Supporting Information

Self-templated synthesis of an orthoformate *in*,*in*-cryptand and its bridgehead inversion by dynamic covalent exchange

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Contents

1. General Experimental Section 3

2. Synthetic Procedures and Characterization Data 4

2.1 Synthesis of Orthoester Cryptates 4

Synthesis of *o*-$(H_{in})_2$-1.1.1 4

Synthesis of [$Li^+ \subset$*o*-$(H)_2$-1.1.1]$BArF^-$ 6

Synthesis of *o*-$(H)_2$-1.1.1 6

Synthesis of [$Na^+ \subset$*o*-$(H)_2$-1.1.1]$BArF^-$ 6

2.2 Interconversion of orthoformate cryptands 8

3. Experimental Binding Studies 9

4. Crystallographic Data 11

Compound *o*-$(H_{in})_2$-1.1.1 11

Compound [$Na^+ \subset$*o*-$(H)_2$-1.1.1]$BArF^-$ 12

Analysis of intramolecular hydrogen bonds in *o*-$(H_{in})_2$-1.1.1 13

Analysis of M^+-O distances, O-C-O angles and R-C-O-M torsion angles in orthoformate and orthoacetate cryptands 13

5. References 14

1. General Experimental Section

Reagents and instruments

All commercially available reagents were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics or TCI and were used without further purification. Molecular sieves and aluminum oxide were dried for 3 days at 150 °C under reduced pressure (10^{-2} mbar) before use. $CDCl_3$ was dried for at least 3 days over molecular sieves. All solvents were dried over molecular sieves for at least 24 hours. All orthoester exchange reactions (catalyzed by TFA) were carried out under nitrogen. NMR spectra were recorded on Bruker Avance 400 or Bruker Avance 500 (^{1}H: 400 or 500 MHz) spectrometers at 298 K and referenced to the residual solvent peak (^{1}H: $CDCl_3$, 7.26 ppm; CD_3CN, 1.94 ppm, CD_2Cl_2: 5.32 ppm; ^{13}C: $CDCl_3$, 77.0 ppm; CD_3CN, 1.32 ppm, CD_2Cl_2: 53.84 ppm). Coupling constants (*J*) are denoted in Hz and chemical shifts (δ) in ppm. Mass spectra were obtained on a Bruker SolariX (HRMS-ESI$^+$, Solvent: methanol or acetonitrile) instrument.

Lithium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate was synthesized according to literature procedures.[1]

General Procedures

General Procedure A (metal-templated cryptate syntheses):

Drying of starting materials: Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate or Lithium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate was dissolved in anhydrous acetonitrile, trimethyl orthoformate (1 mL per gram MBArF) and a catalytic amount of TFA were added. The solvent was removed under reduced pressure and the salt was dried under high vacuum. Diethylene glycol was dried and stored over 3 Å MS and aluminum oxide.

Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (60 µmol, 1.0 equiv., 54 mg) or Lithium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (60 µmol, 1.0 equiv., 52 mg), diethylene glycol (180 µmol, 3.0 equiv., 17.3 µL) and anhydrous trimethyl orthoformate (120 µmol, 2.0 equiv., 13.3 µL) were dissolved in anhydrous chloroform (6 mL) under inert atmosphere. TFA stock solution (1.2 µmol, 0.01 equiv., 10 µL) was added. After equilibration of the reaction mixture, 5 Å MS was added. The reaction progress was monitored by ^{1}H-NMR spectroscopy. If needed, more TFA stock solution was added. Upon completion, the reaction was quenched by addition of triethylamine and the solvent was removed under reduced pressure. The crude product was purified by passing it over a short plug of silica gel. The plug was rinsed with anhydrous chloroform and removal of the solvent under reduced pressure gave the corresponding salts as colourless solids.

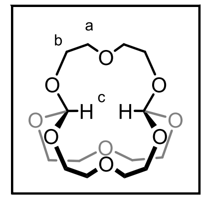
General Procedure B (NMR titrations):

Stock solutions of cryptand and NaBArF in $CDCl_3$ were prepared. The precise quantity of cryptand or metal salt was determined with 1,4-dinitrobenzene as internal standard. A cryptand stock solution with precise concentration was prepared *via* dilution. To the solution of metal salt, cryptand stock solution was added to keep the concentration of cryptand during the titration constant. 600 µL of cryptand stock solution were added to a standard NMR tube, varying amounts of metal salt stock solution were added. The titration was monitored by ^{1}H NMR spectroscopy (temperature: 298 K). Binding constants were fitted using Bindfit. All raw data, calculated fits and related data can be accessed *via* www.supramolecular.org.

2. Synthetic Procedures and Characterization Data

2.1 Synthesis of Orthoester Cryptates

Synthesis of *o*-(H$_{in}$)$_2$-1.1.1



Diethylene glycol (3.6 mmol, 3.0 equiv., 345 µL) and trimethyl orthoformate (2.4 mmol, 2.0 equiv., 265 µL) were dissolved in anhydrous chloroform (60 mL) under inert atmosphere. TFA (24 µmol, 0.01 equiv., 1.86 µL) was added. After equilibration of the reaction mixture, 5 Å MS was added. The reaction progress was monitored by ^{1}H-NMR spectroscopy. After 1 day more TFA (24 µmol, 0.01 equiv., 1.86 µL) was added. After 3 days in total the reaction was quenched by addition of triethylamine and the solvent was removed under reduced pressure. The crude product was purified by washing with diethyl ether to give ***o*-(H$_{in}$)$_2$-1.1.1** as crystalline solid (206 mg, 51%).

