PROTON-IONIZABLE MACROCYCLES CONTAINING 1,2,4-TRIAZOLE AND 4-AMINO-1,2,4-TRIAZOLE SUBUNITS

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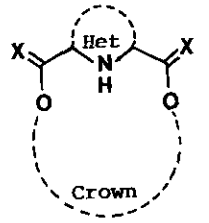
Abstract- Macrocycles 2a and 2b, containing a proton-ionizable 1,2,4-triazole subcyclic unit, have been obtained from the appropriate 3,5-disubstituted N-amino-1,2,4-triazoles and tetraethyleneglycol derivatives. The N-amino function was used as a protective group in the macrocyclization step. The method allowed the preparation of the chiral macrocycle 2b in three steps, from S-lactic acid, in high optical purity and an overall yield of 16%. Triazolyl lone pairs of the macrocycles 2a and 2b, and of their N-aminated precursors 1a and 1b, participate in the complexation of $Eu(fod)_3$ and $Pr(fod)_3$, as well as the crown ether moieties, but not N-amino groups which, when present, were found to be inside the cavity. Ion transport rates towards alkali-metal ions through a bulky chloroform phase were low and showed little selectivity.

Crown compounds containing proton-ionizable functional groups have recently proved of interest in complexation, extraction, and transport of ions without requiring an independent counterion. The ionizable group can be attached to the ring as a pendant arm, or directly incorporated into the macrocyclic framework. Examples of the former approach, with carboxylic acids as the proton-ionizable functions have been studied mostly by Bartsch et al.,[1,2] whereas macrocycles containing an ionizable heterocyclic subunit within the cavity have been extensively developed more recently by Bradshaw, Izatt, and their coworkers at Brigham Young University. The heterocycles so far incorporated belong only to the 4-hydroxypyridine[3-7] and 1,2,4-triazole[8-10] series, and the crowns synthesized were at first of the diester-polyether type (I).[3,6,8,9] Despite the ease of access to structures of type (I) (high-dilution cyclization from the heterocyclic diesters or diacyl chlorides), diester-polyether heterocyclic crowns were not devoid of some inconvenients. Although they were found to form stable complexes with amines, ammonium salts, and even water molecules, the proneness of the ester functions to hydrolyze in basic or acidic aqueous media make them unsuitable

candidates for transport studies in liquid membrane systems.[3] On the other hand, the presence of the ester groups greatly affects the reactivity, acid-base properties, complexation behaviour and structures of the macrocycles.[4] For these reasons, a second generation of proton-ionizable crowns emerged, with full-non ester O-donor atoms in the chain (type II).[4,5,7,10]

The synthesis of these type (II) structures requires additional steps for the protection and deprotection of the ionizable proton (-OH or -NH in hydroxypyridines, -NH in triazoles), and this was achieved by the use of classical benzyl or tetrahydropyranyl (THP) protecting groups.

