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Crown ethers derived from cyclohexane. Influence of their stereochemistry in complexation and transport

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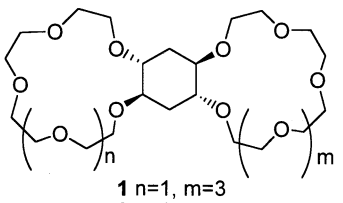
Abstract—Crown ethers derived from cyclohexane have been prepared. The *trans* stereochemistry of the substituents on the carbocyclic ring makes that only one conformation can complex cations. The influence of the stereochemistry in complexation has been studied.

Our research group has been interested for several years in the preparation of crown ether derives from cyclohexane. The rigidity shown by the crown ether directly bound to a cyclohexyl moiety has been previously used by our research group in controlling the ability of ligands to complex and transport cations.[1] Thus, the negative allosteric cooperativity observed in compounds **1** and **2** (Chart 1) greatly increased the transport of cations through organic membranes. The allosteric behaviour observed in these ligands was due to the stereochemistry of the cyclohexane derivative in which only one site at a time has a favourable conformation for binding. On the other hand, the rigidity of the cyclohexyl system provides a direct connection between the crown ether and the substituents on the cyclohexane. Thus, it has been reported that in *trans*-cyclohexyl crown ethers with a bulky substituent in position 3, conformations with the equatorial substituent are more stable than those with the axial disposition.[2] Making use of the same principle, we prepared compound **3** which showed different conformation of the cyclohexane system depending on the pH of the medium. Because of its stereochemistry compound **3** is only able to complex cations if the crown ether moiety adopts a *trans*-diequatorial conformation (lone pair on the oxygen atoms directed toward the centre of the cavity). In addition, the rigidity of the cyclohexyl moiety fixes the conformation in such a way that compound **3** is able to form more stable complexes under basic conditions rather than in an acid medium.[3]

In the course of these studies, several crown ethers derived from cyclohexane have been prepared. These compounds do not only show different stereochemistry but can also present two conformations in the cyclohexane moiety. These two factors can affect their complexation and transport properties.

1. Synthesis and conformational studies

Compounds **7** and **7b** were synthesised as shown in Scheme 1. Compound **4** was prepared using a Diels–Alder reaction between diethyl fumarate and butadiene sulfone.[4] Epoxidation of **4** under standard conditions gave compound **5**[5] that was transformed into diol **6** by reaction with ethyleneglycol in the presence of sulfuric acid.[1b] Compound **6** was the main product in this reaction but the other diasteroisomer, **6a**, was



1 n=1, m=3
2 n=1, m=2

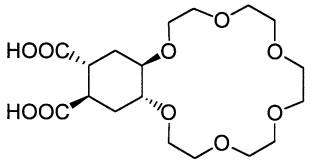


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Chart 1.

Keywords: complexation; cyclohexyl-crown ethers; conformational regulation.

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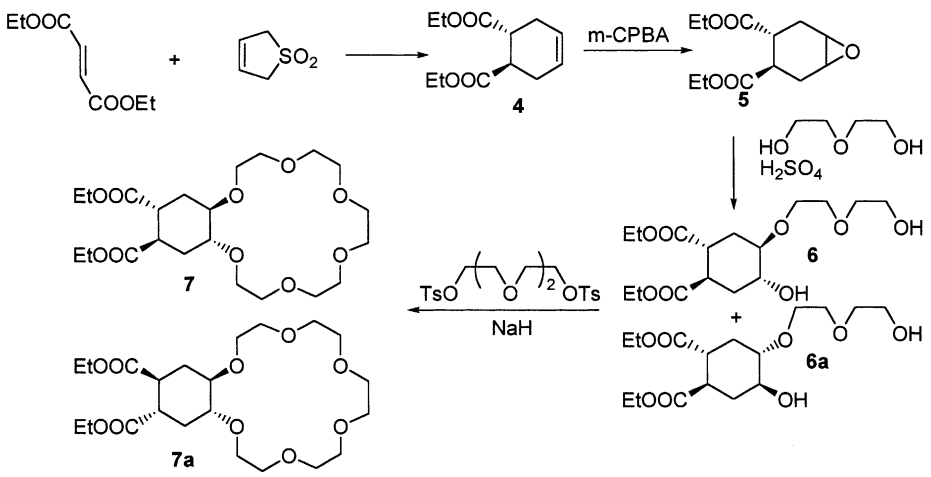


