Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

Anion binding by pyrrole-pyridine-based macrocyclic polyamides

E. A. Katayev[a]; E. N. Myshkovskaya[a]; N. V. Boev[a]; V. N. Khrustalev[a]
[a] A. N. Nesmeyanov Institute of Organoelement Compounds RAS, Moscow, Russia

To cite this Article Katayev, E. A. , Myshkovskaya, E. N. , Boev, N. V. and Khrustalev, V. N.(2008) 'Anion binding by pyrrole-pyridine-based macrocyclic polyamides', Supramolecular Chemistry, 20: 7, 619 — 624
To link to this Article: DOI: 10.1080/10610270701561342
URL: http://dx.doi.org/10.1080/10610270701561342

Supramolecular Chemistry
Vol. 20, No. 7, October–November 2008, 619–624

Taylor & Francis
Taylor & Francis Group

Anion binding by pyrrole–pyridine-based macrocyclic polyamides

E.A. Katayev*, E.N. Myshkovskaya, N.V. Boev and V.N. Khrustalev

A. N. Nesmeyanov Institute of Organoelement Compounds RAS, Moscow, Russia

(*Received 15 May 2007; final version received 1 October 2007*)

The synthesis, characterisation and anion-binding properties of new pyrrole–pyridine-based macrocyclic polyamides **7a** and **7b** are presented. Chloride anion templation in the macrocyclisation reaction has been shown to control [1 + 1] acylation. The anion-binding properties of the receptors have been determined by UV–vis titrations in a DMSO solution and compared with systems with a similar design. The new receptors have been found to display a 10-fold selectivity for hydrogensulphate, dihydrogenphosphate and acetate anions over other anions studied.

Keywords: receptor; anion templation; phosphate binding; host–guest chemistry; macrocyclic polyamide

Introduction

Amide- and urea-based receptors have been widely exploited in the design of anion receptors due to their ability to form strong hydrogen bonds and their structural similarity to polypeptides (*1*, *2*). They are good candidates for pharmaceutical developments such as anion transporters through biological membranes (*3*) and functional models of phosphatases or kinases (*4*). Possessing a high affinity towards anions, they can also find analytical (*5*) and nuclear waste remediation applications (*6*). In recent years, much attention has been devoted to the investigation of the structure–selectivity relationship of amide-based receptors (*7–10*) and their phosphate anion binding (*11–14*). It has been shown by Gale and co-workers that diamidodipyrromethanes can be efficient binding motifs for phosphate recognition (*14*). We have also found that the amido-imine hybrid macrocycle **1** (*15*) and bipyrrole-based receptors (*16*, *17*) can efficiently and selectively bind the dihydrogen phosphate anion in an acetonitrile solution. Structurally, similar receptors bearing only amido functionalities can possess better chemical stability and binding affinity towards anions due to the increased number of NH groups. The anion-controlled formation of macrocyclic ligands has been clearly observed in imine bond formation reactions (*15*, *16*, *18*) and has been suggested in amide (*19*) and urea (*20*) syntheses and the rotaxane and catenane self-assembly (*21*). In this work, we describe the anion-controlled synthesis, characterisation and anion-binding properties of new macrocyclic polyamides containing 2,6-diamidopyridine, 2,2′-diamidodipyrromethane and 2,2′-diamidobipyrrole anion-binding motifs.

Results and discussions

Target macrocyclic polyamides **7a** and **7b** have a design similar to receptors **1** and **2**, except that imino groups are replaced by amido groups. The synthesis of these receptors can be accomplished following two possible routes: the acylation of the starting diamine **3** with oligopyrrole precursors or the acylation of the starting diamines **5a** and **5b** with 2,6-pyridinedicarbonyl dichloride. According to our previous investigations (*22*), the first method is more difficult due to the low stability of oligopyrrole acylating reagents; therefore, in this work we have used the second method. The synthesis of the starting diamines **5a** and **5b** has been described by us recently (*22*). The introduction of an electron-deficient phenyl substituent in the 3-position of pyrrole ring is very important for the stability of the amidopyrroles (*22*) (Figure 1).

