Crown Ethers Derived from 2,7-Dihydroxyacridine and 2,7-Dihydroxyacridan-9-one

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Received March 16, 1994®

We report the synthesis of nine acridine-crown ethers **11a**, **11b**, **12a**, **12b**, **13a**, **13b**, **14b**, **15b**, and **16b** having one or two acridine rings linked by poly(ethylene glycol) chains. Their ^1H and ^{13}C NMR spectra have been analyzed and the chemical shifts related to conformational aspects of the chain and to the tautomerism of the acridan-9-one ring. The transport rates have been determined for compounds **11b** and **12b** against a large variety of ions. While compound **11b** is devoid of complexing properties, compound **12b** transports Fe^{2+}, Cu^+, and Ag^+ but not alkali-metal cations.

Introduction

The importance of crown ethers in organic chemistry is well established.[1] A great variety of such compounds exists, one class being the crown ethers containing heterocyclic subunits and amongst them the proton ionizable crown compounds of Bradshaw.[2–7] These compounds, generally pyridin-4-one derivatives, have a double interest: they allow the study of the influence of the crown ether on the tautomerism of the heterocycle[8] and the determination of the modification of the complexing properties of the crown ether by a heterocycle possessing an acidic proton. Only two authors have reported macrocycles containing acridine residues: Lehn *et al.*[9,10] have prepared bicyclobisintercalands based on acridine subunits and Rebek has used the spatial geometry of the acridine ring to build up macrocyclic receptors.[11]

In this paper we will describe, for the first time, the preparation of crown ethers containing 2,7-acridine subunits (Scheme 1) as well as their properties.

Results and Discussion

Synthesis. 4,4′-Dimethoxy-9-chloroacridine (**2**) was obtained in two steps from 2-bromo-5-methoxybenzoic acid and *p*-anisidine through (4,4-dimethoxyphenyl)-anthranilic acid (**1**).[12] Cyclization of **1** with phosphorus oxychloride yielded **2**. The conversion of **2** into 2,7-dimethoxyacridan-9-one (**3**) has been described to take place by treatment with concd hydrochloric acid in 3 h;[12] however, even after 3 days the reaction was incomplete and the starting material had to be removed by washing the precipitate with hot chloroform. Finally, compound **4** was obtained by treating **3** with hydrobromic acid.

N-Methylation of **3** is better carried out in PTC conditions (methylene chloride, 50% sodium hydroxide, and TEBAC as catalyst). The resulting 10-methyl-2,7-dimethoxyacridan-9-one (**5**) can be *O*-demethylated by hydrobromic acid to obtain **6**. Similarly, the reaction of **2** with hydrobromic acid yields 2,7-dihydroxy-9-chloroacridine (**7**). In this last case, care must be taken with the reaction time: to complete demethylation 18 h are necessary while longer times produce partial hydrolysis of the 9-chloro substituent; for instance, after 24 h, compound **7** is contaminated with 10% of the acridan-9-one **4**.

The transformation of **7** into the amino derivatives **8**–**10** was carried out, in the first case, by ammonium carbonate in the presence of phenol, and in the last two cases, by 3-(dimethylamino)propylamine (formation of **9**) or by 3-(diethylamino)propylamine (formation of **10**). 9-[[3′-(Dialkylamino)propyl]amino]acridines **9** and **10** were prepared since analoguous derivatives present interesting biological properties.[13,14]

To prepare the crown ethers from the 2,7-dihydroxy derivatives **4** and **6**–**10** we selected, after several attempts, a procedure described by Bush[15] and Reinhoudt.[16] This procedure entails the reaction of the dihydroxy derivative with the ditosylate of the corresponding poly(ethylene glycol) in the presence of cesium fluoride using high dilution techniques. It has been used for *o*-dihydroxybenzenes, like pyrocatechol, but never for two hydroxy functions so wide apart, and this is the possible