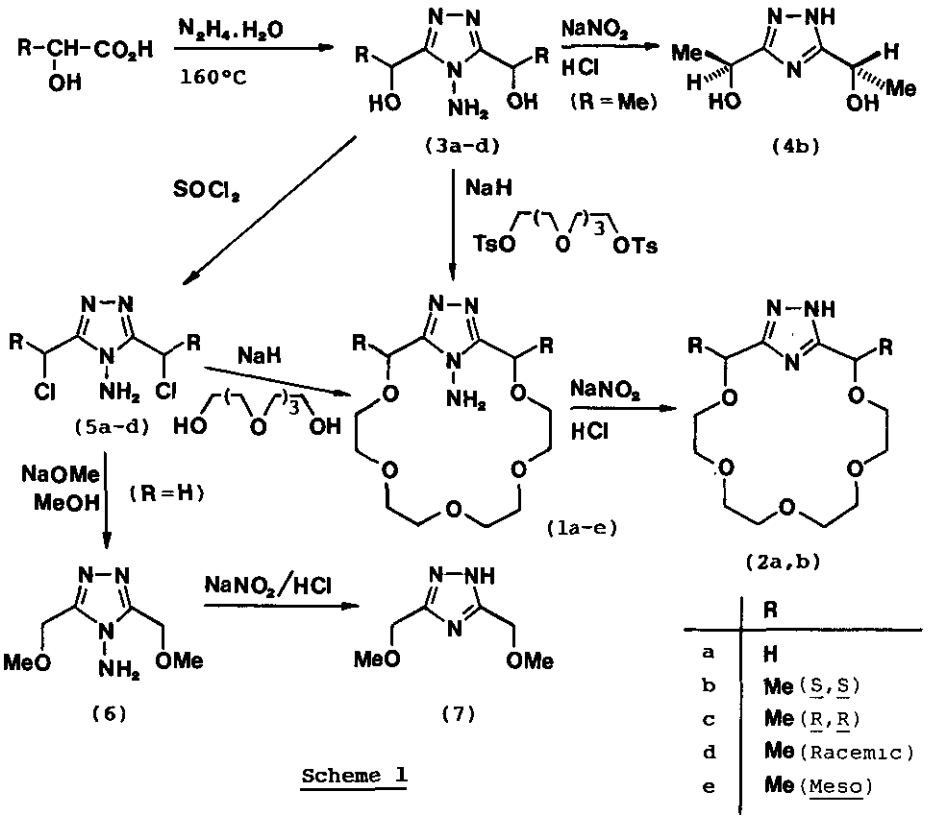


I X=O
II X=H_2

A recent publication by Bradshaw et al.[7,10] on the synthesis of some 1,2,4-triazolyl crowns of type (II) by this methodology prompted us to report our own results in the field. We found that N-aminoazoles could serve as useful starting materials for the synthesis of these macrocycles. The N-NH_2 group, acting as a protecting function during the synthesis, could be either preserved in the final structure to provide an additional pendant arm, or removed by nitrous acid to give the proton-ionizable compounds. The strategy was specially straightforward in the case of 4-amino-1,2,4-triazole, since the heterocycle building unit (which can include chirality) can be obtained in a one-pot reaction from hydrazine and a large variety of carboxylic acids.[11] The syntheses of macrocycles 1 and 2 from hydroxyacetic (glycolic) and 2-hydroxypropanoic (racemic and S-lactic) acids are summarized in Scheme 1.

A high yield (ca. 96%) of 4-amino-3,5-bishydroxymethyl-1,2,4-triazole 3a was obtained following the method of Adamek.[12] A similar procedure was followed with S-lactic acid, and a compound of mp 130-132°C, $[\alpha]_D^{25}$=+22.3°(H_2O) was obtained (78% yield). Surprisingly, a mp 174-175°C had been previously reported in the literature for the same substance, obtained from lactic esters.[13] To cast some light on this discrepancy, we submitted racemic lactic acid to the same reaction conditions, and a mixture of the two diastereoisomers of 4-amino-3,5-bis(1-hydroxyethyl)-1,2,4-triazole was obtained, from which one of mp 171-172°C and another of mp 130-132°C were isolated by fractional crystallization. The compound of mp 130-132°C was identical in every respect (^1H and ^{13}C nmr, ir, EI-MS, mixed mp) to that of the same mp obtained from S-lactic acid, except obviously in its optical inactivity. We concluded, therefore, that compounds of mp 130-132°C, obtained from S- and racemic lactic acids, corresponded to (S,S)- and racemic 4-amino-3,5-bis(1-hydroxyethyl)-1,2,4-triazoles 3b and 3d, respectively,

whereas compound of mp 171-172°C (which probably corresponds to that reported in the literature[13]) is actually the R*,S* (meso) form 3e.



	R
a	H
b	Me (S,S)
c	Me (R,R)
d	Me (Racemic)
e	Me (Meso)

Scheme 1

The optical purity was checked both in 3b and in its N-deaminated derivative 4b,[14] by means of their bis-(S)- α -methoxy- α -trifluoromethylphenyl-O-acetyl (MTPA) derivatives.[16] It is noteworthy that the ^{1}H nmr spectra (200 MHz) of these derivatives did not reveal any splitting of the methyne quadruplets, showing that both the N-deamination of 3b and the condensation of S-lactic acid with hydrazine had taken place without racemization, despite the high temperatures attained at the end of the cyclization step (ca. 160°C).

The reaction of 3a and 3b with thionyl chloride, according to the literature procedure,[15] afforded the corresponding dichloro derivatives 5a and 5b in 84 and 52% yields, respectively. As expected, the reaction with 3b was not completely selective, and two diastereoisomers were isolated in approximate 3:1 ratio.[17]

The synthesis of the macrocycle 1a was accomplished in a 13% yield from 5a and tetraethyleneglycol in tetrahydrofuran, in the presence of sodium hydride (2.5 mol. equiv.), and without high-dilution conditions. Small amounts of the deaminated

macrocycle 2a were found. The synthesis from the bis-alcohol 3a and tetraethyleneglycol ditosylate was unpractical due to the insolubility of 3a in DMF or THF. On the contrary, the chiral macrocycle 1b was obtained in a 23% yield from the corresponding chiral alcohol 3b (high-dilution, room temperature, excess of sodium hydride, DMF, tetraethyleneglycol ditosylate), whereas a mixture of diastereoisomers resulted from the bis-chloromethyl derivative 5b, tetraethyleneglycol and sodium hydride in DMF.[18]

For the deamination of macrocycles 1a and 1b, a standard methodology with nitrous acid was followed. Compounds 2a and 2b resulted in 82 and 89% yields, respectively. The compound 2a was coincident in every respect with the product described by Bradshaw.[10]