In the first stage, pincer diamines **5a** and **5b** were acylated with 2,6-pyridinedicarbonyl chloride (Figure 2). Anion templation has recently attracted a huge amount of interest due to the high level of functionality and selectivity of systems generated by this method (*24*). Due to the presence of six NH groups in the macrocycles **7a** and **7b**, their formation should be highly dependent on the anions present in the reaction mixture. Obviously, the chloride anion as one of reaction products can template the polyamide formation. The acylation reactions were carried out by the slow addition of a THF solution of 2,6-pyridinedicarbonyl chloride to a solution of diamines **5a** or **5b** and excess pyridine as a base in THF. For both diamines, complexes **7a**·Cl^-PyH^+ and **7b**·Cl^-PyH^+ were separated by crystallisation with a 45% yield. The presence of inorganic anions in the final product was first

*Corresponding author. Email: katayev@ineos.ac.ru

ISSN 1061-0278 print/ISSN 1029-0478 online

DOI: 10.1080/10610270701561342
http://www.informaworld.com

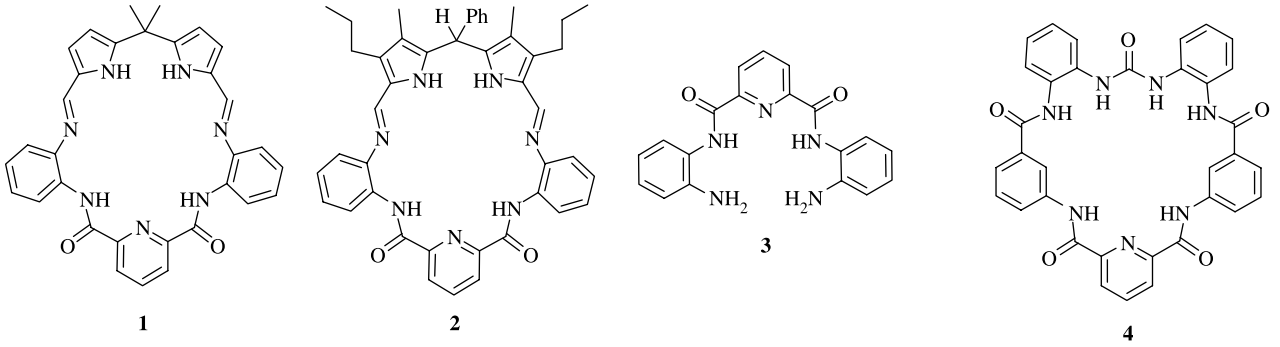

Figure 1. Structure of artificial phosphate-selective receptor **1** (*15*), sulphate-selective receptor **2** (*23*), pincer starting diamine **3** used for synthesis of macrocycles **1** and **2**, and acetate-selective receptor **4** (*19*) developed by Gale and co-workers.

suggested due to the pyridinium cation signals in the ^{1}H NMR of the product and was later proved by elemental analysis and X-ray crystal structure analysis. The anion salt can be easily removed by passing the product through the small plug of silica.

The coordination of the chloride anion to the amidopyrrole and amidopyridine fragments can be suggested as a possible mechanism for the chloride anion templation of the acylation reaction. For this purpose, we conducted several experiments where 2,6-pyridinedicarbonyl chloride was added to the solution of diamine containing one equivalent of a Cl^-, HSO_4^-, $H_2PO_4^-$, CH_3COO^- and ReO_4^-. The presence of tetrabutylammonium chloride increased the yields of the final macrocycle up to 74%. Interestingly, the addition of tetrabutylammonium dihydrogenphosphate or hydrogensulphate to diamine **5b** resulted in the precipitation of the complex TBA^+**5b**·[anion]$^-$, according to the ^{1}H NMR analysis. These complexes were dissolved upon reaction with 2,6-pyridinedicarbonyl chloride producing **7b** with the same high yield (74%). However, in this experiment crystallisation of the product yielded the chloride salt **7b**·TBA^+Cl^- instead of the expected dihydrogenphosphate or hydrogensulphate, according to the X-ray crystal structure analysis (Figure 4). This behaviour can be explained in terms of the relative anion affinity in THF towards competing anions; the ligand has more preference to bind chloride than dihydrogenphosphate. Tetrabutylammonium perrhenate, as a source of larger anion, gave a mixture of 1 + 1 and 2 + 2 products of acylation and polymeric impurities, according to mass spectrometry. However, these experiments provide clear evidence that the presence of an anion in the reaction of macrocyclic polyamide synthesis has a dramatic effect on the resulting product and can template the acylation reaction.

