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Supporting Information for

Highly Selective Monomethylation of Primary Amines Through Host-Guest Product Sequestration

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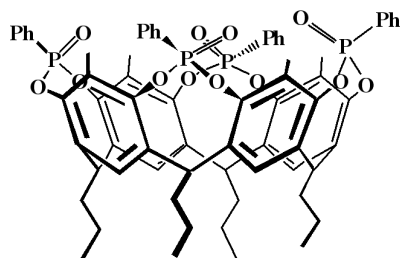
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1. General Methods.

^1H NMR spectra were obtained with a Bruker AC-300 (300 MHz) or a Bruker AVANCE 300 (300 MHz) spectrometer. All chemical shifts (δ) were reported in ppm relative to the proton resonances resulting from incomplete deuteration of the NMR solvents. ^{31}P NMR spectra were obtained with a Bruker AMX-400 (172 MHz) spectrometer and Varian INOVA 600 (600 MHz). All chemical shifts (δ) were recorded in ppm relative to external 85% H_3PO_4 at 0.00 ppm. Electrospray ionization ESI-MS experiments were performed on a Waters ZMD spectrometer equipped with an electrospray interface. The GC-MS were performed on Agilent Technologies (mod.6890N) equipped with MS HEWLETT-PACKARD (mod. 5970) detector. The temperature programme used for the separation of samples and the internal standard started at 60 °C (held 3 min), set at 20 °C /min from 60 °C to 260 °C and held isothermally at 260 for 5 min. Column chromatography was performed by using silica gel 60 (MERCK 70-230 mesh). Microanalyses were performed by using the facilities at Parma University. All solvents were dried and distilled using standard procedures. All commercial reagents were ACS reagent grade and used as received.

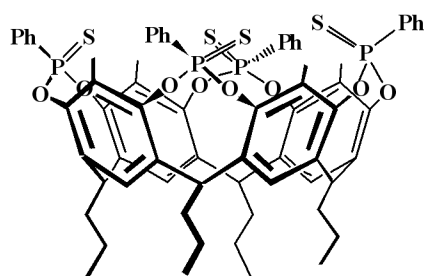
2. Synthesis of the cavitand receptors

Tiiii [C_3H_7 , CH_3 , Ph]



The **Tiiii** [C_3H_7 , CH_3 , Ph] cavitand was synthesized following the procedure reported in literature (Biavardi, E.; Battistini, G.; Montalti, M.; Yebeutou, R. M.; Prodi, L.; Dalcanale, E. *Chem. Commun.*, **2008**, 1638-1640).

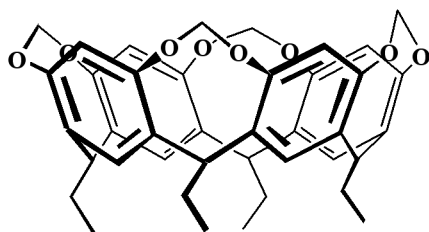
TSiiii [C_3H_7 , CH_3 , Ph]



To a solution of propyl-footed resorcinarene (2.5 g, 3.5 mmol) dissolved in 20 mL of freshly distilled pyridine, dichlorophenylphosphine (1.93 mL, 14.3 mmol) was slowly added at room temperature. The reaction mixture was stirred for 3h at 80°C then cooled at room temperature after the addition. An excess of S_8 was added and left to stir for 1h. The solvent was removed under vacuum. 50 mL of water were added and the resulting yellow suspension was filtered out. Purification by column chromatography on silica gel with a mixture 9:1 of methylene chloride and hexane yielded the product (2.74 g, 62%)

¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.05 (t, 12H, CH₂CH₃, J = 7.2 Hz), 1.43 (m, 8H, CH₂CH₃), 2.10 (s, 12H, ArCH₃), 2.31 (m, 8H, CH₂CH₂CH₃, J = 7.5 Hz), 4.72 (t, 4H, CHCH₂, J = 7.8 Hz), 7.24 (s, 4H, ArH), 7.53 (m, 8H, O=PArH_m), 7.60 (m, 4H, O=PArH_p), 8.20 (m, 8H, O=PArH_o). **³¹P NMR** (172 MHz, CDCl₃) δ (ppm): 72.00 (s, P=S). **ESI-MS**: calculated for C₆₈H₆₈NO₈P₄S₄: 1265.4. Found: 1265.3 (M + H)⁺ and 1304.6 (M + K)⁺.

Mecav[C₂H₅, H]



To a solution of ethyl-footed resorcinarene (3.0 g, 5 mmol) dissolved in 20 mL of dry DMSO, K₂CO₃ (11.06 g, 80-mmol) and CH₂Br₂ (2.0 mL, 36-mmol) were added, under nitrogen. The purple mixture was stirred in a sealed tube at 90°C for 3 hours. The reaction was quenched in water, acidified with HCl and the resulting mixture was extracted with CH₂Cl₂. The organic layer