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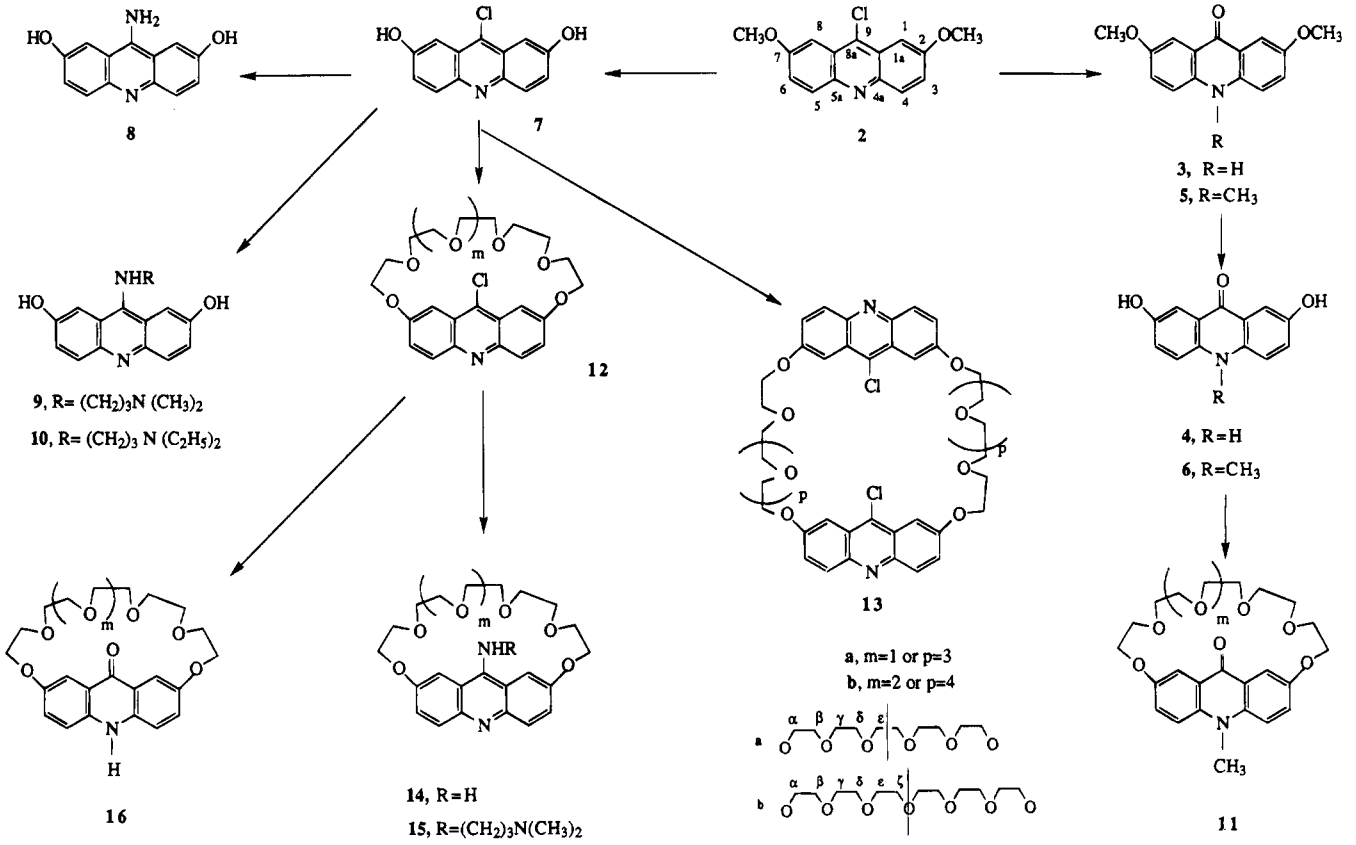
® Abstract published in *Advance ACS Abstracts,* July 15, 1994.

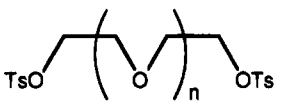
(1) Gokel, G. W. *Crown Ethers and Cryptands*; Royal Society of Chemistry: Cambridge, 1991.
(2) Bradshaw, J. S.; Colter, M. L.; Nakatsuji, Y.; Spencer, N. O.; Brown, M. F.; Izatt, R. M.; Arena, G.; Tse, P. K.; Wilson, B. E.; Lamb, J. D.; Dalley, N. K.; Morin, F. G.; Grant, D. M. *J. Org. Chem.* **1985**, *50*, 4865.
(3) Bradshaw, J. S.; Nakatsuji, Y.; Huszthy, P.; Wilson, B. E.; Dalley, N. K.; Izatt, R. M. *J. Heterocycl. Chem.* **1986**, *23*, 353.
(4) McDaniel, C. W.; Bradshaw, J. S.; Izatt, R. M. *Heterocycles* **1990**, *30*, 665.
(5) Bradshaw, J. S.; McDaniel, C. W.; Krakowiak, K. E.; Izatt, R. M. *J. Heterocycl. Chem.* **1990**, *27*, 1477.
(6) Bradshaw, J. S.; Huszthy, P.; McDaniel, C. W.; Zhu, C. Y.; Dalley, N. K.; Izatt, R. M.; Lifson, S. *J. Org. Chem.* **1990**, *55*, 3129.
(7) Izatt, M. R.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721.
(8) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocycles*; Academic Press: New York, 1976.
(9) Claude, S.; Lehn, J. M.; Vigneron, J. P. *Tetrahedron Lett.* **1989**, *30*, 941.
(10) Claude, S.; Lehn, J. M.; Pérez de Vega, M. J.; Vigneron, J. P. *New J. Chem.* **1992**, *16*, 21.
(11) Rebek, J. *Acc. Chem. Res.* **1990**, *23*, 399.
(12) Kshatriya, K. C.; Patel, S. R.; Nargund, K. S. *J. Univ. Bombay* **1946**, *A15*, 42.
(13) Berny, H.; Bsiri, N.; Charbit, J. J.; Galy, A. M.; Soyfer, J. C.; Galy, J. P.; Barbe, J.; Sharples, D.; Mera Valle, C. M.; Mascaró, C.; Osuna, A. *Arznimi. Forsch.* **1992**, *42*, 674.
(14) Mannani, R.; Galy, J. P.; Sharples, D.; Barbe, J.; Barra, Y. *Chem. Biol. Interact.* **1990**, *74*, 291.
(15) Bush, D. H. *J. Am. Chem. Soc.* **1969**, *91*, 4690.
(16) Reinhoudt, D. N.; de Jong, F.; Tomassen, H. P. M. *Tetrahedron Lett.* **1979**, *22*, 2067.

