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Guest Binding Drives Reversible Atropisomerism in Cavitand Hosts

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Cram's cavitand bowls are rigid host compounds derived from resorcinarenes.[1] These hosts have enjoyed widespread application in supramolecular chemistry,[2] particularly as building blocks for double cavitand molecules such as hemicarcerands[3] and more recently, for larger covalent structures.[4] Single cavitand bowls generally bind guests weakly on their shallow, concave, π-basic surface. Indeed, solution-phase binding between simple cavitand bowls and (solvent) guests has only been detected by taking advantage of the hydrophobic effect, that is, employing water-soluble cavitands in aqueous environments.[5] Landmark contributions from Dalcanale[6] demonstrated that placement of a fixed, inwardly-directed phosphonate binding substituent on a cavitand bowl leads to a sensor host capable of much stronger and more selective, two-point guest binding. In elegant studies, Rebek has introduced deep cavity cavitands carrying fixed "introverted functionality",[7] which exhibit unprecedented behavior by virtue of the shielding afforded to a bound guest from the bulk phase. Herein, we introduce a new class of cavitand bowl structures carrying rim substituents that can reversibly switch from inwardly- to outwardly-directed orientations. We show that a preference for either form can be established through purely physical means, and we demonstrate that this system provides—for the first time—a means of measuring relative solvent guest binding affinities without recourse to the hydrophobic effect.

Mono-aryl cavitands **4** and **5** are readily prepared by Suzuki–Miyaura coupling of cavitand mono-boronate ester **2**[8] with *ortho*-iodoarenes **3** (Table 1). Under optimized conditions, isolated yields for the 2,2′,6-trisubstituted biaryl products **4** and **5** are in the 60–85% range.[9] Reactions leading to the *ortho*-bromophenyl (**4c**/**5c**) and 1-naphthyl substituted cavitands (**4b**/**5b**) took considerably longer than the others. Intriguingly, all but two of these reactions furnish mixtures rich (83–99%) in the *inside* atropisomer **4**. We attribute the kinetic preference for the *inside* stereoisomer in the cross-coupling reaction to steric hindrance at play in the biaryl bond-forming step (Table 1). Thus, in the three-centered transition state of the reductive elimination step, the [Pd(Pfu$_3$)$_2$] group will occupy the less sterically hindered *outside* position and the R substituent will avoid the phosphine ligands, thereby adopting an orientation that leads to *inside* isomer **4**. A similar mechanism has been put forward to explain π-facial selectivities in Suzuki coupling reactions involving (arene)chromium complexes.[10] Irrespective of the mechanism, the kinetic *inside* stereoselectivity appears to be a general feature of these reactions: in the two systems furnishing mixtures rich in the *outside* cavitand isomer **5** (Table 1, entries d and g), the *inside* isomer **4** is atropisomerically unstable under the reaction conditions.

The *inside* and *outside* atropisomers were readily separated by chromatography and the stereochemistry of each was assigned through ^{1}H NMR chemical shifts, NOE experiments, X-ray crystallographic analysis (of **5f**[11]), and the results of interconversion experiments (see below). Informative regions of ^{1}H NMR spectra of selected compounds are reproduced in Figure 1. All protons associated with the substituents of *inside* atropisomers of the methyl (**4d**), ethyl (**4e**), and *n*-propyl (**4f**) esters display upfield chemical shifts, by virtue of their close proximity to the shielding zone of the aromatic cavity. The upfield shift is greatest with the ethyl (**4e**) and *n*-propyl (**4f**) esters, the terminal methyl protons of which resonate at δ −2.05 and −2.71 ppm, respectively, some 3–3.5 ppm upfield of the usual chemical shift for such protons. Surprisingly, the *inside* isomer of the corresponding *n*-butyl ester (**4g**) shows only small upfield chemical shifts. Presumably, whereas the ethyl and *n*-propyl groups are close to the ideal size to reach to the bottom of the cavity, the *n*-butyl group is prohibitively large for a snug fit. The *inside* isomer of the isobutyl ester (**4h**) can be