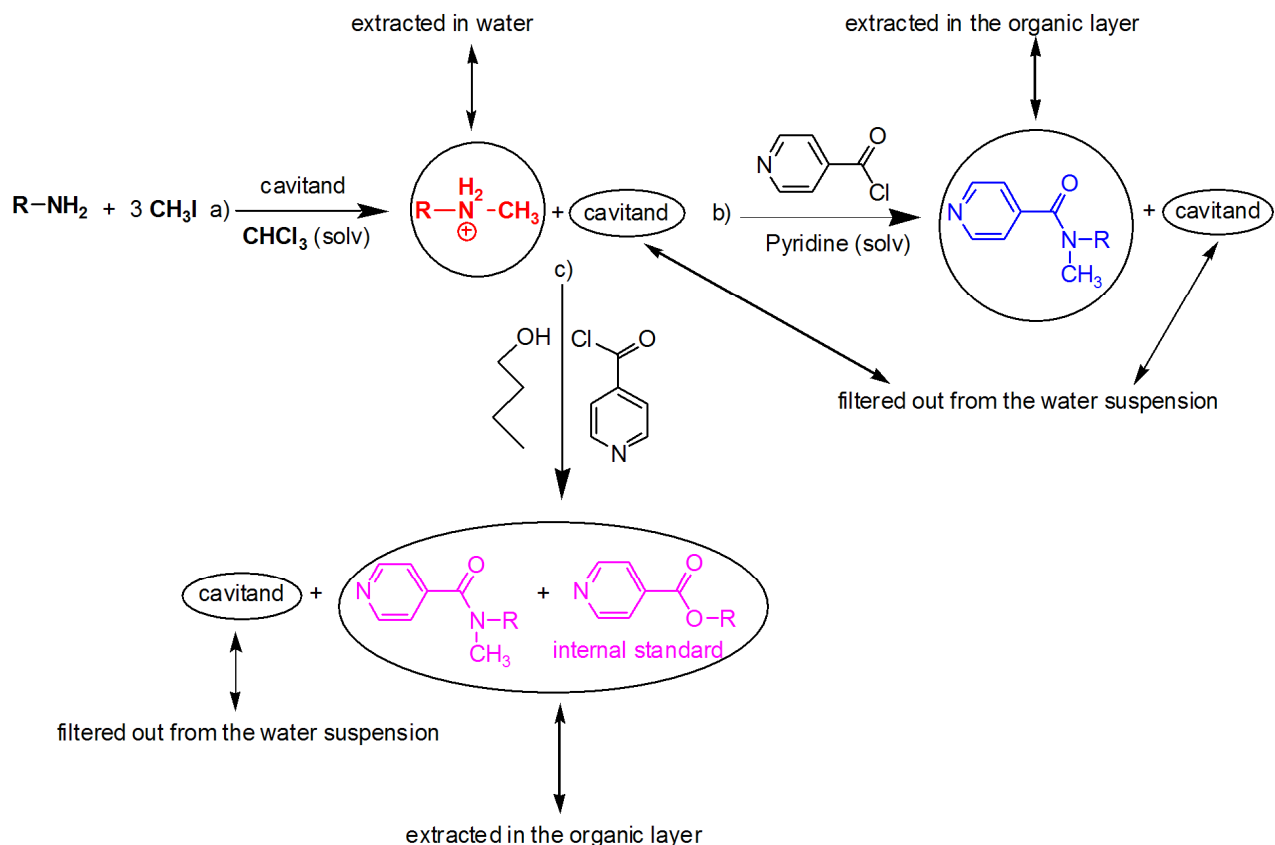
was washed with water (3 x 15 mL), dried over Na₂SO₄ and evaporated. The crude product was purified by column chromatography on silica gel by using hexane/ethyl acetate (6/4) as eluant to give the product (2.85 g, 88 %).

¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.00 (t, 12H, CH₃), 2.30 (m, 8H, CHCH₂CH₃), 4.40 (d, 4H, CH_{in}, J = 7.2 Hz), 4.70 (t, 4H, CHAr₂, J = 8.1 Hz), 5.71 (d, 4H, CH_{out}, J = 7.2 Hz), 6.52 (s, 4H, ArH). **ESI-MS**: *m/z* (%): calculated for C₄₀H₄₀O₈: 649.3; Found: 650.7 (M+H)⁺.

3. Characterization Procedures

Three different procedures were used to determine the yields of the N-monomethylated products reported in Table 2.

- Procedure 1: the yields were determined gravimetrically by weighting and characterizing the crystallized monomethylated ammonium salt (¹H NMR, ESI-MS, E.A.), obtained by treating the crude product with water (Scheme S1-a).
- Procedure 2: the yields were determined gravimetrically by weighting and characterizing (¹H NMR, GC-MS) the corresponding nicotinamide, resulting from the derivatization reaction on the crude (Scheme S1-b).
- Procedure 3: the yields were determined from the GC-MS injection of a solution 60 µg L⁻¹ obtained from the derivatization reaction in the presence of the n-butanol as precursor of the internal standard (Scheme S1-c). Butyl isonicotinate was used for calibration.



Scheme S1. Different characterization procedures used.

4. Procedure 1.

To a solution of the primary amine (0.21 mmol) dissolved in 6 mL of chloroform, one equivalent of **Tiii** [C_3H_7 , CH_3 , **Ph**] (252.2 mg, 0.21 mmol) and three equivalents of methyl iodide (39.2 μ L, 0.63 mmol) were added. The mixture was stirred for 16 hr at room temperature. The solvent and the excess of methyl iodide were removed under vacuum. 5 mL of water were added and the suspension of the cavitand **Tiii** [C_3H_7 , CH_3 , **Ph**] was filtered out. This operation was repeated three times in order to maximize the recovery of the ammoniums salts. The resulting colourless water solution was evaporated and the product crystallized from methylene chloride/ethyl ether 1/1.

N-methylethylammonium iodide (Isolated yield: 62%, 24.4 mg, 0.13 mmol): 1H NMR (300 MHz, CD_3CN) δ (ppm): 1.32 (t, 3H, $CH_3CH_2NH_2CH_3$, $J = 7.3$ Hz), 2.99 (m, 2H, $CH_3CH_2NH_2CH_3$), 2.55 (s, 3H, NH_2CH_3), 7.24 (broad, 2H, $CH_3CH_2NH_2CH_3$). **ESI-MS:** calculated for $C_3H_{10}IN$: 187.9; found: m/z 313.9 ($M + 2I$) $^-$. **Elemental Analysis:** Calculated for $C_3H_{10}IN$: C, 19.27; H, 5.39; N, 7.49. Found: C, 19.02; H, 5.26; N, 7.45.