Scheme 1.

also detected but in such a small amount that it was impossible to carry out its identification at this step.

On the other hand, ^{1}H NMR studies carried out with compound **6**, showed that the conformation of this compound in solution depends on the solvent. Thus, conformation **6I** was mainly present in chloroform and conformation **6II** was present in acetone (Chart 2). Even though coupling constants would give more information about the spacial disposition, unfortunately slow exchange on the NMR time scale led to broad signals (even over a range of temperatures) making difficult the determination of coupling constants. Therefore, the intensity of the cross-peaks in COSY experiments turned out to be the most reliable proof of the preferred conformational arrangement. Thus, in chloroform, strong correlations were observed between H_{ax} and H_d, and between $H_{ax'}$ and $H_{d'}$; in addition, cross-peaks due to the simultaneous coupling between H_{eq}–H_c and H_{eq}–$H_{c'}$ (vecinal and W coupling, respectively) and $H_{eq'}$–H_c and $H_{eq'}$–$H_{c'}$ were also detected. In contrast, in acetone, the strongest correlations were observed between H_{ax} and H_c and $H_{ax'}$ and $H_{c'}$, whereas weaker interactions were observed between H_{eq}–H_d; H_{eq}–$H_{d'}$ and $H_{eq'}$–H_d; $H_{eq'}$–$H_{d'}$, respectively. The influence of the solvent on conformation is related to the possibility of the compound to form intra or intermolecular hydrogen bonds. In chloroform, the intramolecular hydrogen bond is more favourable than in acetone and for this reason conformation **6I** was the most abundant conformation in this solvent. Computational studies carried out using a PM3 semiempirical method,[6] implemented in the MOPAC program[7] showed that conformation **6I** was stabilised by intramolecular hydrogen bonds to a higher level than conformation **6II**. In contrast, conformation **6II** became around 4 kcal mol^{-1} more stable than conformation **6I** when intermolecular hydrogen bonds with acetone were considered. In all these studies several conformations related to the rotation around the single bonds have been considered and the reported results correspond to the most stable ones.

Cyclization to give compound **7** was carried out using **6** and tri(ethyleneglycol) ditosilate in a basic medium. When this reaction was directly carried out with the mixture of compound **6** and **6a** obtained in the former step, compounds **7** and **7a** could be isolated. ^{1}H NMR studies carried out with compound **7** showed that **7II** was the most stable conformation not only in acetone but also in chloroform. Thus, strong correlations between H_{ax} and H_c were observed