0022-3263/94/1959-5156$04.50/0

Scheme 1



reason why the reaction failed in some cases. The penta(ethylene glycol) ditosylate is commercially available, the other ditosylates (tri-, tetra-, and hexa(ethylene glycol)) were prepared by treating the glycol with tosyl chloride in pyridine as solvent.[17]



n = 2, 3, 4, 5

In the case of compound **7** its insolubility in acetonitrile or tetrahydrofuran (THF) makes it necessary to carry out the reaction in dimethylformamide (DMF). In these conditions the reaction with penta- and hexa(ethylene glycol) yields a mixture of the intramolecular reaction product, crown ether **12**, and the intermolecular reaction product, crown ether **13**, plus polymeric materials that can be eliminated since they are insoluble in acetone. With tri- and tetra(ethylene glycol)s, the corresponding crown **12** cannot be formed; thus, we expected to obtain dimers **13**, but only polymers were formed.

The synthesis of the crown ethers **14**, **15**, and **16** from the corresponding dihydroxy derivatives **8**, **9**, and **4** failed (in the case of **8** probably because this compound is insoluble in acetonitrile, THF, DMF, and other solvents used to prepare crown ethers). Fortunately, these compounds can be prepared from a common precursor, the 9-chloro derivative **12** (Scheme 1).

In summary, we have obtained the following nine acridine-crown ethers (**a** from penta(ethylene glycol), $n = 4$, $m = 1$, $p = 3$ and **b** from hexa(ethylene glycol), $n = 5$, $m = 2$, $p = 4$): **11a**, **11b** , **12a**, **12b**, **13a**, **13b**, **14b**, **15b**, and **16b**.

Structure of Acridine-Crown Ethers: NMR and Crystallographic Studies. The molecular structure of compounds **11a** and **11b** were determined by X-ray crystallography.[18] The poly(ethylene glycol) chain is folded over the acridanone ring (see Figure 1); we can safely assume that this is true for all macrocycles containing only one acridine ring (**12a**, **12b**, **14a**, **14b**, **15b**, and **16b**) but that the conformation of macrocycles **13a** and **13b**, containing two acridine rings, is probably different.

The ^{1}H NMR chemical shifts (Table 1) should be analyzed in two reciprocal ways: (i) influence of the poly(ethylene glycol) chain on acridine signals and (ii) influence of the acridine ring on the poly(ethylene glycol) signals.

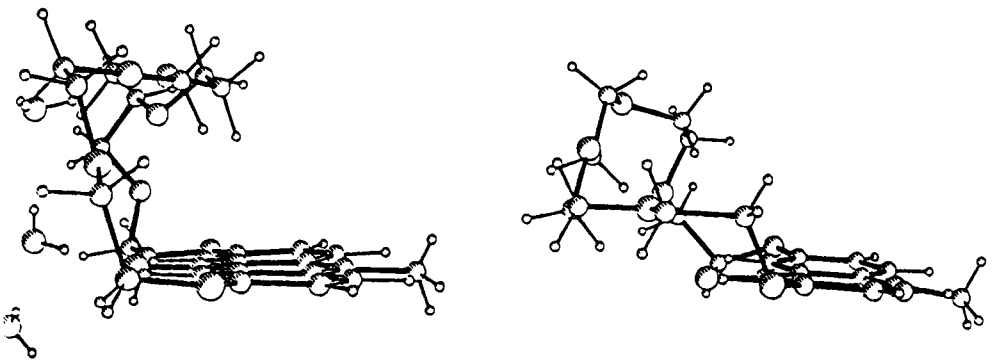
(i) On going from the OH or OMe derivative to the crown ether, only the H_1 signal is affected: a downfield shift of about 0.6 ppm is observed (pairs **2/12**, **4/16**, **5/11**, **8/14**, **9/15**). Bis-crown ethers **13** show an opposite behavior, the signal of H_1 being shifted upfield 0.34 ppm (**2/13a**) and 0.51 ppm (**2/13b**). In the case of compound **13b** the shielded H_1 signal (6.99 ppm) should correspond to a folded conformation in which each acridine ring current shifts the other acridine ring.

(ii) The data concerning the CH_2 signals show that they are ordered: $\delta_\alpha > \delta_\beta > \delta\gamma > \delta_\delta > \delta_\epsilon > \delta_\zeta$; these effects are analoguous to those described by Newkome[19] for macrocyclic naphthyridines. The most noticeable difference is the CH_2 protons on C_α which appear at ~4.2 ppm for bisacridine crown ethers **13a** and **13b** and at ~4.6

(17) Kabalka, G. W.; Varma, M.; Varma, R. S.; Srivastava, P. C.; Knapp, F. F. *J. Org. Chem.* **1986**, *51*, 2386.

(18) Vichet, A.; Galy, J. P.; Baldy, A.; Barbe, J.; Feneau-Dupont, J.; Declercq, J. P. *Acta Crystallogr.* **1991**, *C47*, 2508.

(19) Newkome, G. R.; Garbis, S. J.; Majestic, V. K.; Fronczek, F. R.; Chiari, G. C. *J. Org. Chem.* **1981**, *46*, 833.



11a 11b

Figure 1. Molecular structure of compounds **11a** and **11b**.

