Biphenyl Macrolactams as Colorimetric Sensors for Anions through Displacement Reactions

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Abstract

Macrocyclic ligands **1**–**3** can be used as colorimetric sensor for different anions following the displacement approach. The intense colour of the 4-nitrophenolate anion in MeCN solutions that disappears upon complexation with the ligands is reinstated after the addition of specific anions. The influence of both substituents in the biphenyl moiety and size of the cavity in sensing has been considered. X-ray diffraction studies of ligand **2** are also included.

Introduction

Much work has been directed to the design and synthesis of anion receptors in molecular recognition chemistry [1]. This is due to the crucial roles anions play in biology [2], medicine [3], and environment [4]. Many chemical sensors following the approach of the covalent attachment of signalling subunits and binding sites have been reported. In these sensor molecules the change in a physical property of the host after co-ordination with the guest transmits to the macroscopic world the complexation event. Depending on the modified property of the signalling unit it is possible to observe changes either in the colour (chromogenic chemosensor) [5], in the fluorescence behaviour (fluorogenic chemosensor) [6] or in the redox properties (electrochemical chemosensors) [7]. Another approach to anion detection is the displacement assay. As in the above case, the signalling process is based on the use of binding sites and certain signalling subunits. However, in this approach the subunits are not covalently attached but instead form a molecular ensemble whose spectroscopic characteristics (colour or fluorescence behaviour) have to be as different as possible to those of the free signalling subunit. Then, when a target molecule is added to the solution containing the ensemble, displacement of the signalling unit takes place by the anion and the properties of the released signalling unit return to their non-coordinated state [8]. Among the signalling subunits used in this type of experiments the 4-nitrophenolate anion has given rise to interesting results [9]. Complexation of 4-nitrophenolate anion modifies its electronic proper-

ties giving rise to a colour change that can be used for colorimetric displacement sensing.

During the last years we have been working in the synthesis of ligands derived from biphenyl and able to act as fluorescent or colorimetric sensors for cations and anions [10]. Now we report the synthesis of a new ligand and its use as colorimetric sensor through displacement reactions. In addition, three related compounds previously described have also been studied in order to know the influence of the substituents on the biphenyl system on the sensing behaviour.

Results and discussion

The studied compounds are shown in Chart 1. These ligands present different substituents on the 4,4′ position of the biphenyl being **1** and **3** nitroderivatives and ligands **2** and **4** compounds derived from tetramethylbenzidine. On the other hand, the size of the cavity is different in order to improve selectivity.

The synthesis of ligand **1**–**3** has been previously described and ligand **4** has been prepared following similar

1 R=NO$_2$, n=0
2 R=N(CH$_3$)$_2$, n=0
3 R=NO$_2$, n=1
4 R=N(CH$_3$)$_2$, n=1
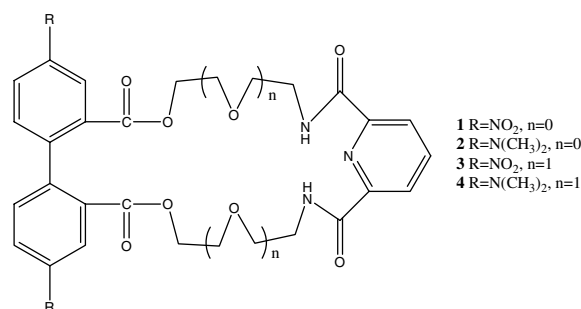
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procedures [11]. Thus, reductive amination of **3** in the presence of aqueous formaldehyde gives rise to compound **4** (51% yield).

Crystal structure of 2

X-ray single-crystal studies with ligand **1** and **3** had been previously reported and now we include X-ray single-crystal studies with ligand **2**. Suitable crystals for ligand **2** were obtained through slow evaporation of dichloromethane. The amides groups are almost coplanar but slightly twisted with respect to the pyridine ring, laying on similar sides of the mean plane of the pyridine ring (C(14)–C(15)–C(5)–O(4) = −9,6°; O(1)–C(1)–C(11)–C(12) = −1,7°). The two amide nitrogens are pointing inward and amide oxygens are pointing outward from the cavity. The macrocycle is stiffened by intramolecular hydrogen bonds (N–H$_{amide}$····N$_{py}$) (Table 1). The presence of such hydrogen bonds is known to stabilise flat syn–syn conformations for compounds containing 2,6-dicarbamoylpyridine moieties [12].