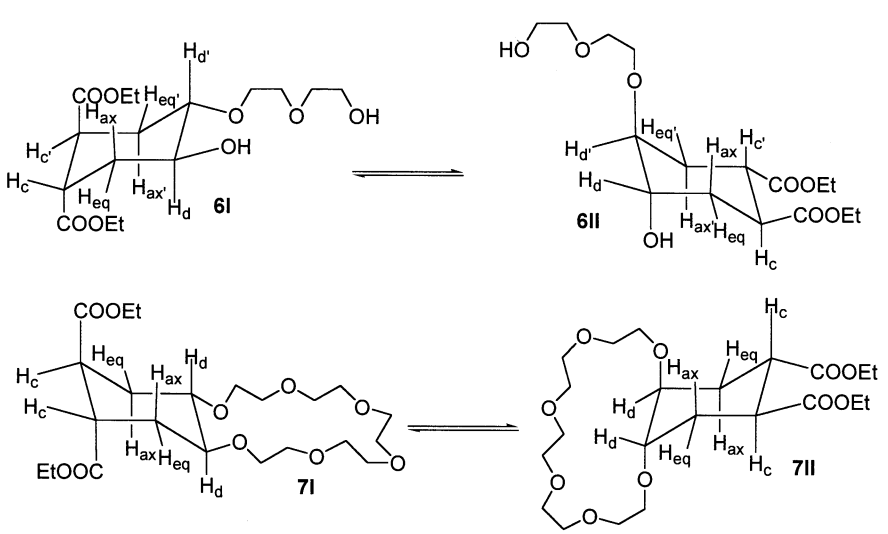
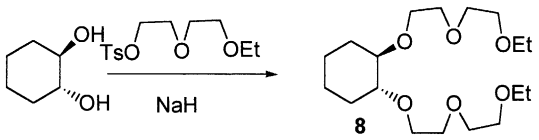


Chart 2.



Scheme 2.

and, in addition, correlations were also detected between H_{eq} and H_d. On the other hand, several conformations in the crown chain must be present because in the ^1H NMR spectrum several signals corresponding to the ethoxycarbonyl groups appear. These signals collapsed to one when the experiment was carried out at high temperature. Compound **7a** was isolated as a minoritary product and was also spectroscopically studied. As expected, a single conformation for the cyclohexane moiety was observed (the one with the four groups in equatorial position).

Computational calculations were carried out in order to have additional information on the stability of the different conformations. Thus, the difference of stability between **7II** and **7I** was around 3 kcal mol^{-1} conformation **7II** being the most stable. On the other hand, compound **7a** in its most stable conformation was around 2 kcal mol^{-1} more stable than **7II** and around 5 kcal mol^{-1} more stable than **7I**.

Complementary studies were carried out with podand **8**. This compound was prepared as shown in Scheme 2 in order to have information on the influence of the macrocyclic effect in systems derived from cyclohexane showing a *trans* configuration. Compound **8** is related to the ligands studied by Raban et al. and described as sterically switched ionophores.[8]

2. Complexation studies

Firstly, complexation of ligand **7** and $Hg(SCN)_2$ was studied. The corresponding 1:1 complex (**9**) could be isolated and the complexation constant determined by using NMR techniques ($\log K$=4.3); the use of this technique for the determination of the constant led to excellent results because a slow exchange occurred on the NMR time scale.

Additionally, association constants of ligand **7** with several alkaline and alkaline-earth cations have been evaluated[9] and compared with compound **8**, dicyclohexyl-18-crown-6 (**10**)[10] (commercial) and *trans*-cyclohexyl-18-crown-6 (**11**) (previously described in the literature[1b]). Data in Table 1 show that stereochemistry is very important in complexation. Thus, macrocyclic compounds derived from cyclohexane with a *trans* stereochemistry (**7**, **11**) make complexes with lower association constant than those observed in the case of compound **10** which presents a *cis*

Table 1. $\log K$ determined by UV methods (picrate salts)

Ligand	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Sr^{2+}
7	4.27	4.67	5.92	6.81	4.47	2.92	1.65
8	3.95	4.14	4.30	3.91	3.59	2.16	1.54
10	5.28	6.37	8.30	6.70	6.25		
11		3.71	3.99				

stereochemistry. On the other hand, comparison between ligands **7** and **11** allowed to affirm that the presence of the ethoxycarbonyl groups in the carbocyclic ring makes compound **7** a better ligand than **11** probably due to lipophilic reasons. Finally, it is very interesting to note that podand compound **8** show values higher than these observed for the related macrocyclic system **11**. A reason for this behaviour can be found in the more open structure of **11** that is not modified by the *trans* stereochemistry. This favourable effect seems to compensate the absence of the macrocyclic effect. In fact, association constants for compound **8** are similar to those obtained for the substituted cyclic ligand **7**.

