CALIXSPHERANDS AS LIGANDS FOR THE COMPLEXATION OF RADIOACTIVE RUBIDIUM-81

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Summary

For the use in medicine we are interested in ligands that form kinetically stable complexes with radioactive alkali cations. The spherands form very stable complexes with Li^+ and Na^+ , but reject the larger alkali cations like K^+ and Rb^+ . Our objective was to synthesize macrocyclic hosts based on a *m*-teranisyl unit and a calix[4]arene moiety that form kinetically stable complexes not only with Na^+ and K^+ but also with Rb^+ .

1. INTRODUCTION

1.1 The $^{81}\text{Rb}/^{81\text{m}}\text{Kr}$ ratio method

Our interest in the complexation of radioisotopes is related to their use in medicine for different purposes¹.

An interesting isotope is rubidium-81, in particular for the non-invasive determination of the blood flow in different parts of the body via the $^{81}\text{Rb}/^{81\text{m}}\text{Kr}$ ratio method². The $^{81}\text{Rb}/^{81\text{m}}\text{Kr}$ ratio method is based on the fact that the radioactive tracer ^{81}Rb is at any time in "radioactive equilibrium" with its decay product krypton-81m, which decays to krypton-81, because of the short half-life of $^{81\text{m}}\text{Kr}$ (13 seconds) compared to ^{81}Rb (4.6 hours). Intravenously injected $^{81}\text{Rb}^+$ is distributed over highly perfused organs such as the kidneys, within which it decays to $^{81\text{m}}\text{Kr}$. This inert gas immediately diffuses over the tissue and is subsequently washed out by the blood at a rate proportional to the blood flow. This leads to a linear relationship between the $^{81}\text{Rb}/^{81\text{m}}\text{Kr}$ ratio of activities measured over the individual kidney and the specific blood flow through the individual kidney.

A disadvantage of the $^{81}\text{Rb}/^{81\text{m}}\text{Kr}$ ratio method is the redistribution of ^{81}Rb over the potassium pool in the surrounding tissues of the kidney.

1.2 Ionophores

The above mentioned problem could in principle be overcome if the rubidium would be "immobilized". Our idea was to complex the rubidium in an ionophore that could be linked to an organ specific compound. However, this ionophore has to meet some requirements. Firstly, because alkali cations, like Na^+ , K^+ , and Rb^+ , cannot be covalently linked to organic compounds, immobilization may only be achieved by complexation of Rb^+ . Secondly, because of the large excess of Na^+ and K^+ present in the blood, the ligand should, if possible, have a high selectivity for Rb^+ . This means that the

K_a = stability constant (M^{-1}), k_c = complexation rate constant ($\text{M}^{-1}\text{s}^{-1}$),

k_d = decomplexation rate constant (s^{-1}), M^+ = metal ion, L = ligand (host)

thermodynamic stability (K_a , see eq. 1) of the Rb^+ -complex should be, at least, 10^6 times higher than the thermodynamic stability for Na^+ and K^+ . Such a high selectivity is very hard to obtain, for this reason we decided to study another possibility, viz. to form kinetically stable complexes with Rb^+ . Kinetically stable means that the decomplexation rate (k_d , see eq. 1) is low at the human time scale. Because of this last requirement simple crown ethers and bicyclic cryptands (figure 1) are not suitable as ligands for the complexation of rubidium, because their decomplexation is fast (table 1)³.

Figure 1

Cation	18-Crown-6		[2.2.2]-Cryptand	
	k_c ($\text{M}^{-1} \cdot \text{s}^{-1}$)	k_d (s^{-1})	k_c ($\text{M}^{-1} \cdot \text{s}^{-1}$)	k_d (s^{-1})
Na^+	2.2×10^8	3.4×10^7	1.2×10^6	1.47×10^2
K^+	1.0×10^{10}	3.7×10^6	2.0×10^6	7.5
Rb^+	4.4×10^8	1.2×10^7	3.1×10^6	1.4×10^2

Table 1 Rate constants for alkali cation complexes of 18-crown-6 and [2.2.2]-cryptand in water at 25°C

In 1979 Cram published a new type of macrocyclic polyether ligand, the spherands, which consist of six anisole moieties (figure 2)⁴. This macrocyclic ligand shows a very strong binding with Li^+ and Na^+ , caused by the fact that the cavity is almost perfectly complementary in size to the diameter of the ions and by the fact that

Figure 2 Spherand

the six methoxy groups shield the cavity from solvent molecules. This can be summarized in the following statement about preorganization: "The more highly host and guests are organized for binding and for low solvation prior to their complexation, the more stable will be their complexes". However, the rigid cavity of the spherands is too small to complex the larger cations like K^+ and Rb^+ .

1.3 Objectives

For the possible application of radioactive Rb^+ isotopes in organ imaging we were interested in macrocyclic host molecules with preorganized cavities that form kinetically stable complexes with Rb^+ .