From a structural point of view, it was noteworthy that a slow proton exchange was observed in 2b by ^{13}C nmr spectroscopy. At room temperature, two signals appeared at 157.4 and 161.1 ppm for quaternary triazole C-atoms, whereas a single broad signal at 159.2 ppm was present above 50°C. This behavior was not observed in the open-chain model. These shift differences are in good agreement with those found for the parent triazole in the solid state (no prototropy).[19] The amino groups of the crowns 1a and 1b showed in the ir spectrum the bands of the $N-NH_2$ stretching, as sharp absorptions at 3350 and 3280 cm^{-1} in 1a and 3340 and 3260 cm^{-1} in 1b. The frequency of these absorptions did not vary appreciably upon dilution over a wide range of concentrations (0.005-0.1M, chloroform), revealing a chelation of the amino group by the crown.

In order to gain some knowledge about the complexing capacity of the heterocyclic and crown ether parts of molecules 1a, 2a, 1b, and 2b, the lanthanide induced shifts (l.i.s.) produced by $Eu(fod)_3$ and $Pr(fod)_3$ in the ^1H and ^{13}C nmr spectra were studied. For comparative purposes the precursors 6 and 7 were also considered. Straight lines were obtained in the range of concentrations used. The results, referred to the most sensitive signal (100%) are reported in Table 1. Contact terms[20] are responsible for the negative values observed on quaternary carbons (Table 1, ^{13}C nmr spectra of compounds 1a and 6). Since contact terms are more important for Eu than for Pr and since they are β effects in heteroaromatic molecules, these observations prove that the lone pairs of triazole participate in the complexation.

The amino group (X in Fig. 1), when present, is inside the cavity (see preceeding discussion concerning ir results). As shown by ^{13}C nmr spectroscopy, the tautomeric proton is at N(1), in agreement with the structure in the solid state.[10] Neither the amino group (compounds 1a and 1b) nor the N(4) lone pair (compounds 2a and 2b) participate in the complexation.

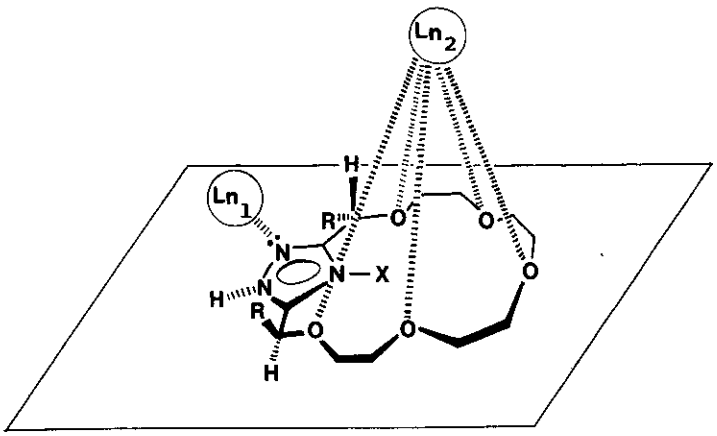


Figure 1. Complexation sites proposed for triazolyl crowns 1 and 2

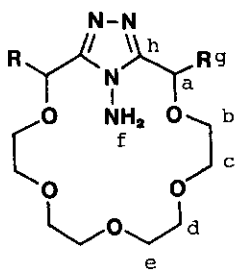
	^{1}H NMR						^{13}C NMR						
Ligand/Complex	CH_a	CH_b	CH_c	CH_{de}	NH_{2f}	CH_g	C_a	C_b	C_c	C_d	C_e	C_g	C_h
1a + Eu(fod)$_3$	100	44	25	19	71	--	100	77	38	38	23	--	-150
1a + Pr(fod)$_3$	100	46	24	18	48	--	100	48	36	25	22	--	140
1b + Eu(fod)$_3$	100	40	31	20	88	40	100	48	36	30	27	61	61
1b + Pr(fod)$_3$	100	47	27	23	69	65	100	47	34	22	19	67	170
2a + Eu(fod)$_3$	100	53	38	23	--	--							
2b + Eu(fod)$_3$	100	41	*	19	--	44							
6 + Eu(fod)$_3$	100	69	--	--	87	--	100	80	--	--	--	--	-15
7 + Eu(fod)$_3$	100	77	--	--	--	--							

* Not observed

Table 1. Lanthanide-induced shifts in ^{1}H and ^{13}C nmr spectra in $CDCl_3$

Ligand	Li^+	Na^+	K^+	Na^+/Li^+	K^+/Na^+
1a	2.14	2.19	3.72	1.02	1.70
1b	0.28	0.49	0.22	1.75	0.45
2b	1.53	2.36	4.08	1.54	1.73
DB-18-C-6	0.56	16.71	177.40	29.84	10.62

Table 2. Transport rates (x10^{-8} mol.h^{-1}) of alkali-metal ions across a $CHCl_3$ phase.



