Anticancer Activity of Host-Guest Systems: Dendrimers Encapsulated in Arene Ruthenium Metalla-Prisms

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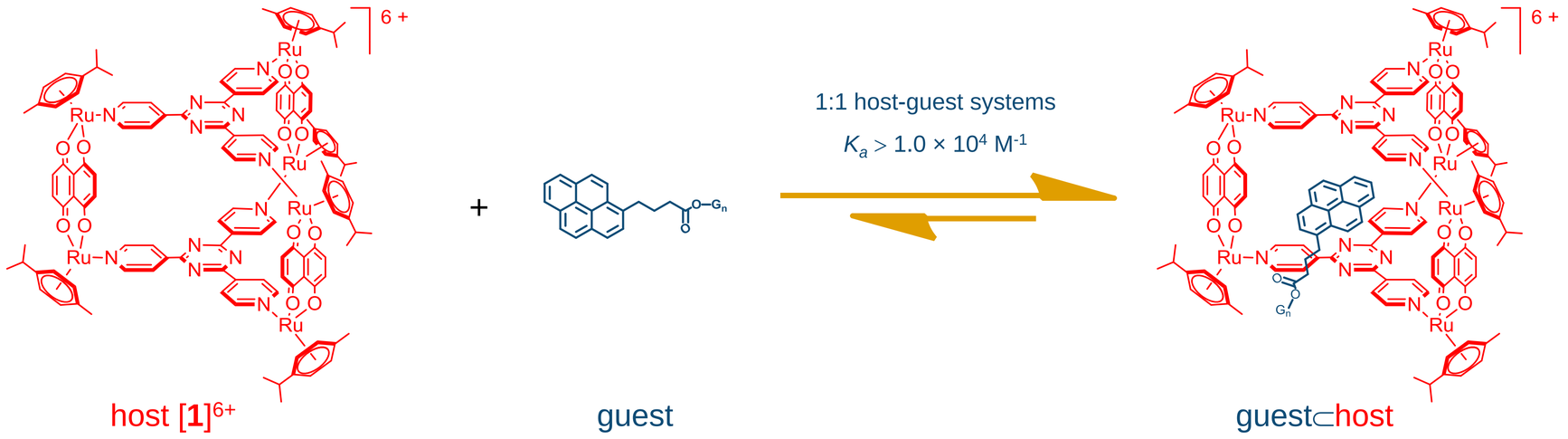
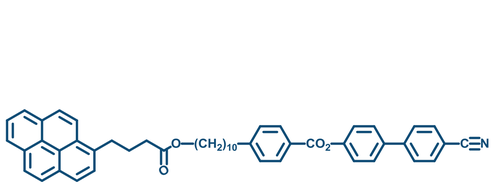
Introduction

Many examples of dendrimers as biological agents[1] and drug carriers[2] can be found in the literature. The combination of poor tissue drainage and increased tumour vascular permeability of cancer cells results in an enhanced permeability and retention (EPR) effect. Consequently, macromolecular drugs are retained in the tumour interstitium for longer periods than in healthy tissues and the selectivity of nanomedicines towards cancer cells can be up to 100 fold greater.[3]

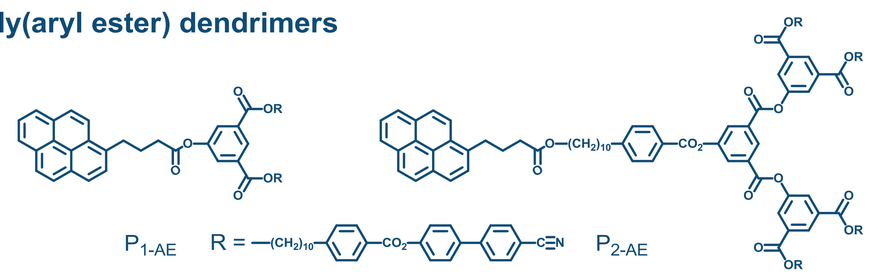
We have developed water-soluble arene ruthenium metalla-cages that possess cavities able to host planar aromatic molecules.[4] The physical and chemical behavior of two types of dendrimers together with the biological activity of metalla-prism $[\mathbf{1}]^{6+}$ and of the dendrimers included in $[\mathbf{1}]^{6+}$ ($[P_n\subset\mathbf{1}][CF_3SO_3]_6$) are presented.[5]