Table 1. ^{1}H-NMR Data of Acridine Derivatives (δ, ppm; J, Hz)

compd	solvent	$H_1(H_8)$	$H_3(H_6)$	$H_4(H5)$	substituents	$^aJ_{13} = {}^4J_{68}$	$^3J_{34} = {}^3J_{56}$
2	$CDCl_3$	7.50	7.45	8.10	4.03 (OCH_3)	2.6	9.3
3	CF_3CO_2H		7.6–8.2		4.10(OCH_3)	*a*	*a*
4	DMSO-d_6	7.50	7.21	7.40		2.8	8.9
5	DMSO-d_6	7.74	7.47	7.86	3.88 (OCH_3), 3.96 (N-CH_3)	3.0	9.6
6	DMSO-d_6	7.63	7.30	7.70	3.87 (N-CH_3)	3.0	9.4
7	DMSO-d_6		7.38–8.04			*a*	*a*
8	DMSO-d_6	7.76	7.60	7.82	12.50 (NH_2)	2.4	9.2
9	DMSO-d_6	7.62	7.47	7.82		2.3	9.3
10	DMSO-d_6	7.56	7.30	7.80		2.3	9.3
11a	$CDCl_3$	8.38	7.37	7.48	3.92 (N-CH_3)	3.0	9.3
11b	$CDCl_3$	8.19	7.37	7.50	3.92 (N-CH_3)	2.9	9.3
12a	$CDCl_3$	8.09	7.43	8.09		*a*	*a*
12b	$CDCl_3$	7.90	7.45	8.08		2.7	9.4
13a	$CDCl_3$	6.99	7.29	7.83		2.6	9.4
13b	$CDCl_3$	7.16	7.33	7.95		2.8	9.4
14b	$CDCl_3$	8.50	7.48	7.85	7.77 (NH_2)	2.4	9.3
15b	$CDCl_3$	8.38	7.38	7.82	10.3 (NH)	2.3	9.3
16b	$CDCl_3$	8.03	7.16	7.37	10.2 (NH)	2.9	9.0

compd	solvent	C_α	C_β	C_γ	C_δ	C_ϵ	C_ζ
11a	$CDCl_3$	4.53	3.84	3.57	3.57	3.57	
11b	$CDCl_3$	4.47	3.90	3.67	3.58	3.47	3.37
12a	$CDCl_3$	4.63	3.91	3.71	3.60	3.47	
12b	$CDCl_3$	4.58	3.95	3.68	3.58	3.47	3.24
13a	$CDCl_3$	4.16	4.00	3.82	3.82	3.82	
13b	$CDCl_3$	4.21	3.95	3.80	3.80	3.80	3.80
14b	$CDCl_3$	4.47	3.88	3.75	3.75	3.75	3.75
15b	$CDCl_3$	complex multiplet including the propyl chain					
16b	$CDCl_3$	4.32	3.80	3.59	3.51	3.44	3.33

[a] Second order.

ppm for monoacridine crown ethers **12a** and **12b**. We assign the shielding of bisacridine derivatives to the effect of a conformational change linked to the anisotropic effect of the acridine ring.

In ^{13}C NMR spectroscopy (Table 2) [HETCOR experiments related the chemical shifts of Tables 1 and 2, particularly important for the signals of the polyethylene glycol chain] the assignment of different carbons is based on a series of previous publications on acridine and acridanone derivatives.[20–25] The most interesting observation concerns the effect of N-methylation in acridan-9-one derivatives. In simple derivatives (pair **3/5** in CF_3CO_2H and pair **4/6** in DMSO-d_6), carbon atoms C_1, C_{1a}, and C_{4a} are deshielded while carbon atom C_4 is shielded (between 1 and 2 ppm). In crown ethers (pair **16b/11b** in $CDCl_3$) opposite effects are observed: carbon atoms C_1, C_{1a}, and C_{4a} are shielded while carbon atoms C_3 and C_4 are deshielded (by about the same amount, 2 ppm). We associate these opposite effects to differences in the acridan-9-one/9-hydroxyacridine tautomerism due to the crown ether. This explanation seems to be in contradiction with the fact that the signal of C_9, which corresponds to the carbon atom closest to the tautomeric change, is almost the same for both compounds (177.06 and 176.35 ppm, respectively). However, we have established previously that the chemical shift of this carbon has little sensitivity to the acridan-9-one/9-hydroxyacridine tautomerism.[20,21]

The changes in conformation between single crowns **12a** and **12b** on one hand and double crowns **13a** and

(20) Faure, R.; Galy, J. P.; Vincent, E. J.; Elguero, J.; Galy, A. M.; Barbe, J. *Chem. Scripta* **1980**, *15*, 62.
(21) Faure, R.; Mahamoud, A.; Galy, J. P.; Vincent, E. J.; Galy, A. M.; Barbe, J. *Spectrosc. Lett.* **1981**, *14*, 223.
(22) Faure, R.; Galy, J. P.; Vincent, E. J.; Galy, A. M.; Barbe, J.; Elguero, J.; *Spectrosc. Lett.* **1983**, *16*, 431.
(23) Faure, R.; Poulallion, P.; Galy, J. P.; Giovanangeli, G.; Soyfer, J. C.; Barbe, J. *Magn. Reson. Chem.* **1985**, *11*, 991.
(24) Dhif, D.; Galy, J. P.; Vincent, E. J.; Barbe, J. *Heterocycles* **1989**, *29*, 1149.
(25) Faure, R.; Galy, J. P.; N'Gadi, L.; Barbe, J. *Magn. Reson. Chem.* **1989**, *27*, 92.