Similarly, both polyamide ligands have high affinities towards chloride since all three crystallographic experiments revealed chloride complexes with the ligand (Figures 3 and 4). The inner cavity sizes of the receptors are almost the same, the average hydrogen bond distance between the Cl and the H–N group is 2.62 Å for **7a** and 2.50 Å for **7b**. However, a comparison of the Cl···NH lengths suggest that the major contribution to the hydrogen bonding with chloride is provided by amido groups in **7a** (the shortest distances are Cl1···H–N3, 2.40 Å and Cl1···H–N6, 2.44 Å) and pyrrole NH groups in **7b** (Cl1···H–N4, 2.47 Å and Cl1···H–N5, 2.37 Å) . Analysis of the crystal structures of **7a** and **7b** with chloride and **2** with sulphuric acid revealed interesting

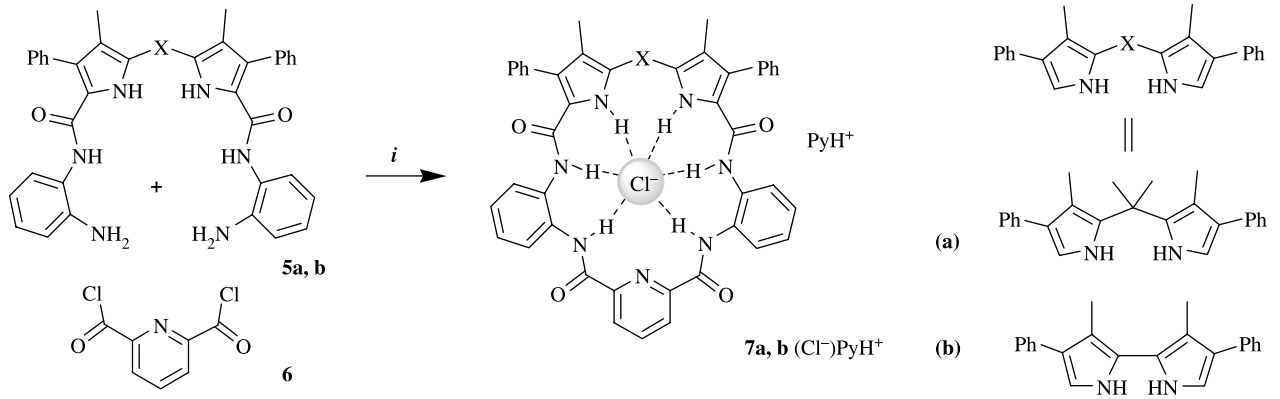

Figure 2. Synthesis of **7a** and **7b**. (*i*) THF, Py (pyridine).

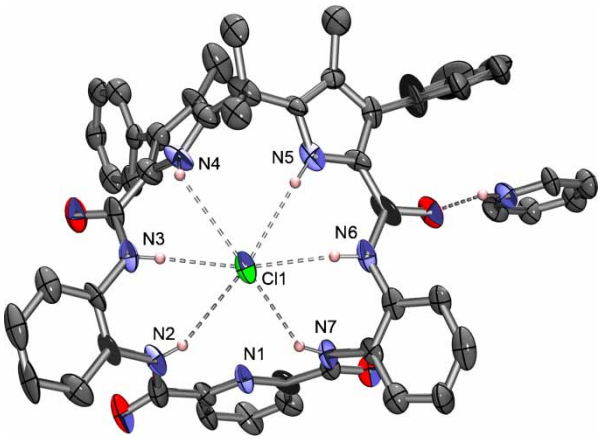

Figure 3. Structure of **7a**·Cl^-PyH^+ according to the X-ray diffraction analysis. Ellipsoids are scaled in 50% probability level. The hydrogen atoms that are not participating in the hydrogen bonds are omitted for clarity.

