Boosting the salt recognition abilities of L-ornithine based multitopic molecular receptors by harnessing a double cooperative effect

by

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GENERAL INFORMATIONS

Unless specifically indicated, all other chemicals and reagents used in this study were purchased from commercial sources and used as received. 18-Aza-crown-6 was prepared according to literature procedure.1 Compounds 1a, 1c and S2 were prepared according to literature procedure.2 Purification of products was performed using column chromatography on silica gel (Merck Kieselgel 60, 230-400 mesh) with mixtures of chloroform/methanol. Thin-layer chromatography (TLC) was performed on silica gel plates (Merck Kieselgel 60 F254).

1H and 13C NMR spectra used in the characterization of products were recorded on Varian Unity 200 spectrometer using a TMS (δ=0.00) or residual protonated solvent as internal standard. The following abbreviations are used to indicate the multiplicity: s - singlet; d - doublet; t - triplet; q - quartet; m - multiplet, b – broad signal.

High resolution mass spectra (HRMS) were measured on a Quattro LC Micromass unit using ESI technique.

UV-vis analyses were performed using Thermo Spectronic Unicam UV500 Spectrophotometer. Atomic absorption measurements were performed using Perkin Elmer AAnalyst 300 spectrometer.

The conductance was measured using a conductance meter, Radiometer model CDM230, with a CDC241-9 conductivity cell.
SYNTHESIS

Receptor 1b

Scheme S1. Synthesis of receptor 1b. *Reagents and conditions:* a) DCC, 1-aza-18-crown-6, CH₂Cl₂, 0°C to r.t., 92%; b) TFA-CH₂Cl₂ (1:1), r.t., quantitative; c) 4-nitrophenyl isocyanate, THF, 73%.

Receptor 1d

Scheme S2. Synthesis of receptor 1d. *Reagents and conditions:* a) DCC, 1-aza-18-crown-6, CH₂Cl₂, 0°C to r.t., 92%; b) H₂, Pd/C, MeOH-THF, r.t., quantitative; c) trifluoroacetyl anhydride, Et₃N, CH₂Cl₂, 0°C to r.t., 72%; d) TFA-CH₂Cl₂ (1:1), r.t., quantitative; e) 4-nitrophenyl isocyanate, Et₃N, THF, 60%.
**Scheme S3.** Synthesis of receptor 1e. *Reagents and conditions:* a) DCC, 1-aza-18-crown-6, CH$_2$Cl$_2$, 0°C to r.t., 91%; b) H$_2$, Pd/C, MeOH-THF, r.t., quantitative; c) 4-nitrophenyl isocyanate, THF, 81%; d) TFA- CH$_2$Cl$_2$ (1:1), r.t., quantitative; e) trifluoroacetyl anhydride, Et$_3$N, CH$_2$Cl$_2$, 0°C to r.t., 73%.

**Scheme S4.** Synthesis of receptor 1f. *Reagents and conditions:* a) DCC, 1-aza-18-crown-6, CH$_2$Cl$_2$, 0°C to r.t., 92%; b) H$_2$, Pd/C, MeOH-THF, r.t., quantitative; c) trifluoromethanesulfonyl chloride, Et$_3$N, CH$_2$Cl$_2$, 0°C to r.t., 91%; d) TFA- CH$_2$Cl$_2$ (1:1), r.t., quantitative; e) 4-nitrophenyl isocyanate, Et$_3$N, THF, 72%.
Receptor 1d:
Compound S5:
Compound S6:
Receptor 1f:
NMR TITRATIONS

The $^1$H NMR titrations were performed on a Varian UnityPlus 200MHz spectrometer, at 298K in CD$_3$CN. The anion TBA and cation PF6 salts were dried under high vacuum at 30−45 °C prior to use. In each case, a 500 μL of freshly prepared 2.7 mM solution of receptor 1 was added to a 5mm NMR tube. Where applicable the solution also contained 1 molar equivalent of sodium hexafluorophosphate. Small aliquots of 10-20 mM solution of tetrabutylammonium anion salts, containing 1 at 2.7 mM concentration, were added and a spectrum was acquired after each addition. Titration isotherms for NH protons were fitted to a 1:1 binding model using the HypNMR 2000 program. The 1:1 binding stoichiometries were verified by a Job plot analysis.

Selected binding isotherms:

![Diagram of receptor 1](image)

<table>
<thead>
<tr>
<th></th>
<th>$K_{TBA}$</th>
<th>$K_{Na}$</th>
<th>$K_{Na}/K_{TBA}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO$_2^-$</td>
<td>1 450</td>
<td>19 000</td>
<td>13.1</td>
</tr>
</tbody>
</table>
Nitrate titration

\[
\begin{array}{|c|c|c|c|}
\hline
\text{NO}_3^- & K_{\text{TBA}} & K_{\text{Na}} & K_{\text{Na}}/K_{\text{TBA}} \\
\hline
150 & 1250 & 8.2 \\
\hline
\end{array}
\]

Bromide titration

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Br}^- & K_{\text{TBA}} & K_{\text{Na}} & K_{\text{Na}}/K_{\text{TBA}} \\
\hline
390 & 3450 & 8.8 \\
\hline
\end{array}
\]
### UV-VIS MEASUREMENTS

UV/vis spectra changes of receptor 1d CH$_3$CN solution in the presence of excess of NaPF$_6$ and TBANO$_2$.

#### Table

<table>
<thead>
<tr>
<th></th>
<th>$K_{TBA}$</th>
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</thead>
<tbody>
<tr>
<td>Cl$^-$</td>
<td>3 100</td>
</tr>
</tbody>
</table>
EXTRACTION and TRANSPORT EXPERIMENTS

The 1.5 mM aqueous solution of NaNO₂ or selected solid salts was extracted with 14 mM of CHCl₃ solution of 1d. After phase separation a sample of organic phase was diluted with ethyl acetate and methanol (1:9:2 v:v:v, chloroform, ethyl acetate, methanol) and the content of extracted sodium cation was determined via atomic absorption spectroscopy. A calibration curve was generated using a standard solution of sodium hexafluorophosphate in chloroform/ethyl acetate/methanol (1:9:2 v:v:v). The results are summarized in Table below.

Calibration curve generated by measuring the peak intensities produced by NaPF₆ standard solutions.

Summary of extraction data.

<table>
<thead>
<tr>
<th>1d</th>
<th>1.5M NaNO₂</th>
<th>NaNO₂</th>
<th>NaBr</th>
<th>NaNO₃</th>
<th>NaCl</th>
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</thead>
<tbody>
<tr>
<td>Extraction efficiency [%]</td>
<td>3.1</td>
<td>47.2</td>
<td>30.1</td>
<td>40.5</td>
<td>26.3</td>
</tr>
</tbody>
</table>

Membrane transport procedure.

Membrane transport experiments were performed with magnetic stirring in a conventional U-tube glass cell at room temperature. The feed phase was a 2 ml of 1M NaNO₂ salt; the membrane phase consisted of 3.9·10⁻²M solution (3 ml) of 1d in chloroform and the receiving phase consisted of 2 ml of distilled water. The salt concentration was determined by conductivity at appropriate intervals.
Calibration curve generated by measuring the conductivity produced by NaNO₂ standard solutions.

Concentration of sodium nitrite in receiving phase in function of time.
