Tetrahedron Letters 52 (2011) 5176–5179

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Resorcin[4]arene-based anion receptors with four phenylurea substituents

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ARTICLE INFO

Article history:
Received 20 June 2011
Revised 25 July 2011
Accepted 27 July 2011
Available online 4 August 2011

Keywords:
Anion binding
Resorcin[4]arene
Urea
Carboxylate anion

ABSTRACT

Cavitand-based anion receptors were developed by the introduction of four phenylurea moieties on the upper rim of a resorcin[4]arene. Their binding properties for various anions were investigated in DMSO-d_6 using ^{1}H NMR spectroscopic methods, and the high 1:1 binding affinity for carboxylates was observed due to hydrophobic as well as charge-dipole interactions between host and guest.

Anions play important roles in biological, medical, environmental, and chemical sciences.[1] Due to these facts, there have been intensive efforts on exploring efficient artificial receptors for targeted anion recognition in supramolecular chemistry.[2,3] Urea,[4] amide,[5] and amidourea[6] groups have been used as useful structural moieties for calix[4]arene-based anion receptors because they function as good hydrogen-bonding donors as well as acceptors with the proper directionality important for binding-site organization. A variety of functional groups have been attached on the upper rim of resorcin[4]arene-based cavitands having concave molecular structure, which enables resorcin[4]arene-based cavitands to be attractive supramolecular building blocks for various organic receptors.[7] However, there are only a few resorcin[4]arene-based anion receptors capable of selective anion recognition.[8] Herein, we have developed new anion receptors with four phenylurea moieties that can recognize anions through hydrogen-bonding.

The syntheses of tetraphenylurea-cavitands **4** started with the Pd(0)-catalyzed Suzuki coupling reaction between cavitand **1** and 3-nitrobenzeneboronic acid using $Pd(PPh_3)_4$ as a catalyst which gave tetra(3-nitrophenyl)cavitand **2** in 64% yield (Scheme 1).[9] Subsequent transformation of cavitand **2** into tetra(3-aminophenyl)cavitand **3** was accomplished under catalytic hydrogenation using H_2/Raney Ni in toluene.[10] The target cavitands **4** were synthesized in 78–82% yield from the reaction of tetra(3-aminophenyl)cavitand **3** with the corresponding isocyanate (Y = H or NO_2) in triethylamine/THF (Scheme 1).[11] Pure cavitands **4** were obtained by recrystallization from a 4:1 mixture of CH_2Cl_2 and MeOH, and were fully characterized with ^{1}H and ^{13}C NMR, high-resolution MALDI-TOF mass spectrometry, and elemental analyses.

The recognition properties of tetrakis(phenylurea)cavitands **4** toward anions of various geometries were investigated using ^{1}H NMR spectroscopic methods with tetra-*n*-butylammonium salts ($Bu_4N^+X^-$). Cavitands **4** are hardly soluble in common organic solvents such as CH_2Cl_2 or $CHCl_3$, but soluble in highly polar solvents such as DMSO. Due to their limited solubility, titration experiments were carried out in DMSO-d_6.

Despite of the high hydrogen-bonding acceptor property of DMSO-d_6, the addition of various anions such as $CH_3CO_2^-$, $H_2PO_4^-$, BF_4^-, PF_6^-, NO_3^-, and I^- to the DMSO-d_6 solution of receptor **4a** or **4b** exhibited the peak broadening and a significant down-field shift of the urea –N*H* protons. No noticeable shifts of other signals of receptor could be observed. This imply that the anions were bound by urea N*H*···X$^-$ hydrogen bonding. The ^{1}H NMR titration curves of cavitand **4a** with various anionic guests are shown in Figure 1.