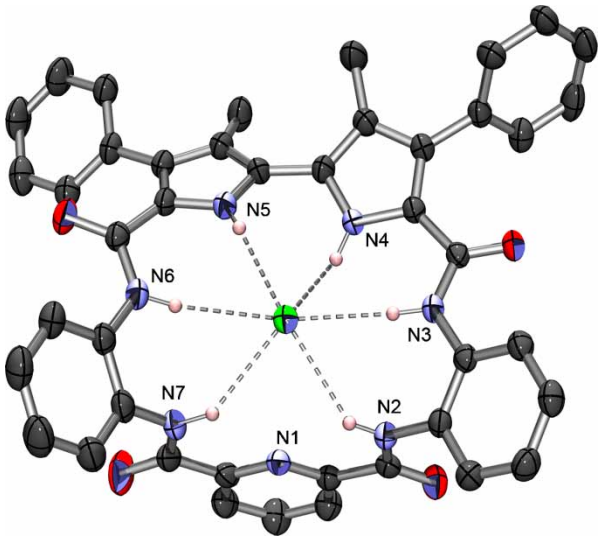

Figure 4. Structure of **7b**·Cl^-TBA^+ according to the X-ray diffraction analysis. Ellipsoids are scaled in a 50% probability level. The hydrogen atoms not participating in the hydrogen bonds and tetrabutylammonium cation are omitted for clarity.

features. In spite of a rather bowl-like conformation of the receptors, their donor NH groups are situated almost in one plane (Figure 5). However, in **7a** the chloride anion is deviated by 0.83 Å from the geometrical centre of six NH groups and in **7b** the distance is even longer, 1.09 Å These observations lead to the suggestion that careful design of the receptors will not provide the selectivity for anion geometries other than spherical. It can be clearly seen in Figure 5 that the direction of the pyrrole NH groups determines the side of guest coordination. Hence, in case of structures (a) and (b) (Figure 5), the coordination can occur only from the right side, while in (c) it can occur from both sides since the pyrrole rings have different orientation with the angle about 30° relative to the centre of the ligand.

Association constants of new receptors were determined by a standard UV–vis titration method in dry DMSO and experimental data were refined by the Hyperquad computer program (Table 1) (*25*). The remarkable feature of our polyamide receptors is their relatively high affinities towards this selection of anions even in DMSO (association constants are as high as $\log K_a = 6$). Taking into consideration the macrocyclic structures with six NH groups located around the circle uniformly, a selectivity towards the halogen anions can be expected; however, the ligands **7a** and **7b** have lower affinity for chloride and fluoride anions than for oxoanions. Addition of the nitrate anion does not cause visible changes in the UV spectrum. Dipyrromethane-based receptor **7a** was found to be selective for the hydrogensulphate anion with association constants an order of magnitude higher than other inorganic anions (Table 1). We have compared the crystal structure of **7a** with structurally similar amido-imine receptor **2** (*23*) known to be selective for hydrogensulphate. A strong similarity between the two structures was found; the torsion angle between pyrrole rings differs only by 10° in **7a**, the distances between opposite NH groups (i.e. amides, imines) are 0.1 Å longer than those in **2** . Hence, we can conclude that this design of the receptor (binding motifs and geometry) has inherited the selectivity for the hydrogensulphate anion. The bipyrrole-based receptor **7b** was found to be selective for dihydrogenphosphate and acetate anions. Unexpectedly, it was observed to bind two dihydrogenphosphate anions. Interestingly, the binding of two dihydrogenphosphate anions was observed by us for the ligand **1** in acetonitrile, and not for the bipyrrole-based receptors (*16*). Taking into consideration the X-ray crystal structure of **7b**, namely planarity of the receptor and different orientation of the pyrrole ring, the two possible binding sites in the receptors can be suggested (*26*). This fact and geometry of chloride coordination suggest that receptors **7a** and **7b** have the preorganised conformation for oxoanion binding and this process is more preferable than binding of chloride anion in DMSO solution.

