Silver complexes of peptidomimetic polyazapyridinophanes. The influence of the bonding cavity size and the nature of side chains

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Several peptidomimetic macrocycles containing a pyridine spacer and ring sizes ranging from 15 to 17 have been efficiently synthesized starting from valine and phenylalanine. The complexes formed have been investigated by potentiometry and NMR. Log *K* values show that phenylalanine derivatives **8** are consistently more stable than valine derivatives **7**, whilst macrocycles with ring sizes of 16 members are the most appropriate for the complexation. The NMR data, in combination with molecular modeling, allow rationalization of the structure of the complexes formed and the participation of the aromatic rings from the side chain of phenylalanine in π-Ag^+ interactions to be discarded.

Introduction

The design and synthesis of novel supramolecular ligand architectures is closely connected to promising application options in different areas.[1] Up to now, a large number of macrocyclic and spherical ligands as well as their open-chain counterparts have been synthesised and characterised and applications found in separation processes, sensing and analyte detection, materials science, catalysis, biomedical uses and development of nanoscopic devices.[2] One important topic in supramolecular chemistry, originating from a biomimetic approach, has been the use of aromatic units of different kinds to build up complex molecular architectures and supramolecular assemblies characterised by π-electronic interactions.[3] In this context, polyazacyclophanes represent a very interesting class of macrocyclic receptors being able to interact with either cationic or anionic guests.[4] One of the most attractive structural features of polyazamacrocycles and, in general, of receptors containing amine groups, is the possibility of using the nitrogen atoms to introduce sidearms of different classes. Those sidearms can substantially affect the properties of the receptor,[5] in particular when they contain additional donor functionalities or its introduction changes the lipophilic/lipophobic balance.[6]

Silver(I) complexes of organic ligands derived from arene donors have a large potential for the construction of organometallic solid-state devices such as electrical conductors, photoactive switches, chemical sensors, *etc.*[7] The highly active field of the synthesis of novel families of compounds containing aromatic units, including diarylalkanes (-alkenes and -alkynes), cyclophanes, deltaphanes, cylindrophanes, *etc.* provides the desired molecular diversity for this purpose.[8–10] The use of the appropriate arene ligands containing several aromatic subunits gives the possibility of assembling silver(I) in complex architectures in which the metal centre can form part of a polymeric linear structure or be encapsulated within a 3D network.[7,11] Additionally, metal complexes that contain Ag(III) and possess sufficient stability *in vivo*, have a high potential for being used in chemotherapy treatments.[12]

Here we present our studies directed to the preparation of several peptidomimetic polyazapyridinophanes and the study of their complexes with Ag(I) revealing that aromatic side groups in the constituent aminoacids can have a significant role in determining the stability of such complexes, even if those aromatic rings are not directly involved in the coordination to the metal.

Results and discussion

Synthesis of receptors

The synthesis of peptidomimetic cyclophanes such as **1** and **2** has been recently described by our group and takes place very efficiently owing to the high degree of preorganization of open-chain pseudopeptidic precursors **5**.[13] Preliminary studies have shown, however, that compounds such as **1** and **2**, under neutral conditions, do not have a high affinity for metal cations for the limited number of strong donor atoms available for coordination.

Thereby, the substitution of the benzene aromatic ring in **1** or **2** by a 2,6-substituted pyridine ring could greatly contribute to improve the stability of the resulting metal complexes.

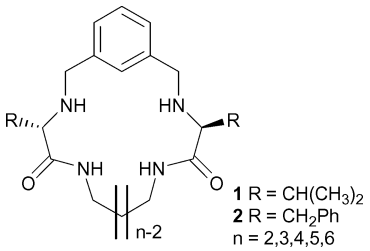

Chart 1

Accordingly, the synthesis of the corresponding macrocyclic pyridinophanes (**7** and **8**) was carried out following the general procedure used for the preparation of **1–2** and related systems (Scheme 1).[13,14]

