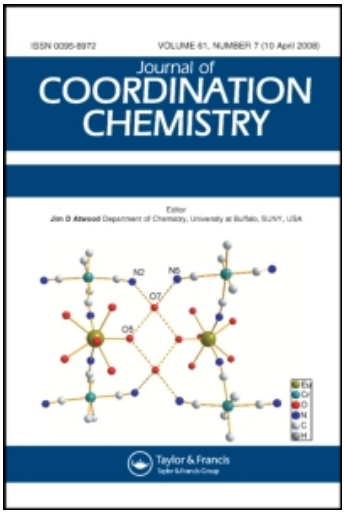

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

Sulfonamides as Ion-Carriers

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To cite this Article Bocheńska, M. , Biernat, J. F. and Bradshaw, J. S.(1992) 'Sulfonamides as Ion-Carriers', Journal of Coordination Chemistry, 27: 1, 129 — 143
To link to this Article: DOI: 10.1080/00958979209407949
URL: http://dx.doi.org/10.1080/00958979209407949

J. Coord. Chem. 1992, Vol. 27, pp. 129-143
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SULFONAMIDES AS ION-CARRIERS

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A short review of the noncyclic, cyclic and bicyclic ligands with sulfonamido groups is presented. The synthesis and the application of the compounds are described.

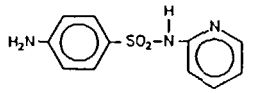
Keywords: Sulfonamides, podands, crowns, cryptands, structures, complexes, ion-selective electrodes

INTRODUCTION

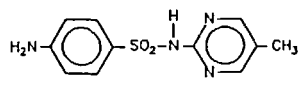
The discovery in the early thirties of the antibacterial activity of benzenesulfonamide was the first step to chemotherapy and also was an invitation to the further investigation of this group of compounds. A history of this discovery and the development of sulfonamide drugs is reviewed by Behnisch.[1] Among the many tested compounds of that kind, only few possess high antibacterial activity and low toxicity, enabling them to act as drugs similar in behaviour to the antibiotics. The therapeutic activity is typical for sulfonamides in which one hydrogen atom of the sulfonamido group is replaced by a heterocyclic or aromatic residue, as for example α-sulfanilamidopyridine, sulfamerazine or sulfathiazole shown below. Sulfonamides behave as important drugs despite the fact that they are not found in nature. The structure, properties, pharmacokinetics and side effects of sulfonamides have been reviewed by F. Bricaire *et al.*[2] There are also quite a few publications dealing with the chelating tendencies of sulfa drugs. Complexation with many divalent cations such as Cu(II), Zn(II), Ni(II), Co(II), Mn(II), Hg(II), Sn(II) and also trivalent Sb(III) was studied.[3-9] Sulfonamide derivatives of amino acids such as Gly, Ala, Glu, Ser, Thr, Met were prepared and the stability constants of their complexes with Co(II), Ni(II), Zn(II) and Cu(II) were compared.[10-12]

Sulfonamides such as saccharine or succaryl, being extremely sweet, are used as artificial sweeteners.

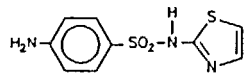
A recent application for the sulfonamides is their use as electrolyte components in high energy lithium batteries.[13]



sulfanilamidopyridine



sulfamerazine



sulfathiazole

Sulfonamides are of interest also because of their chemical properties. The acidity of the sulfonamides with one dissociating proton is similar to that of phenols (pK_a=9). They are chemically stable. These compounds are much more resistant to hydrolysis and to oxidation than phenols and carboxamides. They can be readily prepared and modified. A comparative study of the electronic properties of sulfonamides and carboxamides shows that there is no electronic analogy between these two classes. Sulfonamides seem to be incapable of conjugation in contrast to planar carboxamides.[14]