***N*-methylpropylammonium iodide (Isolated yield: 62%, 26.2 mg, 0.13 mmol):** ^1H NMR (300 MHz, CD_3CN) δ (ppm): 0.96 (t, 3H, CH_3CH_2 , $J = 7.3$ Hz), 1.73 (m, 2H, CH_3CH_2), 2.57 (s, 3H, NH_2CH_3), 2.91 (t, 2H, $\text{CH}_2\text{NH}_2\text{CH}_3$, $J = 7.5$ Hz), 7.15 (broad, 2H, $\text{CH}_2\text{NH}_2\text{CH}_3$). **ESI-MS:** calculated for $\text{C}_4\text{H}_{12}\text{IN}$: 201.0; found: m/z 328.0 ($\text{M} + 2\text{I}$) $^-$. **Elemental Analysis:** Calculated for $\text{C}_4\text{H}_{12}\text{IN}$: C, 23.90; H, 6.02; N, 6.97. Found C, 23.71; H, 5.86; N, 6.92.

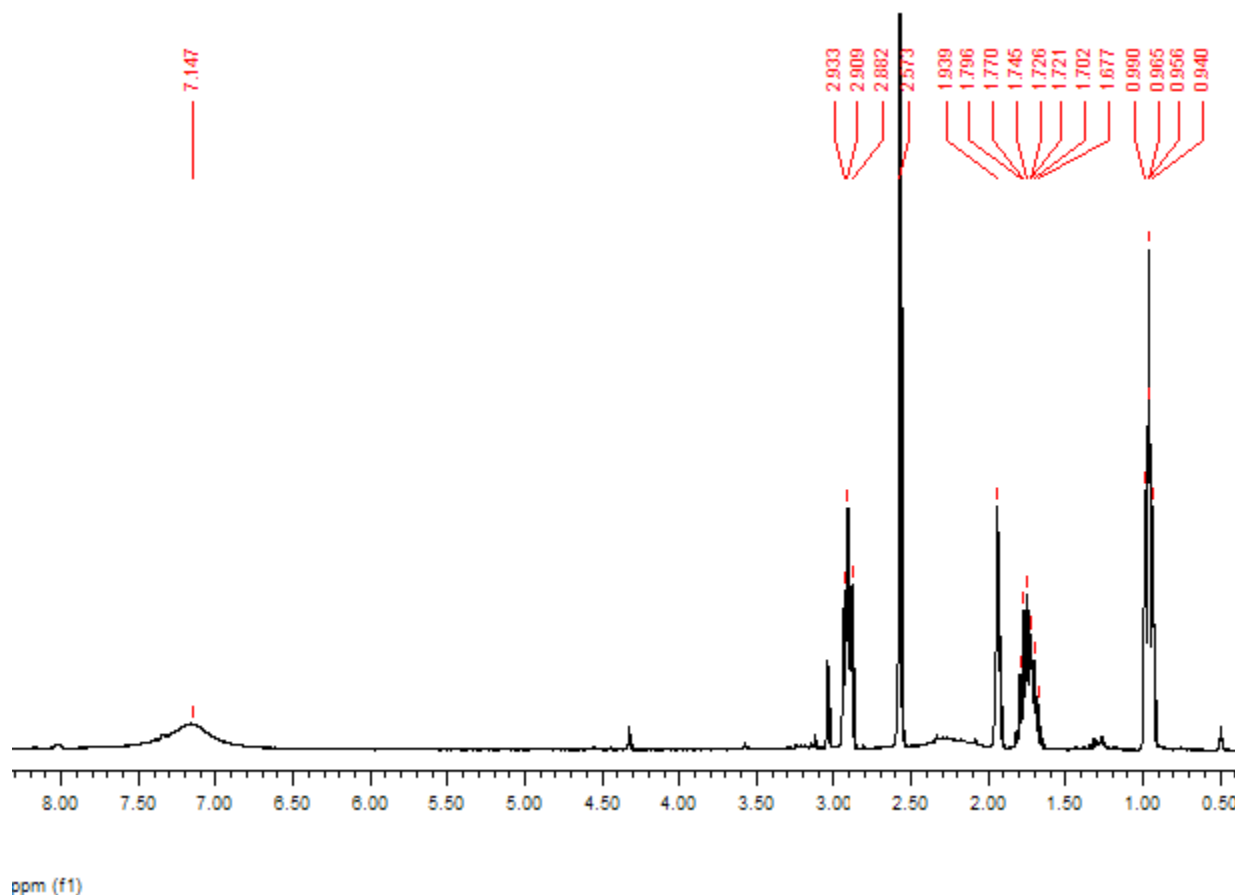


Figure S1. ^1H NMR spectrum of *N*-methylpropylammonium iodide in CD_3CN .

***N*-methylbutylammonium iodide (Isolated yield: 62%, 28.0 mg, 0.13 mmol):** ^1H NMR (300 MHz, CD_3CN) δ (ppm): 0.91 (t, 3H, CH_3CH_2 , $J = 7.3$ Hz), 1.40 (m, 2H, CH_3CH_2), 1.70 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$), 2.55 (s, 3H, $\text{CH}_2\text{NH}_2\text{CH}_3$), 2.90 (t, 2H, $\text{CH}_2\text{NH}_2\text{CH}_3$, $J = 7.5$ Hz), 7.50 (broad, 2H, NH_2CH_3). **ESI-MS:** calculated for $\text{C}_5\text{H}_{14}\text{IN}$: 215.0; found: m/z 342.0 ($\text{M} + 2\text{I}$) $^-$. **Elemental Analysis:** Calculated for $\text{C}_5\text{H}_{14}\text{IN}$: C, 27.92; H, 6.56; N, 6.51. Found C, 27.60; H, 6.43; N, 6.14.

***N*-methylheptylammonium iodide (Isolated yield: 67%, 36.0 mg, 0.14 mmol):** ^1H NMR (300 MHz, CD_3CN) δ (ppm): 0.88 (CH_3CH_2 , 3H, $J = 7.4$ Hz), 1.30 (m, 8H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 1.71 (m, 2H, $\text{CH}_2\text{CH}_2\text{NH}_2$), 2.41 (s, 3H, CH_3NH_2), 2.94 (t, 2H, $\text{CH}_2\text{CH}_2\text{NH}_2$, $j = 6.0$ Hz), 6.75 (t, 2H, NH_2 , $J = 50.3$ Hz). **ESI-MS:** calculated for $\text{C}_8\text{H}_{20}\text{IN}$: 257.2; found: m/z 130.3 ($\text{M} - \text{I}$) $^+$. **Elemental Analysis:** Calculated for $\text{C}_8\text{H}_{20}\text{IN}$: C, 37.37; H, 7.84; N, 5.45. Found C, 37.27; H, 7.77; N, 5.30.