3. X-Ray studies

Complex **9**, obtained from **7** and $Hg(SCN)_2$ has been studied by X-ray analysis (Fig. 1). First of all, the obtained data confirm the *trans–anti–trans* stereochemistry of compound **7**. On the other hand, the structure shows that the cyclohexane moiety presents a chair conformation without strong distortions; only angles C(12)–C(13)–C(14) and C(15)–C(16)–C(11) have values slightly higher than the ideal ones (115.0 and 114.2, respectively). In the crown moiety, the oxygen atoms are not symmetrically arranged with respect to the mercury atom. The metal centre is close to O(2) (Hg–O(2) 2.748 Å) and far from O(6) (Hg–O(6) 2.900 Å). The four remaining oxygen atoms are placed approximately equidistant from the mercury atom (on an average 2.845 Å).

Stronger distortions are observed in the ethoxycarbonyl groups. Firstly, angles C(14)–C(17)–O(8) and C(15)–C(20)–O(10) with values of 110.0 and 109.6, respectively, are far from the ideal situation. Additionally, the ethyl groups show a pronounced asymmetry one of them being in antiperiplanar conformation (dihedral angles C(20)–O(10)–C(21)–C(22) and C(14)–C(15)–C(20)–O(10) of 177.7 and 175.1, respectively) and the other in anticlinal conformation (C(17)–O(8)–C(18)–C(19) and C(15)–C(14)–C(17)–O(8) 80.1 and −59.7, respectively). One of the carbonyl groups (C(17)–O(7)) is practically eclipsed with C(14)–C(13) bond while the other one (C(20)–O(9))

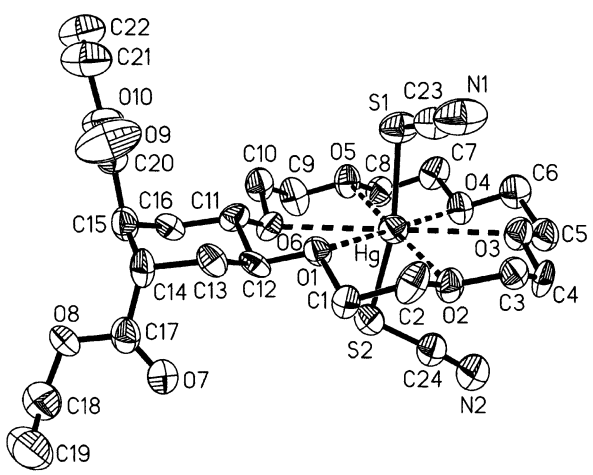


Figure 1. Ellipsoid plot of compound **9**.

is eclipsed with the C(14)–C(15) bond. Finally, both SCN groups are placed close to the ideal positions.

4. Transport experiments

Transport experiments were carried out in a U-tube where two aqueous phases were separated through an organic membrane ($CHCl_3$) and different alkali and alkaline-earth cations were studied.[11] The use of ligands **7** and **7a** allowed to study the influence of the ether configuration on the transport processes. The results observed in these experiments are shown in Table 2. Several interesting results are noteworthy. Thus, as expected, the ligand with a higher association constant does not always induce a higher transport. For example, ligand **7** shows values of association constant of log K_a=4.67, 5.92 and 6.81 for Na^+, K^+ and Rb^+, respectively but the efficiency in transport (after 24 h) is 38.3, 160.7 and 69.6, respectively. Similarly, ligand **10** transports Na^+ more than K^+ (135 and 46, respectively) while the corresponding association constants are in opposite relationship (log K for Na^+ 6.37 and for K^+ 8.30). This behaviour clearly shows that transport depends on the relationship between complexing in the source phase and releasing in the receptor phase.