SULFONAMIDE PODANDS

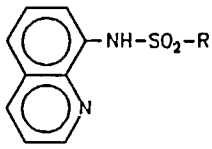
Simple sulfonamide complexing agents such as compounds **1–8** were first introduced in 1960.[15,16] They have been used for the analysis of transition and post-transition metals, such as Cu(II), Zn(II) and Cd(II). After several reports about these compounds they were found to be uninteresting for further investigations.[16] The next report on sulfonamide chelating agents was in 1980[17] showing again the practical application potential of simple sulfonamides (compounds **1–17**). An interesting finding about sulfonamides is that they do not show affinity to Fe(III), Al(III) and alkaline earth metal ions. It makes them useful as solvent extractants for hydrometallurgy of other transition metals. Generally, sulfonamides behave as complexones under alkaline conditions, similarly to phenols. But when electron withdrawing substituents are attached to the sulfonamido group (for instance the trifluoromethyl group in **10**) they can complex Cu(II), Ni(II), Zn(II) under neutral or even acidic conditions.[17]

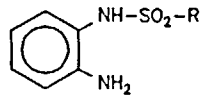
Other types of sulfonamide complexing agents were synthesized with the aim of using them in ion-selective electrodes.[18,19] Compounds **18–34** were synthesized in the reaction of sulfochlorides with the appropriate secondary amines as shown in Scheme 1a–b. They were analogues of carboxamides, known as good ionophores, and were found to behave as potentiometric sensors in membrane electrodes for alkali metal cations, being selective for K^+, although not selective enough for practical applications.

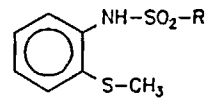
Generally, polydentate macrocyclic ligands form more stable (by about two orders of magnitude) complexes than the corresponding open chain ligands. This phenomenon is known as the macrocyclic effect.[20] Occasionally however the noncyclic ligands appear to be superior to the analogous macrocyclic compounds as determined by ion extraction studies and by membrane transport experiments.[21,22] Many open chain ligands fulfill the requirements of a fast and reversible reaction in ion-selective electrode membranes and therefore may be applied as ionophores.

Fourteen open chain proton-ionizable bis-sulfonamides, podands with 2, 3 or 4 ether oxygen atoms (compounds **35–48**), the analogues of the crown ethers synthesized earlier,[23–25] were synthesized as shown in Scheme 1c. Their properties have been investigated by the solvent extraction method.[26] Their ionophoric properties in ISE have been also studied.[27]

The X-ray crystal structure of the podand with the large polyether chain (4 ether oxygen atoms) showed a linear arrangement with a large degree of flexibility in the backbone chain. The nitrogen atoms are far apart but it appears that the molecule can easily wrap around a metal cation.[26] Also one solvent (i-PrOH) molecule accompanied one molecule of ligand. The tendency to complex organic solvent molecules by sulfonamide podands resembles similar behaviour of sulfonester





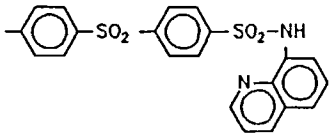


1 R = 

2 R = 

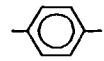
3 R = $-CH_3$

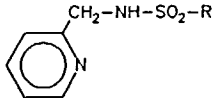
4 R = $-n-C_8H_{17}$

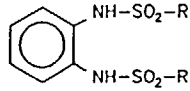
5 R = 

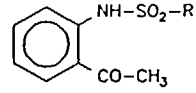
6 R = 

7 R = $-n-C_8H_{17}$

8 R = 







9 R = $-CH_3$

10 R = $-CF_3$

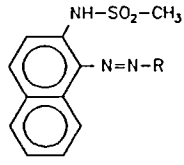
11 R = $-CH_3$

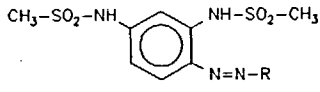
12 R = $-n-C_8H_{17}$

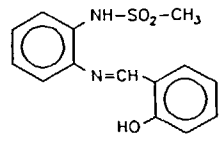
13 R = $-n-C_8H_{17}$

podands.[28] It was reported that such ligands form easily complexes with neutral solvent molecules, such as benzene (of 1:2 stoichiometry) or toluene (of 1:1 stoichiometry).