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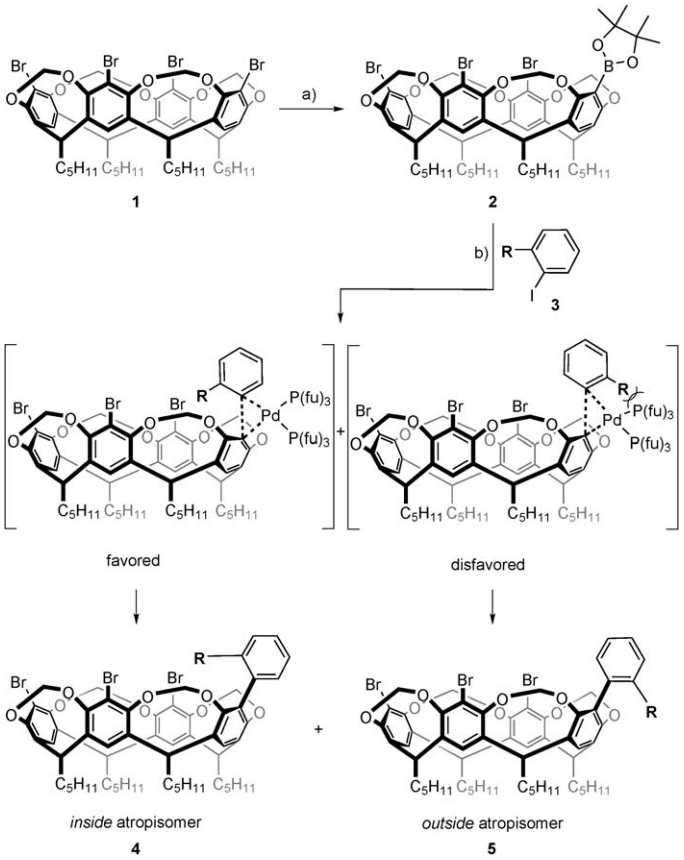
Table 1. Synthesis of mono-aryl cavitands.[a]



Entry	R	Total isolated yield [%]	Kinetic ratio *inside*/*outside* (**4**/**5**)[b]
a	Me	70	86:14
b	1-naphthyl[c]	70	97:3
c	Br	85	98:2
d	CO_2Me	75	25:75[d]
e	CO_2Et	60	83:17
f	CO_2nPr	70	83:17
g	CO_2nBu	70	5:95[d]
h	CO_2iBu	65	99:1

[a] a) *n*BuLi (1.1 equiv), THF, −78 °C; then $B(OMe)_3$ (1.5 equiv), −78 → 25 °C; then pinacol (1.1 equiv), $MgSO_4$ (4.1 equiv), CH_2Cl_2, 25 °C, 18 h. b) Iodoarene **3** (3.0 equiv), Ag_2CO_3 (2.0 equiv), $[Pd_2(dba)_3]$ (0.12 equiv), P(2-furyl)$_3$ (0.50 equiv), THF, 25 °C, 18–72 h. [b] Average of two NMR runs, difference between runs = ±1 %. [c] The *cavitand* substituent is a 1-naphthyl group in this case. [d] Not kinetic ratios: in these cases, interconversion between *inside* and *outside* forms occurs under the reaction conditions.

viewed as a hybrid of the ethyl and *n*-propyl esters. This derivative is undergoing rapid interconversion between "ethyl" down and "propyl" down conformations at room temperature.[12] Interestingly, a higher upfield shift is evident for the "ethyl" CH_3 than the "propyl" CH_3, a result we interpret as a win for the ethyl over the propyl group as the more readily accommodated substituent.