The main site of complexation (Ln_1 in Fig. 1) is at N(1) or N(2) lone pairs. Due to symmetry in N-amino compounds and to tautomerism in NH triazoles, this complexation takes place at N(1) or N(2), having therefore a symmetry plane perpendicular to the molecule. A second complexation site (Ln_2 in Fig. 1) is above the molecular plane,

typical of crown ethers and similar to that proposed for pyridine analogues.[21] Removal of the amino group (pairs 1a/2a and 1b/2b) slightly increases the relative importance of Ln_1. On the other hand, the presence of C-methyl groups (pairs 1a/1b and 2a/2b) decreases the participation of Ln_1 in the complexation process. This accounts for the lack of contact effect in 1b.

Finally, the transport rates of some alkali-metal ions across a bulky $CHCl_3$ phase[22] were determined for 1a, 1b, and 2b. The results are shown in Table 2. Both transport rates and selectivities were found to be low, if compared to dibenzo-18-crown-6 (DB-18-C-6). However, removal of the $N-NH_2$ group enhanced the transport rate significatively. Better results were obtained for the unsubstituted macrocycle 1a than for 1b.

EXPERIMENTAL

Melting points are uncorrected. ^1H and ^{13}C nmr spectra were registered on a Bruker WP 200 SY instrument, mass spectra on a Hewlett-Packard 5985, and infrared spectra on a Perkin Elmer 257. Optical activities were measured on a Perkin Elmer 141 polarimeter. Concentration values (c) are given in g/100 ml. All new compounds gave elemental analyses according to their structures, within a 0.3% error.

Silica gel Merck 70-230 mesh, 230-400 mesh, and DC-Alufolien 60 were used for conventional, flash, and analytical thin layer chromatography, respectively. T.l.c. plates were revealed using a 5% aqueous potassium permanganate solution.

Most chemicals were purchased from Aldrich Co., and used as received without further purification. Thionyl chloride was purified by distillation from quinoline and stored under an inert atmosphere. Organic solvents were purified by standard procedures. N,N-dimethylformamide (DMF) (Carlo Erba) was dried over 3Å molecular sieves before use. Anhydrous tetrahydrofuran (THF) was distilled from benzophenone and sodium under an argon atmosphere, immediately prior to use.

4-Amino-3,5-bis(chloromethyl)-1,2,4-triazole, 5a. This compound was obtained by neutralization with a saturated solution of sodium carbonate of the corresponding hydrochloride.[15] Extraction with ethyl acetate followed by evaporation afforded the free base in quantitative yield, mp 93-95°C. Ir (nujol), 3225 and 3105 (broad, NH), 1660, and 1515 cm^{-1}. ^1H Nmr (DMSO-d_6), δ4.86(s,2H,CH_2Cl) and 6.12(s,2H,NH_2) ppm. ^{13}C Nmr (DMSO-d_6), δ33.2(CH_2Cl) and 152.4(N-C=N) ppm. EI-MS, m/z(%), 182 and 180 (M^+,20,32), 145(100), 147(32), and 110(2).

4-Amino-3,5-Bis(methoxymethyl)-1,2,4-triazole, 6. 4-Amino-3,5-bis(chloromethyl)-1,2,4-triazole 5a (3.61 g, 0.02 mol) was added slowly to a solution of sodium (1.2 g) in

methanol (70 ml). The mixture was stirred at room temperature for 24 h, and then the solvent was evaporated and the residue extracted with chloroform. The solution was evaporated to give 6 (2.58 g, 75%) as a colorless viscous oil. Ir (film), 3325 and 3200(NH), 1645, 1515, and 1200 cm^{-1}. ^1H Nmr ($CDCl_3$), δ3.32(s,3H,OCH_3), 4.56(s,2H, CH_2O), and 5.14(s,2H,NH_2) ppm. ^{13}C Nmr ($CDCl_3$), δ58.5(OCH_3), 63.5(CH_2O), and 152.0(N-C=N) ppm. EI-MS, m/z(%), 172(M^+,0.5), 142(100), 112(28), and 110(24).

3,5-Bis(methoxyxmethyl)-1,2,4-triazole, 7. A solution of sodium nitrite (1.93 g, 0.028 mol) in water (30 ml) was added dropwise over a stirred and cooled solution (0°C) of 6 (3.44 g, 0.02 mol) in 6N hydrochloric acid (20 ml). The temperature was kept below 5°C during the addition. After an additional 1 h under stirring, the solution was neutralized with a saturated solution of sodium bicarbonate to pH~7, and then extracted with chloroform (5x20 ml). The organic solution was dried over anhydrous sodium sulfate, and evaporated to give 7 (2.67 g, 85%), colorless oil. Ir (film), 3500-2500(broad), 1650, and 1560 cm^{-1}. ^1H Nmr ($CDCl_3$), δ3.48(s,3H,OCH_3) and 4.63(s,2H,CH_2O) ppm. ^{13}C Nmr ($CDCl_3$), δ58.7(OCH_3), 66.6(CH_2O), and 157.5(N-C=N) ppm. EI-MS, m/z(%), 127(80), 95(100), and 66(46).