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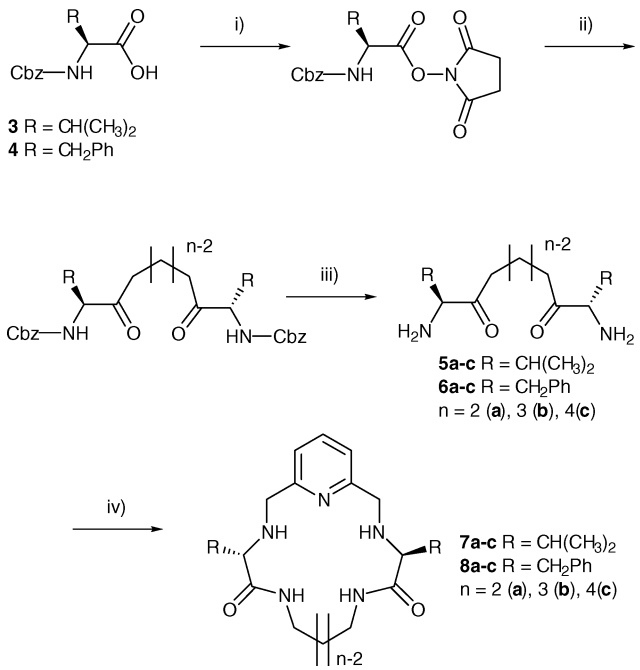

Scheme 1 (i) DCC, *N*-hydroxysuccinimide, THF; (ii) $H_2N(CH_2)_nNH_2$, DME; (iii) HBr/AcOH; (iv) aq. NaOH, (v) 2,6-bis(bromomethyl)-pyridine, K_2CO_3/CH_3CN.

Table 1 Results obtained for the synthesis of polyazapyridinophanes

Entry	Compound	*n*	R	Yield (%)[a]
1	**7a**	2	$CH(CH_3)_2$	62
2	**7b**	3	$CH(CH_3)_2$	50
3	**7c**	4	$CH(CH_3)_2$	63
4	**8a**	2	CH_2Ph	62
5	**8b**	3	CH_2Ph	56
6	**8c**	4	CH_2Ph	65

[a] Yields refer to isolated products after chromatographic purification.

As can be seen in Table 1, the different pyridinophanes were obtained, as pure compounds after chromatographic purification, in 50–65% yields, bearing in mind that purification step responsible for a significant decrease in the final yields. Nevertheless, these yields are comparable to those obtained for related systems such as **1**, and the synthetic methodology does not require the use of high dilution techniques. This is in good agreement with the fact that the U-turn preorganization of the open-chain compounds **5** and **6** seems to be at the origin of this easy macrocyclization.[13c]

According to the goals of our work, we considered two main structural variations for the design of macrocyclic receptors **7** and **8**. First, three different sizes were selected for the macrocyclic cavity through a variation in the number of methylene groups in the central aliphatic spacer. Thus, the synthesized pyridinophanes contained 15 ($n = 2$, **7a** and **8a**), 16 ($n = 3$, **7b** and **8b**) and 17 ($n = 4$, **7c** and **8c**) membered rings. The second point for molecular diversity was the nature of the side chain. In this regard, the two starting amino acids selected were valine and phenylalanine, as this provides a macrocyclic species of C_2 symmetry containing either aliphatic (R=$CH(CH_3)_2$, **7**) or aromatic (R=CH_2Ph, **8**) side chains. This could allow us to explore the possible participation of the aromatic side-chains in the three-dimensional coordination to the metal center through π interactions.[15]

In order to gain some information on the geometrical constrains in the involvement of the phenyl groups of the side chains in the coordination to a metal center sitting in the cavity, we carried out different theoretical calculations. In this context, three different basic conformations can be considered as defined in figure 1. For the *in–in* conformation, the two phenyl rings are expected to be bent towards the macrocyclic ring. According to the C_2 symmetry of the molecule, each one of the aromatic rings should be situated on opposite sides of the cavity to provide a complete encapsulation of a metal cation sitting in the cavity. For the *in–out* conformation, only one aromatic ring is bent over the cavity, while the second one is pointing outwards. Finally, for the third conformation, *out–out*, both phenyl rings are pointing outwards, not providing any possible interaction with a metal cation in the macrocyclic cavity.

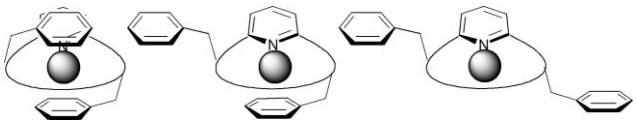

Fig. 1 General description of the three different phenyl rings dispositions around the cavity of the ligand (*in–in*, *in–out*, *out–out*).

Monte Carlo random conformational search (MMFF94 force field as implemented in Spartan Pro) showed that these receptors are very flexible, as confirmed by the large number of minima obtained. However, some interesting trends can be pointed out. Although the most favorable conformations for the phenylalanine derivatives set the side chains pointing out of the macrocyclic cavity, some conformers with this Ph residue folded to the main cyclic structure are also energetically accessible. Thus, for compound **8b** ($n = 3$) the lowest energy minimum as well as the one with the folded residue are depicted in figure 2. The computed difference of energy is only 0.9 kcal mol^{-1}, supporting the theoretical possibility of coexisting populations of these conformations at room temperature. Besides, if some additional stabilization were acting, such as π-cation interactions, it would be clearly easy to obtain conformations of this kind.