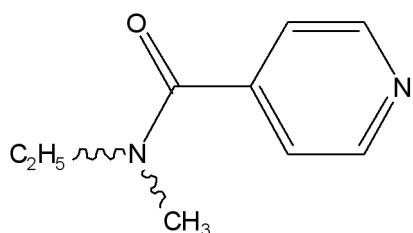
N-methylcyclohexylammonium iodide (Isolated yield: 72%, 36.4 mg, 0.15 mmol): ^1H NMR (300 MHz, CD_3CN) δ (ppm): 1.16 - 2.09 (broad, 10H, $\text{CH}_2(\text{CH}_2)_2(\text{CH}_2)_2$), 2.53 (s, 3H, CH_3NH_2), 3.08 - 3.24 (m, 2H, CHNH_2). 4.96 (broad, 2H, NH_2). **ESI-MS:** calculated for $\text{C}_7\text{H}_{16}\text{IN}$: 241.1; found: m/z 115.8 ($\text{M} - \text{I}$) $^+$. **Elemental Analysis:** Calculated for $\text{C}_7\text{H}_{16}\text{IN}$: C, 34.87; H, 6.69; N, 5.81. Found C, 34.68; H, 6.51; N, 5.69.

N-methylanilinium iodide. (Isolated yield: 72%, 35.5 mg, 0.15 mmol): ^1H NMR (300 MHz, CD_3CN) δ (ppm): 2.99 (s, 3H, CH_3), 7.45 - 7.53 (broad m, 5H, C_5H_5). **ESI-MS:** calculated for $\text{C}_7\text{H}_{10}\text{IN}$: 235.1; found: m/z 108.7 ($\text{M} - \text{I}$) $^+$. **Elemental Analysis:** Calculated for $\text{C}_7\text{H}_{10}\text{IN}$: C, 35.77; H, 4.29; N, 5.96. Found C, 35.58; H, 4.13; N, 5.76.

5. Procedure 2 (isolated yields of derivatized products).

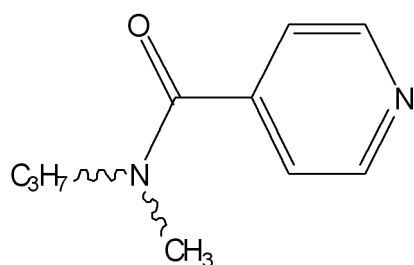
After the monomethylation reaction, the solvent and the excess of methyl iodide were removed under vacuum. The crude was dissolved in 6 mL of pyridine and divided in 2 equal portions. In the case of reaction with the internal standard, one equivalent of butanol (10.1 μL , 0.11 mmol) was added to one of the portions. After the addition of an excess of isonicotinoyl chloride hydrochloride, the solutions were stirred for 3 h at 100 $^\circ\text{C}$. The solvent was removed under vacuum. The resulting crudes were treated with water and the cavitand suspension was filtered out. The colourless water solutions were basified with solid K_2CO_3 and then they were extracted with CH_2Cl_2 . The organic layer was rinsed with acidic and neutral water to neutrality, the solvent evaporated leading to a colourless liquid for aliphatic amines, white and yellow crystals for cyclohexylamine and aniline respectively.

N-ethyl, N-methyl isonicotinamide



(Isolated yield: 75%, 13.0 mg, 0.079 mmol): ^1H NMR (300 MHz, CD_3CN) δ (ppm): 1.16 and 1.06 (t, 3H, CH_2CH_3 , $J = 7.2$ Hz), 2.97 and 2.82 (s, 3H, CH_3N), 3.48 and 3.15 (t, 2H, CH_2N , $J = 7.2$ Hz), 7.26 (d, 2H, H_{mpy} , $J = 4.5$ Hz), 8.62 (d, H_{opy} , $J = 4.5$ Hz). **GC-MS:** $r_t = 8.23$ min. m/z (%): (M^+) = 164 (27.2), 106 (100), 163 (51.2), 78(50.9), 51 (23.6), 58 (8.7), 79 (5.9), 135 (5.3), 149 (3.6).

N-methyl, N-propyl isonicotinamide



(Isolated yield: 79%, 14.8 mg, 0.083 mmol): ^1H NMR (300 MHz, CD_3CN) δ (ppm): 0.93 and 0.70 (t, 3H, CH_2CH_3 , $J = 7.3$ Hz), 1.64 and 1.51 (m, 2H, CH_2CH_3), 2.97 and 2.82 (s, 3H, CH_3N), 3.43 and 3.09 (t, 2H, NCH_2 , $J = 7.2$ Hz), 7.26 (d, 2H, H_{mpy} , $J = 3.6$ Hz), 8.61 (d, 2H, H_{opy} , $J = 3.6$ Hz). GC-MS: rt = 8.77 min. m/z (%): (M^+) = 178 (12.5), 106 (100), 78(29.4), 177 (10.7), 149 (12.5), 51 (12.5), 107 (6.25), 135 (5.3), 163 (1.7).