In conclusion, we have synthesised new macrocyclic polyamide receptors based on amido-pyridine and amido-pyrrole-binding motifs. The chloride-templated acylation can be an effective method for the preparation of polyamide receptors with appropriate cavity size. The receptors display high affinities ($\log K_a = 6$) towards hydrogensulphate, dihydrogenphosphate and acetate anions according to UV–vis titrations in DMSO solution. The present study of anion-dependent acylation opens future perspectives for the development of polyamide strategic synthesis and artificial models of proteins.

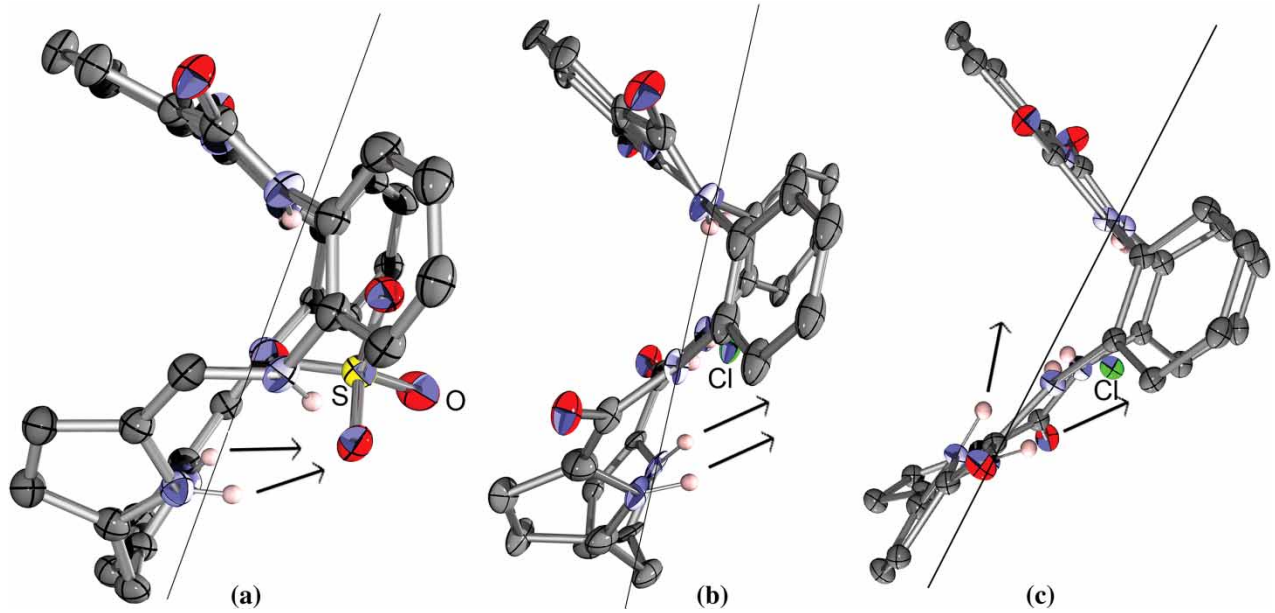

Figure 5. A comparison of host–guest complexes of receptors (a) **2**·H_2SO_4, (b) **7a**·Cl^- and (c) **7b**·Cl^-. The lines show average geometrical planes between donor NH groups. The arrows show the direction of the pyrrole NH groups.

We are currently investigating the biological activity of these polyamide receptors, namely the ability of the ligands to perform RNA cleavage.