poly(aryl ester) dendrimers

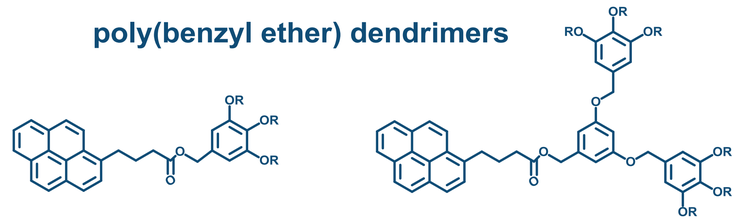


$P_{0\text{-}AE}$



$P_{1\text{-}AE}$ $P_{2\text{-}AE}$

poly(benzyl ether) dendrimers

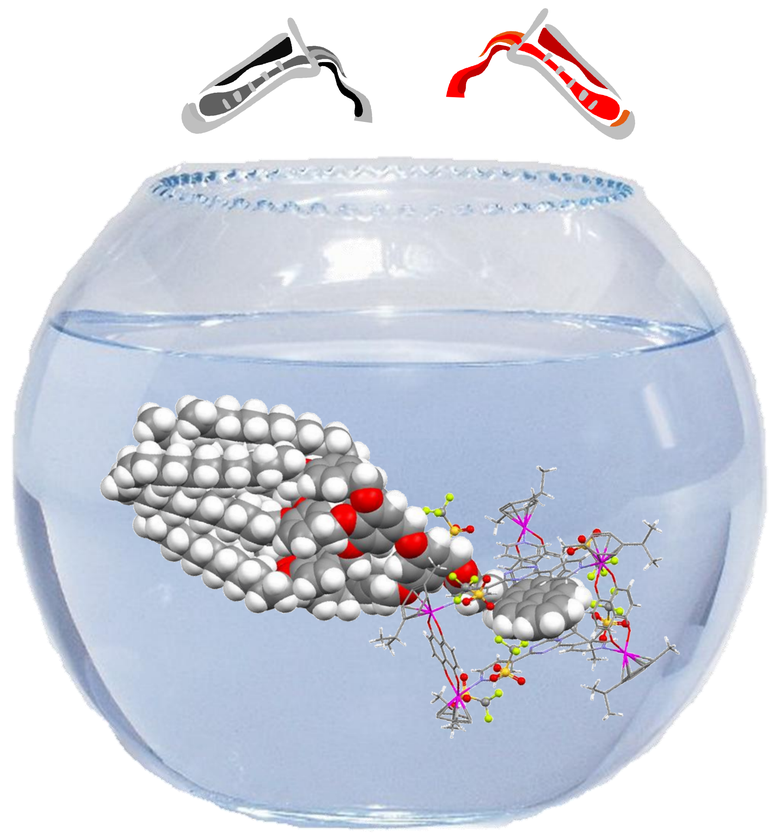


$P_{1\text{-}BE}$ $P_{2\text{-}BE}$

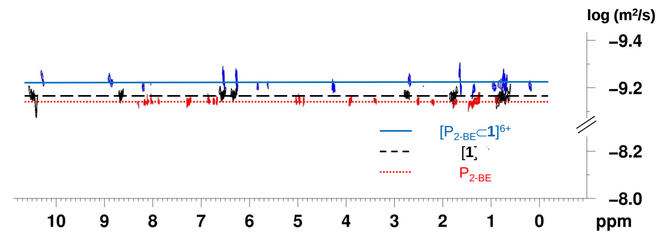
Thermodynamic studies

	K_a (10^4 M^{-1})		ΔG° (kcal/mol)	
	NMR data	UV-Vis data	NMR data	UV-Vis data
$[P_{1\text{-}BE}\subset\mathbf{1}]^{6+}$	4.2	4.9	-6.30	-6.39
$[P_{2\text{-}BE}\subset\mathbf{1}]^{6+}$	3.5	3.9	-6.19	-6.25
$[P_{0\text{-}AE}\subset\mathbf{1}]^{6+}$	4.1	7.8	-6.29	-6.67
$[P_{1\text{-}AE}\subset\mathbf{1}]^{6+}$	1.9	2.7	-5.83	-6.04
$[P_{2\text{-}AE}\subset\mathbf{1}]^{6+}$	n.a.	0.8	n.a.	-5.36