(S,S)-4-Amino-3,5-bis(1-hydroxyethyl)-1,2,4-triazole, 3b. A mixture of (S)-lactic acid (90% pure, 105.5 g, 1.05 mol) and hydrazine hydrate (105.0 g, 2.10 mol) was heated at 100°C for 5 h, under stirring. Excess hydrazine and water were distilled off as the temperature was raised up slowly to 160°C (about 3 h), and the mixture was kept at this temperature for 5 h more. All the process was monitored by ^1H nmr for the disappearance of open-chain intermediates. Vacuum evaporation of volatile residues afforded an oil which readily solidified and was recrystallized stepwise in a large amount of acetonitrile (80 ml per gram). The yield was 70.0 g of 3b (78%), mp 130-132°C, $[\alpha]_D^{25}$=+22.3° (c=1.5, water). Ir (KBr), 3400 and 3340(NH), 3200(broad, OH), 1630, and 1090 cm^{-1}. ^1H Nmr (DMSO-d_6), δ1.47(d,J=6.6Hz,6H,CH_3), 4.90(m,2H,CH), 5.37(d,J=5.7Hz,2H,OH), and 5.76(s,2H,NH_2) ppm. ^{13}C Nmr (DMSO-d_6), δ22.1(CH_3), 60.4(CH), and 157.6(N-C=N) ppm. EI-MS, m/z(%), 172(M^+,6), 157(7), 155(19), and 154(100). The optical purity of the compound was established by means of the MTPA derivative, obtained from 3b (0.023 g, 0.13 mmol) and α-methoxy-α-trifluoromethylphenylacetyl chloride[16] (0.100 g, 0.4 mmol) in dichloromethane (2 ml) in the presence of anhydrous pyridine. After 48 h stirring at room temperature, the reaction mixture was poured into water (15 ml) and extracted with ethyl acetate (5x5 ml). The organic layer was washed successively with 10% hydrochloric acid (5x5 ml), a saturated solution of sodium carbonate (3x5 ml), and water, and finally dried ($MgSO_4$)

and evaporated to give the corresponding diester (0.045 g, 57%). ^{1}H Nmr ($CDCl_3$), δ1.78(d,J=6.8Hz,6H,CH_3), 3.49(s,6H,OCH_3), 5.13(s,2H,NH_2), 6.08(q,J=6.8 Hz,2H,CH), and 7.3-7.6(m,10H,aromatic) ppm. EI-MS, m/z(%), 604(M^+,0.5), 589(0.5), 574(12), 387(11), 371(31), 189(100), 137(60), and 105(35).

(Meso)-4-amino-3,5-bis(1-hydroxyethyl)-1,2,4-triazole, 3e. The compound was obtained following a similar procedure as for the chiral isomer 3b. Fractional crystallization in acetonitrile gave the optically inactive compound 3e, mp 171-172°C, ir (nujol), 3345, 3250, and 3170(NH,OH), and 1625 cm^{-1}. ^{1}H Nmr (DMSO-d_6), δ1.47(d,J=6.6Hz,6H, CH_3), 4.90(m,2H,CH), 5.38(d,J=5.6Hz,2H,OH), and 5.75(s,2H,NH_2) ppm. ^{13}Nmr (DMSO-d_6), δ22.0(CH_3), 60.4(CH), and 157.6(N-C=N) ppm. EI-MS, m/z(%), 172(M^+,6), 157(7), 155(20), and 154(100). A second crop of crystals was obtained upon concentration of the acetonitrile solution. This material was identical in every respect (mp and mixed mp, ir, nmr, and MS spectra) to 3b, except for the fact that it was optically inactive, and was therefore identified as the racemic combination 3d.

(S,S)-3,5-Bis(1-hydroxyethyl)-1,2,4-triazole, 4b. The general deamination procedure described for the bismethoxymethyl derivative 7 was used, from 3b (6.0 g, 0.035 mol), with the following modification: after the reaction was completed, solvents were removed in vacuo and the residue was extracted with hot acetonitrile. Evaporation of the solution gave 4b (5.05 g, 92%), mp 134°C, $[\alpha]_D^{25}$=-18.5° (c=1.5, water). Ir (KBr), 3250 and 3160(broad,NH,OH) cm^{-1}. ^{1}H Nmr (DMSO-d_6), δ1.48(d,J=6.7Hz,6H,CH_3) and 5.00(q,J=6.7Hz,2H,CH) ppm. ^{13}C Nmr (DMSO-d_6), δ21.9(CH_3), 60.8(CH), and 159.1(N-C=N) ppm. EI-MS, m/z(%), 157(M^+,1), 143(6), 142(92), and 124(100). MTPA derivative, obtained as for 3b (see above) with a 39% yield. ^{1}H Nmr ($CDCl_3$), δ1.70(d,J=6.7Hz,6H, CH_3), 3.52(s,6H,OCH_3), 6.20(q,J=6.7Hz,2H,CH), and 7.3-7.6(m,10H,aromatic) ppm. EI-MS, m/z(%), 530(1), 357(1), 356(6), 190(11), 189(100), 139(9), 122(38), and 105(34).