Table 2. ^{13}C-NMR Data of Acridine Derivatives (δ, ppm)

compd	solvent	$C_1(C_8)$	$C_2(C_7)$	$C_3(C_6)$	$C_4(C_5)$	C_9	$C_{1a}(C_{8a})$	$C_{4a}(C_{5a})$	substituents
2	DMSO-d_6	99.66	158.30	126.45	131.34	144.04	125.41	144.08	55.63 (OCH_3)
3	CF_3CO_2D	101.37	160.09	132.68	122.27	166.33	118.13	137.93	57.33 (OCH_3)
4	DMSO-d_6	107.84	151.35	123.76	118.56	175.54	120.38	134.54	
5	CF_3CO_2D	103.11	159.92	133.13	119.48	166.54	119.48	140.03	37.87 (N-CH_3), 57.58 (OCH_3)
6	DMSO-d_6	109.15	151.65	123.90	117.47	175.63	122.00	136.18	33.79 (N-CH_3)
7	DMSO-d_6	102.26	156.55	124.35	130.96	141.96	125.24	142.17	
8	DMSO-d_6	105.23	153.90	127.25	120.55	154.22	122.40	133.42	
9	DMSO-d_6	105.12	152.02	125.50	122.98	153.37	114.79	136.09	44.00 [$N(CH_3)_2$][a]
10	DMSO-d_6	104.74	150.37	124.95*	124.20*	153.27	115.41	137.22	46.25, 10.15 [$N(C_2H_5)_2$][b]
11a	$CDCl_3$	110.46	153.74	125.24	115.83	176.76	122.58	137.46	33.73 (N-CH_3)[c]
11b	$CDCl_3$	109.62	153.72	123.90	116.11	176.35	122.47	137.38	33.77 (N-CH_3)[d]
12a	$CDCl_3$	103.42	157.67	125.51	130.27	143.92	125.51	143.92	*e*
12b	$CDCl_3$	102.60	157.83	125.23	131.19	144.29	125.63	144.29	*f*
13a	$CDCl_3$	100.32	157.20	124.08	131.39	144.40*	125.32	143.92*	*g*
13b	$CDCl_3$	100.83	157.53	124.25	131.66	144.35	125.26	144.35	*h*
14b	$CDCl_3$	104.23	155.78	128.52	122.34	153.18	111.86	135.30	*i*
15b	$CDCl_3$	105.58	155.25	126.67	121.93	154.45	114.25	135.66	45.03 [$N(CH_3)_2$][j]
16b	$CDCl_3$	107.68	153.67	125.42	118.56	177.06	120.38	135.65	*k*

[a] 47.71, 25.90, 56.45 ($-CH_2-$)$_3$. [b] 49.75, 25.89, 47.78 ($-CH_2-$)$_3$. [c] 68.38 (C_α), 70.72*(C_β), 70.92* (C_γ), 71.53# (C_δ), 71.84# (C_ϵ). [d] 68.48 (C_α), 70.63 (C_β), 71.50 (C_γ), 71.15 (C_δ), 70.52 (C_ϵ), 70.29 (C_ζ). [e] 68.22 (C_α), 70.21* (C_β), 70.98* (C_γ), 71.19# (C_δ), 72.20# (C_ϵ). [f] 68.48 (C_α), 70.98 (C_β), 71.45 (C_γ), 71.25 (C_δ), 70.45 (C_ϵ), 70.45 (C_ζ). [g] 67.83 (C_α), 69.62* (C_β), 70.80* (C_γ), 70.95* (C_δ), 71.07* (C_ϵ). [h] 68.05 (C_α), 68.70* (C_β), 70.96* (C_γ), 70.96* (C_δ), 71.21* (C_ϵ), 71.21* (C_ζ). [i] 69.67 (C_α), 70.65* (C_β), 70.77* (C_γ), 70.82# (C_δ), 70.15# (C_ϵ), 70.15 (C_ζ). [j] 49.28, 25.58, 58.28 ($-CH_2-$)$_3$, 69.08 (C_α), 70.12* (C_β), 70.96* (C_γ), 70.12# (C_δ), 70.12# (C_ϵ), 70.12* (C_ζ). [k] 68.03 (C_α), 70.65* (C_β), 71.32* (C_γ), 71.06# (C_δ), 70.36# (C_ϵ), 70.17* (C_ζ).

Table 3. Transport Rates (10^{-7} mol L^{-1} h^{-1}) of Ions through a Chloroform Phase

crown	Li^+	Na^+	K^+	Cs^+	Ca^{2+}	NH_4^+	Ni^{2+}	Co^{2+}	Cu^{2+}	Ag^+	Fe^{2+}
DB18C6[28]	61	200	1980	870							
DB18C6	60	190	4130	1720	0	3300	N.m.[a]	N.m.	0	0	0
11b	0	0	0	0	0	0	0	0	0	0	0
12b	0	0	0	0	0	0	0	0	340	360	620

[a] N.m. = not measured.

13b affect essentially carbon atom C_1 which is shielded in the last compounds (between 1.8 and 3.1 ppm).

Ionophore properties of crown ethers **11b** and **12b**. Transport rates for compounds **11b** and **12b** and for dibenzo-18-crown-6 (DB18C6) used as reference compounds are reported in Table 3. Acridan-9-one derivative **11b** is devoid of complexing properties while 9-chloroacridine derivative **12b** is not a "classical" crown ether but it transports $Fe^{2+} > Ag^+ = Cu^{2+}$. This property is not only due to the acridine since 2,7-dimethoxy-9-chloroacridine **2** is devoid of such behavior. Crown ethers are known to transport Ag^+ and Cu^{2+}.[7, 26-28]

We have also determined for compound **12b** the kinetics of complexation and decomplexation: decomplexation is quick and complete for the three cations. This makes acridine-crown **12b** an interesting compound with unusual complexation properties although with weak selectivity.