2. HEMISPHERANDS AND CRYPTAHEMISPHERANDS

2.1 Hemispherands⁵

In order to obtain kinetically stable complexes of Rb^+ it was necessary to synthesize macrocyclic hosts with a larger cavity than the spherands but of comparable rigidity. A possibility is to substitute one part of the spherand molecule by another building block. Cram and coworkers synthesized the so called hemispherands (see figure 3) in which a *m*-teranisyl moiety is combined with a polyethylene glycol chain. In

Figure 3

the hemispherand three of the binding sites are preorganized prior to complexation, the ethylene oxy bridges however are not organized. This results in a lower kinetic stability compared to the spherand complexes.

We have synthesized a number of hemispherands with modified *m*-terphenyl units and studied their complexation⁶.

2.2 Cryptahemispherands⁷

It is known that cryptand complexes have a higher stability than the crown ether complexes (see table 1). For this reason the combination of a *m*-teranisyl unit with a diazacrown ether might have a higher stability than the hemispherands. At the time we had decided to synthesize these molecules we learned that Cram and coworkers had already synthesized the so called cryptahemispherands (see figure 3). Cram *et al.* showed that the cryptahemispherands had higher thermodynamic stabilities than the hemispherands. Although, they did not report the kinetic stability of the alkali complexes of the cryptahemispherands, these macrocycles should form kinetically stable complexes, at least in apolar solvents like chloroform. To determine the kinetic stability of the cryptahemispherand complex of Rb^+ , with a cavity complementary to the larger cations, we have synthesized cryptahemispherand 1 according to the procedure described by

Cram *et al.*

The stability of 1.RbCl was determined by stirring a homogeneous solution of 1.RbCl (0.001 M), NaCl (0.150 M), and KCl (0.030 M) in 100 mL of water at pH 7.4 (Ringers solution) at room temperature⁸. The exchange of Rb⁺ for Na⁺ and K⁺ was monitored by ¹H NMR. After 2 h an equilibrium was established with almost exclusively the K⁺ complex present (K⁺/Na⁺ and K⁺/Rb⁺ ≥ 30:1). The rate of exchange of Rb⁺ for K⁺ and Na⁺ was much faster than expected from the calculated rate in chloroform. This might be due to the fact that the exchange is a bimolecular process instead of a simple decomplexation of 1.RbCl as the rate determining step, or to a more accessible cavity for solvent molecules. This facilitates the solvation of the cation and of the ligand^{3b}.

3. CALIXSPHERANDS

3.1 Calixarenes⁹

The condensation of *para*-substituted phenols with formaldehyde under basic conditions is known for many years. Gutsche showed that the ratio of products depends on the solvent, the temperature, the amount of base etc., and reported that by choosing the right conditions calix[8]arene, calix[6]arene, and calix[4]arene could be obtained as pure compounds in good yields (50-75%)¹⁰.

Calix[4]arene¹¹ is a rather flexible molecule that can exist in four different conformations: the cone, the partial cone, the 1,3-alternate, and the 1,2-alternate conformation (see figure 4). The conformational mobility is decreased by alkylating part of the phenolic oxygens.

Figure 4 The different conformations of calix[4]arene

We have synthesized a number of so-called calixcrowns and we showed that the calixcrowns could complex alkali cations^{8,11}. The kinetic stability of these compounds is not very high, because of the flexible ethylene oxy bridge and the rather open cavity.

3.2 Calixspherands⁸

The complexation of alkali cations with calixcrowns suggested that the combination of calix[4]arene with a more rigid bridge might form more stable complexes. CPK molecular models showed that it should be possible to bridge 1,3-alkylated calix[4]arene with a *m*-teranisyl moiety. This combination might give a

$$\frac{d[4.M^+Pic^-]}{dt} = k_c \frac{[4][L.M^+Pic^-]}{K_L[L]} \quad \text{eq 4}$$

Guest	Temp, K	$k_c, M^{-1}.s^{-1}$	k_d, s^{-1}	$K_a = k_c/k_d, M^{-1}$
Na ⁺	358		4.0×10^{-5}	
	343		3.4×10^{-6}	
	328		6.4×10^{-7}	
K ⁺	298	1.3×10^4	6.0×10^{-9}	2.1×10^{12}
	358		5.5×10^{-6}	
	353		2.5×10^{-6}	
	348		9.2×10^{-7}	
Rb ⁺	298	2.2×10^5	1.0×10^{-8}	2.2×10^{13}
	298	2.5×10^5	6.9×10^{-5}	3.6×10^9

Table 2 Complexation (k_c) and decomplexation (k_d) constants and association constants for the calixspherand.

developed by Cram and Lein for the spherand complexes^{12b}. Since the endo methoxy group provided an excellent probe, we have synthesized the hexadeuteriocalixspherands (4-*d*₆) by using 25,27-bis(methoxy-*d*₃)-*p*-*tert*-butylcalix[4]arene instead of 25,27-dimethoxy-*p*-*tert*-butylcalix[4]arene. Assuming that the rate of decomplexation is the rate determining step in the exchange reaction ($K_a \geq 10^9 M^{-1}$), the rate of decomplexation of 4.RbPic was determined at 298 K.