More interesting results are those related to the influence of stereochemistry in transport. It seems that the stereochemistry of the ligands gives rise to different cavity sizes and for this reason the same cation can be transported with very different efficacy depending on the ligand used. Thus, the sodium cation is transported by ligand **7a** with an efficiency that is around four times that shown by ligand **7**. On the other hand, strong differences between Mg^{2+} and Sr^{2+} were found for compound **7** which transports around 200 times more Sr^{2+} than Mg^{2+}. In addition, some differences between Na^+ and Sr^{2+} (Na^+/Sr^{2+}=2.2) were also observed. This is important because there are not many ligands useful for separating Na^+ from Sr^{2+}. Finally, complexation of Mg^{2+} and Sr^{2+} with ligand **7** and **7a** shows an opposite tendency. Thus ligand **7a** transports 77.5 times more Mg^{2+} than **7** but this ligand transports three times more Sr^{2+} than ligand **7a**.

In addition, comparative studies were carried out with the commercial dicyclohexyl-18-crown-6 (**10**) that has traditionally been reported as a good Sr^{2+} extractant.[12] However, ligand **7** transports 6.3 times more strontium than **10** and even podand **8** shows an efficacy 3.3 times higher for the same cation. Probably the observed behaviour for compound **10** is due to the high association constant values that this ligand shows and the release of the cation at the receiving phase is difficult.

Table 2. Transport efficacy after 24 h with ligands **7** and **7a**, **8** and **10**

	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Sr^{2+}	NH_4^+
7	9.0	38.3	160.7	69.6	52.2	0.4	82.8	89.7
7a	35.0	152.1	148.6	77.0	70.9	31.1	27.8	65.9
8	<1	27	43	28	20	35	44	19
10	46	135	46	51	–	21	13.1	29

All the salts were picrates.

In conclusion, it has been established that the stereochemistry of crown ethers substituted by a cyclohexane moiety has a strong influence on the cation complexation and the transport efficacy. This behaviour can be related to the size of the crown cavity that depends on the stereochemistry of the compound. The relationship between the capacity of the ligand to bind the cation in the source phase and to release it in the receiving phase is also important. Additionally, it has been observed that the conformation of the cyclohexane and consequently the conformation of the crown cavity depend on a high number of factors.

5. Experimental

5.1. Data for compounds

5.1.1. Synthesis of *trans*-1,2-bis(ethoxycarbonyl)-4-cyclohexane (4). Butadiene sulfone (10 g, 0.0846 mol), diethyl fumarate (13.6 g, 0.0846 mol) and hydroquinone (116 mg, 1 mmol) were dissolved in ethanol (20 ml). The mixture was kept in a sealed reactor at 120°C for 16 h. After cooling, 150 ml of a solution of $NaHCO_3$ (10%) was added and the reaction was extracted with dichloromethane (3×50 ml). The organic phase was dried with anhydrous Na_2SO_4 and the solvent evaporated to give **4** as a pale yellow oil (97%). ^1H NMR (250 MHz, $CDCl_3$) δ 5.68 (m, 2H), 4.15 (q, 4H, J=7.12 Hz), 2.82 (m, 2H), 2.39 (m, 2H), 2.21 (m, 2H), 1.25 (t, 6H, J=7.12 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.7 (s), 124.8 (d), 60.4 (t), 41.1 (d), 27.8 (t), 14.0 (q). HRMS (IE^+) calcd for $C_{12}H_{18}O_4$ m/z 226.1205; found 226.1210.