The biphenyl unit shows a dihedral angle between the aromatic rings (C(31)–C(32)-C(22)–C(21) = 110.9°) higher than in compound **1** that showed a value of 62.5°. On the other hand, each carbonyl group of the ester functions is almost coplanar with its corresponding aromatic ring (O(3)–C(4)–C(21)–C(26) = 8.8° and C(36)–C(31)–C(8)–O(6) = 159.4°). Finally, the pyridine ring is close to one of the aromatic rings of biphenyl, being the angle between both rings around 21°. In conclusion, the cavity is bent in such a way that the free space inside is very small (Figure 1).

Complexation studies

Ligands **1–3** were able to complex 4-nitrophenolate as its tetrabutylammonium salt. Complexation studies were carried out using UV/vis spectroscopic techniques and with the three ligands the characteristic yellow colour of tetrabutylammonium 4-nitrophenolate is partially discoloured after addition of an excess of ligand (Figure 2). This change in the colour that is naked-eye detectable is due to the co-ordination of the phenoxide group to NH amide groups in the ligands. Similar behaviour has been described for different type of receptors. [9]

UV/vis experiments using the molar ratio method with the studied ligands demonstrated that the stoichiometry was 1:1 (Figure 3). The complexation constants were determined by using the Clinp software [13] and
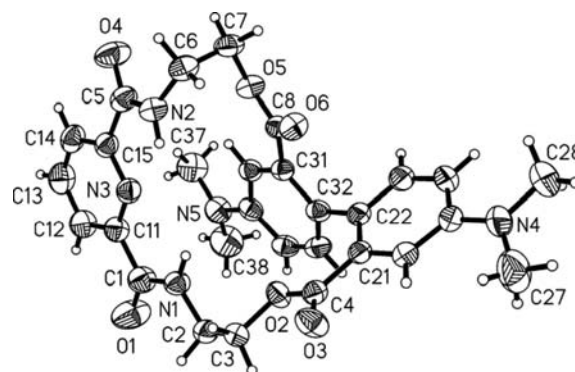

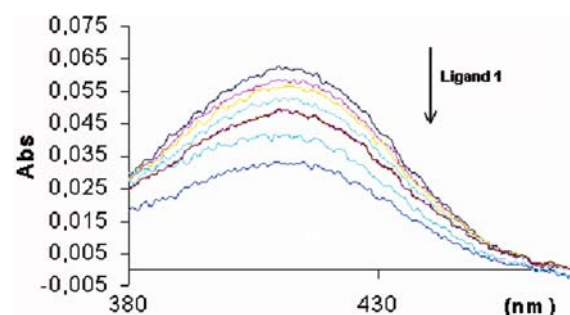*Figure 1.* Ellipsoids plot (40% probability) of compound **2** showing the labelling scheme.

Figure 2. Decreasing absorbance of the 4-nitrophenolate anion (1.44×10^{-5} M) upon addition of ligand **1** (3.6×10^{-4} M) in MeCN at 25 °C.

are shown in Table 2. By contrast, ligand **4** was unable to form stable complex with the guest under these conditions and the characteristic colour of the guest solution remained unchanged even after addition of large amount of host.

The results shown in Table 2 indicate that compounds with nitro groups in the biphenyl moiety form stronger complex than ligands containing dimethylamino groups. Thus, the complex formed by ligand **1** is ten times more stable than the complex formed by ligand **2**. These two ligands have the same size and donor atoms being the only difference the substitution in the biphenyl system. The same behaviour is observed with ligands **3** and **4**. With these two hosts the influence of the biphenyl substitution is so strong that ligand **4** is unable to form stable complexes.