Experimental Section

The proton and carbon-13 NMR spectra were obtained in the indicated solvent at 200 MHz. Elemental analyses were performed by "Service Central de Microanalyse du CNRS". Molecular weights were determined by the electron impact method. Starting materials were purchased from Aldrich Chemical Co. 4,4'-Dimethoxyphenyl)anthranilic acid (**1**)[12] and 2,7-dimethoxy-9-chloroacridine (**2**)[12] were prepared as reported. The ditosylates were obtained according to the general procedure and used without further purifications.[17]

The complexation properties of the acridine-crown ethers have been assessed by the "liquid–liquid extraction method" previously described.[29,30]

Preparation of 2,7-Dimethoxyacridan-9-one (3). By heating a mixture of **2** (5 g, 18 mmol) and hydrochloric acid (20% v/v) (172 mL) at 140 °C with vigorous stirring during 72 h, pouring the resulting solution over ice, and neutralizing with diluted ammonia a yellow solid was obtained. After careful washing with water, 4 g of a dry solid was obtained. The compound was extracted with hot chloroform, and the insoluble residue (3.37 g, 65% yield) was pure compound **3**: mp > 300 °C; ^{1}H NMR (CF_3CO_2H) δ 4.1, 7.6–8.2. Anal. Calcd for $C_{15}H_{13}O_3N$: C, 70.58, H, 5.13, N, 5.49. Found: C, 70.47, H, 5.10, N, 5.49.

Preparation of 2,7-Dihydroxyacridan-9-one (4). By heating a mixture of **3** (0.40 g, 1.6 mmol) and 62% hydrobromic acid (20 mL) at reflux during 24 h, pouring the resulting solution over ice, and neutralizing with aqueous ammonia, a yellow-green precipitate was isolated (0.2 g, 56% yield): mp > 300 °C, lit.[31] mp = 275 °C); ^{1}H NMR (DMSO-d_6) δ 7.21, 7.40, 7.50, 9.48. Anal. Calcd for $C_{13}H_9O_3N$: C, 68.72, H, 3.99, N, 6.16. Found: C, 68.66, H, 3.96, N, 6.17.

Preparation of 2,7-Dimethoxy-10-methylacridan-9-one (5). By stirring a mixture of **3** (2.5 g, 10 mmol), triethylbenzylammonium chloride (TEBAC) (0.49 g, 2.15 mmol), 50% NaOH (80 mL), CH_2Cl_2 (80 mL), and dimethyl sulfate (4.4 mL, 46 mmol) for 24 h at room temperature two phases were obtained. There was a precipitate in the aqueous phase which was filtered off. The organic phase was washed with 20% aqueous ammonia and evaporated under vacuum. The solid thus obtained was identical with the solid filtered from the aqueous phase; thus, both were mixed, dissolved in ethanol at room temperature, and then diluted with water. A yellow precipi-

(26) Maeda, T.; Kimura, K.; Shono, T. *Fresenius Z. Anal.* **1979**, *298*, 363.
(27) Buschmann, H. J. *Chem. Ber.* **1985**, *118*, 2746.
(28) Chandler, C. J.; Deady, L. W.; Reiss, J. A. *Austr. J. Chem.* **1988**, *41*, 1051.
(29) Samat, A.; Bibout, M. E. M.; Elguero, J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1717.
(30) Izatt, M. R.; Christensen, J. J. *Progress in Macrocyclic Chemistry*; Wiley: New York, 1979; Vol. 2, pp 52–72.
(31) Linnel, H.; Stuckey, R. E. *Quart. J. Pharm. Pharmacol.* **1940**, *13*, 162.

tate was formed which was collected by filtration, 2 g (90% yield) of compound pure **5**: mp = 222.5 °C; ^{1}H NMR (DMSO-d_6) δ 3.88, 3.96, 7.47, 7.74, 7.86. Anal. Calcd for $C_{16}H_{15}O_3N$: C, 71.37, H, 5.57, N, 5.20. Found: C, 71.19, H, 5.43, N, 5.36.

Preparation of 10-Methyl-2,7-dihydroxyacridan-9-one (6). By heating a mixture of **5** (1 g, 3.72 mmol) and 62% hydrobromic acid (50 mL) at reflux during 18 h, pouring the resulting solution over ice, and neutralizing with 20% aqueous ammonia, a yellow solid was obtained which was washed with water and dried. It was dissolved in ethanol at room temperature and then diluted with water. A yellow precipitate was formed which was collected by filtration, 0.75 g (85% yield) of pure compound **6**; mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 3.87, 7.30, 7.63, 7.70, 9.60. Anal. Calcd for $C_{14}H_{11}O_3N$: C, 69.71, H, 4.57, N, 5.81. Found: C, 69.65, H, 4.82, N, 5.97.

