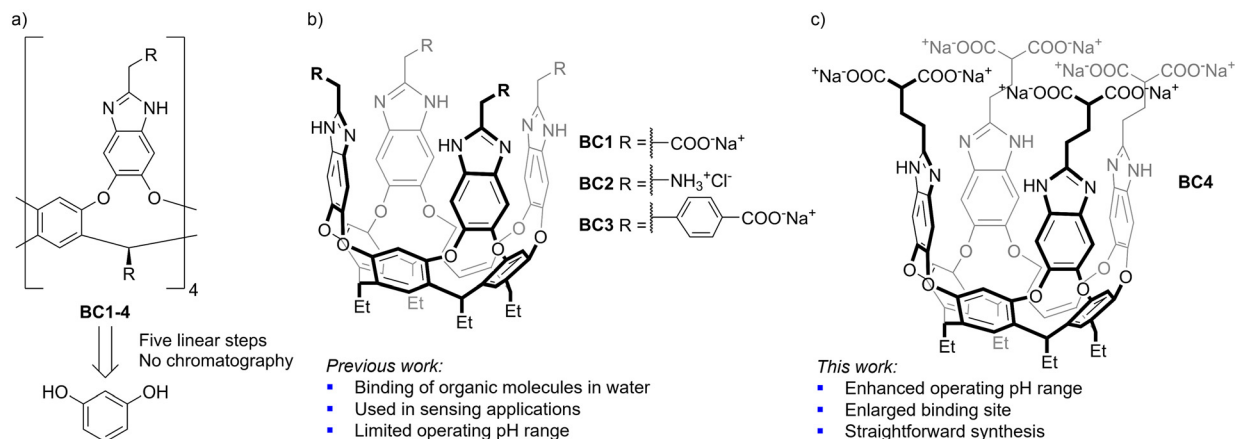
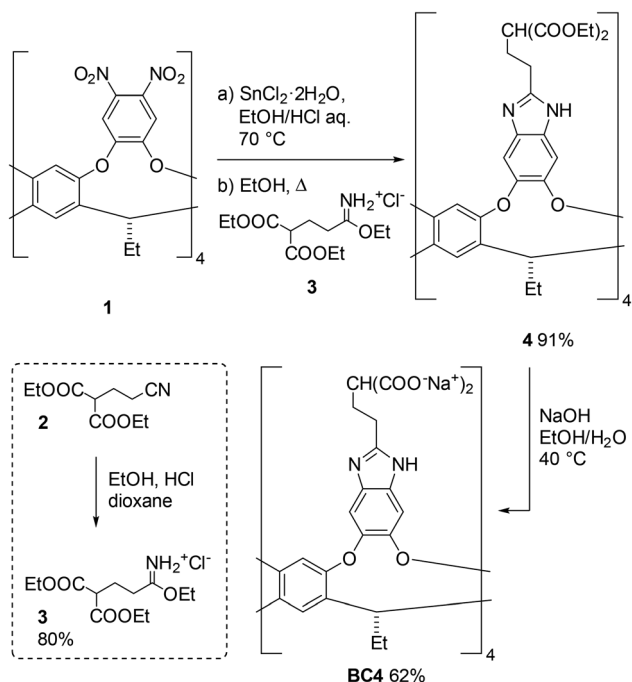


Fig. 1 (a) Schematic structure and retrosynthesis of water soluble benzimidazole cavitands (BC). (b) Previously reported BC receptors. (c) Newly developed octacarboxylate BC receptor BC4.



Scheme 1 Synthesis of cavitant BC4. Inset: synthesis of imidate precursor 3.

ble from readily available nitrile 2, enabling an efficient entry into a novel derivative of the BC family, BC4. The resulting cavitant would feature 8 carboxylate units, increasing solubility. In addition, the 3-carbon spacer between the core and the hydrophilic rim would significantly deepen the cavity. Receptor BC4 was synthesized according to Scheme 1. Known octanitro derivative 1²⁴ was reduced to the corresponding octaamino hydrochloride salt and subsequently reacted with imidate 3 to furnish octaester cavitant 4. Upon basic hydrolysis of 4, sodium octacarboxylate BC4 was obtained in good yield after dialysis. Importantly, no chromatographic purifi-

cations were required throughout this sequence, which can be carried out easily on gram scale.