5.1.2. Synthesis of *trans*-4,5-bis(ethoxycarbonyl)-epoxycyclohexane (5). 18.33 g (0.08 mol) of **4** were dissolved in 100 ml of dichloromethane. The solution was cooled to 0°C and then a solution of *m*-CPBA (70%), 30 g (0.12 mol) in 300 ml of dichloromethane was added dropwise. The reaction was kept at this temperature for 20 h and then a solution of Na_2CO_3 (10%) (125 ml) was added. The mixture was stirred for 10 min and the organic phase was washed three times with the solution of Na_2CO_3 (10%). The organic phase was dried with anhydrous Na_2SO_4 and the solvent evaporated to give compound **5** as a transparent oil (96%). ^1H NMR (250 MHz, $CDCl_3$) δ 4.10 (q, 4H, J=7.2 Hz), 3.24 (m, 2H), 2.80 (m, 1H), 2.00 (m, 1H), 2.31 (m, 2H), 2.03 (m, 2H), 1.23 (t, 6H, J=7.2 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.0 (s), 173.2 (s), 60.1 (t), 51.3 (d), 49.7 (d), 39.6 (d), 37.3 (d), 26.8 (t), 25.7 (t), 13.3 (q). HRMS (EI^+) calcd for $C_{12}H_{18}O_5$ m/z 242.1154; found 242.1153.

5.1.3. Synthesis of compounds 6 and 6a. A solution of **5** (10 g, 1.65 mol) in 100 ml of chloroform was added to diethyleneglycol (175 g, 1.65 mol). The mixture was stirred and then 60 μl of H_2SO_4 were added. The reaction was kept under reflux for 20 h and then cooled and washed with water. The organic phase was dried with anhydrous $MgSO_4$ and the crude was purified by distillation to give a mixture of both diastereoisomers **6** and **6a** (80%). ^1H NMR (250 MHz, $CDCl_3$) δ 4.11 (q, 4H, J=7.0 Hz), 3.77 (m, 1H), 3.58 (m, 8H), 3.38 (m, 1H), 3.04 (m, 2H), 2.07 (m, 2H), 1.77 (m, 2H), 1.20 (t, 6H, J=7.0 Hz). ^{13}C NMR δ (62.5 MHz, $CDCl_3$) δ 174.4 (s), 78.1 (d), 73.5 (t), 70.7 (t),

68.4 (t), 68.0 (t), 61.6 (t), 60.8 (t), 39.7 (d), 39.4 (d), 30.5 (t), 27.2 (t), 14.1 (q). HRMS (EI^+) ($M-H_2O$) calcd for $C_{16}H_{26}O_7$ *m/z* 330.1678; found 330.1691.

5.1.4. Synthesis of compounds 7 and 7a. A suspension of a mixture of **6** and **6a** (4 g, 0.0115 mol) and NaH (827 mg, 0.034 mol) in THF (150 ml) was heated at reflux under inert atmosphere for 2 h. Then, a solution of triethylene glycol di-*p*-tosylate (5.22 g, 0.0115 mol) in anhydrous THF (70 ml) was added dropwise during 4 h. After the addition, the reaction was additionally heated for 48 h. The solvent was removed and the product was dissolved in water. The aqueous phase was acidified with HCl (10%) and extracted with chloroform and ethyl acetate several times. All the organic phases were dried with anhydrous Na_2SO_4 and the solvent was evaporated to give an oil. Purification by column chromatography (silicagel, hexane/ethyl acetate 1:3) allowed to separate both diasteroisomers **7** (transparent oil, 17%) and **7a** (transparent oil, 3%). **7** ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.09 (q, 4H, J=7.12 Hz), 3.74 (m, 2H), 3.62 (m, 20H), 2.86 (m, 2H), 1.98 (m, 2H), 1.79 (m, 2H), 1.19 (t, 6H, J=7.12 Hz). ^{13}C NMR δ (62.5 MHz, $CDCl_3$) δ 175.0 (s), 74.2 (d), 71.2 (t), 70.6 (t), 68.0 (t), 60.3 (d), 38.9 (d), 27.5 (t), 14.1 (q). HRMS (FAB^+) (M+H) calcd for $C_{22}H_{30}O_{10}$ *m/z* 463.2543; found 463.2546. Combustion analysis calcd for $C_{22}H_{30}O_{10}\cdot H_2O$: 55.00% C, 8.33% H; found 55.02% C, 8.34% H. **7a** ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.09 (q, 4H, J=7.10 Hz), 3.80 (m, 2H), 3.67 (m, 20H), 3.25 (m, 2H), 2.60 (d, 2H, J=12.3 Hz), 2.30 (d, 2H, J=12.3 Hz), 1.19 (t, 6H, J=7.10 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.3 (s), 80.6 (d), 71.2 (t), 70.7–69.7 (t), 60.6 (t), 42.8 (d), 32.1 (t), 13.1 (q). HRMS (FAB^+) (M+Na) calcd for $C_{22}H_{30}O_{10}Na$ *m/z* 485.2362; found 485.2376.