In order to have some information about the structure of the complexes formed between ligands **1–3** and tetrabutylammonium 4-nitrophenolate several ^{1}H NMR experiments were carried out. The results obtained indicated that with ligand **1** only the signals corresponding to the NH hydrogen atoms were shifted downfield ($\Delta\delta$ = 0.20 ppm). The small modifications observed in the ^{1}H NMR spectrum after complexation agree with this is showed in Figure 4 in which the aromatic ring of the 4-nitrophenolate lies far from any of the ligands hydrogen atoms except the amide groups. This geometry also corresponded to a minimum of energy in the modelisation carried out using molecular mechanic calculations [14].

Table 1. Hydrogen bond geometry for **2**

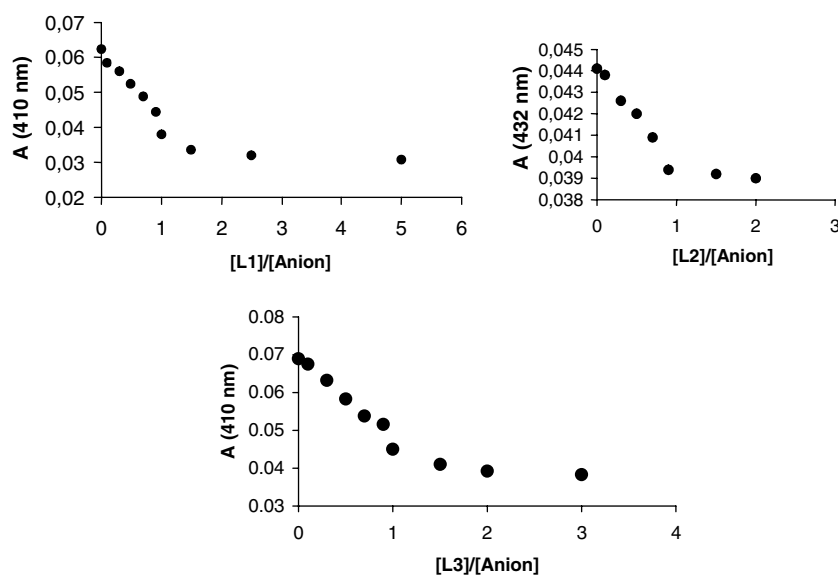| D–H····A	d(H····A) (Å)	d(D····A) (Å)	(D–H····A) (°)
N2–H2N····N3	2.29(3)	2.700(4)	109(2)
N1–H1N····N3	2.34(3)	2.711(3)	107(2)
N2–H2N····O5	2.97(3)	2.725(4)	65(2)
N1–H1N····O5	2.72(3)	2.924(5)	96(3)

Figure 3. Stoichiometry determination for complexation of 4-nitrophenolate anion by ligands **1, 2** and **3** (A = absorbance at the showed λ).

Table 2. Complexation constants of tetrabutylammonium 4-nitrophenolate in CH$_3$CN at 25 °C using UV/vis spectroscopy

Ligand	1	2	3
Log K	4.55 ± 0.03	3.22 ± 0.02	4.09 ± 0.02

Table 3. Value of the chemical shifts for the biphenyl, pyridine and NH hydrogen of ligand **3**: free and in the presence of tetrabutylammonium 4-nitrophenolate

	$\delta(H_a)$	$\delta(H_b)$	$\delta(H_c)$	$\delta(H_d)$	$\delta(H_e)$	$\delta(NH)$
3	8.71	8.42	7.49	8.13–8.11	8.27	8.38
3 4-nitrophenolate	8.67	8.28	7.39	7.92–7.94	8.00	9.17
	8.34	8.16	7.35			

A similar behaviour was observed in ¹H NMR spectrum obtained from the complex formed with ligand **2**. By contrast, complexation of ligand **3** with 4-nitrophenolate gave rise to clear modifications in its ¹H NMR spectrum (Table 3). Thus, the anion co-ordination produces loss of symmetry and two different aromatic rings for the biphenyl moiety are observed. A similar behaviour has been described in the complexation of this ligand with fluoride. The different environment observed for both aromatic rings in the biphenyl system suggests that the nitrophenolate anion is now close to one of these rings in the complex. This idea is consistent with the theroretical calculation that shows the nitrophenyl anion being close to the pyridine moiety and also to one of the aromatic rings of the biphenyl system.