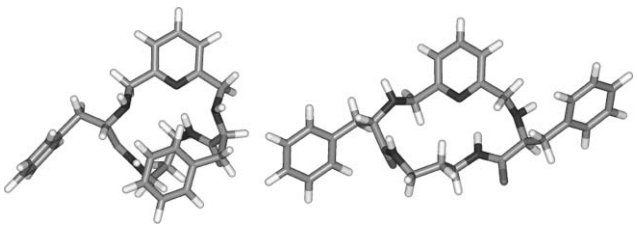

Fig. 2 Minimum energy conformers: *in–out* (left) and *out–out* (right) for compound **8b**.

Study of the interaction with Ag^+. Potentiometric studies

Taking the former considerations into account, the interaction of receptors **7** and **8** with the Ag^+ cation was studied by potentiometric titrations using a Ag^+ ion selective electrode. The low solubility of some of the ligands precluded an accurate analysis of the complexes formed in water. Nevertheless, conditional stabililty constants for AgL complex formation could be determined in

Table 2 Logarithms of the stability constants for the formation of the AgL complexes for ligands **7** and **8** in MeOH, determined at 298.1 K in 0.05 M $(C_2H_5)_4NClO_4$

Ligand	*n*	R	Log *K*[a]
7a	2	$CH(CH_3)_2$	5.68(3)
7b	3	$CH(CH_3)_2$	5.82(2)
7c	4	$CH(CH_3)_2$	5.50(2)
8a	2	CH_2Ph	6.46(3)
8b	3	CH_2Ph	6.55(2)
8c	4	CH_2Ph	5.72(3)

[a] Standard deviation on the last significant figure are given in parenthesis.

MeOH. Table 2 gathers the values for the stability constants determined in MeOH at 298.1 K in 0.05 M $(C_2H_5)_4NClO_4$.

The emf measurements excluded the formation of complexes with stoichiometries differing from the 1 : 1 ligand : metal ratio. The same conclusion was obtained with ESI-MS experiments. In all cases, the only peaks detected correspond to the formation of the corresponding $Ag^+ \cdot L$ complexes with no indication for the formation of complexes with other stoichiometries.

According to the data in Table 2, it can be observed that, in both cases, valine and phenylalanine derivatives, the highest stability constants are obtained for the macrocyclic receptors that possess a 16 membered ring (**7b** and **8c**, $n = 3$), even if differences with receptors having other ring sizes are small in some cases. On the other hand, it seems that the presence of the aromatic side groups (**8**, R=CH_2Ph) provides an additional stabilization factor for the complexes formed. The magnitude of this stabilization, almost an order of magnitude for receptors **8a** and **8b**, could suggest that some kind of π-cation interactions are involved in complex formation.

NMR studies

In order to analyse this possible participation of aromatic rings in more detail, an NMR analysis of the corresponding complexes was undertaken. In this regard, the ^1H and ^{15}N NMR spectra of AgL species in CD_3OD were recorded and studied.

In the case of the ^{15}N NMR spectroscopy, all the assignments were made on the basis of 2D ^1H–^{15}N correlation experiments (gHMBC pulse sequence).[16] Fig. 3 shows the long range ^1H–^{15}N correlation spectra obtained for different L : Ag^+ stoichiometries using compound **7c** as the ligand and $AgNO_3$ as the source for the silver(I) ion. The assumed atom numbering for H and N signals is depicted in figure 4.

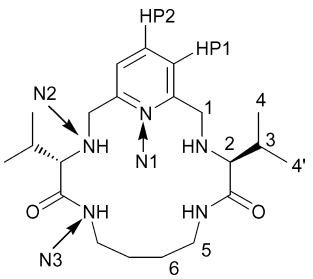

Fig. 4 Structure of **7c** with the corresponding atom numbering.