5.1.5. Synthesis of compound 8. 7.6 g (26.6 mmol) of diethyleneglycol monoethylether tosilate were added to a suspension of NaH in DMSO (8.5%, 6 ml) and 1.6 g (13.5 mmol) of *trans*-cyclohexanediol. The mixture was heated at 45°C for 20 h. Then, 25 ml of water were added and the mixture was extracted with ethyl acetate (3×25 ml). The organic phase was dried and the product was purified by column chromatography (silicagel, hexane/ethyl acetate 1:1) to give compound **8** (65%) as a light yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.49–3.70 (m, 16H), 3.47 (q, 4H, J=7 Hz), 3.13 (m, 2H), 1.90 (m, 2H), 1.54 (m, 2H), 1.19 (m, 4H), 1.11 (t, 6H, J=7 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 82.2 (d), 69.1–70.8 (t), 66.8 (t), 30.5 (t), 23.8 (t), 15.4 (q). HRMS (FAB^+) (M+) calcd for $C_{18}H_{37}O_6$ *m/z* 349.2590; found 349.2578.

5.1.6. Synthesis of 7·Hg(SCN)$_2$ (9). 1 equiv. of $Hg(SCN)_2$ in acetone was added to 1 equiv. of **7** in acetone. After stirring for 1 min, the solution was kept at room temperature for 24 h. After this time **9** was separated by filtration. Suitable crystals for X-ray were obtained by diffusion in MeOH/hexane.

5.2. Determination of association constants

The experiments to determine association constants with the different ligands were carried out as described in Ref. 1b.

5.3. Transport experiments

Transport experiments were done in a U-tube cell at 25°C. A solution 0.003 M of the ligand in free-ethanol chloroform (12 ml) was placed at the bottom of the cell, and two portions of aqueous solutions (2 ml) were carefully added on top of them. The source phase was a 0.01 M aqueous of the corresponding salt and the receiving phase was desionized water. Both surface areas were 1.75 cm^2. The organic phase was magnetically stirred at 500 rpm. The concentration of the picrate anion after 24 h was obtained by calculation based on the absorption of 354.0 nm for KPic and 356.0 nm for $SrPic_2$ in the UV spectrum. Each experiment was repeated at least three times, and the results are reported as the average of the three determinations.

5.4. X-Ray crystal structure determination of 9

A colourless lath of 0.62×0.24×0.07 mm^3 size grown by *n*-hexane/methanol diffusion, monoclinic, space group $P2_1/n$, a=8.369 (2), b=16.764 (3), c=21.638 (4) Å, β=93.26 (3)°, V=3031 (11) Å^3, Z=4, 2θmax=50°, diffractometre Nonius CAD4, Mo K_α (λ=0.71073 Å), ω-scan, T=293 (2) K, 5961 reflections collected of which 5302 (R_{int}=0.03) were independent, heavy atom method primary solution and refinement on F^2 using SHELX97 program,[13] 342 refined parameters. Hydrogen atoms were included using a riding model. $R1[\sum||F_o|-|F_c||/\sum|F_o|$, $I>2\sigma(I)]$=0.0548, max Δ/σ=0.001, max $\Delta\rho$=1.03 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 167759. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax +44(0)-1223-336033 or e-mail deposit@ccdc.cam.ac.uk).

Acknowledgments

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