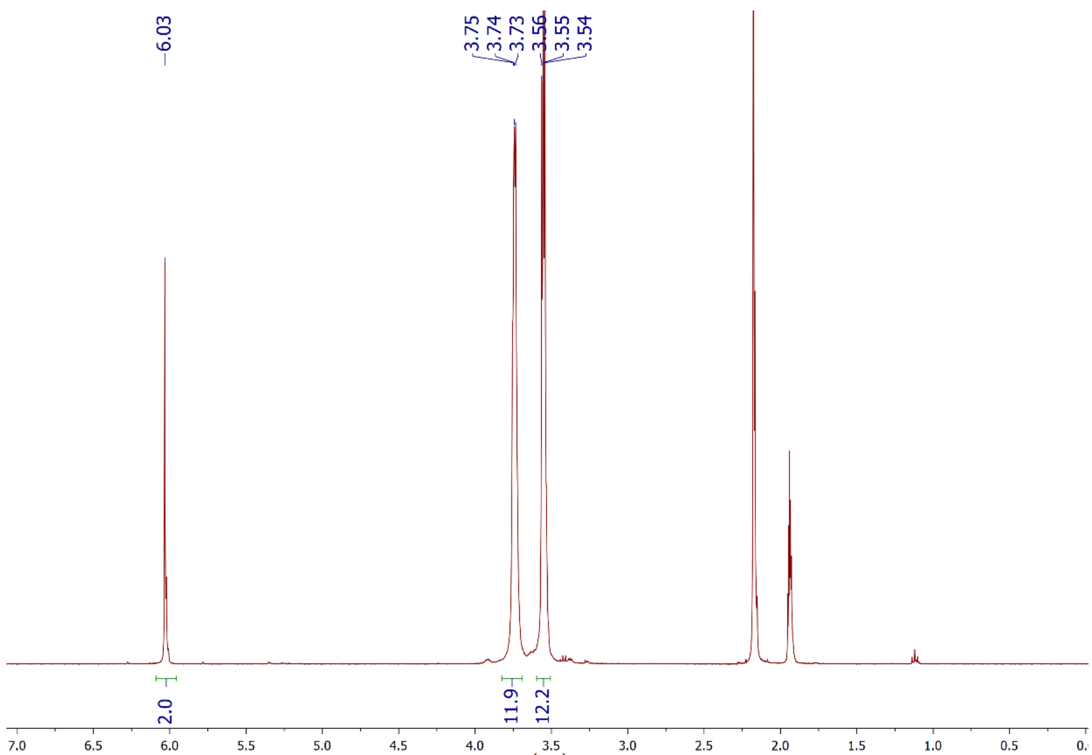
^{1}H-NMR (500 MHz, CD_3CN, 298 K): δ (ppm) = 6.03 (s, 2H, c), 3.78 – 3.70 (m, 12H, b), 3.58 – 3.51 (m, 12H, a).

^{13}C-NMR (125 MHz, CD_3CN, 298 K): *δ* (ppm) = 118.6, 73.7, 64.6.

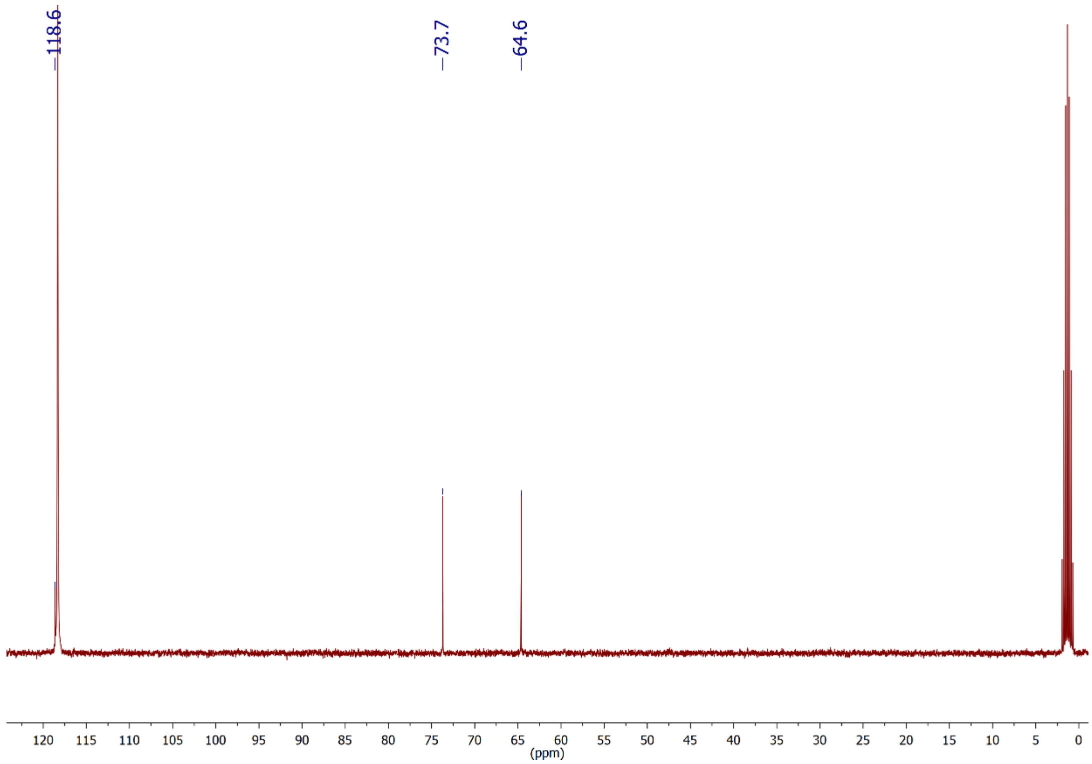
HRMS (ESI$^+$): *m/z* = 361.1471 [M+Na]$^+$ (calcd. 361.1469 for $C_{14}H_{26}NaO_9$).

m.p.: degradation >250 °C.