Atropisomeric stability varies considerably throughout the series of compounds prepared (Table 2). Thus, in $[D_8]$toluene solution, a pure sample of either atropisomer of

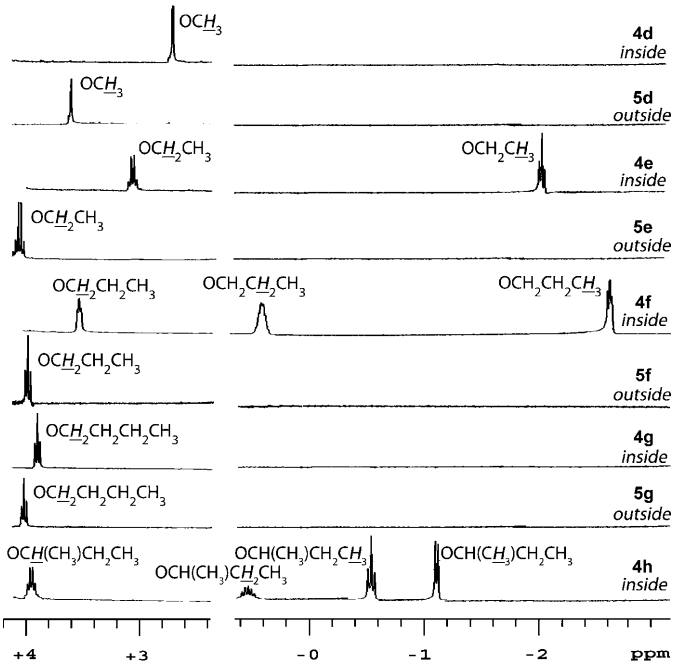


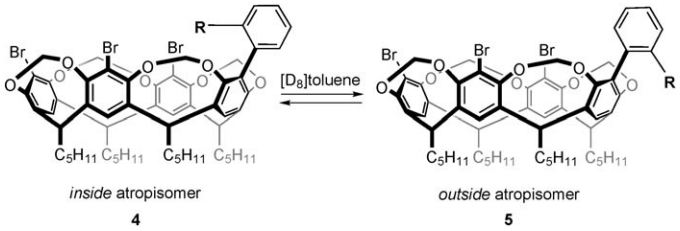
Figure 1. Pertinent sections of ^{1}H NMR spectra of *inside* and *outside* esters, **4d**–**h** and **5d**–**g**, respectively (300 MHz, $CDCl_3$, 25 °C).

the *ortho*-CO_2Me-phenyl-substituted cavitand **4d/5d** is converted into an equilibrium mixture at ambient temperature overnight, whereas the two atropisomers of the *ortho*-bromophenyl-cavitand (**4c/5c**) are kinetically stable at 100 °C for several days. A substituent's influence upon the relative atropisomeric stability of an arylated cavitand (order of stability: *ortho*-Br phenyl > 1-naphthyl > *ortho*-Me phenyl ≫ *ortho*-CO_2R phenyl) is broadly consistent with substituent effects observed during racemization studies with chiral biphenyls.[13] Nevertheless, within the ester substituent family, a curious atropisomeric stability order $CO_2Et > CO_2nPr \gg CO_2Me > CO_2nBu$ is witnessed.

Further unexpected and unprecedented properties begin to emerge during more detailed investigations into the thermodynamic equilibration of these compounds (Table 2). In general, the thermodynamically more stable isomer in toluene is the *outside* form. The exceptions are the CO_2Et and CO_2nPr compounds (Table 2, entries e and f), which favor the *inside* isomer. Interestingly, the equilibrium ratios of atropisomers are temperature dependent: the majority of derivatives examined (Table 2, entries c–g) display an enhanced preference for the *inside* isomer as the temperature is increased.[14] At even higher temperature, something remarkable happens with the methyl ester atropisomers **4d/5d**: the *inside* isomer becomes dominant (*inside* **4d**/*outside* **5d** thermodynamic ratio at 200 °C in $[D_8]$toluene 54:46).[15] Thus, it is possible to prepare a mixture rich in either atropisomer by simply holding a solution of the mixture at a particular temperature.

These results are best explained by the equilibrium depicted in Table 3, which takes into account the influence of solvation upon the relative stabilities of the *inside* and *out-*

Table 2. Temperature and substituent effects on atropisomer ratio.