As can be seen in the figure, only three different signals, corresponding to the three different kinds of nitrogen atoms: pyridine

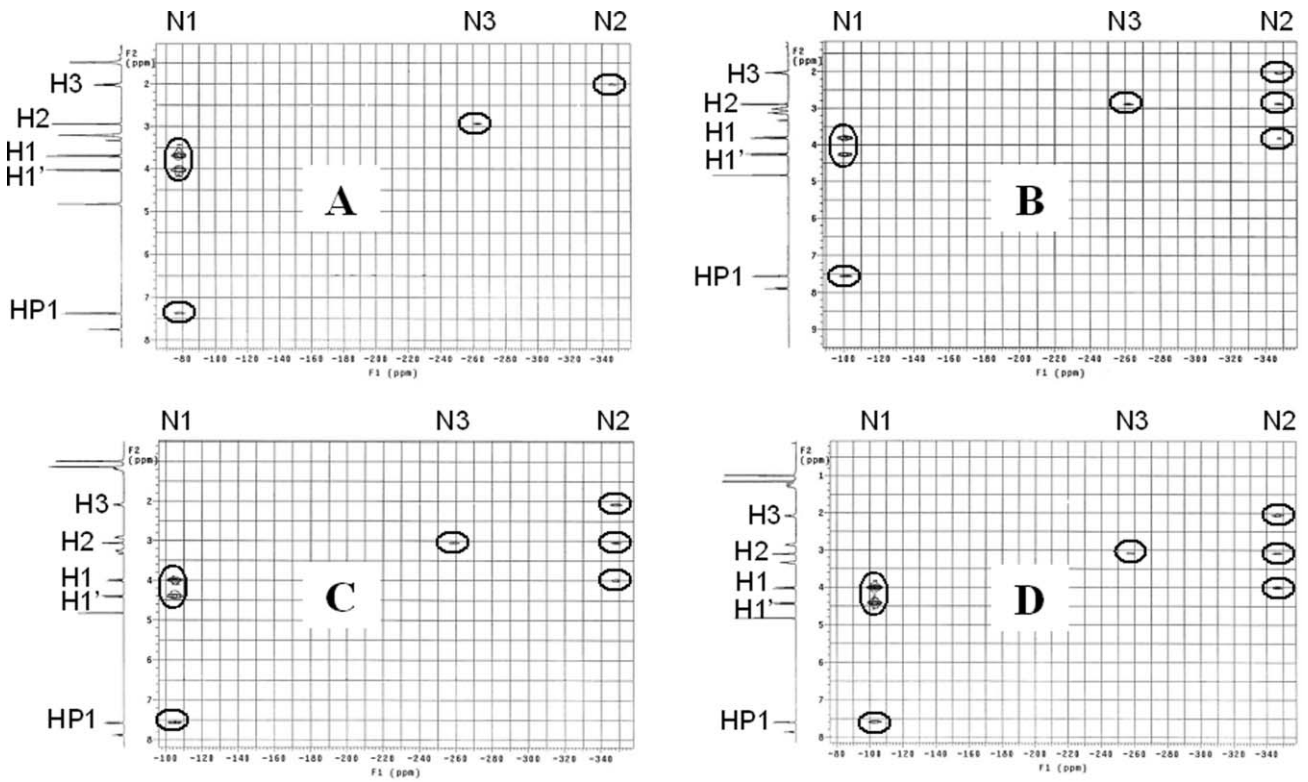

Fig. 3 Long range ^1H–^{15}N correlation spectra (HMBC) obtained in CD_3OD for **7c**-$AgNO_3$ at different ligand : metal ratios: (a) 1 : 0, (b) 2 : 1, (c) 1 : 1, (d) 1 : 2.

(N1), amine (N2) and amide (N3) are observed for all complexation stages. This indicates that complexation–decomplexation equilibria are fast on the NMR time scale. The peak at *ca.* −80 ppm for the free ligand can be assigned to the nitrogen atom from the pyridine subunit (N1). During complexation, this signal is shifted more than 20 ppm upfield and reaches a shift value of almost −105 ppm when the complexation ratio is 1 : 1. No further changes in this shift were observed when an excess of Ag^+ ions was added, confirming the 1 : 1 stoichiometry of the complexes formed. Only very small changes are detected, however, for the signals corresponding to the other nitrogen atoms. Signals for the amine nitrogen (N2) appear at −346 and −348 ppm, while the ones for the amide nitrogen (N3) are observed at −263 ppm for the free ligand and are upfield shifted to −258 ppm when the complex is formed. This indicates that only the pyridine nitrogen atom (N1) is directly involved in the coordination to the silver cation. Participation of the amide groups seems to occur, but data suggest that this should happen through the involvement of the oxygen carbonyl atoms. Accordingly, ^{13}C NMR spectra of silver complexes showed a downfield shift of the carbonyl signals ($\Delta\delta$ 2.2 and 0.7 ppm for **7c**·Ag and **8a**·Ag, respectiveley) supporting this proposal for the mode of interaction. The NMR data also reveal that deprotonation of the N–H amide group does not take place. Similar trends were observed for the other macrocycles studied.