Tetrakis(4′-nitrophenylurea)cavitand **4a** showed the large down-field shifts of the urea –NH_b peak from 9.35 ppm to 11.53 ppm ($\Delta\delta$ = 2.18 ppm) and –NH_c from 8.85 ppm to 10.91 ppm ($\Delta\delta$ = 2.06 ppm) upon the complexation with acetate anion. And small down-field shifts ($\Delta\delta$ = 0.14–0.25 ppm) for the *ortho*- protons of the phenyl rings (H_a, H_d, and H_e) were observed in the same conditions. Cavitand **4a** also shows a moderate down-field shifts of the urea –N*H* signal ($\Delta\delta$ = 1.02 ppm) with $H_2PO_4^-$. But only small complexation-induced chemical shifts were observed in the case of BF_4^-, PF_6^-, NO_3^-, and I^-. The strong affinity of acetate anion may be attributed to its geometry. Due to Y-shaped geometry of acetate, the hydrogen bonding interactions between the carboxylate group and the two across urea –N*H* groups become more feasible. Together with the cavity filling effect of methyl group acetate anion was proved to be a favorable guest.

The same trends can be seen for tetrakis(phenylurea)cavitand **4b**. For cavitand **4b**, the signal of urea –N*H* is unresolved and

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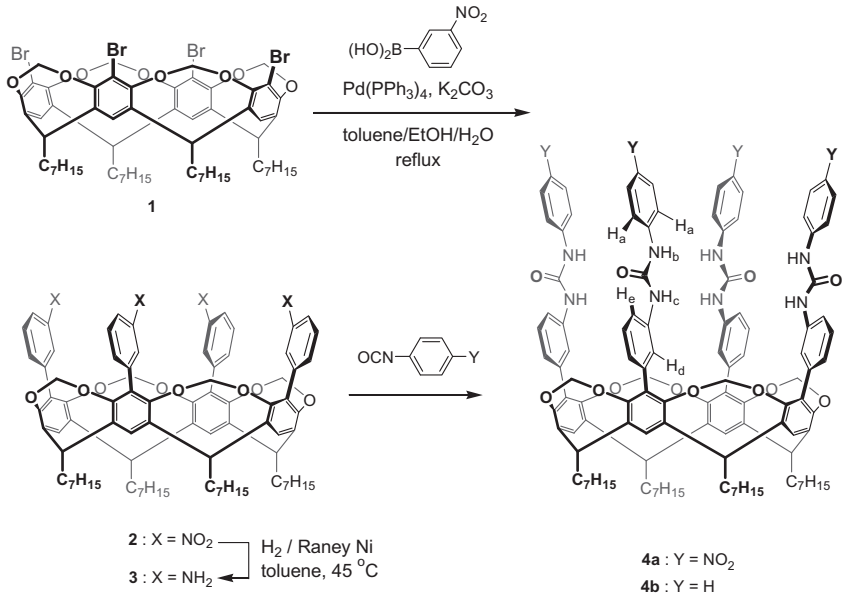
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.07.119



Scheme 1. Synthesis of tetrakis(phenylurea)cavitands **4.**

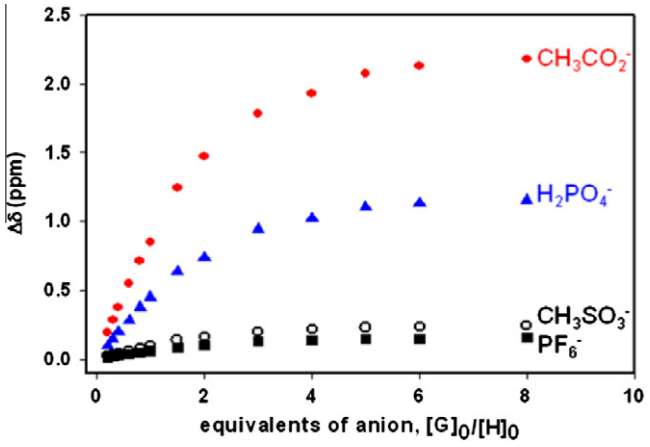


Figure 1. ^{1}H NMR titration curve of cavitand **4a** with tetrabutylammonium salts of anionic guests in DMSO-d_6. (Δδ: complexation-induced chemical shifts of the urea –NH_b protons).