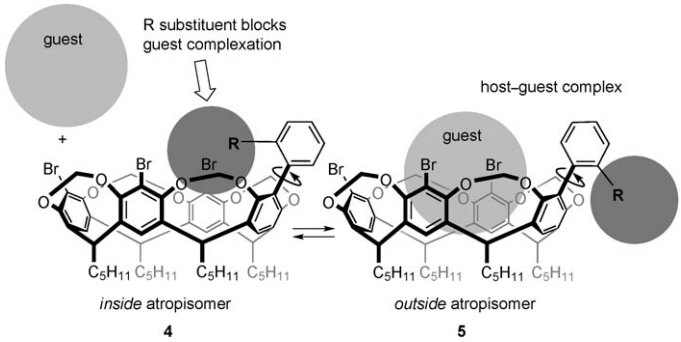


Entry	R	$t_{1/2}$ at 65 °C[a]	Equil. ratio *in*/*out* (**4**/**5**) at 65 °C[b]	Equil. ratio *in*/*out* (**4**/**5**) at 100 °C[b]	Isomer favored at higher *T*
a	Me	28 h	13:87 ± 3	6:94 ± 2	*outside*
b	1-naphthyl[c]	400 h	28:72 ± 1	17:83 ± 2	*outside*
c	Br	–[d]	20:80[e] ± 2	29:71[f] ± 1	*inside*
d	CO_2Me	5 min	30:70 ± 2	43:57 ± 2	*inside*
e	CO_2Et	50 min	83:17 ± 2	86:14 ± 1	*inside*
f	CO_2nPr	40 min	75:25 ± 1	77:23 ± 2	*inside*
g	CO_2nBu	10 min	16:84 ± 2	23:77 ± 2	*inside*

[a] *Outside* atropisomer. [b] *in*/*out* ratios are the average of 4–8 runs and standard deviations are quoted. [c] The *cavitand* substituent is a 1-naphthyl group in this case. [d] No measurable change after 1000 h at 65 °C. [e] Equil. ratio at 120 °C. [f] Equil. ratio at 140 °C.

side atropisomers. The cavity of the *inside* isomer **4** is occupied by the *ortho*-substituent of the aryl group, which precludes guest (i.e., solvent) binding. In contrast, the *outside* isomer **5** is free to serve as a host for a complementary guest molecule. The increased preference for the *inside* isomer **4** at higher temperatures (Table 2) now becomes evident: *outside* → *inside* switching leads to the expulsion of a guest molecule, an entropically driven process.

Table 3. Relative guest binding affinities measured through atropisomer ratios.



Solvent	Equil. ratio *in*/*out* (**4e**/**5e**) at 50 °C[a]
no solvent[b]	99:1
Me_2NCHO	98:2
CCl_4	85:15
PhMe	81:19
Me_2CO	80:20
PhH	76:24
$CHCl_3$	73:27
Me_2SO	69:31
EtOAc	41:59

[a] Average of three NMR runs, difference between runs = ±1%. [b] The solid **4e/5e** mixture was heated to 50 °C, then immediately dissolved in $CDCl_3$ at 25 °C and a ^{1}H NMR spectrum was recorded.

At first glance, the atropisomeric stability order CO_2Et > CO_2nPr ≫ CO_2nBu > CO_2Me (Table 2, $t_{1/2}$) appears curious. If steric effects alone were determining the barrier towards rotation about the biaryl bond, one would expect that as the size of the ester substituent is increased, atropisomeric stability would increase. We suggest an additional (Goldilocks) factor at play here, which relates to how well the ester substituent fits into the cavity: the methyl ester is too small for the cavity and the *n*-butyl is too large, whereas the ethyl and *n*-propyl esters are within the correct size range (but the ethyl fits best of all). Evidently, the self-fulfilling[7c] nature of the inside ethyl and *n*-propyl groups causes a ground-state stabilization which increases the barrier towards biaryl bond rotation. The methyl and *n*-butyl groups have a lower interconversion barrier since the inside isomers lack such a high degree of stabilization.