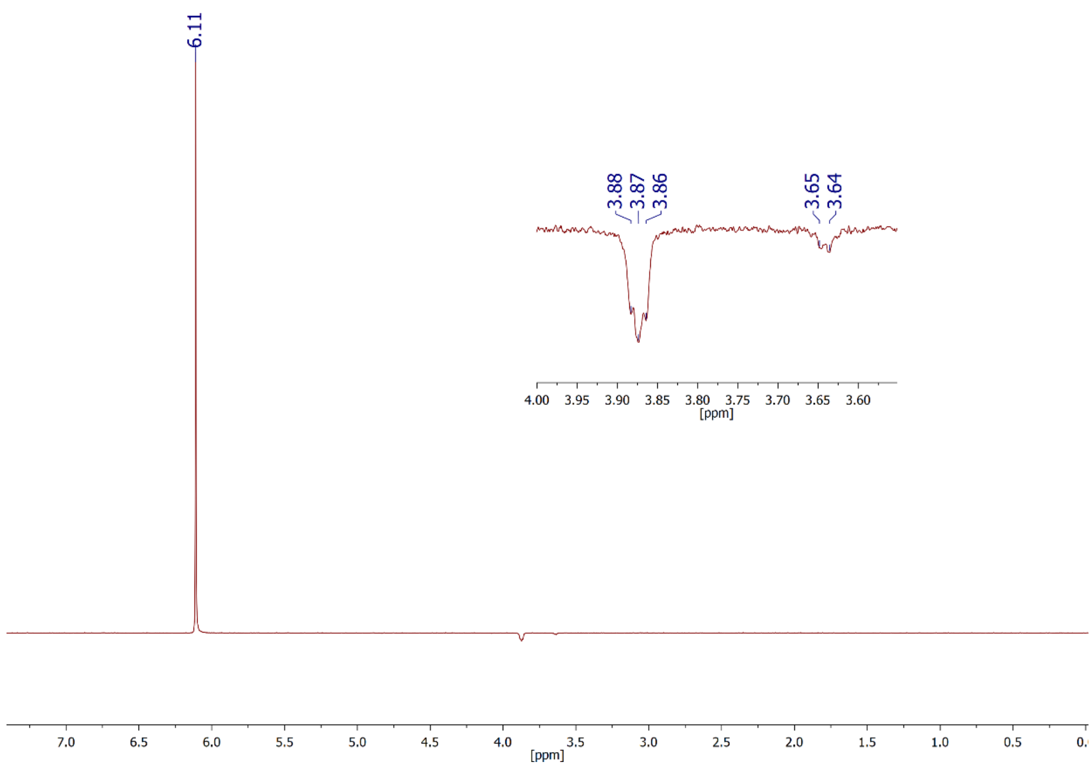
^{1}H NMR spectrum (500 MHz, CD_3CN, 298 K):



^{13}C NMR spectrum (125 MHz, CD_3CN, 298 K):

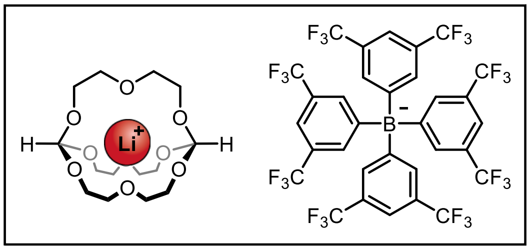


^{1}H NOE NMR spectrum (400 MHz, $CDCl_3$, 298 K):



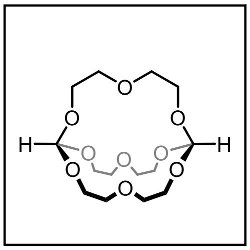
Synthesis of [Li$^+$⊂*o*-(H)$_2$-1.1.1]BArF$^-$

The synthesis of **[Li$^+$⊂*o*-(H)$_2$-1.1.1]BArF$^-$** was reported previously.[2] **[Li$^+$⊂*o*-(H)$_2$-1.1.1]BArF$^-$** was prepared according to general procedure A. The yield was improved to 55% (40 mg).



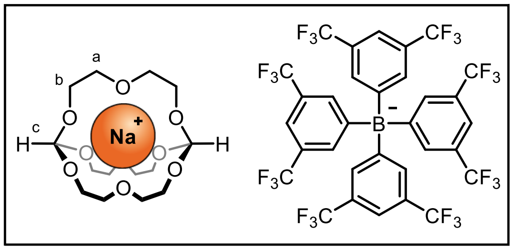
Synthesis of *o*-(H)$_2$-1.1.1

The synthesis of Synthesis of ***o*-(H)$_2$-1.1.1** was reported previously.[2]



Synthesis of [Na$^+$⊂*o*-(H)$_2$-1.1.1]BArF$^-$

***o*-(H)$_2$-1.1.1** (14.7 µmol, 1.0 equiv., 5.0 mg) was dissolved in acetonitrile and NaBArF (14.7 µmol, 1.0 equiv., 13.1 mg) was added. The mixture was stirred for 5 min, removal of the solvent gave the product **[Na$^+$⊂*o*-(H)$_2$-1.1.1]BArF$^-$** as colourless solid (18.1 mg, quant).