Receptor BC4 proved to be completely soluble in pure water at mM concentrations. A 4 mM solution of pure BC4 has a pH of *ca.* 8. To assess the solubility of BC4 at varying pH values, solutions of the octacarboxylate salt in D₂O were monitored by ¹H NMR upon addition of increasing amounts of DCl ([BC4] = 1.3 mM). Remarkably, the cavitant remained completely soluble upon adjusting the pH of the solution down to 4, and resonances assigned to the receptor were clearly observed in the corresponding ¹H NMR spectra. At pH < 4 the solution appeared cloudy, indicating precipitation, and no signals from the cavitant could be detected by ¹H NMR spectroscopy in these solutions. In contrast, tetracarboxylate BC1 is only soluble at basic pH (pH ≥ 7.8 or 9 depending on the reports).^{8,25}

The spectroscopic features of pure BC4 in D₂O solution reproduce those previously observed for BC1–BC3. Resorcin[4] arene derived cavitands can adopt two extreme conformations, the folded (*vase*) conformer, suitable for binding of guests, or the open (*kite*) conformer.²⁶ In the absence of a suitable organic guest, the cavitant adopts the kite conformer, as ascertained by the number of resonances observed in the ¹H NMR spectrum, corresponding to D_{2d} averaged symmetry (Fig. 2).²⁷ Kite conformers are postulated to exist as dimers in solution to minimize exposure of the hydrophobic surface to the aqueous media. Upon addition of THF to the aqueous cavitant solution, an abrupt change was observed in the spectrum, indicating the formation of the vase conformer upon binding of THF molecules, despite the accumulation of negatively charged dicarboxylate units that could potentially disfavour folding through repulsive electrostatic interactions. A shift of the methine resonance from 3.96 ppm (D₂O) to 5.53 ppm (D₂O/THF-*d*₈ 95 : 5) is observed, which is diagnostic of the kite-vase transition.^{26,28} In addition, the aromatic resonances are shifted downfield and collapse into three resonances, corresponding to the C_{4v} averaged symmetry expected for the vase



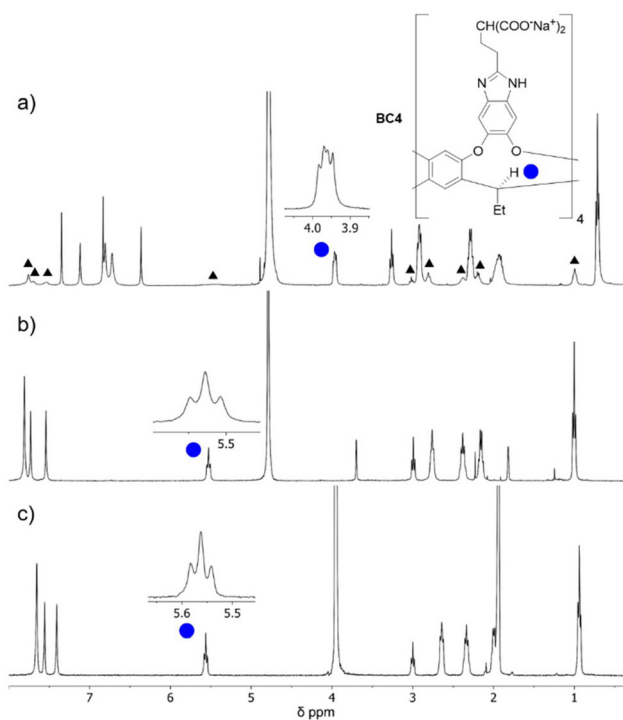


Fig. 2 ^1H NMR spectra of BC4 in different solvents, with the diagnostic methine resonance highlighted (blue dots). (a) D_2O , black triangles indicate small amounts of the vase form, encapsulating residual ethanol. (b) $\text{D}_2\text{O}/\text{THF}-d_8$ (95 : 5). (c) $\text{CD}_3\text{CN}/\text{D}_2\text{O}$ (3 : 1).

conformer. In $\text{CD}_3\text{CN}/\text{D}_2\text{O}$ mixtures the vase form is also favoured, despite the fact that the hydrophobic cavity of resorcin[4]arene cavitands typically abhors highly polar molecules.