The ^1H NMR spectra also provided some interesting information. A representative example is given in Fig. 5 which shows the ^1H NMR spectra in CD_3OD for the free ligand **7c** (lower trace) and its 1 : 1 complex with $Ag(NO_3)$ (upper trace).

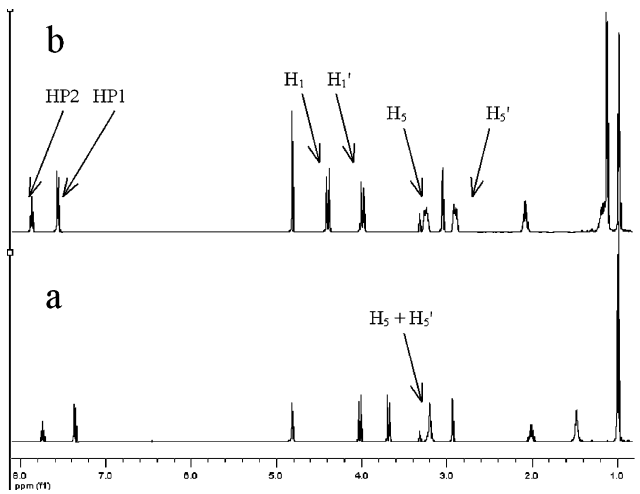

Fig. 5 ^1H NMR spectra for the free (a) and complexed (b) (1 : 1 ligand:metal ratio) **7c** in CD_3OD.

In the region corresponding to the pyridine protons, all of the investigated compounds showed a downfield shift of both signals (HP1 and HP2) ($\Delta\delta$ 0.15–0.25 ppm) upon complexation. A more significant downfield shift was even observed for the benzylic like protons H1 and H1′ that in the free ligand (for **7c**) appear as two doublets at 3.6 and 4.0 ppm and experience downfield shifts of 0.25–0.45 ppm when the complex is formed.

Less distinct trends are observed for the other protons, but the presence of a rather rigid structure for the complex is clearly indicated by the comparison of the spectra of L and AgL species. Thus, for **7c**, a splitting of some of the signals is observed for the complex. This is particularly significant for the methyl signals of the isopropyl group ($\Delta\delta = 0.14$ ppm) and for protons H5 on the butylenic spacer ($\Delta\delta = 0.34$ ppm). Even for H1 and H1′ the anisochrony is incremented in the complex ($\Delta\delta = 0.09$ ppm). In the case of H5, one of the resulting signals remains essentially unshifted, whilst the second one is more shielded, shifting from *ca.* 3.2 to 2.9 ppm. Also protons H6 show a clear shielding in the complex shifting from about 1.5 to about 1.2 ppm, but in this case no splitting is observed, perhaps because of the partial overlapping with the signal corresponding to one of the methyl groups. Most likely, the shielding of some of the butylenic protons takes place as a consequence of the involvement of amide oxygen atoms in the coordination to the metal that locates the electron density of the carbonyl group in close proximity of those hydrogen atoms.

In the case of the macrocycles **8** derived from phenylalanine, having phenyl groups at the side chain, the NMR did not provide any indication of the involvement of this aromatic ring in the coordination to the metal centre. As can be observed in Fig. 6, for **8c**, a significant downfield shift is observed, in the aromatic region for pyridine protons HP1 and HP2, but the shifts corresponding to the protons of the aromatic side chain remain essentially unchanged. The same is observed in the case of the ^{13}C NMR spectra. No changes in the signals corresponding to the phenyl group are detected when the complex is formed.

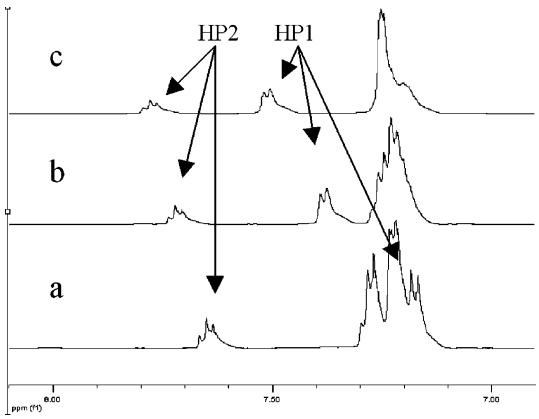

Fig. 6 Aromatic region of the ^1H NMR spectra of compound **8c** as free ligand (a) and in the presence of $AgNO_3$ for 2 : 1 (b) and 1 : 1 (c) L : metal ratios, in CD_3OD.