Preparation of 2,7-Dihydroxy-9-chloroacridine (7). A solution of **2** (3 g, 11 mmol) in 62% hydrobromic acid (150 mL) was heated under reflux for 17 h. The solution was poured into ice and neutralized with concentrated ammonia solution. The resulting red solid was filtered off, washed with water, and dried. The dry solid was extracted with hot chloroform. The insoluble residue (2.45 g, 90% yield) was pure compound **7**: mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 7.38–8.04, 10.55. Anal. Calcd for $C_{13}H_8O_2NCl$: C, 63.65, H, 3.26, N, 5.71. Found: C, 63.71, H, 3.45, N, 5.86.

Preparation of 2,7-Dihydroxy-9-aminoacridine (8). First, compound **7** (2 g, 8.15 mmol) was dissolved in phenol (4.4 g, 46.7 mmol) at 75 °C, and then ammonium carbonate (2.31 g, 20.2 mmol) was added. The mixture was stirred and heated during 1 h at 120 °C. The resulting oil was mixed with acetone (25 mL) at which time it crystallized. The solid was filtered off, washed first with acetone then with diluted hydrochloric acid, and dried. One (1.00) g (58% yield) of a green compound was obtained: mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 7.60, 7.76, 7.82, 9.30, 12.50. Anal. Calcd for $C_{13}H_{10}O_2N_2$: C, 69.03, H, 4.43, N, 12.39. Found: C, 68.84, H, 4.59, N, 12.54.

Preparation of 2,7-Dihydroxy-9-[3′-(dimethylamino)propyl]acridine (9). By heating a mixture of **7** (1 g, 4 mmol) and phenol (2.2 g, 2.3 mmol) for 30 min at 80 °C a clear solution was obtained. Then, 3-(dimethylamino)propylamine (0.6 mL, 4 mmol) was added, and the temperature raised to 110 °C and maintained during 3 h. The oily residue was mixed with acetone (25 mL) and it crystallized. The solid was filtered off, washed twice with hot acetone (400 mL), and dried. A brown powder (1.16 g, 93% yield) was obtained: mp = 170 °C; ^{1}H NMR (DMSO-d_6) δ 1.99, 2.40, 2.74, 3.96, 7.47, 7.62, 7.82. Anal. Calcd for $C_{18}H_{21}O_2N_3$: C, 69.45, H, 6.75 N, 13.50. Found: C, 69.63, H, 6.60, N, 13.37.

Preparation of 2,7-Dihydroxy-9-[3′-(diethylamino)propyl]acridine (10). Using the same procedure but with 2-(diethylamino)ethylamine, compound **7** (1 g) yields 0.80 g (60%) of a brown powder: mp = 180 °C; ^{1}H NMR (DMSO-d_6) δ 2.00, 2.10, 2.70, 2.95, 3.85, 7.30, 7.56, 7.80. Anal. Calcd for $C_{20}H_{25}O_2N_3$: C, 70.80, H, 7.37, N, 12.39. Found: C, 70.92, H, 7.18, N, 12.21.

Preparation of Macrocycles 11–13. Reaction of 10-Methyl-2,7-dihydroxyacridan-9-one (6) with Penta(ethylene glycol) Ditosylate. Compound **6** (1.00 g, 4.15 mmol) was dissolved in anhydrous DMF (400 mL) at 100 °C under nitrogen. To this mixture was added potassium *tert*-butoxide (1.86 g, 16.6 mmol), and the solution was stirred during 3 h. A solution of penta(ethylene glycol) ditosylate (2.5 g, 4.45 mmol) in anhydrous DMF (50 mL) was slowly added. The resulting solution was kept at 100 °C under nitrogen for 5 days. The solvent was evaporated under reduced pressure and the residue extracted with hot anhydrous acetonitrile (400 mL). The insoluble part was filtered off and eliminated. The acetonitrile solution was evaporated and the oily residue mixed with acetone. The insoluble part (potassium tosylate) was filtered off and eliminated. The acetone solution was evaporated, and the residue mixed with ethanol–diethyl ether (1:1) yielded a solid and a solution. By evaporation of the solution, 220 mg of a yellow solid which was pure compound **11a** was obtained (12% yield): mp = 147.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.57, 3.84, 3.92, 4.53, 7.37, 7.48, 8.38. Anal. Calcd for $C_{24}H_{29}O_7N$: C, 65.01, H, 6.54, N, 3.16. Found: C, 64.98, H, 6.73, N, 3.34.

Reaction of 10-Methyl-2,7-dihydroxyacridan-9-one (6) with Hexa(ethylene glycol) Ditosylate. With the same procedure but using hexa(ethylene glycol) ditosylate (2.69 g, 4.56 mmol), 350 mg of crown ether **11b** was obtained (17% yield): yellow solid; mp = 104.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.37, 3.47, 3.58 , 3.67, 3.90, 3.92, 4.47, 7.37, 7.50, 8.19. Anal. Calcd for $C_{26}H_{33}O_8N$: C, 64.06, H, 6.77, N, 2.87. Found: C, 63.90, H, 6.82, N, 2.97.

Reaction of 2,7-Dihydroxy-9-chloroacridine (7) with Penta(ethylene glycol) Ditosylate. Under nitrogen atmosphere, compound **7** (1 g, 4 mmol) was dissolved in anhydrous DMF (400 mL) at 100 °C, and then cesium fluoride (3.1 g, 20.35 mmol) was added and the solution stirred for 3 h. To this solution was slowly added penta(ethylene glycol) ditosylate (2.4 g, 4.4 mmol) in anhydrous DMF (50 mL). The resulting mixture was kept at 100 °C under nitrogen atmosphere during 3 days. The solvent was removed under reduced pressure and the oily residue extracted with hot acetonitrile (400 mL). The insoluble solid was filtered off and eliminated and the solution evaporated under reduced pressure. The oily residue was treated with acetone (100 mL): a solid insoluble in acetone appeared which was filtered off.