The ability of ligands **1**–**3** in anion complexation had been previously studied and the observed results suggested the possibility of carrying out displacement assays in order to study the behaviour of these hosts as colorimetric sensors. Thus, addition of anions to solutions of 4-nitrophenolate complexes gives rise to a displacement reaction that restores the yellow colour of the free 4-nitrophenolate (Figure 5). Table 4 shows the relative absorbance values for solutions of ligands **1**–**3** (3.6 × 10⁻⁴ M) and 4-nitrophenolate (3.6 x 10⁻⁴ M) in MeCN upon addition of different anions (until 100 equivalents).
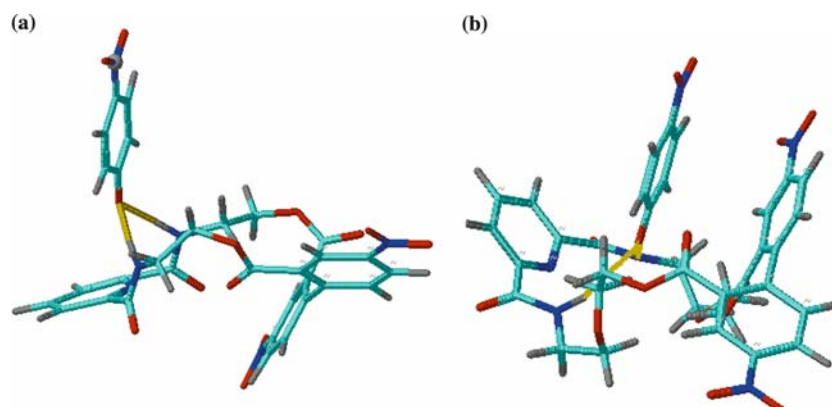

Figure 4. Theoretic model: (a) **1**· 4-nitrophenolate complex (b) **3**· 4-nitrophenolate complex.
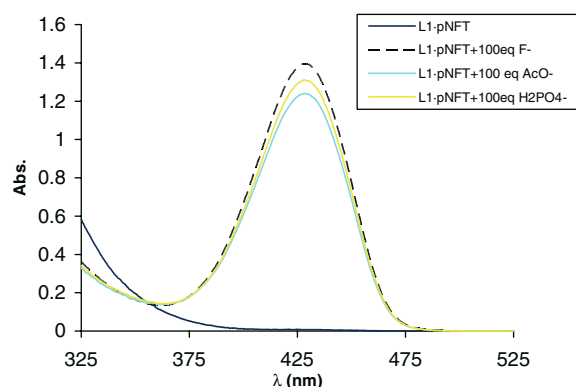
Figure 5. 4-nitrophenolate UV absorption recovery in the presence of different anions.

Figure 6. Selectivity of anion recognition with ligands **1–3**.

Experiments of anion recognition carried out with ligands **1** and **3** demonstrated that these ligands developed a red colour in the presence of fluoride. However, this colour development is strongly dependent not only on the ligand concentration but also on time. For this reason, there are not interferences in the experiments now described because the displacement of 4-nitrophenolate and so, the recovery of the yellow colour is very fast [10b]. Figure 6 clearly shows the different selectivity of ligands **1–3** in front of anions. As it was expected anion basicity is one of the most important factors in the displacement reaction; thus, ligands **1** and **2** give rise to similar results in the presence of F^-, AcO^- and $H_2PO_4^-$ which have a similar basic character. By contrast, ligand **3** shows a more selective behaviour. In fact, it is clear that this ligand forms stronger complex with AcO^- or $H_2PO_4^-$ than with F^- what can be related to the different geometry shown by these three ligands. The remaining anions show lower affinity with the three studied ligands.