For a proposal of the Ag complex with the peptidomimetic macrocycle, some molecular modeling has been also undertaken. The optimized geometry at the HF/3-21G* level of theory for a 16-membered ring receptor is shown in figure 7. As side chains seem not to directly interact with the cation, they have been omitted for computational simplicity. A nitrate counterion has been used for completing the coordination sphere of the metal center. Interestingly, the Ag atom is very close to the pyridine nitrogen as well as to the amide carbonyls, but not to the benzylic nitrogens, supporting the observed ^{15}N chemical shift changes. In addition to that, the carbonyl groups set their anisotropy cones pointing to H5 protons, suggesting an explanation for the shielding of one of the corresponding diastereotopic protons on that position. The optimized geometry set the metal atom on top of the macrocyclic main plane, almost equidistant to pyridine nitrogen and amide carbonyls (see distances in figure 7). This arrangement would make

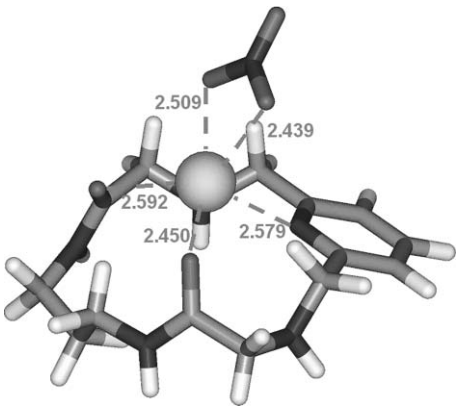

Fig. 7 Proposed model of coordination of Ag cation to 16-membered-ring pepetidomimetic pyridinophane (HF/3-21G*). Selected distances to the metal centre (dashed lines) are given in angstroms.

both faces of the receptor chemically inequivalent, suggesting an explanation for the increased anisochrony of diasterotopic methylene signals upon complex formation. Finally, space filling view of the optimized geometry showed how the Ag cation fits nicely inside the 16-membered ring macrocyclic cavity.

Conclusions

C_2 symmetric macrocyclic peptidomimetics can be easily and efficiently synthesised according to our general methodology. Those ligands are able to form some interesting 1 : 1 complexes with Ag^+ in CH_3OH that involve the coordination of only the pyridine nitrogen atoms. Neither the amine nor the amide nitrogen atoms seems to participate in the coordination to the metal cation. Instead, the oxygen atoms of the amide moiety are properly located to participate in the coordination to silver, so that complexation takes places without deprotonation of the amide hydrogen atom. As could be expected, the strength of the complexes formed is dependent on the size of the macrocyclic cavity. For both, valine and phenylalanine derivatives (**7** and **8** respectively) the 16 member macrocyclic ring size is the most suited for complex formation. Nevertheless, differences observed in log K values, between macrocycles with ring sizes of 15, 16 and 17 members, are small. More significant, almost one order of magnitude in some cases, are the variations in log K values detected when the isopropyl substituent at the side chain is changed to phenyl. NMR experiments ruled out the direct participation of phenyl groups through π-cation interactions. In this regard, those differences could be related to the different roles that both substituents may play in either defining the solvation spheres of the ligands and complex cations or affecting the steric environment about the macrocycle cores.

Experimental

General procedure for the preparation of the macrocycles

All of the bis(aminoamide) derivatives (**5a–c** and **6a–c**) used throughout our synthetic sequence were obtained as previously described.[13c]

Synthesis of 7a. Compound **5a** (0.5 g, 1.29 mmol), anhydrous K_2CO_3 (1.77 g, 12.9 mmol), tetrabutylammonium bromide (0.210 g, 0.65 mmol) and 2,6-bis(bromomethyl)pyridine (0.335 g, 1.29 mmol) were placed in a flask containing dry CH_3CN (175 mL) and were refluxed for 12 h under argon atmosphere. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. The crude product was dissolved in $CHCl_3$ (50 mL) and extracted with aqueous 0.01 M NaOH (3 × 50 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was purified by silica flash chromatography using $MeOH/CH_2Cl_2$ (1 : 40) as the eluent to give 0.437 g of **3a** in the form of a white solid. Yield 62%; mp. 190–192 °C; IR (KBr) ν 3300, 3087, 2952, 1634, 1551 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.93 (d, 6H, $J = 6.9$ Hz), 0.99 (d,6H, $J = 6.9$ Hz), 2.04 (m, 2H), 2.98 (d, 2H, $J = 5.5$ Hz), 3.22 (m, 4H), 3.647 (d, 2H, $J = 13.5$ Hz), 4.07 (d, 2H, $J = 13.5$ Hz), 7.25 (d, 2H, $J = 7.7$ Hz), 7.88 (t, 1H, $J = 7.7$ Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 18.5, 19.8, 32.6, 32.6, 40.2, 55.9, 56.0, 56.1, 69.9, 122.8, 122.9, 138.5, 138.7, 161.0, 177.3; ESI-MS $m/z = 362.3$ ($M + H^+$), 384.2 ($M + Na^+$). Anal. Calcd. for $C_{19}H_{31}N_5O_2$ C, 63.1; H, 8.6; N, 19.4. Found C, 62.7; H, 9.0; N, 19.2.