Having established that the conformational behaviour of BC4 in aqueous solution is analogous to that of other water-soluble BCs, we set out to gauge the binding space of BC4 by testing its capacity to extract and bind a diverse set of biologically relevant guests in aqueous solutions, including monoterpenes, and sesquiterpenes (G1–G22, Fig. 3 and 4). These experiments were carried out at 2 mM concentration of host and excess guest. § For a number of guests, direct evidence of binding was obtained from the appearance of bound guest signals in the far upfield region of the ^1H NMR spectrum—in addition of the characteristic resonances of the vase form (Fig. 3). These upfield shifted resonances indicate the formation of complexes that are in slow exchange regime relative to the ^1H NMR time-scale, a typical feature of BC hosts and related cavitands. For some of these guests, the resonances in the far upfield region are sufficiently resolved to infer directly the guest orientation. For myrtenol (G9) and camphor (G16) for instance, the appearance of two characteristic singlets that integrate three protons each (relative to the smaller bound guest resonances) is indicative of the *gem*-dimethyl portion of the guest being fixed at the deepest region of the cavity where

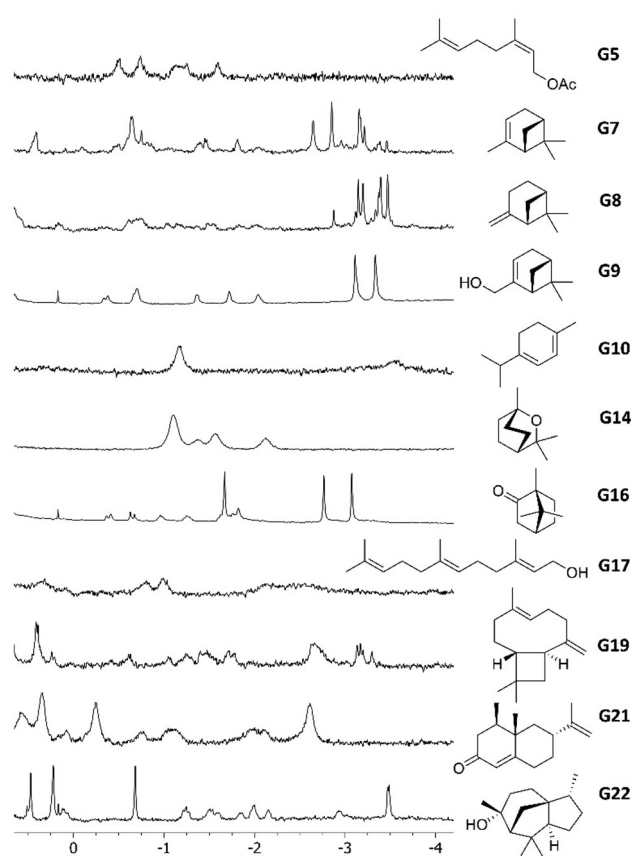


Fig. 3 Far upfield region of the ^1H NMR spectra of BC4 in the presence of different guests, indicating binding in the deep cavity.

the magnetic anisotropy is stronger. For α -pinene (G7) and β -pinene (G8) similar resonances are observed in the same region, although the splitting of these signals indicates that the guest is present in two different orientations under slow exchange kinetics.

Sesquiterpenes are also taken in the cavity as indicated by ^1H NMR (G17, G19, G21, G22). In the case of cedrol (G22) the orientation of the guest can also be deduced: a single methyl resonance around -3.5 ppm indicates that the cyclopentyl ring is oriented towards the deep section of the cavity. This is orientation is reasonable: it places the bulkier bicyclo[3.2.1]octane fragment of G22 on the wider upper section of the cavitand, exposing at the same time the alcohol function to the aqueous environment and the polar rim of the cavity.