Conclusions

Ligands **1–3** can be successfully used in the sensing of F^-, AcO^- and $H_2PO_4^-$ through displacement of previously complex with 4-nitrophenolate. The electronic character of the substituents on the biphenyl moiety seems to exert influence on the complexation ability. In that sense ligands **1** and **3** with nitro groups at the 4,4′
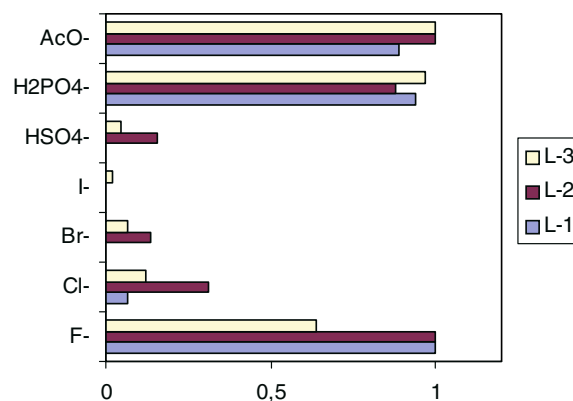
positions of the biphenyl give rise to stronger complex than ligands **2** and **4** that present dimethylamino groups at the same positions. In addition, the importance of the cavity size and the flexibility of the system is so strong that ligand **4** is unable of complexing tetrabutylammonium 4-nitrophenolate. By contrast, ligand **3** with the same cavity size not only is able to act as a colorimetric sensor but also shows higher selectivity than ligands **1** and **2**.

Experimental

General methods

All commercially available reagents were used without further purification. Water sensitive reactions were performed under argon. Column chromatography was carried out on SDS activated neutral aluminium oxide (0.05–0.2 mm; activity degree 1). IR spectra were recorded on a Perkin-Elmer 1750 FT-IR and a Bruker Equinox 55 FT-IR. NMR spectra were recorded with Bruker Avance 300/500 and Varian Unity-300/400 spectrometers. Chemical shifts are reported in parts per million downfield from TMS. Spectra were referenced to residual undeuterated solvent. High resolution mass spectra were taken with a Fisons VG-AUTOSPEC and those using the eletrospray ionizing technique were recorded on an HPLC-MS with ion trap Bruker 3000-Esquire Plus. UV spectra were run at 20 °C (thermostated) on a Shimadzu UV-2102 PC.

Table 4. Relative absorbance values for ligands **1–3** + 4-nitrophenolate solutions containing equimolar concentrations of different anions (all anions were used as their tetrabutylammonium salts)

Ligand/anion		F^-	Cl^-	Br^-	I^-	HSO_4^-	$H_2PO_4^-$	AcO^-
1	Δ(Absorbance)	1.3875	0.0879	0.0002	0.0004	0.0002	1.3036	1.2328
	Relative absorbance	1	0.06336	0.00014	0.00029	0.00014	0.93955	0.88852
2	Δ(Absorbance)	0.7233	0.2252	0.0969	0.0004	0.1143	0.6373	0.7225
	Relative absorbance	1	0.31135	0.13397	0.00055	0.15803	0.88110	0.99889
3	Δ(Absorbance)	0.3931	0.0733	0.0416	0.0129	0.0284	0.5992	0.6182
	Relative absorbance	0.63588	0.11857	0.06729	0.02087	0.04602	0.96926	1