Experimental

General method for preparation of 7a and 7b

To a solution of 50 mg of diamine **5a** or **5b** (0.08 mmol) and 0.06 ml (0.8 mmol) of pyridine (in 25 ml of THF) under an argon atmosphere, 19.83 mg of 2,6-pyridinedicarbonyl dichloride (0.09 mmol in 25 ml solution in THF) was slowly added dropwise (*ca.* 20 min). The mixture was stirred at room temperature for 24 h. The resulting precipitate was filtered (chloride salt), dissolved in a solution of dichloromethane–methanol (95/5 v/v) and passed through a small silica plug. The solution was evaporated giving the desired product in 45% yield. In the case of anion-templated syntheses, the reactions were carried out in the presence of an anion and the product was separated by column chromatography using a solution of dichloromethane–methanol (95/5 v/v) for eluting. The crystallisation of the chloride salts was accomplished by slow diffusion of pentane (in the case of **7a**) or ether (in the case of **7b**) into dichloromethane solution.

Table 1. Association constants of receptors **7a** and **7b** determined by UV–vis titration with tetrabutylammonium salts of corresponding anions in DMSO solution at 25°C.

Receptor/anion log K_a	**7a**	**7b**
$H_2PO_4^-$	3.83(3)	5.24(8) 8.29(7)
HSO_4^-	5.26(8)	3.32(7)
CH_3COO^-	4.36(1)	6.00(6)
Cl^-	4.37(4)	4.60(5)
F^-	4.63(4)	4.70(4)

Ligand **7a.** Anal. calcd for $C_{51}H_{45}ClN_8O_4$: C, 70.46; H, 5.22; N, 12.89. Found: C, 70.21; H, 5.02; N, 12.87. ^{1}H NMR for **7a**·Cl^-PyH^+ (DMSO-d6): δ (ppm): 10.87 (s, 2H), 10.44 (s, 2H), 9.77 (s, 2H), 8.91 (m, 4H), 8.55 (m, 2H), 8.29 (m, 3H), 8.03 (m, 4H), 7.82 (m, 2H), 7.38 (m, 2H), 7.25–7.14 (m, 10H), 1.84 (s, 6H), 1.68 (s, 6H). ^{1}H NMR for the free ligand (DMSO-d6): δ (ppm) 10.66 (s, 2H), 9.68 (s, 2H), 8.73 (s, 2H), 8.36 (m, 3H), 7.50 (m, 4H), 7.19 (m, 14H), 1.79 (s, 6H), 1.60 (s, 6H). ^{13}C NMR (DMSO-d6): δ (ppm) 160.3, 157.2, 148.1, 134.9, 134.2, 132.0, 131.1, 128.7, 127.1, 126.8, 126.6, 126.0, 125.4, 125.1, 124.5, 123.4, 122.5, 121.1, 115.8, 30.5, 25.3, 10.9. MALDI-TOF: 776 $[M + Na]^+$.

Ligand **7b.** Mp 215°C. Anal. calcd for $C_{59}H_{69}ClN_8O_4$: C, 71.60; H, 7.03; N, 11.32. Found: C, 71.30; H, 6.85; N, 11.17. ^{1}H NMR for **7b**·Cl^-PyH^+ (DMSO-d6): δ (ppm): 11.34 (s, 2H), 10.99 (s, 2H), 9.74 (s, 2H), 8.86 (m, 2H), 8.43 (t, 1H, $J = 7.8$ Hz), 8.36 (d, 2H, $J = 7.8$ Hz), 8.26 (m, 3H), 7.93 (m, 4H), 7.42 (m, 2H), 7.35 (m, 6H), 7.27 (m, 4H), 7.17 (m, 2H), 1.97 (s, 3H). ^{1}H NMR for the free ligand (DMSO-d6): δ (ppm) 11.24 (s, 2H), 10.29 (s, 2H), 8.90 (s, 2H), 8.33, 8.01 (d, 1H), 8.00 (t, 2H), 7.36 (m, 18H), 1.98 (s, 6H). ^{13}C NMR (DMSO-d6): δ (ppm) 163.8, 158.7, 149.5, 139.3, 134.5, 134.4, 130.0, 129.9, 128.7, 127.8, 127.5, 127.0, 126.3, 125.1, 123.9, 123.8, 122.6, 122.2, 117.2, 10.9. MALDI-TOF: 711 $[M + Na]^+$.

Table 2. Crystallographic data for **7a** and **7b**.