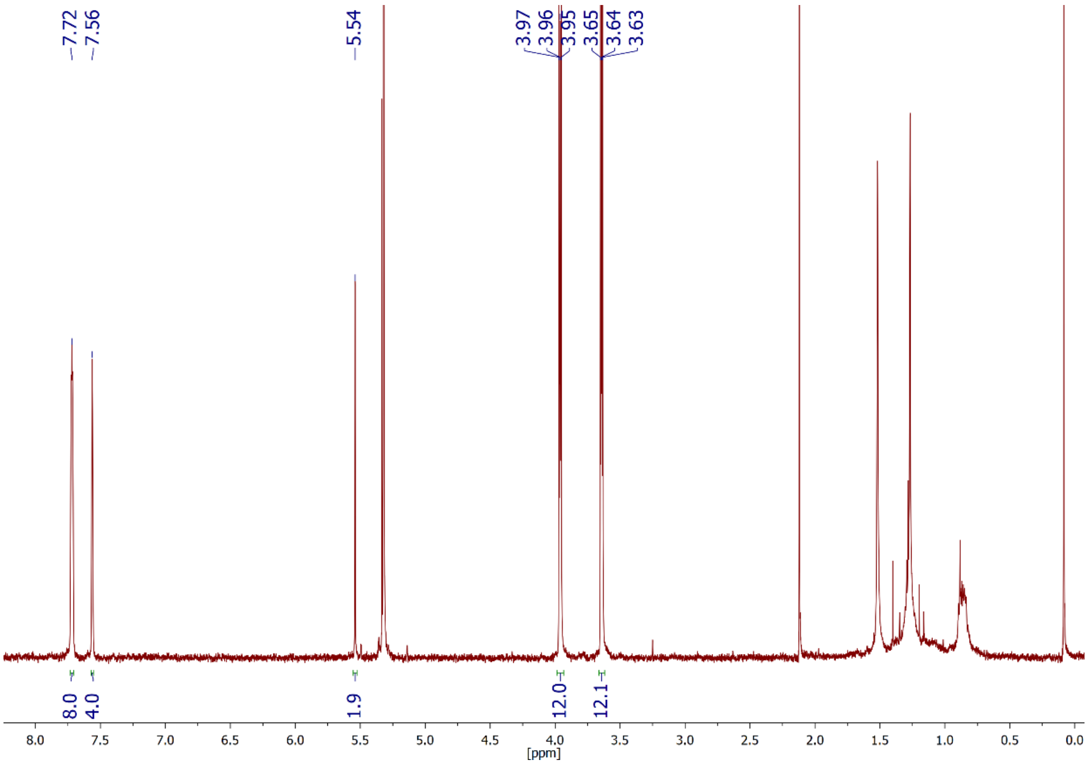
^{1}H-NMR (500 MHz, CD_2Cl_2, 298 K): δ (ppm) = 7.74 – 7.70 (m, 8H), 7.58 – 7.55 (m, 4H), 5.54 (s, 2H, c), 3.97 – 3.95 (m, 12H, b), 3.65 – 3.63 (m, 12H, a).

^{13}C-NMR (125 MHz, CD_2Cl_2, 298 K): *δ* (ppm) = 162.0, 161.6, 135.2, 128.3, 126.1, 123.9, 117.9, 117.9, 117.9, 117.8, 107.4, 70.4, 63.4.

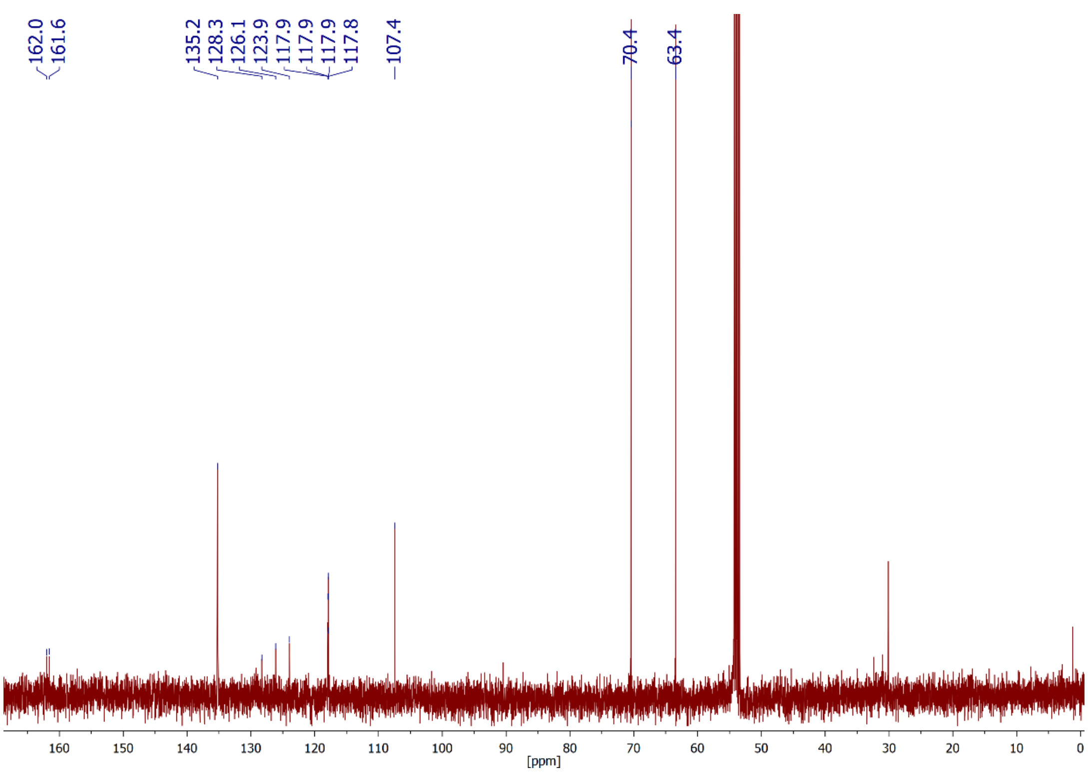
HRMS (ESI$^+$): *m/z* = 361.1470 [M+Na]$^+$ (calcd. 361.1469 for $C_{14}H_{26}NaO_9$).

m.p.: 182 °C.