Secondary bis-sulfonamides of similar structure, compounds **49–52** were synthesized as prospective ionophores for ion-selective electrodes.[29]





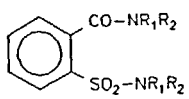


14 R = 

15 R = 

16 R = 

17



18 $R_1 = R_2 = -C_2H_5$

19 $R_1 = R_2 = -n-C_4H_9$

20 $R_1 = R_2 = -C_4H_9$

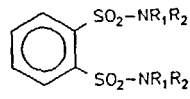
21 $R_1 + R_2 =$ 

22 $R_1 + R_2 =$ 

23 $R_1 = R_2 = -CH_2-C_6H_5$

24 $R_1 = -C_2H_5$, $R_2 = -C_6H_5$

25 $R_1 = H$, $R_2 = n-C_{14}H_{29}$

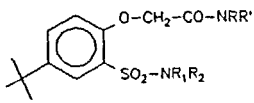


26 $R_1 = R_2 = -n-C_4H_9$

27 $R_1 = R_2 = -i-C_4H_9$

28 $R_1 + R_2 =$ 

29 $R_1 = -C_2H_5$, $R_2 = -C_6H_5$



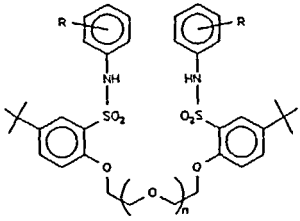
30 $R = R' = -n-C_4H_9$; $R_1 = -C_2H_5$,

31 $R = R' = -n-C_4H_9$; $R_1 + R_2 =$ 

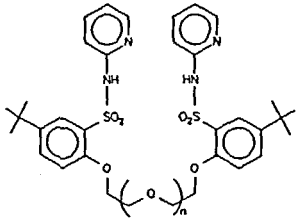
32 $R = R' = R_1 = R_2 = -i-C_4H_9$

33 $R = R' = -i-C_4H_9$; $R_1 = -C_2H_5$, $R_2 = -C_6H_5$

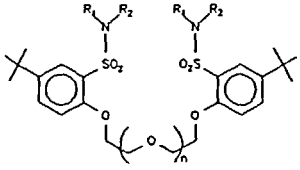
34 $R = R' = -n-C_4H_9$; $R_1 = R_2 = -CH_2-C_6H_5$



35 n = 0 R = –H
36 n = 1 R = –H
37 n = 2 R = –H
38 n = 0 R = –p–NO_2
39 n = 1 R = –p–NO_2
40 n = 2 R = –p–NO_2
41 n = 0 R = –o–OCH_3
42 n = 1 R = –o–OCH_3
43 n = 2 R = –o–OCH_3
44 n = 2 R = –p–OCH_3
45 n = 1 R = –o–OCH_3
46 n = 2 R = –p–CH_3



47 n = 0
48 n = 1



49 n = 1 $R_1 = R_2 = -n-C_8H_{17}$

50 n = 1 $R_1 + R_2 =$ 

51 n = 2 $R_1 = -C_6H_5$, $R_2 = -CH_2-C_6H_5$

52 n = 2 $R_1 = R_2 = -C_6H_{11}$

SULFONAMIDE CROWN ETHERS

The classical crown ethers first synthesized by Pedersen[30] possess an unique property of binding salts and forming complexes in which an anion neutralizes the positive charge of the cation complexed by the crown. Different anions may substantially change properties of the formed complex such as stability, solubility, lipophilicity, etc. This might be disadvantageous when cations are extracted together with different anions from aqueous solutions into organic solvents using crown ethers, as the anions affect the partition coefficients of the complexes.