Empirical formula	**7a**·[PyH][Cl]·$4CH_2Cl_2$	**7b**·[NBu_4][Cl]·$2CH_2Cl_2$
FW	1209.1	1159.52
T (K)	120(2)	180(2)
Crystal size (mm)	0.30 × 0.06 × 0.06	0.20 × 0.20 × 0.15
Crystal system	Triclinic	Triclinic
Space group	P–1	P–1
a (Å)	13.814(2)	12.9616(7)
b (Å)	14.072(2)	14.3035(7)
c (Å)	16.970(2)	16.8358(9)
α (°)	96.902(5)	85.645(5)
β (°)	96.919(5)	84.506(5)
γ (°)	114.713(5)	76.606(5)
V ($Å^3$)	2921.2(7)	3017.8(3)
Z	2	2
dc ($g\,cm^{-3}$)	1.375	1.276
F(000)	1248	1224
m (mm^{-1})	0.483	0.293
$2q_{max}$ (°)	48	50
Index range	$-15 \le h \le 15$ $-16 \le k \le 16$ $-19 \le l \le 19$	$-15 \le h \le 15$ $-16 \le k \le 16$ $-20 \le l \le 19$
No. of rflns collected	20697 ($R_{int} = 0.0937$)	22709 ($R_{int} = 0.0261$)
No. of unique rflns	8954	10096
No. of rflns with $I > 2s(I)$	2834	8076
Data/restraints/parameters	8954/61/437	10096/40/621
R1; wR2 ($I > 2s(I)$)	0.1123; 0.1473	0.0577; 0.1552
R1; wR2 (all data)	0.2248; 0.1710	0.0692; 0.1642
GOF on F2	0.938	1.029
T_{min}; T_{max}	0.868; 0.972	0.949; 0.959

X-ray structure determination

Data were collected on a Bruker SMART 1000 CCD diffractometer (λ($MoK_α$)-radiation, graphite monochromator, ω and φ scan mode) and corrected for Lorentz and polarisation effects, and for absorption (Table 2) (*27*). The structures were determined by direct methods and refined by full-matrix least-squares technique with anisotropic thermal parameters for non-hydrogen atoms. In the crystal **7b**, two *n*-butyl groups of the cation were disordered each over two sites, with the occupancies of 0.5:0.5 and 0.7:0.3. The hydrogen atoms were placed in calculated positions and refined in riding model with fixed thermal parameters ($U_{iso}(H) = 1.5\,U_{eq}(C)$ for the CH_3 groups and $U_{iso}(H) = 1.2U_{eq}(C)$ for the other groups). One dichloromethane molecule in **7b**·[NBu_4][Cl]·$2CH_2Cl_2$ and all four dichloromethane molecules in **7a**·[PyH][Cl]·$4CH_2Cl_2$ were found to be strongly disordered and could not be modelled satisfactorily. The contribution to the scattering by these molecules was removed by using the utility SQUEEZE in PLATON98 (*28*). All calculations were carried out by using the SHELXTL PLUS (PC Version 5.10) program package (*29*). Crystallographic data for **7a** and **7b** have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 645410 and 645411. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; Email: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

Acknowledgements

Financial Support from Russian Foundation for Basic Research (grants no. 05-03-32684 and 05-03-08017) is acknowledged.

References

(1) Sessler, J.L.; Gale, P.A.; Cho, W.-S. *Anion Receptor Chemistry*; Royal Society of Chemistry: Cambridge, UK, 2006.
(2) Schmuck, C. *Coord. Chem. Rev.* **2006**, *250*, 3053–3067.
(3) McNally, B.A.; Leevy, W.M.; Smith, B.D. *Supramol. Chem.* **2007**, *19*, 29–37.
(4) Garipova, I.Y.; Silnikov, V.N. *Russ. Chem. Bull. Int. Ed.* **2002**, *51*, 1112–1117.
(5) Anslyn, E.V. *J. Org. Chem.* **2007**, *72*, 687–699.
(6) Custelcean, R.; Sellin, V.; Moyer, B.A. *Chem. Commun.* **2007**, 1541–1543.
(7) Kang, S.O.; Begum, R.A.; Bowman-James, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 7882–7894.
(8) Kang, S.O.; Hossain, M.A.; Bowman-James, K. *Coord. Chem. Rev.* **2006**, *250*, 3038–3052.
(9) Gale, P.A. *Acc. Chem. Res.* **2006**, *39*, 465–475.
(10) Andrievsky, A.; Ahuis, F.; Sessler, J.L.; Vogtle, F.; Gudat, D.; Moini, M. *J. Am. Chem. Soc.* **1998**, *120*, 9712–9713.