The acetone solution by evaporation yielded an oil which treated with ethanol–diethyl ether (1:1) partly solidified. The precipitate was eliminated by filtration and the solution evaporated. A pale brown solid was obtained which was pure compound **12a** (100 mg, 6% yield): mp 125 °C; ^{1}H NMR ($CDCl_3$) δ 3.47, 3.60, 3.71, 3.91, 4.63, 7.43, 8.09. Anal. Calcd for $C_{23}H_{26}O_6NCl$: C, 61.68, H, 5.81, N, 3.13. Found: C, 61.75, H, 5.89, N, 3.26.

The solid insoluble in acetone was extracted with hot $CHCl_3$ (25 mL). Cesium tosylate was insoluble in these conditions and can be eliminated. The chloroform solution was evaporated and the oily residue mixed with acetone (25 mL); a solid was formed which was filtered, washed with acetone, and dried. A brown solid (130 mg, 8% yield) was isolated which was pure compound **13a**: mp 177 °C; ^{1}H NMR ($CDCl_3$) δ 3.82, 4.00, 4.16, 6.99, 7.29, 7.83. Anal. Calcd for $C_{46}H_{52}O_{12}N_2Cl_2$: C, 61.67, H, 5.81, N, 3.12. Found: C, 61.51, H, 5.97, N, 3.23.

Reaction of 2,7-Dihydroxy-9-chloroacridine (7) with Hexa(ethylene glycol) Ditosylate. With an identical procedure but using hexa(ethylene glycol) ditosylate (2.6 g, 4.4 mmol) a mixture of two compounds was obtained.

Fraction soluble in acetone, **12b**: mp = 129 °C (170 mg, 9% yield); mass spectrometry, M (m/z) = 491; ^{1}H NMR ($CDCl_3$) δ 3.24, 3.47, 3.58, 3.68, 3.95, 4.58, 7.45, 7.90, 8.08. Anal. Calcd for $C_{25}H_{30}O_7NCl$: C, 61.04, H, 6.10, N, 2.85. Found: C, 61.12, H, 6.24, N, 2.91.

Fraction insoluble in acetone, **13b**: mp = 160.5 °C (170 mg, 9% yield); mass spectrometry, M (m/z) = 983; ^{1}H NMR ($CDCl_3$) δ 3.80, 3.95, 4.21, 7.16, 7.33, 7.95. Anal. Calcd for $C_{50}H_{60}O_{14}N_2Cl_2$: C, 61.03, H, 6.10, N, 2.84. Found: C, 60.89, H, 5.98, N, 3.00.

Reactivity of Macrocycle 12b. Reaction with Ammonium Carbonate. Compound **12b** (200 mg, 0.4 mmol) was dissolved in phenol (200 mg, 0.4 mmol) at 80 °C, and then NH_4CO_3 (45 mg, 0.4 mmol) was added. The mixture was heated at 100 °C during 2 h. The residue was mixed with acetone (50 mL), and the pale green insoluble residue was filtered off. After being washed with acetone and dried compound **14b** weighed 50 mg (26% yield): mp > 300 °C; ^{1}H NMR ($CDCl_3$) δ 3.75, 3.88, 4.47, 7.47, 7.85, 8.52. Anal. Calcd for $C_{25}H_{32}O_7N_2$: C, 63.56, H, 6.78, N, 5.93. Found: C, 63.54, H, 6.79, N, 5.88.

Reaction with 3-(Dimethylamino)propylamine. A solution of **12b** (200 mg, 0.4 mmol) in phenol (220 mg, 2.3 mmol) at 80 °C was kept at this temperature for 20 min and then 3-(dimethylamino)propylamine (0.06 mL, 0.4 mmol) was added and the mixture maintained at 105 °C during 3 h. The resulting oil crystallizes after several hours by adding a small amount of acetone. Compound **15b**, a orange solid soluble in water, was obtained (80 mg, 34% yield): mp = 142 °C; ^{1}H NMR

($CDCl_3$) δ 2.18–4.53, 7.38, 7.82, 8.38. Anal. Calcd for $C_{30}H_{43}O_7N_3$: C, 64.63, H, 7.72, N, 7.54. Found: C, 64.74, H, 7.82, N, 7.50.

Hydrolysis. By heating compound **12b** (200 mg, 0.4 mmol) in 15% hydrochloric acid (10 mL) at 100 °C during 65 h, then pouring the solution into ice and neutralizing the solution with 15% aqueous sodium hydroxyde a solid precipitated which was filtered off. The solution was evaporated under vacuum and the residue was extracted with hot $CHCl_3$ (4 × 25 mL). The chloroform solution yielded, after evaporation, an oil which solidified after several days by adding a small quantity of ethanol. Yellow crystals of compound **16b** were thus obtained: mp = 142 °C (50 mg, 24% yield); ^1H NMR ($CDCl_3$) δ 3.33, 3.44, 3.51, 3.59, 3.80, 4.32, 7.16, 7.37, 8.03. Anal. Calcd for $C_{25}H_{31}O_8N$: C, 63.42, H, 6.55, N, 2.96. Found: C, 63.40, H, 6.58, N, 3.02.