Intriguingly, some of the guests tested triggered the appearance of the vase form resonances without evidence of any far upfield shifts, making it impossible to distinguish between specific 1 : 1 binding in the cavity of BC4 under fast exchange conditions or unspecific interactions outside the cavitand. This was puzzling since the differences of some of these guests with others bound in slow regime are very subtle (*e.g.* G10 vs. G11–G12, Fig. 4). This phenomenon has been previously observed with BC-type hosts by Rebek.²⁹ During studies of BC1 in combination with sodium dodecylsulfate (SDS), it

§The majority of the guests tested have marginal solubility in pure water. See ESI† for details of the ^1H NMR experiments.



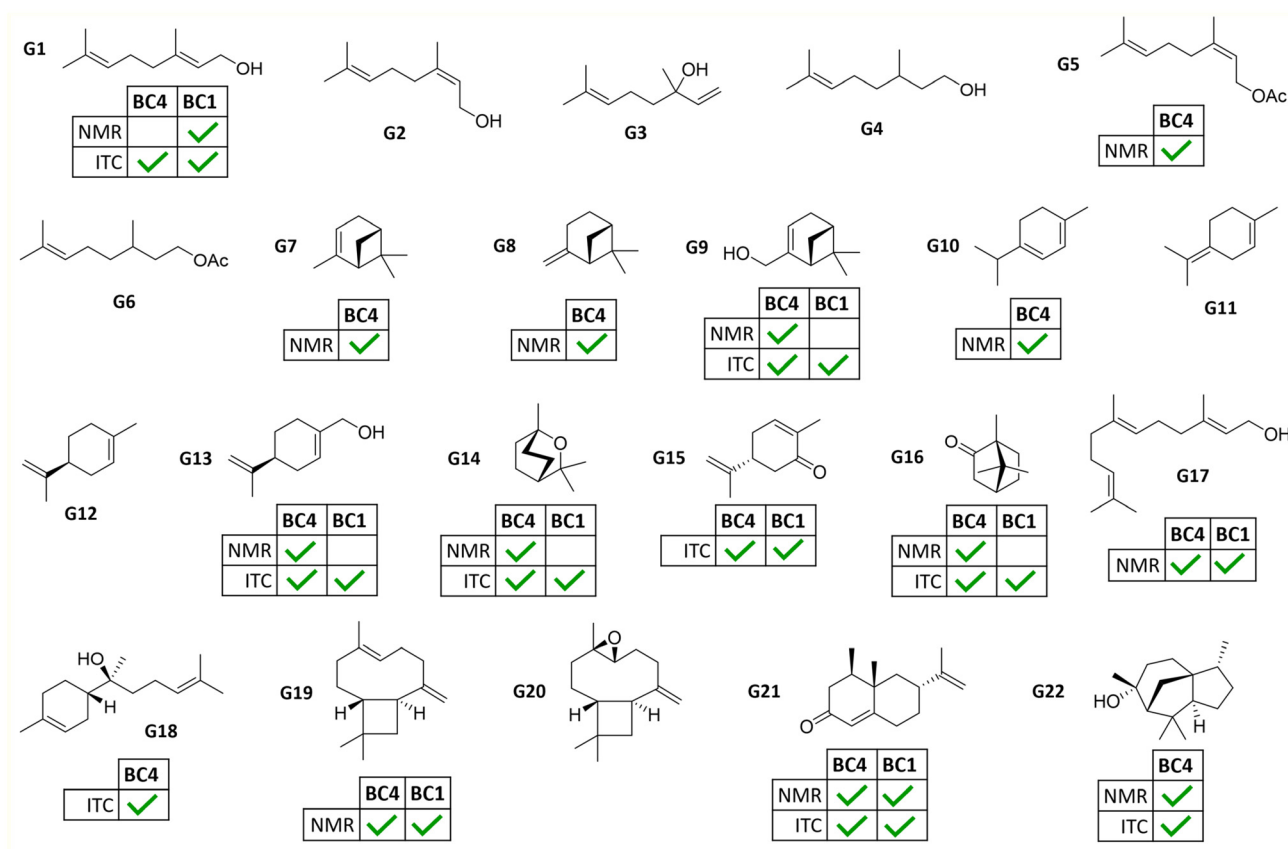


Fig. 4 Guests tested in this study. Green check marks indicate positive evidence of specific binding (1 : 1, slow exchange regime) in the cavity of BC4 and/or BC1, respectively.