The influence of different anions on the extraction of metal cations can be avoided by the application of "proton-ionizable" crown ethers introduced to crown ether chemistry by Cram,[31–33], Lehn[34–37] and Bartsch.[38–41] Proton ionizable crown ethers dissociate in solutions and, depending on the pH, the proton might be even fully removed from the parent crown compound which forms the respective crown-derived anion. The anionic crowns bind the respective cations forming complexes in which the positive charge of the bonded metal ion is neutralized only by the negative charge of the anionic crown residue. Thus the complex formed by electron donor atoms of the macrocycle and metal cation is already neutral and does not need to be accompanied by an anion. The first proton dissociating residue introduced into crown ethers was the carboxylic group located in the pendant arm of the crown.[31–41] Also phenolic groups located inside the crown ether ring play a similar role.[42–44]

A completely new approach to this field was introduced by Bradshaw and co-workers, who synthesized many new crowns, which contain ionizable groups as a part of the macroring.[45–48] They were the triazolo and 4-hydroxypyridino esters,[45] 4-pyridone,[46] triazole[47] and the 4-thiopyridono crowns.[48] All these compounds behave as weak acids. The pK_a values for 4-pyridono, 4-thiopyridono and triazolo crowns are 10.98, 8.3 and 9.55, respectively.[48] The anion formed during dissociation of the proton has a negative charge located on the electron donor nitrogen atom which is a part of the macroring. The additional charge should lead to an increase in stability of the complex formed by the crown anion and cations. The effect of complexation using proton dissociating crown ethers is apparently electrostatic in nature but the additional effect of an anion also plays a significant role.[43,44] The increased stability of alkali metal complexes with some ionizable crown ethers led to more efficient solvent extraction metal cations from aqueous solutions into organic media. The distinct advantage of such crowns is that transport of the metal cation does not involve anion co-transport and gives an opportunity to construct a proton driven alkali metal cation pump.[38] A schematic mechanism of counter transport of alkali metal cations and protons is as follows[45a]:

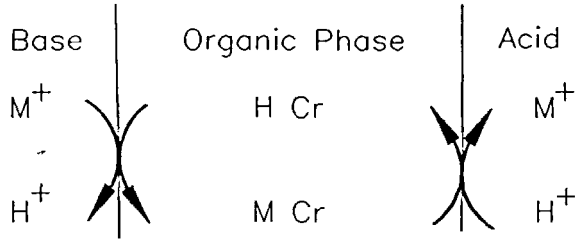
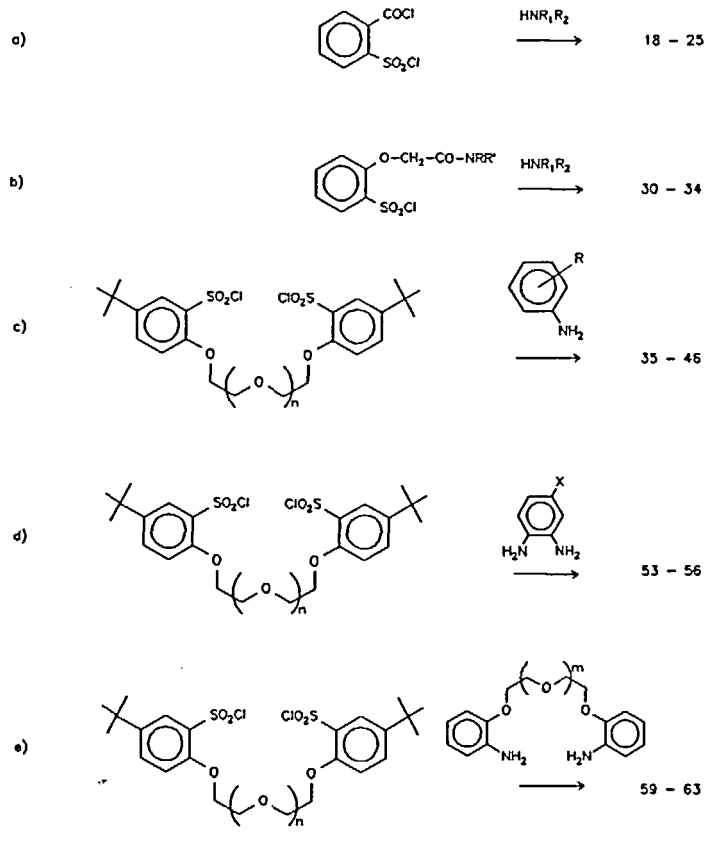


TABLE I
Properties of noncyclic sulfonamides.