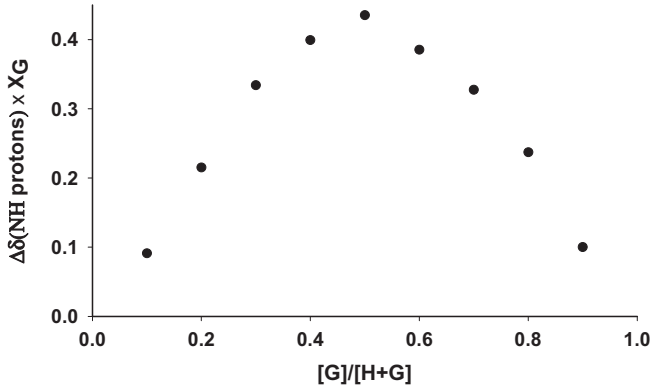


Figure 2. Job plot of cavitand **4a** with $Bu_4N^+CH_3CO_2^-$ in DMSO-d_6.

gradually moved to down-field from 8.62 ppm to 10.58 ppm (Δδ = 1.96 ppm) upon the addition of up to 8 equiv of acetate anion.

To determine the binding stoichiometry of cavitands **4** with anions, Job plot experiments[12] were used. Figure 2 shows the Job plot of cavitand **4a** with $CH_3CO_2^-$. The concentration of caviplex $CH_3CO_2^-$ **@4a** approaches a maximum when the molar fraction of anion is about 0.5, which indicates that $CH_3CO_2^-$ forms a 1:1 complex with cavitand **4a**.

The binding constant, K was determined through the monitoring of the complexation induced shifts of the urea –NH_b protons using the WinEQNMR,[13] a nonlinear least squares regression computer program. The binding constant values for cavitands **4a** and **4b** with various anions in DMSO-d_6 are summarized in Table 1.

Tetrakis(4-nitrophenylurea)cavitand **4a** showed a significant binding affinity toward carboxylate anions ($K_{acetate}$ = 421 M^{-1} and $K_{propionate}$ = 433 M^{-1}). Also, the binding of the tetrahedral $H_2PO_4^-$ is moderate ($K_{dihydrogen\ phosphate}$ = 213 M^{-1}). These affinities may be due to the basicity of carboxylate anions and $H_2PO_4^-$, allowing it to form stronger hydrogen-bonding with the urea –N*H*.[14] On the other hand, the complexation of other anions (BF_4^-, PF_6^-, NO_3^-, and I^-) exhibited weak binding affinities (K <30 M^{-1}).

Table 1
Binding constants (K, M^{-1}) of cavitand **4** with tetrabutylammonium salts in DMSO-d_6 at 25 °C

Host	$C_3H_7CO_2^-$	$CH_3CO_2^-$	$H_2PO_4^-$	BF_4^-	PF_6^-	NO_3^-	I^-
4a	433	421	213	21	23	17	13
4b	352	343	200	19	23	25	12

The binding affinity of cavitand **4a** is stronger than cavitand **4b**. The introduction of electron-withdrawing *para*-substituents, $-NO_2$, to the urea phenyl ring of cavitand **4a** increase the acidity of the urea –N*H* and accordingly strengthen the hydrogen bonding interaction between the urea –N*H* and anions.[13]

To estimate the orientation of anion in the cavity of cavitand **4a**, ^{1}H NMR titration experiments were performed with the larger $C_3H_7CO_2^-$ (Fig. 3). As $C_3H_7CO_2^-$ was added to the solution of cavitand **4a**, ^{1}H NMR spectra showed the up-field shift of the methyl protons of the complexed anion from 0.93 to 0.72 ppm (Δδ = −0.21 ppm). The relatively small upfield chemical shift and binding constant of complexed $C_3H_7CO_2^-$ seem to be due to the fast