was reported that above the critical micellar concentration of SDS, BC1 was found to be in the folded state although no far upfield shifts for bound SDS were observed in the ^1H NMR spectrum, indicating that incorporation of BC hosts into micelles or similar aggregates enhances guest exchange in and out of the cavity. Given that the barriers to self-exchange in resorcin[4]arene derived cavitands have been determined to be always above 16 kcal mol^{-1} , we assessed the energy barrier associated to the kite-vase transition of BC4 to understand the observed behaviour. Using an EXSY experiment,^{30,31} a Gibbs free energy barrier of $18.2 \text{ kcal mol}^{-1}$ was obtained, in good agreement with that obtained for other resorcin[4]arene based cavitands (Fig. S1†).³² This result suggests that some guests may be able to slip out of the cavity without unfolding or with partial unfolding—for a structurally related cavitand, the calculated exchange barrier to partial opening of one wall is around 15 kcal mol^{-1} in chloroform—³³ and that this slippage mechanism may be favoured when the cavitand is incorporated in micelles or similar aggregates. Fast exchange kinetics may also be the result of poor shape complementarity, as exemplified by the case of geraniol (G1). In the presence of G1, BC4 adopts the folded vase conformation but the upfield resonances indicative of slow exchange are not observed. A possible explanation is that G1 features a narrower shape than the bulkier polycyclic monoterpenes (G7–G9, G14, G16), significantly redu-

cing the available attractive contacts with the hydrophobic cavity. Structurally related farnesol (G17) appears to bind in the cavity, but the broad upfield shifts observed also suggest that the guest is on the verge of fast chemical exchange (Fig. 3).

For completeness, we assessed the inclusion of guests in receptor BC1 under the same conditions (Fig. 5). Somewhat surprisingly, both geraniol and farnesol bind in slow exchange regime within cavitand BC1, providing well resolved resonances that indicate the encapsulation of the terminal *gem*-dimethyl groups at the deepest section of the host. Evidence of internalization was also obtained for caryophyllene (G19), nootkatone (G21) and cedrol (G22).

Considering the previous findings and in order to establish a systematic comparison between the binding abilities of BC4 and BC1 that is not blurred by exchange kinetics, we evaluated the association constants (K_a) for a representative selection of guests by isothermal titration calorimetry (ITC, Table 1 and ESI†). The selected guests were chosen to provide sufficient solubility in aqueous solution. We were able to fit the obtained calorimetric data to 1 : 1 stoichiometry isotherms, confirming the formation of well-defined inclusion complexes as opposed to unspecific binding on the outside of the host. With the exception of geraniol, all the guests tested provided increased affinity for BC4, with association constants up to one order of



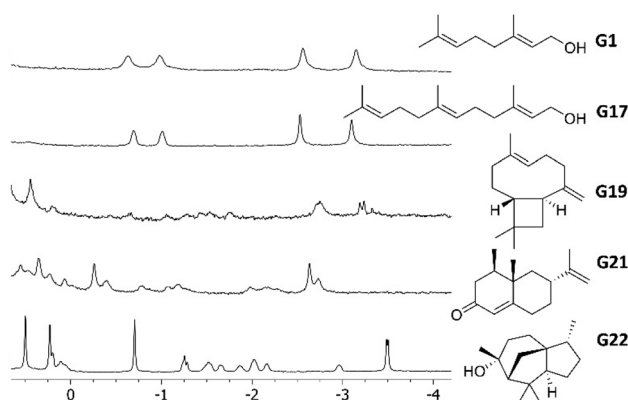


Fig. 5 ^1H NMR evidenced for the 1 : 1 encapsulation of different guests within host BC1 in D_2O at 25 $^\circ\text{C}$.