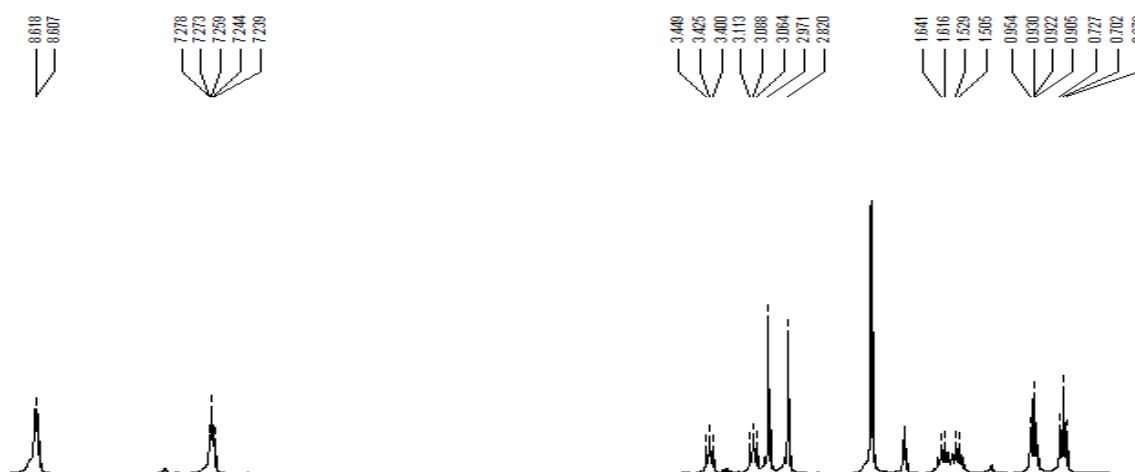
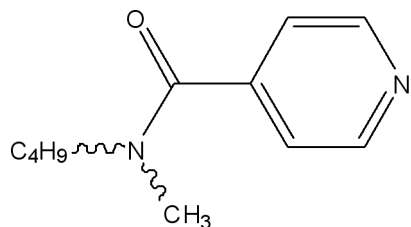


Figure S2. ^1H NMR spectrum of N-methyl, N-propyl isonicotinamide in CD_3CN .

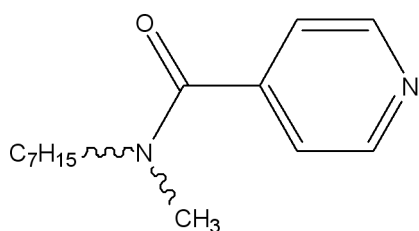
N-butyl, N-methyl isonicotinamide



(Isolated yield: 87%, 17.6 mg, 0.091 mmol): ^1H NMR (300 MHz, CD_3CN) δ (ppm): 0.95 and 0.76 (t, 3H, CH_2CH_3 , $J = 7.2$ Hz), 1.38 and 1.12 (m, 2H, CH_2CH_3), 1.60 and 1.50 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.97 and 2.82 (s, 3H, CH_3N), 3.46 and 3.11 (t, 2H, NCH_2 , $J = 7.2$ Hz), 7.26 (d, 2H, H_{mpy} , $J = 4.5$ Hz), 8.61 (d, 2H, H_{opy} , $J = 4.5$ Hz).

GC-MS: rt = 9.28 min. m/z (%): (M^+) = 192 (3.6), 106 (100), 78(28.6), 149 (19.6), 51 (10.7), 114 (8.9), 135 (5.3), 163 (2.9), 191 (2.5).

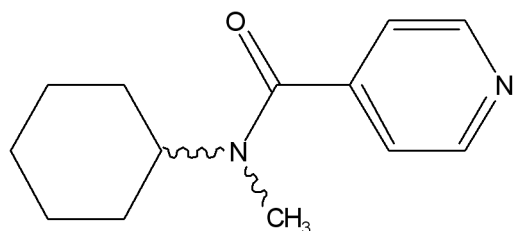
N-heptyl, N-methyl isonicotinamide



(Isolated yield: 75%, 18.5 mg, 0.079 mmol): ^1H NMR (300 MHz, CDCl_3) δ (ppm): 1.33 – 0.81 (broad, 2H, CH_2CH_3), 1.33 – 1.17 (broad, 6H, $\text{CH}_2(\text{CH}_2)_4\text{CH}_3$), 1.62 and 1.50 (m, 2H, $\text{O}=\text{CCH}_2\text{CH}_2$), 3.05 and 2.87 (s, 3H, CH_3N), 3.45 and 3.13 (t, 2H, NCH_2 , $J = 7.2$ Hz), 7.24 (d, 2H, H_{mpy} , $J = 4.5$ Hz), 8.66 (d, 2H, H_{opy} , $J = 4.5$ Hz).

GC-MS: rt = 10.87 min. m/z (%): (M^+) = 234 (3.8), 106 (100), 149 (37.7), 78 (32), 51 (9.4), 156 (9.4), 135 (7.1), 177 (1.8), 233 (1.8).

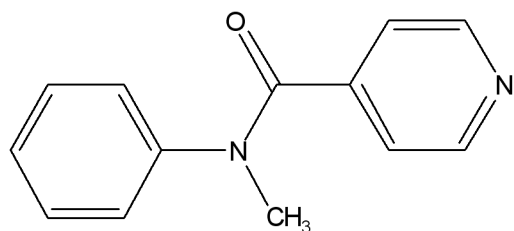
N-cyclohexyl, N-methyl isonicotinamide



(Isolated yield: 64%, 14.7 mg, 0.067 mmol): ^1H NMR (300 MHz, CD_3CN) δ (ppm): 1.85 – 1.02 (broad, 10H, $\text{CH}_3\text{NCH}(\text{CH}_2)_3$), 2.88 and 2.69 (s, 3H, CH_3N), 4.35 and 3.24 (m, 1H, NCH), 7.25 (d, 2H, H_{mpy} , $J = 4.5$ Hz), 8.62 (d, 2H, H_{opy} , $J = 4.5$ Hz). **GC-MS:** rt = 10.76 min. m/z (%):

(M^+) = 218 (25.3), 106 (100), 137 (60.16), 78(41.6), 161 (16.6), 175 (15), 51 (14.2), 217 (6.6), 55 (6.6), 123 (4.5), 219 (3.3).

N-methyl N-phenyl, isonicotinamide



(Isolated yield: 82%, 18.3 mg, 0.086 mmol): ^1H NMR (300 MHz, CD_3CN) δ (ppm): 3.41 (s, CH_3N), 7.24 - 7.04 (m, 7H), 8.43 (d, 2H, H_{opy} , $J = 4.5$ Hz). **GC-MS:** rt = 10.25 min. m/z (%): (M^+) = 212 (34.4), 106 (100), 78(60.6), 119 (24.6), 51 (23.7), 77 (16.4), 211 (8.2), 213 (3.2).