Compound no.	m.p. [°C]	Yield [%]	Application ions of preference	X-ray ref.	Reference
1	153–4	76.4	Very efficient solvent extraction agent		16, 17
2	148–9	76.5	for Cu(II), Zn(II), Co(II), Cd(II) used		16
3	143–4	69.0	for qualitative screening process; forms coloured, insoluble chelates with Ag, Hg, Cu, Pb, Co, Zn ions		16
4	—	—	Very efficient solvent extraction agent for Cu(II), Zn(II), Co(II), Cd(II)		16, 17
5	203–4	50.0	Similar to 1, 2 and 3		16
6	135–6	80.0	Behaves similarly as 4		15, 16
7	—	—	Behaves similarly as 4		16, 17
8	—	—	Behaves similarly as 4		16, 17
9	—	—	Forms stable Cu(II) complex		17
10	—	—	Stable complexes with Cu(II), Ni(II), Zn(II) at any conditions.		17
11	—	—	Forms neutral complexes of HL A type with Co(II), Ni(II), Cu(II), Zn(II), A = NH_3, en		17
12	—	—	Extracts Cu(II) and Zn(II)		17
13	—	—	Extracts Cu(II), Ni(II), Zn(II) in presence of NH_3		17
14	—	—	Stable complexes with divalent		17
15	—	—	metals without significant colour		17
16	—	—	change		17
17	—	—	Forms stable Cu(II) complex		17
18	oil	50	ISE Na-selective		18
19	oil	55	ISE Ca-selective		18
20	76–8	30	ISE K-selective	19	18, 19
21	173–5	75	ISE K-selective		18
22	103–5	43	ISE K-selective		18
23	155–8	62	ISE K-selective		18
24	82–5	21	ISE K-selective		18
25	56–8	54	ISE Ca-selective		18
26	66–9	70	ISE K-selective		18
27	74–8	50	ISE K-selective		18
28	163–5	88	ISE K-selective		18
29	121–3	25	ISE K-selective		18
30	103–5	35	ISE K-selective		18
31	oil	43	ISE K-selective		18
32	132–4	40	ISE K-selective		18
33	105–8	25	ISE K-selective		18
34	oil	33	ISE Ca-selective		18
35	205–6	63	Solvent extraction Na,K		26
36	173–5	25	Solvent extraction Na,K		26
37	170–1	50	Solvent extraction Na,K		26
38	261–3	33	ISE: K, G; solvent extraction Na < K		26, 27, 59
39	213–5	80	ISE: K, G; solvent extraction Na > K		26, 27, 59
40	158–9	40	ISE: K, G; solvent extraction Na < K		26, 27, 59
41	213–5	57	ISE: K, G; solvent extraction Na > K		26, 27, 59

TABLE I—*continued.*

Compound no.	m.p. [°C]	Yield [%]	Application ions of preference	X-ray ref.	Reference
42	134–5	60	ISE: K, G; solvent extraction Na > K		26, 27, 59
43	67–9	50	ISE: K, G; solvent extraction K > Na	26	26, 27, 59
44	176–7	71	ISE: K, G; solvent extraction K > Na		26, 27, 59
45	153–5	60	ISE: K, G; solvent extraction Na > K		26, 27, 59
46	188–9	73	ISE: K, G; solvent extraction Na,K		26, 27, 59
47	272–4	40	No application		26
48	250–1	80	No application		26
49	oil	90	JSE: G, K		52, 29
50	185–9	89	JSE: G, K		52, 29
51	oil	30	JSE: G, K		52, 29
52	172–4	25	JSE: G, K		52, 29