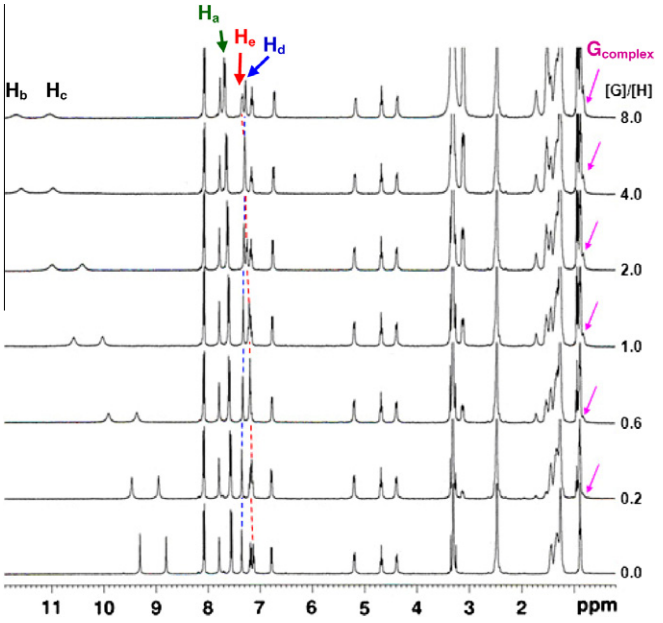


Figure 3. ^{1}H NMR spectra showing the chemical shift changes of cavitand **4a** (4 mM) by the addition of $Bu_4N^+C_3H_7CO_2^-$ in DMSO-d_6 at 25 °C.

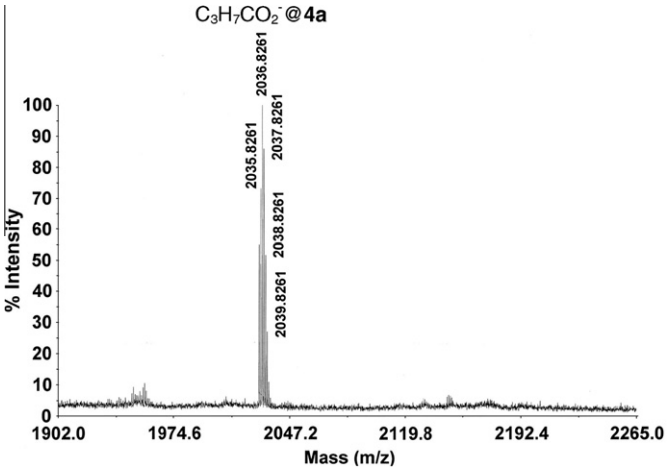


Figure 4. Negative mode MALDI-TOF mass spectrum of $C_3H_7CO_2^-$@**4a**.

complexation–decomplexation dynamic process of anion on the NMR time scale in polar DMSO-d_6 at 25 °C. However this implies that the alkyl group in the $C_3H_7CO_2^-$ is heading to inner cavity and Y-shaped $-CO_2^-$ binds with the urea –N*H* of cavitand **4a** in the upper part.[15] The binding constant was calculated to be 433 M^{-1} by WinEQNMR.

In negative mode MALDI-TOF mass spectrum (Fig. 4) a peak at m/z 2036.8261 corresponding to $C_3H_7CO_2^-$@**4a** was clearly observed.

The energy-minimized structures of tetrais(4-nitrophenylurea) cavitand **4a** and tetrakis(4-nitrophenylurea)caviplex $C_3H_7CO_2^-$@**4a** using Spartan'04 V1.03 (Molecular Mechanics MMFF) showed that four phenylurea groups of cavitand **4a** are directing in-ward and a well defined 1:1 caviplex $C_3H_7CO_2^-$@**4a** (Fig. 5).

In summary, new anion receptors **4** with four phenylurea moieties on the upper rim of a resorcin[4]arene cavitand were synthesized and their anion binding properties were studied by ^{1}H NMR titration in DMSO-d_6, negative mode MALDI-TOF mass spectrum, and molecular mechanics calculations. These new receptors