The complementary fit of the ethyl and *n*-propyl substituents in the cavitand bowl not only affects the barrier towards atropisomerism, it is sufficiently strong to override the usual thermodynamic preference for the *outside* form in toluene (Table 2, *in*/*out* equilibrium ratios).

This unique system[16] offers a very convenient method for the measurement of relative solvent–guest binding strengths (Table 3). Evidently, this remarkable solvent influence upon *inside*/*outside* atropisomer ratio is the result of competition between the *ortho*-CO_2Et substituent and the solvent for the cavitand bowl cavity. In the absence of solvent or in poorly binding solvents, the equilibrium is dominated by *inside* isomer **4e**. In contrast, a solvent that binds in the bowl well (i.e., ethyl acetate) is signaled by an equilibrium dominated by the *outside* isomer **5e**. The equilibrium ratio in a particular solvent is, therefore, a direct measure of relative solvent–guest binding affinity for cavitands. A simple explanation of different atropisomer ratios resulting from solvent polarity effects can be ruled out, since there is no correlation between atropisomer ratios and solvent dipoles or dielectric constants.[17] In contrast, the relative solvent-binding affinities recorded here through switchable *in*/*out* cavitand **4e/5e** display an excellent correlation with association constants reported by Sherman, in studies employing an ammonium phosphate-derivatized cavitand.[5,18] The ability of this new method to measure relative[19] guest binding strengths of organic solvents in an operationally straightforward manner, that is, by simply measuring atropisomer ratios, and without recourse to the hydrophobic effect, clearly demonstrates its unprecedented simplicity and sensitivity.

Experimental Section

Typical procedure: Under nitrogen, an oven-dried round-bottom flask was charged with C-pentyltribromocavitandboronate pinacolyl ester **2** (100 mg, 84 μmol), 2-iodotoluene (55.4 mg, 254 μmol, 3.0 mol equiv), silver carbonate (46 mg, 170 μmol, 2.0 mol equiv), tris(dibenzylideneacetone)dipalladium(0) (10 mg, 10 μmol, 0.12 mol equiv), and tri-2-furylphosphine (10 mg, 42 μmol, 0.5 mol equiv). The flask was evacuated and refilled with nitrogen three times then dry tetrahydrofuran (5 mL) was added. The reaction mixture was stirred at 25 °C in the dark for 18 h then

filtered through a short plug of celite and the solvent was evaporated to afford the crude product. ^{1}H NMR analysis of the crude product indicated an 86:14 mixture of *inside*/*outside* isomers. The crude product was purified by flash chromatography (100 g silica, 6:4 dichloromethane/hexane then 50 g silica, 1:9 ethyl acetate/hexane) to give *inside* isomer **4a** (58 mg, 60%) and *outside* isomer **5a** (9 mg, 10%).[17]

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Keywords: atropisomerism · cavitands · host–guest systems · molecular recognition

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[12] The triplet at $\delta = -0.5$ ppm and doublet at $\delta = -1.1$ ppm are the result of an averaging of the up and down conformations of the "ethyl" CH_3 and the "propyl" CH_3 groups. The rate of interconversion between these two forms is too rapid, even at $-90\,^{\circ}C$, to observe discrete conformations. See the Supporting Information for details.

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[15] See the Supporting Information for van't Hoff analysis.

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[17] See the Supporting Information for details.

[18] We observe the same relative binding strengths: PhMe < PhH < $CHCl_3$ < EtOAc. Sherman obtained a much lower binding affinity for acetone, a result that we ascribe to competitive H-bonding by water in his system. Since such competitive H-bonding is absent in the present system, we believe that this new data provides a better value for the binding affinity of acetone.

[19] This *in*/*out* cavitand system offers an operationally simple method for relative guest affinities. We are investigating the use of related systems to provide equilibrium constants for host–guest binding events.

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