Synthesis of 7b. This compound was obtained as described above starting from **5b**. Yield 50%; mp. 221–224 °C; IR (KBr) ν 3288, 3074, 2952, 1634, 1538 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.967 (d, 6H, $J = 6.8$ Hz), 0.99 (d, 6H, $J = 6.8$ Hz), 1.66 (m, 2H), 1.99 (m, 2H, 2.95 (d, 2H, $J = 5.9$ Hz), 3.12 (m, 2H), 3.22 (m, 4H), 3.65 (d, 2H, $J = 14.1$ Hz), 4.06 (d, 2H, $J = 14.1$ Hz), 7.29 (d, 2H, $J = 7.7$ Hz), 7.71 (t, 1H, $J = 7.7$ Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 18.9, 19.8, 29.8, 32.5, 37.2, 55.4, 55.4, 70.0, 122.5, 122.6, 138.8, 139.0, 160.8, 176.9; ESI-MS $m/z = 376.2$ ($M + H^+$). Anal. Calcd. for $C_{20}H_{33}N_5O_2$ C, 64.0; H, 8.9; N, 18.7. Found C, 64.2; H, 9.3; N, 18.7.

Synthesis of 7c. This compound was obtained as described above starting from **5c**. Yield 63%; mp. 228–231 °C; IR (KBr) ν 3299, 3076, 2957, 1638, 1549 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.98 (t, 12H, $J = 7.3$ Hz), 1.47 (m, 4H),2.00 (m, 2H), 2.92 (d, 2H, $J = 5.8$ Hz), 3.20 (m, 4H), 3.68 (d, 2H, $J = 14.2$ Hz), 4.01 (d, 2H, $J = 14.2$ Hz), 7.36 (d, 2H, $J = 7.7$ Hz), 7.73 (t, 1H, $J = 7.7$ Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 17.8, 19.9, 26.3, 31.2, 38.1, 55.4, 68.9, 121.0, 137.5, 159.3, 173.0; ESI-MS $m/z = 390.0$ ($M + H^+$), 412.5 ($M + Na^+$); Anal. Calcd. For $C_{21}H_{35}N_5O_2$ C, 64.8; H, 9.1; N, 17.9. Found C, 64.6; H, 9.4; N, 17.5.

Synthesis of 8a. This compound was obtained as described above starting from **6a**. Yield 62%; mp. 173–175 °C; IR (KBr) ν 3290, 3085, 2930, 1634, 1552 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 2.78 (m, 2H), 3.08–3.22 (m, 6H), 3.43 (dd, 2H, $J = 5.8$, 8.2 Hz), 3.61 (d, 2H, $J = 13.5$ Hz), 3.88 (d, 2H, $J = 13.5$ Hz), 7.14 (d, 2H, $J = 7.7$ Hz), 7.22–7.28 (m, 10H), 7.63 (t, 1H, $J = 7.7$ Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 40.1, 54.6, 65.2, 122.9, 127.76, 129.6, 130.2, 138.8, 139.1, 160.5, 176.5; ESI-MS $m/z = 458.5$ ($M + H^+$), 480.5 ($M + Na^+$); Anal. Calcd. For $C_{27}H_{31}N_5O_2 \times H_2O$ C, 68.2; H, 7.0; N, 14.7. Found C, 68.6; H, 7.3; N, 14.7.

Synthesis of 8b. This compound was obtained as described above starting from **6b**. Yield 56%; mp. 176–178 °C; IR (KBr) ν 3311, 3080, 2953, 1635, 1546 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.58 (s, 4H), 2.84 (m, 2H), 2.94–317 (m, 10H), 3.47 (m, 2H), 3.66

(d, 2H, $J = 14.1$ Hz), 3.90 (d, 2H, $J = 14.1$ Hz), 7.16–7.30 (m, 12H), 7.66 (t, 1H, $J = 7.7$ Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 29.0, 37.6, 40.1, 54.2, 64.8, 122.8, 127.8, 129.6, 130.4, 139.1, 160.2, 176.0; ESI-MS $m/z = 472.2$ (M + H$^+$), 494.2 (M + Na$^+$); Anal. Calcd. For $C_{28}H_{33}N_5O_2$ C, 71.3; H, 7.1; N, 14.9. Found C, 71.4; H, 7.2; N, 14.9.