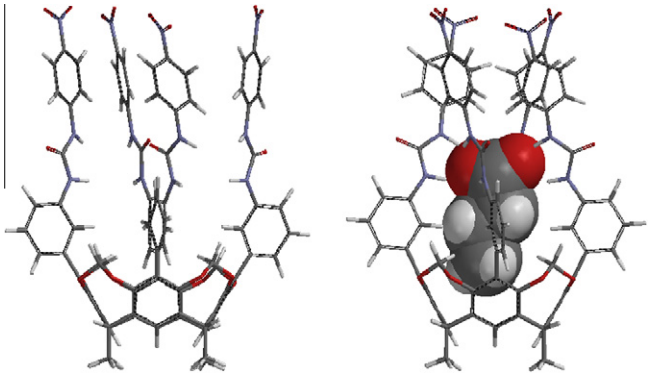


Figure 5. The energy-minimized structures of tetrakis(4-nitrophenylurea)-cavitand **4a** (left) and caviplex $C_3H_7CO_2^-$@**4a** (right) using Spartan'04 V1.03 (Molecular Mechanics MMFF).

showed the high affinities for 1:1 binding with carboxylate anions due to the dual hydrophobic as well as hydrogen bonding interactions. Currently various modifications to increase their solubility are on going.

Acknowledgments

This work was supported by CBMH (Yonsei University) and the Korea Research Foundation Grant funded by the Korean Government (KRF- 2009-0072919).

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9. Cavitand **2**: Tetrabromocavitand **1** (600 mg, 0.48 mmol), 3-nitrophenyl boronic acid (448 mg, 2.69 mmol), $Pd(PPh_3)_4$ (111 mg, 0.10 mmol) and K_2CO_3 (398 mg, 2.88 mmol) were mixed in degassed toluene (30 ml), H_2O (10 ml), and EtOH (10 ml) and heated to reflux for 3 days under argon atmosphere.After cooling the reaction mixture, the solvent was removed by distillation under reduce pressure, and the residue was dissolved in CH_2Cl_2 (30 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and

concentrated. Purification of the crude product by flash column chromatography on silica gel (Hexane:CH_2Cl_2 = 1:4) provided cavitand **2** as a white solid (434 mg, 64%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.0 Hz, 4H, Ar-*H*), 7.89 (s, 4H, Ar-*H*), 7.52 (t, J = 8.0 Hz, 4H, Ar-*H*), 7.45 (d, J = 8.0 Hz, 4H, Ar-*H*), 7.40 (s, 4H, Ar-*H*), 5.27 (d, J = 8.0 Hz, 4H, –OCH_{out}H$_{in}$O–), 4.86 (t, J = 7.8 Hz, 4H, –C*H*–), 4.29 (d, J = 6.8 Hz, 4H, –OCH$_{out}$$H_{in}$O–), 2.37 (m, 8H, –$CH_2$–), 1.54–1.31 (br m, 40H, –(CH_2)$_5$–), 0.92 (t, J = 6.8 Hz, 12H, –CH_3).