(S,S)-4-Amino-3,5-bis(1-chloroethyl)-1,2,4-triazole, 5b. A mixture of (S,S)-4-amino-3,5-bis(1-hydroxyethyl)-1,2,4-triazole 3b (3.0 g, 0.017 mol) and thionyl chloride (4 ml) was stirred at room temperature for 18 h. The excess of reagent was removed in vacuo, the residue was dissolved in water, pH was adjusted to ca. 8 with a saturated solution of sodium bicarbonate, and finally the solution was extracted with ethyl acetate. The resulting organic solution was dried ($MgSO_4$) and evaporated, to give an oil whose ^{1}H nmr spectrum showed a mixture of diastereoisomers (ca. 3:1). Trituration of the crude mixture with ethyl ether-THF (5:1) afforded the major component as a slightly yellowish insoluble compound, identified as a mixture of 5b and 5c (84% e.e. of 5b)[17] (1.9 g, 52%), mp 145°C (ethyl acetate-n-hexane), $[\alpha]_D^{25}$= -189.5° (c=1.5,

ethanol). Ir (KBr), 3345, 3145, 1640, and 1380 cm^{-1}. ^1H Nmr (DMSO-d_6), δ1.90(d,J=6.9Hz, 6H,CH_3), 5.45(q,J=6.9Hz,2H,CH), and 5.98(s,2H,NH_2) ppm. ^{13}C Nmr (DMSO-d_6), δ21.9(CH_3), 46.0(CH), and 155.1(N-C=N) ppm. EI-MS, m/z (%), 210 and 208(M^+,9,15), 175(32), 174(9), and 173(100). Evaporation of the filtered solution afforded the minor component as an oil, which was believed to be the meso form 5e, and was no further purified nor characterized. ^1H Nmr (DMSO-d_6), δ1.89(d,J=6.9Hz,6H, CH_3), 5.46(q,J=6.9Hz,2H,CH), and 6.03(s,2H,NH_2) ppm.

20-Amino-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo[15.2.1]eicosa-17,19-diene, 1a. Tetraethyleneglycol (1.29 g, 6.67 mmol) was added over a well stirred suspension of sodium hydride (0.60 g of 60% purity, 0.015 mol) in dry THF (500 ml). After 10 min, 4-amino-3,5-bis(chloromethyl)-1,2,4-triazole 5a (1.21 g, 6.67 mmol) was added, and the mixture was stirred under argon at room temperature for 72 h. Evaporation of the solvent afforded an oil which was purified by column chromatography (eluant: ethyl ether-methanol 2:1). The yield of 1a was 0.26 g (13%), mp 81-83°C (ethyl acetate-n-hexane). Ir (nujol), 3335 and 3265(NH), 1600, and 1100 cm^{-1}. Ir ($CHCl_3$), 3350 and 3280 (NH) cm^{-1}. ^1H Nmr ($CDCl_3$), δ3.63(s,8H,CH_2 at 7,8,10,11), 3.65(m,4H,CH_2 at 5,13), 3.75(m,4H,CH_2 at 4,14), 4.84(s,4H,CH_2 at 2,16), and 6.05(s,2H,NH_2) ppm. ^{13}C Nmr ($CDCl_3$), δ63.1 (C_2,C_{16}), 68.8(C_4,C_{14}), 70.0, 70.3, and 70.5(C_5,C_{13};C_7,C_{11};C_8,C_{10}), and 150.5(C_1,C_{17}) ppm. EI-MS, m/z(%), 302(M^+,13), 287(12), 286(14), 273(61), 259(30), 243(20), 169(84), 154(72), 126(94), 110(80), and 66(100). CI-MS (methane), m/z(%), 343(M+41,7), 331(M+29,24), and 303(M+1,100).