The rates of decomplexation of 4.NaPic and 4.KPic could not be measured at 298 K, because the exchange processes are too slow. From experiments at three different temperatures, we obtained the values for $\Delta H^\ddagger$ and $T\Delta S^\ddagger$ and extrapolated them to rates of decomplexation at 298 K. From the measured values of k_c and k_d the association constant (K_a) could be calculated. The results of the experiments are summarized in table 2.

The results show that the calixspherands have the potential to be used in medicine. However, to use the calixspherand for organ imaging the calixspherand should be linked to an organ specific compound. Work is in progress to obtain calixspherands that could be linked to organ specific compounds. We are also working on calixspherands with a higher kinetic stability for the alkali cations and on calixspherands that form complexes with higher valent cations.

4. REFERENCES

- 1 Radiopharmaceuticals II, Society Nuclear Medicine, New York, 1979.
- 2 a) G. van Herk, PhD Thesis, Groningen, 1976; b) D. de Zeeuw, PhD Thesis, Groningen, 1980.

- 3 a)R.M. Izatt, J.S. Bradshaw, S.A. Nielsen, J.D. Lamb and J.J. Christensen, *Chem. Rev.* **85**, 271(1985); b)B.G. Cox, J. Garcia-Rosas and H. Schneider, *J.Am.Chem.Soc.* **103**, 1054 and 1384(1981).
- 4 D.J. Cram, T. Kaneda, R.C. Helgeson and G.M. Lein, *J.Am.Chem.Soc.* **101**, 6752(1979).
- 5 K.E. Koenig, G.M. Lein, P. Stuckler, T. Kaneda and D.J. Cram, *J.Am.Chem.Soc.* **101**, 3553(1979).
- 6 a)P.J. Dijkstra, B.J. van Steen and D.N. Reinhoudt, *J.Org.Chem.* **51**, 5127(1986); b)P.J. Dijkstra, H.J. den Hertog Jr., B.J. van Steen, S. Zijlstra, M. Skowronska-Ptasinska, D.N. Reinhoudt, J. van Eerden and S. Harkema, *J.Org.Chem.* **52**, 2433(1987); c)P.J. Dijkstra, M. Skowronska-Ptasinska, D.N. Reinhoudt, H.J. den Hertog Jr., J. van Eerden, S. Harkema and D. de Zeeuw, *J.Org.Chem.* **52**, 4913(1987); d)P.J. Dijkstra, H.J. den Hertog Jr., J. van Eerden, S. Harkema and D.N. Reinhoudt, *J.Org.Chem.* **53**, 374(1988); e)P.J. Dijkstra, B.J. van Steen, B.H.M. Hams, H.J. den Hertog Jr. and D.N. Reinhoudt, *Tetrahedron Lett.* **27**, 3183(1986).
- 7 a)D.J. Cram, S.P. Ho, C.B. Knobler, E. Maverick and K.N. Trueblood, *J.Am.Chem.Soc.* **108**, 2989(1986); b)D.J. Cram and S.P. Ho, *J.Am.Chem.Soc.* **108**, 2998(1986).
- 8 P.J. Dijkstra, J.A.J. Brunink, K.-E. Bugge, D.N. Reinhoudt, S. Harkema, R. Ungaro, F. Ugozzoli and E. Ghidini, *J.Am.Chem.Soc.* **111**, 7567(1989).
- 9 C.D. Gutsche, *Calixarenes*, Royal Society of chemistry, Cambridge, 1989.
- 10 C.D. Gutsche, M. Iqbal and D. Stewart, *J.Org.Chem.* **51**, 742(1986).
- 11 a) G. Alfieri, E. Dradi, A. Pochini, R. Ungaro and G.D. Andreetti, *J.Chem.Soc.,Chem.Comm.* 1075(1983); b) R. Ungaro, A. Pochini and G.D. Andreetti, *J.Inclusion Phenom* **2**, 199(1984); c) E. Ghidini, F. Ugozzoli, R. Ungaro, S. Harkema, A.A. El-Fadl and D.N. Reinhoudt, *J.Am.Chem.Soc.* accepted for publication.
- 12 a)D.J. Cram, T. Kaneda, R.C. Helgeson, S.B. Brown, C.B. Knobler, E. Maverick and K.N. Trueblood, *J.Am.Chem.Soc.* **107**, 3645(1985); b)D.J. Cram and G.M. Lein, *J.Am.Chem.Soc.* **107**, 3657(1985).
- 13 a)F. de Jong, D.N. Reinhoudt, C.J. Smit and R. Huis, *Tetrahedron Lett.* 4783(1976); b)F. de Jong, D.N. Reinhoudt and R. Huis, *Tetrahedron Lett.* 3985(1977).
- 14 G.M. Lein and D.J. Cram, *J.Am.Chem.Soc.* **107**, 448(1985).