10. Cavitand **3**: Tetra(3-nitrophenyl)cavitand **2** (500 mg, 0.35 mmol) was dissolved in toluene (50 mL) in an autoclave, and to this solution was added a catalytic amount of Raney nickel, prewashed with ethanol (2 × 10 mL) and toluene (2 × 10 mL). After the autoclave was flushed and then pressurized with hydrogen (10 atm), the mixture was stirred at 45 °C for 24 h. After cooling to room temperature, catalyst was filtered through a pad of celite and rinsed with 10% CH_3OH/CH_2Cl_2 (2 × 30 mL). The filtrate was concentrated and dried under high vacuum to give tetra(3-aminophenyl)cavitand **3** as a white solid (438 mg, 96%) that was taken directly to the next step: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (s, 4H, Ar-*H*), 6.94 (t, J = 8.0 Hz, 4H, Ar-*H*), 6.42 (d, J = 8.0 Hz, 4H, Ar-*H*), 6.21 (d, J = 8.0 Hz, 4H, Ar-*H*), 6.20 (s, 4H, Ar-*H*), 5.10 (d, J = 8.0 Hz, 4H, –OCH_{out}H$_{in}$O–), 4.96 (s, 8H, –NH_2), 4.64 (t, J = 8.0 Hz, 4H, methine–C*H*–), 4.26 (d, J = 8.0 Hz, 4H, –OCH$_{out}$$H_{in}$O–), 2.44 (m, 8H, –$CH_2$–), 1.47–1.28 (br m, 40H, –(CH_2)$_5$–), 0.87 (t, J = 6.8 Hz, 12H, –CH_3).
11. Typical procedure: To a solution of tetra(3-aminophenyl)cavitand **3** (300 mg, 0.23 mmol) in dry THF (30 mL) was added triethylamine (0.1 mL, 1.0 mmol) and the solution was stirred for 5 min at room temperature. 4-nitrophenyl isocyanate (138 mg, 0.84 mmol) was added to the solution and the mixture was stirred for 14 h. The reaction mixture was concentrated under reduced pressure. The residue was recrystallized from CH_2Cl_2/MeOH (4:1) to give the cavitand **4a** as a yellow solid (362 mg, 82%). Cavitand **4a**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 4H, N*H*), 8.85 (s, 4H, N*H*), 8.12 (d, J = 9.2 Hz, 8H, Ar-*H*), 7.83 (s, 4H, Ar-*H*), 7.59 (d, J = 9.2 Hz, 8H, Ar-*H*), 7.40 (s, 4H, Ar-*H*), 7.23 (t, J = 7.6 Hz, 4H, Ar-*H*), 7.17 (d, J = 7.6 Hz, 4H, Ar-*H*), 6.83 (d, J = 7.6 Hz, 4H, Ar-*H*), 5.24 (d, J = 7.2 Hz, 4H, –OCH_{out}H$_{in}$O–), 4.72 (t, J = 7.8 Hz, 4H, methine–C*H*–), 4.43 (d, J = 7.2 Hz, 4H, –OCH$_{out}$$H_{in}$O–), 2.48 (m, 8H, –$CH_2$–), 1.48–1.28 (m, 40H, –(CH_2)$_5$–), 0.88 (t, J = 6.4 Hz, 12H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.80, 151.75, 146.2, 140.8, 138.3, 138.0, 134.0, 128.9, 128.1, 124.9, 124.2, 121.6, 120.1, 117.2, 99.8, 37.1 31.2, 29.5, 29.1, 28.8, 27.7, 22.0, 13.9; HRMS (MALDI-TOF) Calcd for $C_{112}H_{116}N_{12}NaO_{20}$ 1972.8360, Found 1972.8156 [M+Na]$^+$; Anal. Calcd for $C_{112}H_{116}N_{12}O_{20}$: C, 68.98; H, 6.00; N, 8.62. Found: C, 69.03; H, 5.80; N, 8.91. Cavitand **4b**: white solid (78%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 8H, –CON*H*), 7.82 (s, 4H, Ar-*H*), 7.41 (d, J = 7.6 Hz, 8H, Ar-*H*), 7.38 (s, 4H, Ar-*H*), 7.24 (t, J = 7.6 Hz, 8H, Ar-*H*), 7.19 (t, J = 7.6 Hz, 4H, Ar-*H*), 7.14 (d, J = 7.2 Hz, 4H, Ar-*H*), 6.94 (t, J = 7.2 Hz, 4H, Ar-*H*), 6.77 (d, J = 7.2 Hz, 4H, Ar-*H*), 5.23 (d, J = 7.6 Hz, 4H, –OCH_{out}H$_{in}$O–), 4.72 (t, J = 8.0 Hz, 4H, methine–C*H*–), 4.42 (d, J = 7.6 Hz, 4H, –OCH$_{out}$$H_{in}$O–), 2.48 (m, 8H, –$CH_2$–), 1.47–1.28 (m, 40H, –(CH_2)$_5$–), 0.87 (t, J = 6.8 Hz, 12H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.3, 151.8, 139.6, 139.0, 138.0, 133.9, 129.1, 128.6, 128.5, 128.1, 123.5, 121.7, 121.5, 119.6, 118.1, 118.0, 116.7, 99.9, 37.1, 31.3, 29.6, 29.1, 28.9, 27.7, 22.0, 13.9; HRMS (MALDI-TOF) Calcd for $C_{112}H_{120}N_8NaO_{12}$ 1792.8957, Found 1792.8040 [M+Na]$^+$; Anal. Calcd for $C_{112}H_{120}N_8O_{12}$: C, 75.99; H, 6.83; N, 6.33. Found: C, 75.78; H, 6.96; N, 6.22.
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