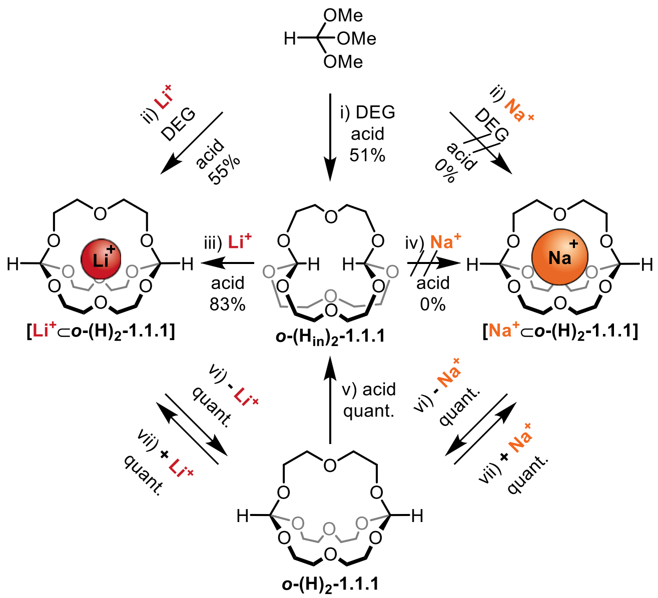
^{1}H NMR spectrum (500 MHz, CD_2Cl_2, 298 K):



^{13}C NMR spectrum (125 MHz, CD_2Cl_2, 298 K):



2.2 Interconversion of orthoformate cryptands



i) Self-assembly of ***o*-(H$_{in}$)$_2$-1.1.1**: See Section 2.1 Synthesis of Orthoester Cryptates.

ii) Self-assembly of **[Li$^+$⊂*o*-(H)$_2$-1.1.1]BArF$^-$** and attempted self-assembly of **[Na$^+$⊂*o*-(H)$_2$-1.1.1]BArF$^-$**: See General Procedure A and Section 2.1 Synthesis of Orthoester Cryptates.

iii) Conversion of ***o*-(H$_{in}$)$_2$-1.1.1** to **[Li$^+$⊂*o*-(H)$_2$-1.1.1]BArF$^-$**: ***o*-(H$_{in}$)$_2$-1.1.1** (60 µmol, 1.0 equiv.) was stirred in $CHCl_3$ (6 mL) with lithium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (60 µmol, 1.0 equiv.) and TFA stock solution (1.2 µmol, 0.01 equiv., 10 µL) for 10 min. The reaction was quenched by addition of triethylamine and the solvent was removed under reduced. The crude product was purified by passing it over a short plug of silica gel. The plug was rinsed with anhydrous acetonitrile and removal of the solvent under reduced pressure gave the product as colourless solid.

iv) Attempted conversion of ***o*-(H$_{in}$)$_2$-1.1.1** to **[Na$^+$⊂*o*-(H)$_2$-1.1.1]BArF$^-$**: ***o*-(H$_{in}$)$_2$-1.1.1** (60 µmol, 1.0 equiv.) was stirred in $CHCl_3$ (6 mL) with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (60 µmol, 1.0 equiv.) and TFA stock solution (1.2 µmol, 0.01 equiv., 10 µL) for 3 d. The reaction progress was monitored by ^{1}H-NMR spectroscopy and no conversion was observed.

v) Conversion of ***o*-(H)$_2$-1.1.1** cryptand to ***o*-(H$_{in}$)$_2$-1.1.1**: ***o*-(H)$_2$-1.1.1** (6 µmol, 1.0 equiv.) was dissolved in $CHCl_3$ (6 mL), TFA stock solution (0.12 µmol, 0.01 equiv., 1 µL) was added. The reaction mixture was left standing without stirring for 10 min. The reaction was quenched by addition of triethylamine and the solvent was removed under reduced pressure to give the product as colourless solid.

vi) Removal of metal salts: **[Na$^+$⊂*o*-(H)$_2$-1.1.1]BArF$^-$** or **[Li$^+$⊂*o*-(H)$_2$-1.1.1]BArF$^-$** (60 µmol, 1.0 equiv.) was stirred in $CHCl_3$ (6 mL) with chloride-loaded anion exchange resin (Lewatit MP-68) for 12 h. The resin was removed by filtration and the solvent was removed under reduced pressure to give the product as colourless oil.

vii) Reintroduction of metals: ***o*-(H)$_2$-1.1.1** (60 µmol, 1.0 equiv.) was stirred in CH_3CN (6 mL) with sodium or lithium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (60 µmol, 1.0 equiv.) for 5 min. Removal of the solvent under reduced pressure gave the products as colourless solids.

3. Experimental Binding Studies

The NMR titrations were carried out according to general procedure B.

	K_a [M^{-1}]	Fit error [M^{-1}]	avg. K_a [M^{-1}]	u [M^{-1}]	$U_{95\%}$ [M^{-1}]
NaBArF (1 mM)	500	30	500	30	±100
	500	20			
	400	10			

Table S1: Association constants obtained for the titration of ***o*-(H)$_2$-1.1.1** with **NaBArF** in $CDCl_3$ at 298 K. Fit method: Nelder-Mead. Binding model: 1:1.; u: standard uncertainty = $s/\sqrt{n}$; s: standard deviation; n: number of measurements; U: 95% confidence interval = $t_{(0.05,2)} \times u$; $t_{(\alpha, n-1)}$: student-t distribution at a probability α.[3]

NaBArF 1 mM	http://app.supramolecular.org/bindfit/view/292f7428-60d2-4ada-ae82-027f57613cfe
NaBArF 1 mM	http://app.supramolecular.org/bindfit/view/53fee8f7-156d-474b-b9d2-568f3128ec79
NaBArF 1 mM	http://app.supramolecular.org/bindfit/view/77054cde-c218-4d67-8d19-2b8eef99546e

Table S2: Links to raw data, calculated fits and statistical information for the titrations.