6. Procedure 3 (GC yields).

The crude product of the monomethylation reaction was derivatized (Scheme S1-c) in order to reduce the polarity of the secondary amines for GC elution.¹ The internal standard was derivatized together

¹ (a) Hiroyuki Kataoka, *Journal of Chromatography A*, **1996**, 733, 19-34. (b) Sacher, F.; Lenz, S.; Brauch, H.-J. *Journal of Chromatography A*, **1997**, 764, 85-93. (c) Halket, J. M.; Waterman, D.; A. Przyborowska, M.; Patel, R. K. P.; Fraser, P. D.; Bramley, P. M. *Journal of Experiment Botany*, **2005**, 56, 219-243

with the crude reaction to take into account the matrix effect during the proceeding of the reaction and the work-up.² The crude of the derivatization reaction was suspended in water and the cavitand was filtered out. The derivatized product and the internal standard were extracted with methylene chloride and injected in GC-MS (60 $\mu\text{g L}^{-1}$). The yield of the monomethylated product was determined from the ratio of the peak areas (average of three injections) (Figure S3 - S4).

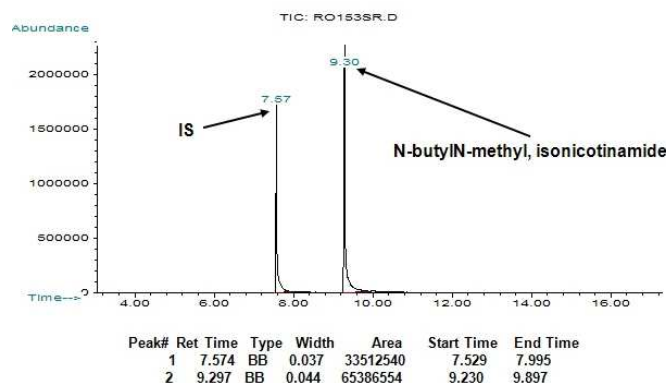


Figure S3. Calibration: GC-MS injection of a solution of derivatized N-butyl methylammium iodide in the presence of one equivalent of butanol for calibration.

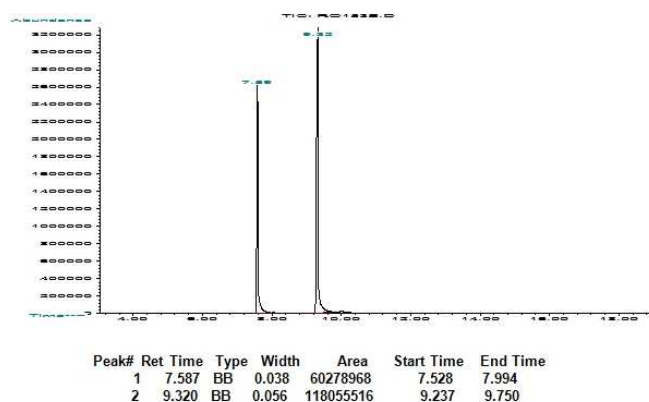
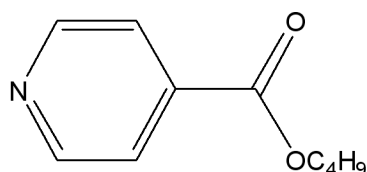


Figure S4. GC-MS injection of a solution of derivatized reaction crude of N-monomethylation of butylamine in the presence of one equivalent of butanol for yield determination.

Synthesis of butyl isonicotinate internal standard (IS) for GC calibration:



To a solution of isonicotinoyl chloride hydrochloride (2 g, 11.2 mmol) dissolved in 80 mL of pyridine, 2.1 mL of n-butanol (22.4 mmol) were added. The reaction mixture was stirred for 3 h at 100 C. The solvent was removed under vacuum. 50 mL of a water solution containing 5 mmol of sodium carbonate were added. Purification by extraction with CH_2Cl_2 led to the formation of butyl isonicotinate as colourless liquid (1.4 g, 7.8 mmol, 70%).

² Mol, H. G. J.; Sumarto, S.; Steijger, O. M. *Journal of Chromatography A*, **2000**, 879, 97-112.

^1H NMR (300 MHz, CDCl_3) δ (ppm): 0.93 (t, 2H, CH_2CH_3 , $J = 7.3$ Hz), 1.43 (m, 2H, CH_2CH_3), 1.71 (m, 2H, OCH_2CH_2), 4.31 (t, 2H, OCH_2CH_2 , $J = 6.7$ Hz), 7.79 (d, 2H, H_{mpy} , $J = 4.5$ Hz), 8.72 (d, 2H, H_{opy} , $J = 4.5$ Hz). **GC-MS**: $\text{rt} = 7.59$ min, m/z (%): (M^+) = 179 (4), 106 (100), 124 (92), 78 (59), 56 (47), 51 (36.7), 123 (36.2), 137(12.2), 164 (10.2), 178 (10.2), 150 (2).

7. Monitoring the reactions via ^{31}P NMR.

As the free and complexed cavitands showed different ^{31}P NMR signals in slow exchange at 4.64 ppm and 8.65 ppm respectively, the reaction was monitored by following the intensity changes of the two signals over time. 3 equivalents of CH_3I were added at once to the NMR tube containing a solution of the 1/1 mixture of cavitand and amine in CDCl_3 at 25 C (0.035 M each).

In the case of n-propylamine, after the first ^{31}P NMR spectrum recorded, only the signal corresponding to the complex was present (Figure S5).