(2S,16S)-20-Amino-2,16-dimethyl-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo[15.2.1]-eicosa-17,19-diene, 1b. Over a well stirred, argon purged, suspension of sodium hydride (60% purity, 3.84 g, 96 mmol) in 1200 ml of dry DMF, were added simultaneously, at room temperature and at a rate of 3 ml/h, via syring pump, two solutions of (S,S)-4-amino-3,5-bis(1-hydroxyethyl)-1,2,4-triazole 3b (3.31 g, 19.2 mmol) and of tetraethyleneglycol ditosylate (9.60 g, 19.2 mmol), in 50 ml DMF each. When the addition was complete (ca. 17 h), the mixture was further stirred at room temperature for two days. The reaction was then filtered and evaporated in vacuo, to give a residue which was treated with a mixture of chloroform and ethyl acetate (1:1) (200 ml). The resulting precipitate was filtered off and the filtrate was evaporated. The residue (6.9 g) was purified by flash column chromatography (eluant: ethyl acetate-methanol from 10:1 to 5:1) to give 1b (1.45 g, 23%), mp 142-144°C (ethyl acetate-n-hexane), $[\alpha]_D^{25}$=+31.3° (c=1.5, chloroform). I.r.(KBr), 3340 and 3270 (NH), 1590, and 1125 cm^{-1}. Ir ($CHCl_3$), 3340 and 3260 (NH) cm^{-1}. ^1H Nmr ($CDCl_3$),

δ1.71(d,J=6.5Hz,6H,CH_3), 3.65(m,12H,CH_2 at 5,7,8,10,11,13), 3.75 (m,4H,CH_2 at 4,14), 4.87(q,J=6.5Hz,2H,CH at 2,16), and 6.20(s,2H,NH_2) ppm. ^{13}C N m r ($CDCl_3$), δ16.2(CH_3), 67.0(C_4,C_{14}), 69.6(C_2,C_{16}), 70.1, 70.2, and 70.5 (C_5,C_{13};C_7,C_{11};C_8,C_{10}), and 152.4(C_1, C_{17}) ppm. EI-MS, m/z(%), 330(M^+,8), 315(19), 301(15), 287(71), 271(34), 183(66), 155(75), 140(99), 139(95), 138(89), and 54(100). CI-MS (methane), m/z(%), 371(M+41,7), 359(M+29,23), and 331(M+1,100).

Reaction of (S,S)-4-amino-3,5-bis(1-chloroethyl)-1,2,4-triazole 5b with the Disodium Salt of Tetraethyleneglycol. Two solutions in DMF (45 ml each) of 5b (0.93 g, 4.45 mmol) and disodium tetraethyleneglycoxide (prepared from 0.87 g, 4.48 mmol, of the glycol and 0.395 g of 60% sodium hydride, 9.9 mmol, in DMF) were added simultaneously, via syring pump, to 250 ml of DMF, under stirring, at a rate of 2 ml/h, at room temperature. The mixture was further stirred for two days at room temperature. After a similar work-up as described above for the preparation of 1b, a mixture of diastereoisomers of 1b (0.088 g, 6%) was isolated in a 3:1 ratio.[18] ^{1}H Nmr ($CDCl_3$), δ1.71(1c+1b) and 1.72(1e) (d,d,J=6.5Hz,6H,CH_3), 3.65(1c+1b and 1e) (m,12H,CH_2 at 5,7,8, 10,11,13), 3.75(1c+1b and 1e) (m,4H,CH_2 at 4,14), 4.87(1c+1b and 1e) (q,J=6.5Hz,2H,CH), and 6.17(1e) and 6.20(1c+1b) (s,s,2H,NH_2) ppm.

3,6,9,12,15-Pentaoxa-18,19,20-triazabicyclo [15.2.1]eicosa-1(19),17-diene, 2a. This compound was obtained following the general method of deamination described above for 7a, from the corresponding N-amino derivative 1a (0.287 g, 1.0 mmol). The yield was 0.235 g (82%), mp 110°C (ethyl acetate-n-hexane) (lit.[10] 112-114°C). Ir (nujol), 3500-2500 (broad), 1645, and 1110 cm^{-1}. ^{1}H Nmr ($CDCl_3$), δ3.65(m,12H,CH_2 at 5,7,8, 10,11,13), 3.70(m,4H,CH_2 at 4,14), 4.73(s,4H,CH_2 at 2,16), and 9.5(broad,1H,NH) ppm. ^{13}C Nmr ($CDCl_3$, 50°C), δ64.5(C_2,C_{16}), 69.6, 70.2(two signals), and 70.5(C_5,C_{13}; C_7,C_{11};C_8,C_{10};C_4,C_{14}), and 156.2(broad,C_1,C_{17}) ppm. EI-MS, m/z(%), 287(M^+,2), 272(2), 258(22), 244(21), 200(20), 198(24), 154(66), 111(55), 95(100), and 66(99). CI-MS (methane), m/z(%), 328(M+41,5), 316(M+29,15), and 288(M+1,100). If the neutralization was avoided the corresponding hydrochloride was isolated. ^{1}H Nmr ($CDCl_3$), δ3.70 (m,8H,CH_2 at 7,8,10,11), 3.75(m,4H,CH_2 at 5,13), 3.85(m,4H,CH_2 at 4,14), 4.93(s,4H,CH_2 at 2,16), and 9.2(broad,NH^+) ppm. ^{13}C Nmr ($CDCl_3$), δ63.5(C_2,C_{16}), 69.6, 70.0, 70.3, and 70.4(C_5,C_{13};C_7,C_{11};C_8,C_{10};C_4,C_{14}), and 153.3(C_1,C_{17}) ppm. EI-MS, m/z(%), 288(M^+,6), 287(4), 272(4), 258(49), 244(44), 200(39), 198(45), 154(82), 111(64), 95(100), and 66(65).