Table 1 Association constants (K_a) of different guests with BC4 and BC1^a

Entry	Guest	K_a (BC4) M^{-1}	K_a (BC1) M^{-1}
1	G1	$1.62 \pm 0.04 \times 10^5$	$1.22 \pm 0.04 \times 10^5$
2	G9	$2.91 \pm 0.05 \times 10^5$	$1.23 \pm 0.05 \times 10^5$
3	G13	$1.19 \pm 0.04 \times 10^6$	$3.7 \pm 0.2 \times 10^5$
4	G14	$9.9 \pm 0.2 \times 10^3$	$2.0 \pm 0.1 \times 10^3$
5	G15	$1.06 \pm 0.01 \times 10^6$	$5.5 \pm 0.3 \times 10^5$
6	G16	$9.5 \pm 0.4 \times 10^4$	$3.9 \pm 0.2 \times 10^4$
7	G18	$1.5 \pm 0.1 \times 10^5$	— ^b
8	G21	$1.34 \pm 0.04 \times 10^5$	$5.0 \pm 0.2 \times 10^4$

^a Determined by ITC at 25 $^\circ\text{C}$ in H_2O (5% v/v EtOH). ^b Not determined due to the low magnitude of K_a and solubility constraints.

magnitude above those obtained for BC1. For bisabolol (G18), the association constant with BC1 could not be properly measured because of solubility constraints, indicating qualitatively an important reduction in affinity with respect to BC4.

To better understand the previous results, we carried out computational modelling of a selection of complexes with BC4 and BC1 as the sodium salts, including 4 water bridging molecules (Fig. 6 and S2†). The spaces between carboxylate units from adjacent panels of the cavita nd provide a good fit for sodium cations. The resulting saline bridges stabilize the vase conformation, which explains the fact that BC4 retains the preference for the vase conformer observed in BC1–3 despite the accumulation of carboxylate units at the upper rim. The different exchange kinetics observed correlate qualitatively with the shape complementarity between host and guest.

Polycyclic monoterpenes (G7–G8, G14, G16) feature a spherical shape that is very complementary to the lower half of the cavita nd surface, maximizing attractive non-covalent interactions with the aromatic panels (Fig. 6). On the contrary, acyclic terpenes favour extended conformations of narrower shape and poorer complementarity, resulting in a reduction of the available attractive interactions with the cavita nd's wall.²² A possible explanation for the binding of geraniol in BC1 under slow exchange regime can be derived from the corresponding