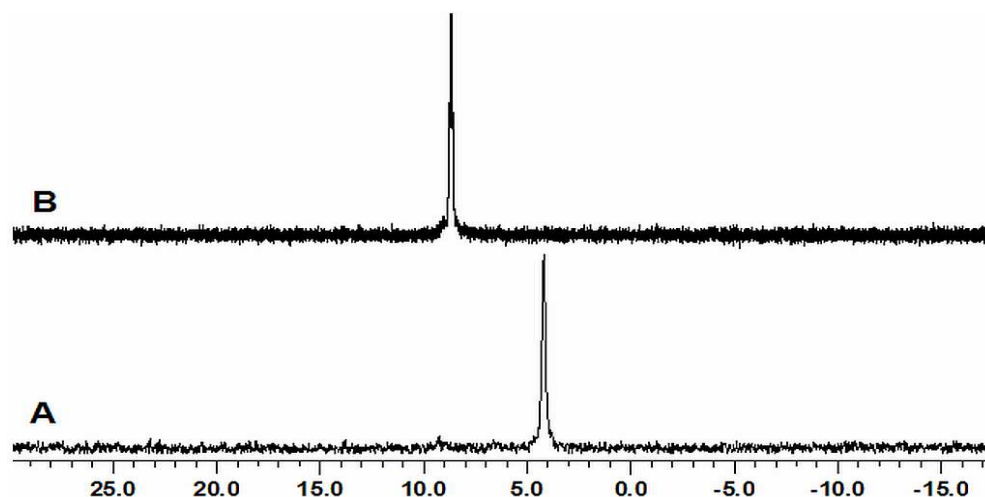


Figure S5. ^{31}P NMR in CDCl_3 of (A) **Tiii** [C_3H_7 , CH_3 , Ph] cavitand + $\text{C}_3\text{H}_7\text{NH}_2$; (B) 2.25 min after addition of 3 eq of CH_3I to the previous solution.

By contrast, the reaction with butylamine and heptylamine were completed after 90 min (Figure S6) and 215 min (Figures S7-S8), respectively.

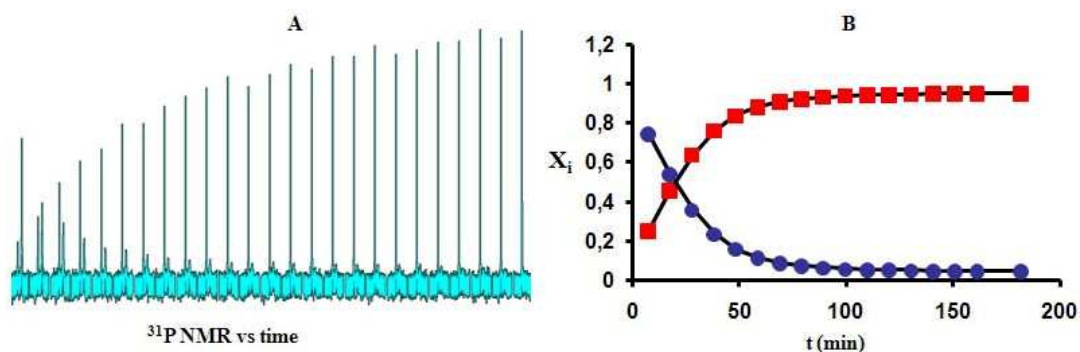


Figure S6. Formation of the **Ti(III)•N-methylbutylammonium** complex monitored via ^{31}P NMR: (A) sequence of the ^{31}P spectra taken at different times; (B) corresponding plot of the normalized areas X_i of the ^{31}P signals versus time. Color code: blue peaks and circles = free **Ti(III)**; red peaks and squares = **Ti(III)•N-methylbutylammonium** complex.

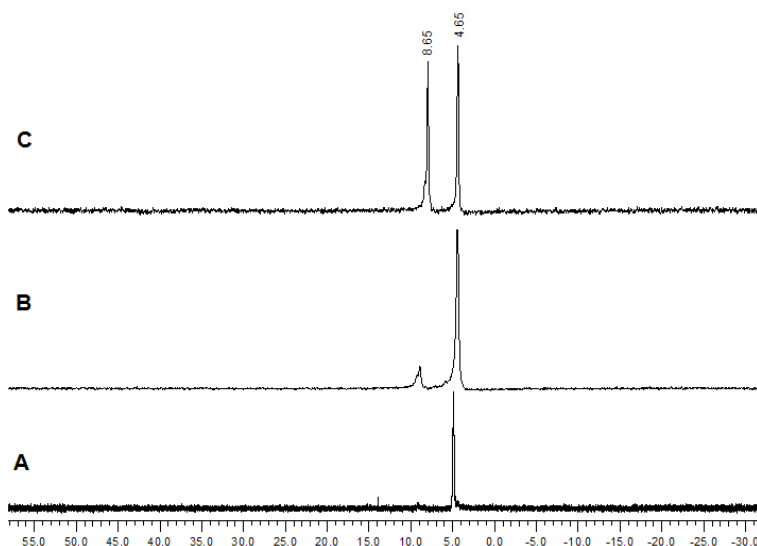


Figure S7. N-monomethylation of heptylamine monitored via ^{31}P NMR. (A) free cavitand + 1 equivalent of n-heptylamine; (B) 10 minutes after addition of CH_3I ; (C) 50 min after addition of CH_3I .

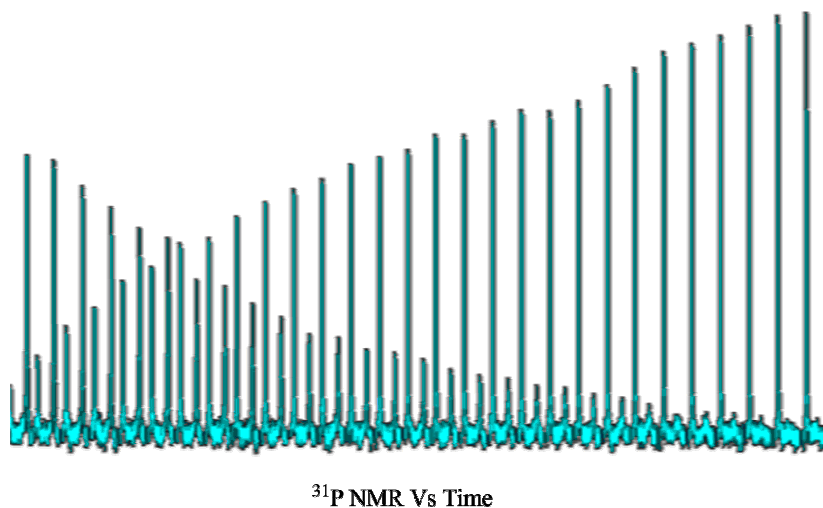


Figure S8. Formation of the **Tiii•N-methylheptylammonium** complex monitored via ^{31}P NMR: sequence of the ^{31}P spectra taken at different times;