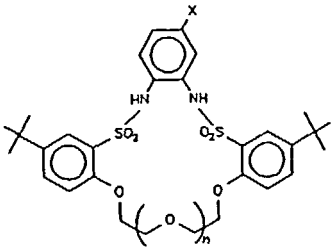


Scheme 1

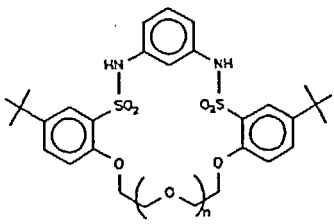
At the basic interface the carrier is deprotonated and cation complexation occurs to give a neutral complex which can diffuse across the membrane. At the acidic interface the reverse process occurs: protonation and metal ion loss regenerates the carrier and completes the cycle.

In principle, exactly the same applies when the dissociating group is of another nature than the groups described so far.

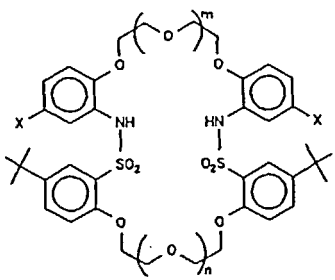
Sulfonamides were known in crown ether chemistry only as intermediate products in the synthesis of azacrowns. Removal of the protecting sulfonyl residue led to the final product—the azacrowns or their derivatives.[49] The idea to introduce the sulfonamido group into crown ether moieties[23] led to the synthesis of several crowns possessing two proton dissociating sulfonamido groups as a part of the macroring and various ring sizes: 17–26 membered rings.[23–25] Among sulfonamide crowns there are compounds in which sulfur is attached to the aromatic group and nitrogen atoms are attached to aromatic or aliphatic groups (compounds **53**–**65**). The synthesis of the sulfonamide crowns is shown in Scheme 1d–e. They were obtained in the reaction of the bis-sulfonyl chloride with the appropriate diamine. All of them are high melting crystalline compounds (see Table 2). Transport of alkali metal cations was studied



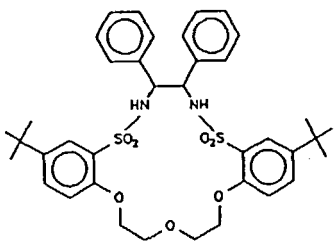
53 n = 1 X = H
54 n = 2 X = H
55 n = 1 X = Cl
56 n = 2 X = Cl



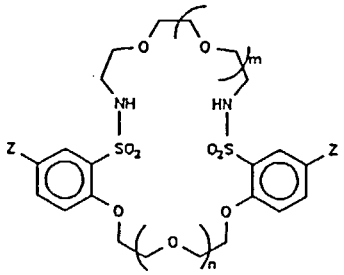
57 n = 1
58 n = 2



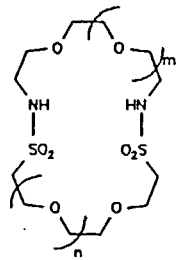
59 m = n = 0 X = H
60 m = 1, n = 0 X = H
61 m = 0, n = 1 X = H
62 m = n = 1 X = H
63 m = n = 0 X = Cl



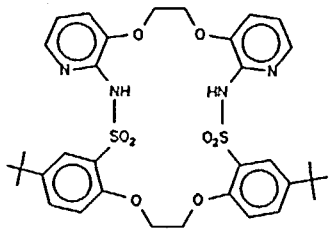
64



65 m = 1 n = 0 Z = t-Bu
66 m = 1 n = 0 Z = CH_3
67 m = 0 n = 1 Z = CH_3
68 m = 1 n = 1 Z = CH_3