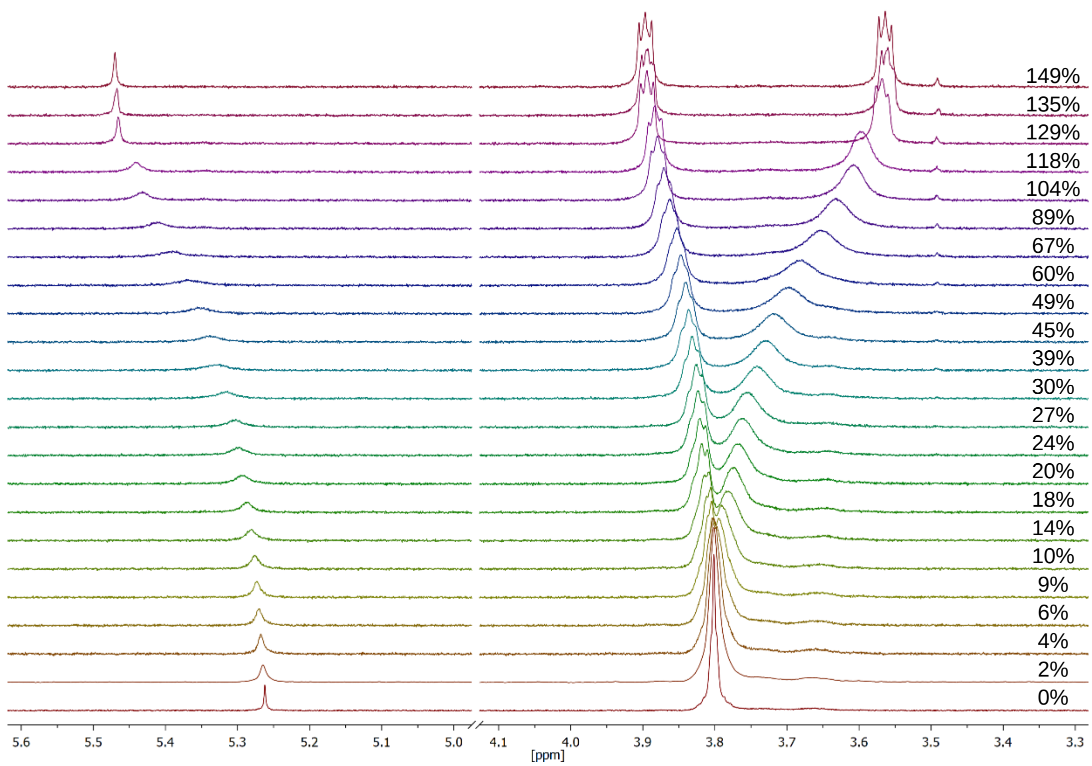


Figure S1: Representative partial ^{1}H NMR (500 MHz, 298 K, $CDCl_3$) stack plot for a titration of ***o*-(H)$_2$-1.1.1** with **NaBArF** from 0-149%.

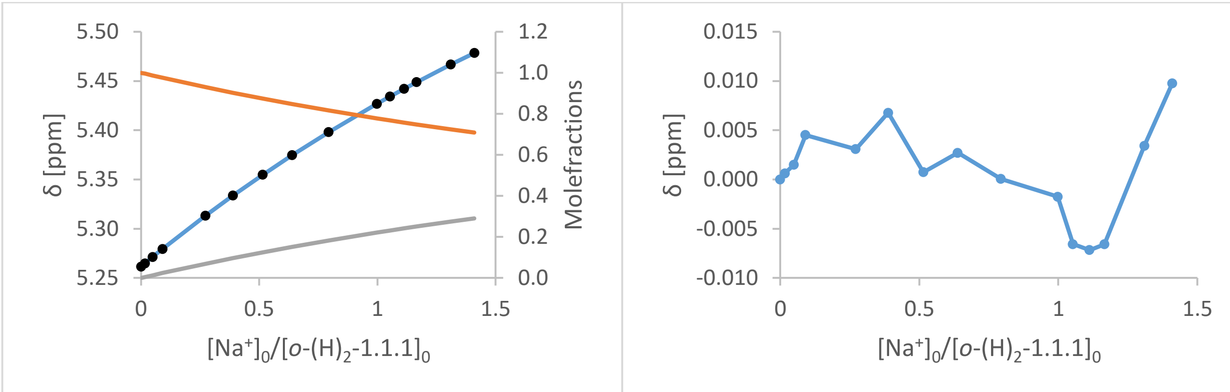


Figure S2: Left: Binding isotherm and species concentration plot for titration of ***o*-(H)$_2$-1.1.1** (1 mM) with **NaBArF** in $CDCl_3$ at 298 K. Black dots: Experimental points; Blue line: Fit according to 1:1 model; orange und grey lines: mole fractions of corresponding species. Right: Residual plot.