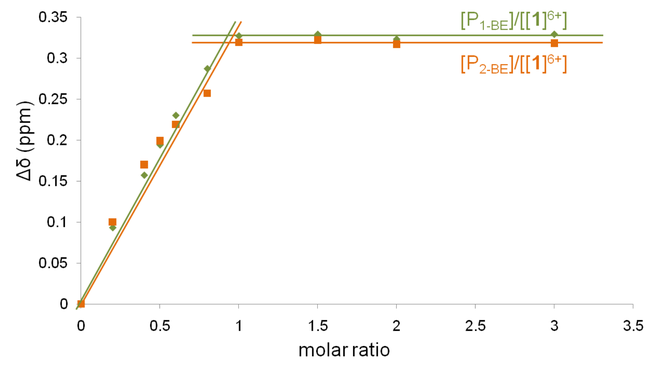
n.a. = not applicable
^{1}H NMR titration in CD_2Cl_2 at 21°C, 4mM of $[\mathbf{1}]^{6+}$
UV/Vis method in CH_2Cl_2 at 21°C



DOSY measurements



^{1}H NMR titrations



^{1}H NMR chemical shift changes for the H_β proton of the tpt ligands *versus* the molar ratio of $P_{1\text{-}BE}$ and $P_{2\text{-}BE}$ to $[\mathbf{1}]^{6+}$ (4.0 mM) in CD_2Cl_2 at 21°C.

Biological studies

	$[P_{1\text{-}BE}\subset\mathbf{1}][CF_3SO_3]_6$	$[P_{2\text{-}BE}\subset\mathbf{1}][CF_3SO_3]_6$	$[P_{0\text{-}AE}\subset\mathbf{1}][CF_3SO_3]_6$	$[P_{1\text{-}AE}\subset\mathbf{1}][CF_3SO_3]_6$	$[P_{2\text{-}AE}\subset\mathbf{1}][CF_3SO_3]_6$	$[\mathbf{1}][CF_3SO_3]_6$	cisplatin
A2780 cell lines (IC_{50}, μM)	2.4 ± 0.5	2.5 ± 0.8	0.4 ± 0.1	2.2 ± 1.1	2.6 ± 0.8	3.1 ± 1.0	1.6 ± 0.6
A2780cisR cell lines (IC_{50}, μM)	2.9 ± 0.7	3.2 ± 0.9	0.5 ± 0.4	2.4 ± 0.8	2.8 ± 1.0	4.6 ± 0.5	8.6 ± 0.6

Conclusion

The cytotoxicity of the host-guest systems is found to be equivalent to that of the empty metalla-prism except for $[P_{0\text{-}AE}\subset\mathbf{1}][CF_3SO_3]_6$ which presents an increase of one order of magnitude. The metalla-cage host systems deliver hydrophobic guest molecules with extremely large appendages into cancer cells. These results open the door for the design of hydrophilic dendrimers with lower molecular weight for biological applications.

1: M. A. Mintzer, M. W. Grinstaff, *Chem. Soc. Rev.* **2011**, *40*, 173; 2: M. E. Fox, F. C. Szoka, J. M. J. Fréchet, *Acc. Chem. Res.* **2009**, *42*, 1141; 3: H. Maeda, *Adv. Enzyme Regul.* **2001**, *41*, 189; 4: B. Therrien, G. Süss-Fink, P. Govindaswamy, A. K. Renfrew, P. J. Dyson, *Angew. Chem. Int. Ed.* **2008**, *47*, 3773; 5: a) A. Pitto-Barry, N. P. E: Barry, O. Zava, R. Deschenaux, P. J. Dyson, B. Therrien, *Chem. Eur. J.* **2011**, *17*, 1966; b) A. Pitto-Barry, N. P. E: Barry, O. Zava, R. Deschenaux, B. Therrien, *Chem. Asian J.* **2011**, *6*, 1595.