Synthesis of 8c. This compound was obtained as described above starting from **6c**. Yield 65%; mp. 192–196 °C; IR (KBr) ν 3306, 3078, 2942, 1634, 1557 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.42 (br, s 4H), 2.82 (m, 2H), 3.06 (m, 2H), 3.40 (m, 2H) 3.64 (d, 2H, $J = 14.1$ Hz), 3.88 (d, 2H, $J = 14.1$ Hz), 7.18 (d, 2H, $J = 7.7$ Hz), 7.22–7.30 (m, 10H), 7.65 (t, 1H, $J = 7.7$ Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 27.2, 39.2, 40.2, 54.3, 65.1, 122.0, 127.7, 129.4, 130.2, 138. 8, 139.0, 160.2, 175.9; ESI-MS $m/z =$ 486.3 (M + H$^+$), 508.2 (M + Na$^+$); Anal. Calcd. For $C_{28}H_{33}N_5O_2$ C, 71.7; H, 7.3; N, 14.4. Found C, 71.8; H, 7.4; N, 14.4.

NMR Measurements

The ^{1}H, and ^{13}C spectra were recorded on Varian INOVA 500 spectrometer operating at 500 MHz for ^{1}H and 125.75 MHz for ^{13}C. The NMR experiments involving ^{15}N were recorded on a Varian INOVA 500 spectrometer equipped with a 5 mm tunable, broadband, inverse-detection probe. The spectrometer operates at 500 MHz for ^{1}H, and 50.7 MHz for ^{15}N. The spectra were determined at 30 °C. Neat nitromethane was used as reference (0 ppm) to calculate ^{15}N chemical shifts. ^{1}H–^{15}N HMBC-type correlation experiments were recorded using the gHMQC Varian pulse sequence setting up the experiment for long-range couplings. The studies were carried out in solutions containing 5–15 mg of the ligands dissolved in 0.6 mL of the corresponding deuterated solvent.

EMF measurements

The potentiometric titration were carried out at 298.1 ± 0.1 K using 0.05 M $(C_2H_5)_4NClO_4$ in MeOH as the supporting electrolyte.

Before each measurement the Nernst's equation was verified in the following system:

$$Ag^0 \,|\, 0.01\ M\ AgNO_3\ (MeOH) + 0.04\ M\ (C_2H_5)_4NClO_4\ (MeOH) \,\|\, 0.05\ M\ (C_2H_5)_4NClO_4\ (MeOH) \,\|\, c_{Ag} + (MeOH) + 0.05\ M\ (C_2H_5)_4NClO_4\ (MeOH) \,\|Ag^0$$

The specific measurements were performed in the system:

$$Ag^0 \,|\, 0.01\ M\ AgNO_3\ (MeOH) + 0.04\ M\ (C_2H_5)_4NClO_4\ (MeOH) \,\|\, 0.05\ M\ (C_2H_5)_4NClO_4\ (MeOH) \,\|\, c^0{}_L\ (MeOH) + c_{Ag} + (MeOH) + 0.05\ M\ (C_2H_5)_4NClO_4\ (MeOH) \,|\, Ag^0$$

where $c^0{}_L$ is the concentration of the ligand at the beginning of the titration, and c_{Ag} is the concentration of the standard solution of silver ion.

Three series of the measurements were performed for three different ligand concentrations $c^0{}_L$, which ranged from 5×10^{-4} to 5×10^{-3} M. The results reproducibility was ± 0.20 mV. The values of formation constants were computed by means of the MINIQUAD program,[17] and the program based on the BEST algorithm.[18]

Molecular modeling

For the molecular modeling studies, a PC version of Spartan Pro program was used. To obtain the minima of energy, the conformer distribution calculation option available in Spartan Pro was used. With this option, an exhaustive Monte Carlo search without constraints was performed for every structure. The torsion angles were randomly varied and the obtained structures fully optimized using the MMFF94 force field. Thus, 100 minima of energy within an energy gap of 10 kcal mol^{-1} were generated. These structures were analyzed and ordered considering the relative energy, being the repeated geometries eliminated. For the Ag complex, the geometry was fully optimized at the HF/3-21G* level of theory implemented in Spartan Pro. Frequencies analysis showed that it is a minimum of energy.

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