Synthesis of ligand **4**

An heterogeneous solution of **3** [10b] (0.3 g, 0.47 mmol), formaldehyde (0.3 mL, 30% in water) and Pd/C 10% (0.1 g) in anhydrous ethanol (50 mL) was stirred under hydrogen (30 lib/inch^2). The mixture was followed by thin layer chromatography until the reaction was finished (45 min), then the reaction was filtered off and the solid was washed with HCl 10%. The aqueous layer was basified accurately (until pH = 8) with potassium carbonate, extracted with ethyl acetate (3 x 25 mL) and washed with brine. Organic layers were joined, dried with anhydrous sodium sulphate. The solvent was evaporated under reduce pressure to give compound **4** as an oil (0.1532 g, 51%). IR absorptions(KBr)v_{max}/cm^{-1}: 3351 (NH), 3329 (Ar–H), 2921 (CH$_3$, CH$_2$), 1720 (C = O), 1667, 1607 (N–C = O), 1538 (C = C), 1223 (C–O), 1064, 815, 646. δ_H (300 MHz; CDCl$_3$) 9.02 (2H, bt, J = 5.3 Hz, NH), 8.33 (2HdJ = 7.7 Hz, Py–H), 8.03 (1H, t, J = 7.7 Hz, Py–H), 7.23 (2H, d, J = 2.8 Hz, Ar–H), 7.07 (2H,d,J = 8.5 Hz, Ar–H), 6.85 (2H, dd, J$_1$ = 2.8 Hz, J$_2$ = 8.5 Hz, Ar–H), 4.22 (4H, m, CH$_2$–OOC), 3.79 (4H, m, CH$_2$–N), 3.48 (4H, m, CH$_2$–O), 3.35 (4H, m, CH$_2$–O). δ_C (75 MHz, CDCl$_3$) 169.0, 164.1, 149.3, 139.1, 132.2, 131.3, 130.9, 125.5, 125.0, 115.4, 113.5, 70.7, 69.7, 63.9, 40.8, 39.7. HMS (E.I.): M$^+$ calc. for C$_{33}$H$_{39}$N$_5$O$_8$ 633.279, found 633.2805. Elemental analysis Found: C, 60.70; H, 6.52; N, 10.43. C$_{33}$H$_{39}$N$_5$O$_8$·H$_2$O required C, 60.82; H, 6.34; 10.75.

Titration experiments with tetrabutylammonium 4-nitrophenolate: General method

Increasing amounts of the ligand solution (3.6 x 10^{-4} M) were added to a solution of tetrabutylammonium 4-nitrophenolate (3.6 x 10^{-4} M, 2 mL) and the UV-vis spectrum was registered. (The results are shown in the supplementary material).

Displacement reaction: General procedure

Three milliliter of a mixture of **L** (3.6 × 10^{-4} M) and tetrabutylammonium 4-nitrophenolate (3.6 x 10^{-4} M) in acetonitrile was placed in a quartz cuvette and the UV-vis spectra were recorded. Then, 10 μl of a solution of anion (as its tetrabutylammonium salt) 0.9 M was added to the cuvette, after 30 s the spectra was recorded again. The difference between the absorbances registered at 428 nm gave the absolute absorbance for every anion. To obtain the relative absorbances all the absolute values were referred to the biggest one. Results are summarized in Table 4.

Crystal structure determination of compound **2**

A colourless tablet of compound **2** suitable for X-ray diffraction was grown by a dichloromethane solution.

Crystal data

C$_{29}$H$_{31}$N$_5$O$_6$, M = 9545.59, monoclinic, a = 15.273(3), b = 16.180(3), c = 11.078(2) Å, β = 103.33(3), U = 2663.8(9) Å^3, T = 293(1) K, space group P2$_1$/c, Z = 4, μ(Mo-K$_\alpha$) = 0.097 mm^{-1}, 11,213 reflections measured, 6477 unique (R$_{int}$ = 0.0565) which were used in all calculations. NH hydrogen atoms were refine as free, methyl as *rigid* and the others using a *riding* model. The final wR2(F^2) was 0.1388 (all data) and R1(F) was 0.0543(I > 2σI). A list of anisotropic displacement parameters for non-hydrogen atoms, bond lengths and angles, hydrogen atoms co-ordinates have been deposited as supplementary material at the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, United Kingdom (CCDC 245998). The list of F$_0$/F$_c$ structure data is available directly form the author until a year after the paper is published.

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14. Optimization of geometry was performed by Molecular Mechanics using MM+ as Force Field and the Polak-Ribiere (conjugated gradient) alogorithm, contained in HyperChem release 7.01 from Hypercube Inc. (www.hyper.com).