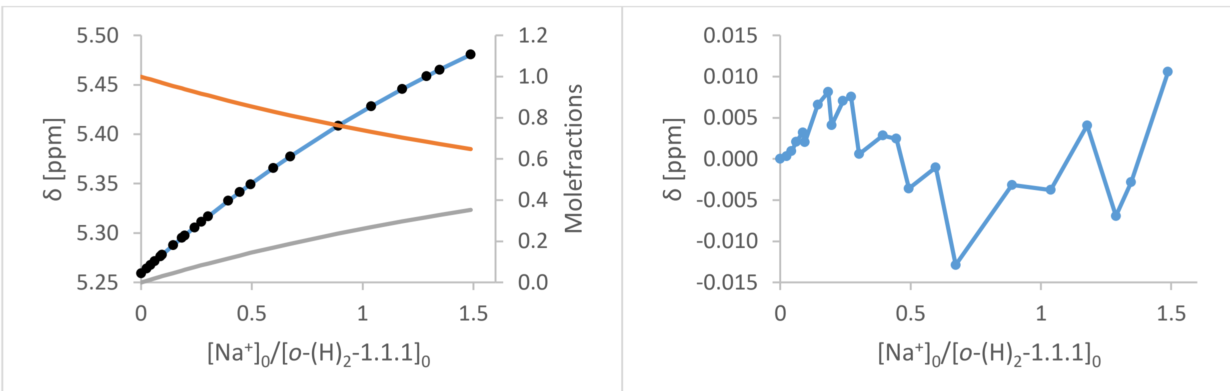


Figure S3: Left: Binding isotherm and species concentration plot for titration of ***o*-(H)$_2$-1.1.1** (1 mM) with **NaBArF** in $CDCl_3$ at 298 K. Black dots: Experimental points; Blue line: Fit according to 1:1 model; orange und grey lines: mole fractions of corresponding species. Right: Residual plot.

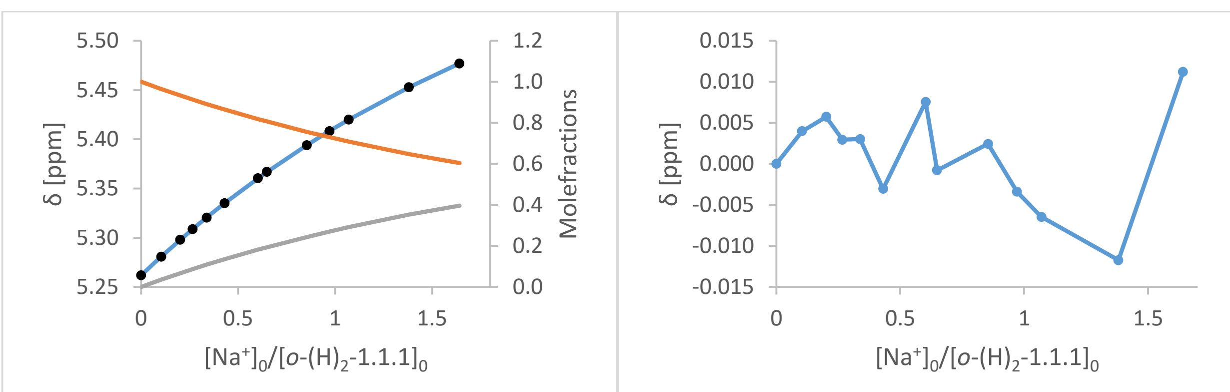
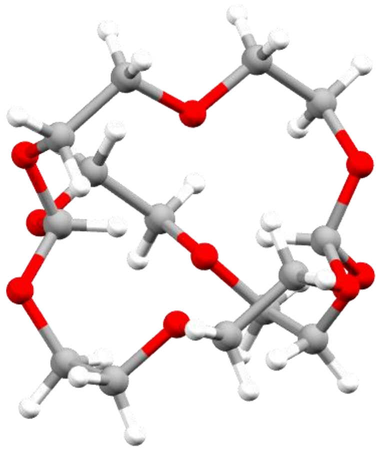


Figure S4: Left: Binding isotherm and species concentration plot for titration of ***o*-(H)$_2$-1.1.1** (1 mM) with **NaBArF** in $CDCl_3$ at 298 K. Black dots: Experimental points; Blue line: Fit according to 1:1 model; orange und grey lines: mole fractions of corresponding species. Right: Residual plot.

4. Crystallographic Data

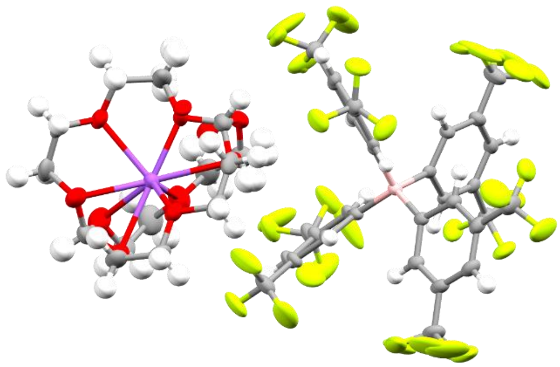
Compound *o*-(H_{in})$_2$-1.1.1



Empirical formula	$C_{14}H_{26}O_9$
Formula weight	338.35
Temperature/K	150.00(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	14.9352(5)
b/Å	8.20386(19)
c/Å	14.9002(4)
α/°	90
β/°	113.530(4)
γ/°	90
Volume/Å^3	1673.87(9)
Z	4
ρ_{calc}g/cm^3	1.343
μ/mm^{-1}	0.959
F(000)	728.0
Crystal size/mm^3	0.228 x 0.197 x 0.168
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	11.95 to 148.172
Index ranges	$-18 \leq h \leq 13$, $-10 \leq k \leq 8$, $-14 \leq l \leq 18$
Reflections collected	10016
Independent reflections	3329 [R_{int} = 0.0338, R_{sigma} = 0.0264]
Data/restraints/parameters	3329/0/209
Goodness-of-fit on F^2	1.054
Final R indexes [I>=2σ (I)]	R_1 = 0.0357, wR_2 = 0.0980
Final R indexes [all data]	R_1 = 0.0434, wR_2 = 0.1039
Largest diff. peak/hole / e Å^{-3}	0.26/-0.21

***o*-(H_{in})$_2$-1.1.1** was crystallized by slow evaporation of a solution of ***o*-(H_{in})$_2$-1.1.1** in diethyl ether. The cif-file was deposited in the Cambridge structural database under identifier CCDC 1876094.

