Kinetically Stable Silver Complexes of Calixspherands

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Calixspherands 1 and 2 form kinetically stable complexes with Ag⁺ in CDCl₃ saturated with D₂O, with half-lives of decomposition of 51 and 131 h, respectively.

We have recently shown that calixspherands 1 and 2 form kinetically very stable complexes with the alkali metal ions Na⁺, K⁺, and Rb⁺. The Rb⁺ complexes have decomposition half-lives, in CDCl₃ saturated with D₂O, of 139 h and 180 d, respectively, whereas the complexes with Na⁺ and K⁺ have decomposition half-lives of several years.¹ The cavity of the calixspherands with its size of ca. 2.2 Å, as calculated from the crystal structure of [3 Na]⁺,² is complementary to Ag⁺ (2.52 Å), and is highly shielded from solvent molecules. Hence the calixspherands should also be able to form kinetically stable complexes with silver, although they lack the soft donor atoms sulfur and nitrogen which are preferred for the complexation of the soft silver cation.³,⁴

Kinetically stable complexes of silver-111 (a β-emitter; Eₘₐₓ 1.04 MeV) may be used in cancer radioimmunotherapy as it produces little (7%) γ-radiation, and has a physical half-life of 179 h. The decay profile ensures that tissue penetration is restricted to ca. 1.1 mm.⁵ In this communication the kinetic stability of silver complexes of calixspherands 1 and 2 is discussed.

Complexation of the free 1 and 2 with silver triflate in chloroform–methanol 1:1 afforded the silver complexes in almost quantitative yields. Complexation was confirmed by fast atom bombardment mass spectrometry and by high field shift in the ¹H NMR spectra for the methoxy group, which is situated in the cavity of the calix[4]arene moiety, from δ ca. 3 (free ligand) to ca. 0.1.

The determination of the decomposition rate constant of [1-Ag]⁺ and [2-Ag]⁺, which determines the kinetic stability, was performed as described for the spherand molecules by Cram and Lehn⁶ and as used for the alkali metal complexes of the calixspherands.¹,² In this method, a time course analysis of the exchange of Ag⁺ from a non-deuterated ligand to a partially deuterated ligand was followed by ¹H NMR spectroscopy.⁶ Decomposition rate constants (kₐ) at 25 °C for the silver complexes of 1 and 2 were calculated from the obtained rates of decomposition at higher temperatures by an Eyring plot. The results are summarized in Table 1. The decomposition rates are the lowest reported for a Ag⁺ complex,⁷ e.g. the Ag⁺ complex of cryptand-[2.2.1] has a kₐ of 5.6 × 10⁻⁴ s⁻¹ in Me₂SO at 25 °C.⁸ Our results show that kinetically stable silver complexes are formed by the calixspherands. Half-lives for decomposition at 25 °C were calculated from the decomposition rate constants [kₐ = ln(2/kₐ)] and are 50.9 h for 1 and 131 h for 2. These half-lives are shorter than those for decomposition of rubidium. The results obtained for 1 and 2 indicate that, although the size-fit between the cavity size and the ionic radius of silver is good and the cavity is highly shielded from solvent molecules, the interaction between the oxygen donor atoms and silver probably is too weak to obtain silve complexes which are sufficiently stable for in vivo use. Furthermore, the longer half-life for decomposition of [2-Ag]⁺ compared with that of [1-Ag]⁺ shows that, just as for alkali metal ion complexes, the kinetic stability of the complexes is increased when the shielding of the cavity is increased.

The results described in this communication show that kinetically stable silver complexes are formed with ligands, which have only oxygen donor atoms and a highly shielded cavity. The substitution of one or more oxygen atoms for sulfur atoms in the calixspherands in order to obtain ligands for silver which may be used for practical application in vivo, for example in radioimmunotherapy, is currently under investigation.

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Table 1 Decomposition rate constants (kₐ) for the silver complexes of calixspherands 1 and 2 in CDCl₃ saturated with D₂O

<table>
<thead>
<tr>
<th>Host</th>
<th>T (°C)</th>
<th>kₐ (s⁻¹)</th>
<th>ΔH (kJ mol⁻¹)</th>
<th>ΔS (kJ mol⁻¹ K⁻¹)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>3.3 × 10⁻⁵</td>
<td>105</td>
<td>1.3</td>
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<tr>
<td></td>
<td>47</td>
<td>6.4 × 10⁻⁵</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>55</td>
<td>2.2 × 10⁻⁴</td>
<td>105</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>3.8 × 10⁻⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
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<td>50</td>
<td>2.8 × 10⁻⁵</td>
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<tr>
<td></td>
<td>25</td>
<td>1.5 × 10⁻⁶</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ 25 °C. ² Extrapolated to 25 °C.

Footnotes

¹ 1: mp > 225 °C; decompy. ¹H NMR (CDCl₃): 7.34 (s, 2 H), 7.33 (s, 2 H), 7.20 (d, 2 H, J = 2.3 Hz), 7.18 (br s, 2 H), 7.02 (br s, 2 H), 6.91 (d, 2 H, J = 2.3 Hz), 6.80 (s, 2 H), 6.80 and 4.19 (ABq, H, J = 11.1 Hz), 4.70 and 3.71 (ABq, H, J = 12.5 Hz), 4.37 (s, 3 H), 3.76 and 3.17 (ABq, H, J = 14.9 Hz), 3.67 (s, 6 H), 2.50 (s, 3 H), 2.38 (s, 6 H), 1.96 (d, 2 H, J = 7.0 Hz), 1.31 and 1.17 (s, 9 H), 1.06 (s, 18 H), -0.02 (s, 3 H), -0.51 (s, 3 H, J = 7.0 Hz); MS m/z (FAB) 1185.5 (M⁺Ag⁺). ²Satisfactory elemental analyses: mp > 240 °C (dec). ³¹H NMR (CDCl₃): 7.30 and 7.27 (s, 2 H), 7.34 (s, 2 H), 7.24 (d, 2 H, J = 2.3 Hz), 7.19 (br s, 2 H), 7.00 (br s, 2 H), 6.96 (d, 2 H, J = 2.3 Hz), 6.88 (s, 2 H), 5.99 and 4.19 (ABq, H, J = 10.8 Hz), 4.71 and 3.74 (ABq, 4 H, J = 12.5 Hz), 4.30 (s, 3 H), 3.91 and 3.31
(ABq, 4 H, J 14.9 Hz), 3.69 (s, 6 H), 2.73–2.63 (m, 1 H), 2.52 (s, 3 H),
2.36 (s, 6 H), 1.30 (s, 9 H), 1.20 (s, 9 H), 1.08 (s, 18 H), 0.04 (s, 3 H),
−0.38 (d, 5 H, J 6.2 Hz); MS m/z (FAB) 1199.6 (2-Ag)−.

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