(11) Hirsch, A.K.H.; Fischer, F.R.; Diederich, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 338–352.
(12) Shimizu, S.; Osuka, A. *Eur. J. Inorg. Chem.* **2006**, 1319–1335.
(13) Liao, J.-H.; Chen, C.-T.; Fang, J.-M. *Org. Lett.* **2002**, *4*, 561–564.
(14) Vega, I.E.D.; Gale, P.A.; Hursthouse, M.B.; Light, M.E. *Org. Biomol. Chem.* **2004**, *2*, 2935–2941.
(15) Sessler, J.L.; Katayev, E.; Pantos, G.D.; Ustynyuk, Y.A. *Chem. Commun.* **2004**, 1276–1277.
(16) Katayev, E.A.; Boev, N.V.; Khrustalev, V.N.; Ustynyuk, Y.A.; Tananaev, I.G.; Sessler, J.L. *J. Org. Chem.* **2007**, *72*, 2886–2896.
(17) Katayev, E.A.; Pantos, G.D.; Reshetova, M.D.; Khrustalev, V.N.; Lynch, V.M.; Ustynyuk, Y.A.; Sessler, J.L. *Angew. Chem. Int. Ed.* **2005**, *44*, 7386–7390.
(18) Bru, M.; Alfonso, I.; Burguete, M.I.; Luis, S.V. *Angew. Chem. Int. Ed.* **2006**, *45*, 6155–6159.
(19) Brooks, S.J.; Garca-Garrido, S.E.; Light, M.E.; Cole, P.A.; Gale, P.A. *Chem. Eur. J.* **2007**, *13*, 3320–3329.
(20) Meshcheryakov, D.; Bohmer, V.; Bolte, M.; Hubscher-Bruder, V.; Arnaud-Neu, F.; Herschbach, H.; Dorsselaer, A.; Thondorf, I.; Mogelin, W. *Angew. Chem. Int. Ed.* **2006**, *45*, 1648–1652.
(21) Beer, P.D.; Sambrook, M.R.; Curiel, D. *Chem. Commun.* **2006**, 2105–2117.
(22) Boev, N.V.; Ustynyuk, Y.A. *Russ. J. Org. Chem.* **2007**, *43*, 297–304.
(23) Sessler, J.L.; Katayev, E.; Pantos, G.D.; Scherbakov, P.; Reshetova, M.D.; Khrustalev, V.N.; Lynch, V.M.; Ustynyuk, Y.A. *J. Am. Chem. Soc.* **2005**, *127*, 11442–11446.
(24) Lankshear, M.D.; Beer, P.D. *Coord. Chem. Rev.* **2006**, *250*, 3142–3160.
(25) Gans, P.; Sabatini, A.; Vacca, A. *Talanta* **1996**, *43*, 1739–1753.
(26) Hisaki, I.; Sasaki, S.-i.; Hirose, K.; Tobe, Y. *Eur. J. Org. Chem.* **2007**, 607–615.
(27) Sheldrick, G.M. *SADABS, V2.01, Bruker/Siemens Area Detector Absorption Correction Program*; Bruker AXS Inc. : Madison, WI, 1998.
(28) Spek, A.L. In *PLATON, A Multipurpose Crystallographic Tool*; Utrecht University: Utrecht, Netherlands, 1998.
(29) Sheldrick, G.M. In *SHELXTL, v. 5.10, Structure Determination Software Suite*; Bruker AXS: Madison, WI, 1998.