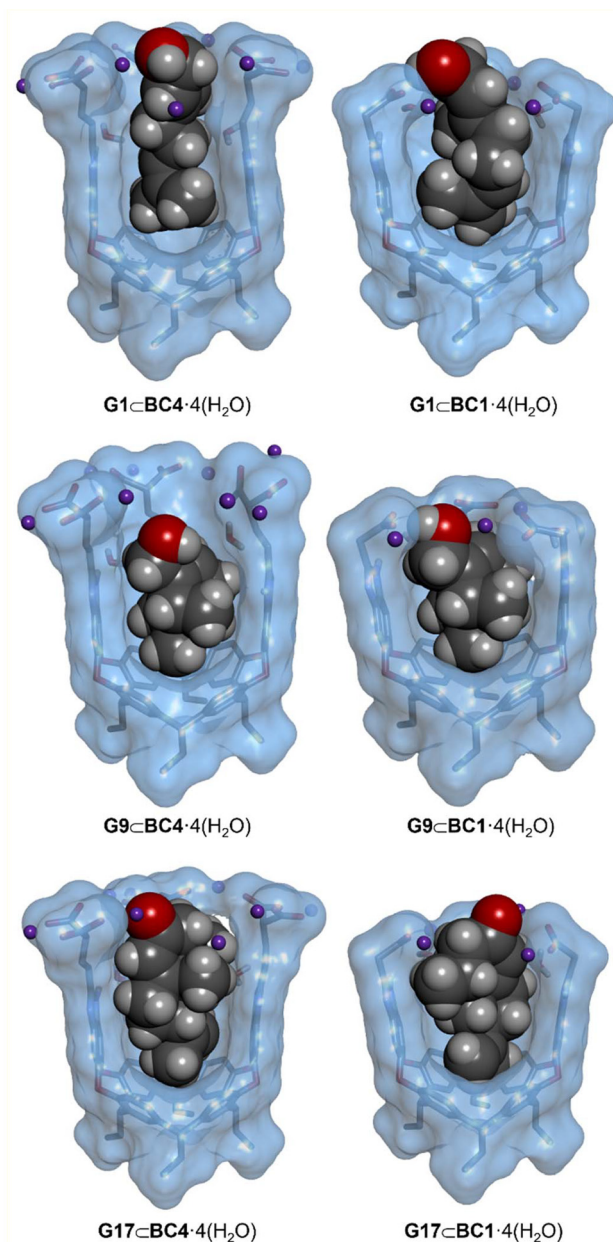


Fig. 6 Molecular models of geraniol (G1), myrtenol (G9) and nootkatone (G17) bound in BC4-4(H_2O) and BC1-4(H_2O) (MMFF). The cavita nds are shown with a superimposed solvent accessible surface (front panel omitted for clarity) illustrating the different degrees of host–guest complementarity along the guest series. Sodium ions are shown as purple spheres.

molecular model. Geraniol engages in hydrogen bonding with the carboxylates on the rim of the cavita nds, forcing the adoption of a contorted and more complementary conformation, enhancing interactions with the cavita nd walls. A similar phenomenon can be invoked for farnesol (G17). Conversely, the carboxylate functions of BC4 are farther apart from the deep section of the cavity, so that hydrogen bonding to G1 favours the less complementary extended conformation that ensures exposure of the hydroxyl group to the aqueous medium.



Molecular modelling also provides a reasonable explanation for the enhanced binding constants of cyclic terpenes in **BC4**. As it can be observed in Fig. 6, the binding of terpenes in **BC1** leads to a slight distortion of the walls towards the exterior in comparison to **BC4**. This “bloating” of the cavitand results in less efficient bridging by the auxiliary water molecules—the hydrogen bonding interactions are stretched. The net effect in terms of association constants is subtle for monoterpenes (Table 1, entry 2), but the higher complementarity of cyclic sesquiterpenes with **BC4** is evident in the complex with nootkatone (**G21**). The most likely orientation of the guest is that with the isopropylidene group positioned in the narrow, tapered end of the receptor, and the bulkier cyclohexenone portion accommodated in the wider upper region defined by the ethylene spacers of **BC4**, providing additional van der Waals interactions that are not available in **BC1**. A similar effect can be appreciated in the complexes of bisabolol, caryophyllene, and cedrol (Fig. S2[†]). For caryophyllene (**G19**) and cedrol (**G22**) the bulkier *E*-cyclonene and bicyclo[3.2.1]octane fragments respectively provide good complementarity with the wider upper region of **BC4** defined by the ethylene spacers.

Conclusions

In summary, we have developed a new benzimidazole-type cavitand based on resorcin[4]arene (**BC4**) that expands and complements the capabilities of the existing family of **BC** receptors. **BC4** presents an improved solubility profile, operating in a wider range of pH. In addition, **BC4** presents an expanded hydrophobic cavity that allows enhanced binding of sizable guests such as sesquiterpenes, while preserving the affinity towards smaller guests typical of analogue **BC1**. The guest exchange kinetics are very sensitive to subtle changes in shape size and shape. **BC4** is readily available on gram scale and requires no chromatographic purifications. Overall, all these features bode well for the implementation of **BC4** in sensing applications of biologically relevant analytes.

Data availability

The data supporting the findings reported in this manuscript has been deposited in the CORA.RDR institutional repository, DOI: [10.34810/data1632](https://doi.org/10.34810/data1632).

The dataset contains raw and processed data in the following categories:

Full NMR characterization data for new compounds.

¹H NMR data for the binding studies reported.

Optimized geometries and optimization files for the computational studies reported.

Conflicts of interest

There are no conflicts to declare.

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