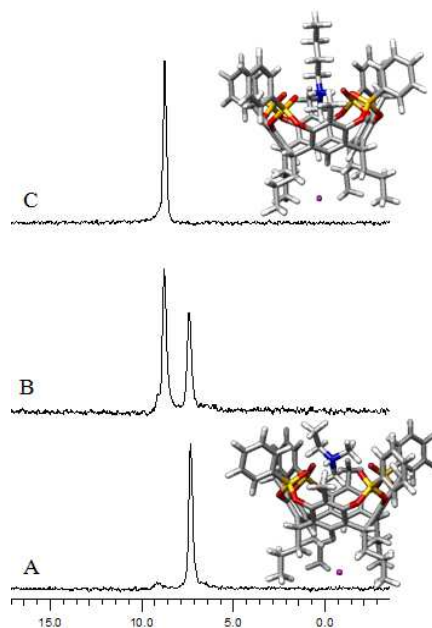


Figure S9. Complexation of N,N-dimethylethylammonium iodide monitored via ^{31}P NMR in $\text{CDCl}_3/\text{D}_2\text{O}$. (A) **Tiii** + 1.2 equivalents of N,N-dimethylethylammonium iodide (**Tiii•N,N-dimethylethylammonium** complex); (B) **Tiii** + 1.2 equivalents of N,N-dimethylethylammonium iodide + 0.6 equivalent of N-butylmethylammonium iodide; (C) **Tiii** + 1.2 equivalents of N,N-dimethylethylammonium iodide + 1 equivalent of N-butylmethylammonium iodide (**Tiii•N-methylbutylammonium** complex).

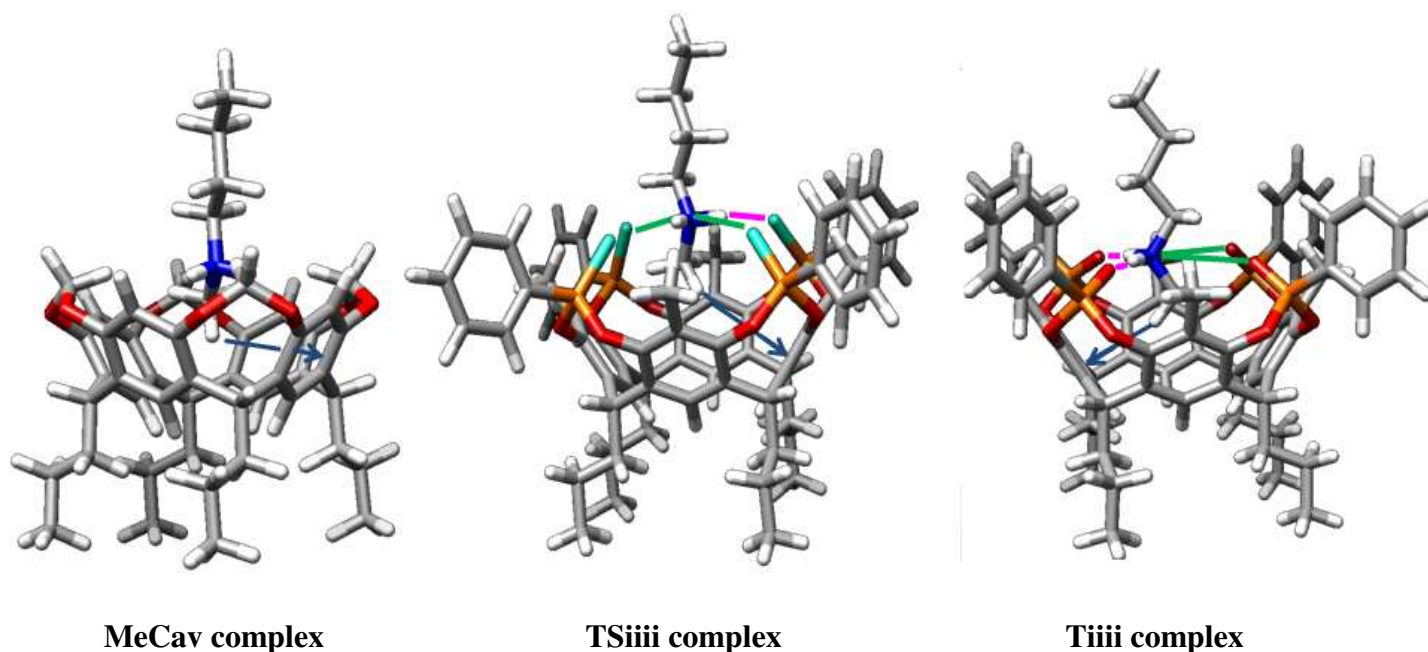


Figure S10. Enlarged Spartan minimized structures of **MeCav**, **TSiiii** and **Tiiii** complexes with **N-methylbutylammonium iodide**. The main interatomic distances calculated for CH- π interactions are (distance H-centroid of the aromatic ring): 2.75 Å for **MeCav**, 3.39 Å for **TSiiii**, 3.00 Å for **Tiiii**. The H-bonding P=S \cdots H-N $^+$ distances are 2.44 and 2.47 Å, while the P=O \cdots H-N $^+$ distances are both 1.60 Å. The corresponding main interatomic P=S \cdots N distances and P=O \cdots N are: 3.23 Å for **TSiiii**, 2.63 Å for **Tiiii**.³

³ The **Tiiii** data are comparable with those obtained from a crystal structure of a similar complex: Delangle, P.; Mulatier, J.-C.; Tinant, B.; Declercq, J.-P.; Dutasta, J.-P. *Eur. J. Org. Chem.* **2001**, 3695-3704