(2S,16S)-2,16-Dimethyl-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo[15.2.1]eicosa-1(19),17-diene, 2b. Obtained from 1b (0.66 g, 2.0 mmol) by the general deamination

procedure described above. Colorless oil (0.56 g, 89%). The compound was further purified by column chromatography (eluant: ethyl acetate-methanol 4:1). $[\alpha]_D^{25}$=-34.2° (c=2.7, $CHCl_3$). I r (nujol), 3600-2500 (broad), 1640, and 1100 cm^{-1}. ^1H Nmr ($CDCl_3$), δ1.62(d,J=6.6Hz,6H,CH_3), 3.5-3.9(m,16H,CH_2 at 4,5,7,8,10,11,13,14), 4.75(q,J=6.6Hz,2H, CH), and 13.3(broad,1H,NH) ppm. ^{13}C Nmr ($CDCl_3$), δ19.8(CH_3), 67.8(C_4,C_{14}), 70.1 and 71.0(C_5,C_{13}; C_7,C_{11};C_8,C_{10};C_2,C_6), 157.4 and 161.1(broad,C_1,C_{17}) ppm. ^{13}C Nmr ($CDCl_3$, 50°C), δ19.8(CH_3), 68.0(C_4,C_{14}), 70.1, 70.3, and 71.1(C_5,C_{13};C_7,C_{11};C_8,C_{10};C_2,C_{16}), and 159.2(broad,C_1,C_{17}) ppm. EI-MS, m/z(%), 315(M^+,0.5), 300(1), 286(1), 272(6), 256(3), 244(2), 226(5), 154(16), 138(25), 123(47), and 122(100). CI-MS (methane), m/z(%), 356(M+41,5), 344(M+29,14), and 316(M+1,100). Hydrochloride, ^1H nmr ($CDCl_3$), δ1.69(d,J=6.2Hz,6H,CH_3), 3.70(m,12H,CH_2 at 5,7,8,10,11,13), 3.84(m,4H,CH_2 at 4,14), and 4.97(q,J=6.2Hz,2H,CH_2 at 2,16) ppm. EI-MS, m/z(%), 316(M^+,0.5), 315(0.5), 300(1), 286(1), 272(8), 256(3), 244(1), 226(4), 154(7), 138(12), 123(32), and 122(100).

Lanthanide-induced Shifts (l.i.s.) Study. Samples of $CDCl_3$ solutions of ligands 1a, 1b, 2a, 2b, 6, and 7, containing increasing amounts of $Ln(fod)_3$ (Ln=Eu or Pr) were prepared by mixing aliquots of a $5x10^{-5}$M solution of each ligand (solution A) with 10^{-5}M solutions of either $Eu(fod)_3$ or $Pr(fod)_3$ in solution A (solution B). The aliquots of solutions A and B were chosen in such a way as to reach final concentration ratios of $Ln(fod)_3$/ligand ranging from 0.05 to 0.2M. Spectra were recorded at room temperature and the corresponding shifts with respect to the free ligand calculated. Straight lines were obtained in the range of concentrations used. Values on Table 1 are reported in % relative to the most sensitive signal in the ^1H nmr spectrum of each ligand, for which a 100% value was given.

Transport Rates Measurements. Measurements were performed with a glass cell composed of two concentric cylinders[22] containing 50 ml of a $CHCl_3$ solution of the macrocycle ($7x10^{-4}$M) and two aqueous phases. The source phase (I) consisted in 10 ml of an alkali picrate solution ($2x10^{-3}$M), the nitrate of the same cation (10^{-1}M), and a small amount of LiOH ($5x10^{-5}$M) in the case of N-aminated macrocycles 1a and 1b. The receiving phase (II) was made with 12.5 cm^3 of pure water. Samples of phase II were periodically analyzed for picrate content (UV, 355 nm). Measured rates ($x10^{-8}$ $mol.h^{-1}$) for Li^+, Na^+, and K^+ are collected in Table 2.

ACKNOWLEDGEMENT

We thank Dr. Marta Bruix for nmr spectral measurements. Financial support from 'Comisión Asesora de Investigación Científica y Técnica (CAICYT)' is also gratefully acknowledged.

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[18] A mixture of two diastereoisomers (3:1 ratio) was isolated, with a total yield of 6%. The major one was assigned to the (R,R)-isomer 1c, which probably contained some (S,S)-isomer 1b. The minor one should correspond to the meso form 1e.

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Received, 28th November, 1986