Compound [Na$^+$⊂*o*-(H)$_2$-1.1.1]BArF$^-$



Empirical formula	$C_{46}H_{38}BF_{24}NaO_9$
Formula weight	1224.56
Temperature/K	149.95(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	13.1390(3)
b/Å	17.7561(3)
c/Å	21.7663(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	5078.00(19)
Z	4
ρ_{calc}g/cm^3	1.602
μ/mm^{-1}	0.174
F(000)	2472.0
Crystal size/mm^3	0.2282 x 0.1705 x 0.0955
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.538 to 59.1
Index ranges	$-13 \le h \le 17$, $-24 \le k \le 24$, $-27 \le l \le 26$
Reflections collected	67161
Independent reflections	12798 [R_{int} = 0.0419, R_{sigma} = 0.0356]
Data/restraints/parameters	12798/481/861
Goodness-of-fit on F^2	1.030
Final R indexes [I>=2σ (I)]	R_1 = 0.0454, wR_2 = 0.0941
Final R indexes [all data]	R_1 = 0.0649, wR_2 = 0.1040
Largest diff. peak/hole / e Å^{-3}	0.65/-0.33
Flack parameter	-0.08(12)

[Na$^+$⊂*o*-(H)$_2$-1.1.1]BArF$^-$ was crystallized by solvent layering of hexane over solution of **[Na$^+$⊂*o*-(H)$_2$-1.1.1]BArF$^-$** in chloroform. The cif-file was deposited in the Cambridge structural database under identifier CCDC 1876120.

Analysis of intramolecular hydrogen bonds in *o*-(H_{in})$_2$-1.1.1

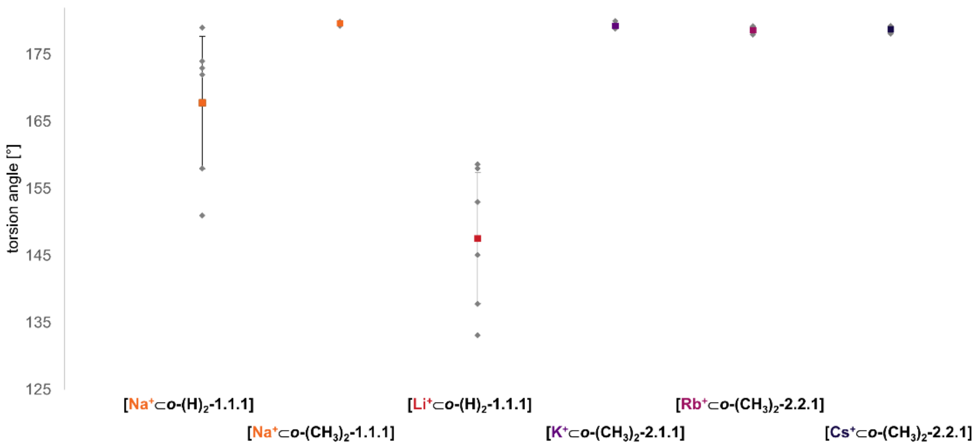
entry	Compound	H···O distance [Å]	C-H···O angles [°]	O-C-O angle [°]
1	***o*-(H_{in})$_2$-1.1.1**	2.4, 2.4, 2.4, 2.5, 2.5, 2.5	119.5, 119.5, 120.6, 121.1, 122.0, 122.3	107.48, 107.58, 107.67, 107.74, 107.91, 108.22

Table S3: H···O distances, C-H···O angles and O-C-O angles derived from solid state structure of ***o*-(H_{in})$_2$-1.1.1**.

Analysis of M^+-O distances, O-C-O angles and R-C-O-M torsion angles in orthoformate and orthoacetate cryptands

entry	Compound	M^+-O distance [Å] (orthoester oxygens)	M^+-O distance [Å] (chain oxygens)	O-C-O angle [°]	Torsion angle R-C-O-M [°]
1	**[Na^+⊂*o*-(H)$_2$-1.1.1] BArF$^-$**	2.242(5), 2.512(3), 2.553(3), 2.553(3), 2.677(3), 3.606(4)	2.433(3), 2.445(3), 2.592(3)	104.3(3), 104.9(3), 107.4(3), 107.7(3), 111.6(3), 116.7(4)	151(2), 159(2), 171(4), 173(2), 175(4), 176(4)
2 ref.:4	**[Na^+⊂*o*-(CH_3)$_2$-1.1.1] BArF$^-$**	-	-	-	179.3, 179.5, 179.7, 179.7, 179.8, 179.9
3 ref.: 2	**[Li^+⊂*o*-(H)$_2$-1.1.1]BArF$^-$**	1.957(5), 1,963(5), 2.940(5), 3.157(5), 3.620(5), 3.672(5)	2.163(5), 2.176(6), 2.232(5)	105.9(2), 106.4(2), 110.4(2), 110.9(3), 112.1(3), 112.2(2)	133.1, 137.8, 145.1, 153.0, 158.0, 158.6
4 ref.:1	**[K^+⊂*o*-(CH_3)$_2$-2.1.1] BArF$^-$**	-	-	-	178.9, 179.0, 179.1, 179.4, 179.4, 180.0
5 ref.:1	**[Rb^+⊂*o*-(CH_3)$_2$-2.2.1] BArF$^-$**	-	-	-	178.0, 178.0, 178.8, 178.8, 179.2, 179.2
6 ref.:1	**[Cs^+⊂*o*-(CH_3)$_2$-2.2.1] BArF$^-$**	-	-	-	178.1, 178.2, 178.9, 179.0, 179.2, 179.2

Table S4: Comparison of M^+-O distances, O-C-O angles and torsion angles in orthoformate and orthoacetate cryptands.



Graph 1: Comparison of R-C-O-M torsion angles of orthoformate and orthoacetate cryptands.[1,2,4]

5. References

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