69 n = 0 m = 0
70 n = 1 m = 1



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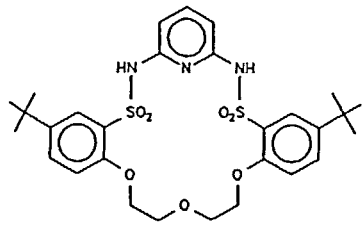
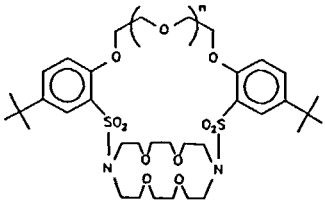
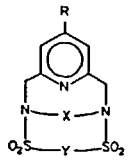


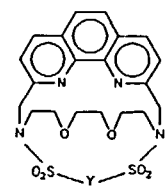
72



73 n = 1
74 n = 2



	X	Y	R
75	$-CH_2(CH_2OCH_2)_2CH_2-$	$-(CH_2)_{10}-$	-H
76	"	"	$-OCH_3$
77	"	$-CH_2(CH_2OCH_2)_3CH_2-$	-H
78	"	"	$-OCH_3$
79	$-CH_2(CH_2OCH_2)_3CH_2-$	$-(CH_2)_{10}-$	-H
80	"	"	$-OCH_3$
81	"	"	$-N(Et)_2$
82	"	$-CH_2(CH_2OCH_2)_3CH_2-$	-H
83	"	"	$-OCH_3$
84	"	"	$-N(Et)_2$
85	$-CH_2(CH_2OCH_2)_4CH_2-$	$-(CH_2)_{10}-$	$-N(Et)_2$
86	"	$-CH_2(CH_2OCH_2)_3CH_2-$	$-OCH_3$



87 Y = $-CH_2(CH_2OCH_2)_3CH_2-$
88 Y = $-(CH_2)_{10}-$

TABLE II
Properties of macrocyclic compounds.

Compound no.	m.p. [°C]	Yield [%]	Application ions of preference	X-ray ref.	Reference
53	268–71	23	ISE: Rb, K, Cs; transport of Cs > Na > K > Rb; solvent extraction: Na > K	23	23, 24, 25, 26, 55, 57, 62
54	302–05	10	ISE: K; transport of Cs, K, Rb, Na; solvent extraction: Na,K		23, 24, 26, 55, 62
55	232–34	10	ISE: Cs, Rb, K; very low transport rate		25, 55, 62
56	305–06	19	ISE: Rb, K; transport of Rb > K > Na > Cs		25, 55, 62
57	230–32	12	ISE: K, Rb, Cs; low transport rate		24, 25, 55, 62
58	256–59	17	ISE: Rb, K; transport of K, Rb, Cs, Na		24, 55, 62
59	229–30	70	ISE: K; transport of Rb, K, Na	24	24, 57, 62
60	277–79	6	Transport of Rb > K > Na	24	24, 57
61	183–84	91	ISE: K; low transport rate		24, 57, 62
62	164–65	10	Transport of K, Rb, Na, Cs		24, 57
63	290–93	25	ISE: K; transport of Rb, K, Cs		25, 57
64	183–86	8.8	No transport		24, 57
65	251–52	72	ISE: K; no transport		24, 57, 62
66	—	—	ISE: Cs; complexation of Ag, Pb, Hg, Cd, Na, K studied by NMR		50
67	—	—	ISE: Cs; complexation of Na, K, NH_4, Ag (by NMR)	50	50
68	—	—	ISE: Cs; complexation of Ag, NH_4, Cs (by NMR)		50
69	—	—	Complexation of Na, K, Ag, Pb, Hg (NMR study)		51
70	—	—	Complexation of Na, K, Ag, Pb, Hg		51
71	131–33	1	—		25
72	252–56	6	—		25

using sulfonamide crowns. They were also used as potentiometric sensors in ion-selective electrodes.

X-ray crystal structures of two crowns **59** and **60** (20- and 23-membered rings) reveal that each structure contains two crystallographically different molecules.[24] The X-ray structure of **53** is also known.[23] Attempts to obtain solid sulfonamide complexes with the appropriate metal ions for X-ray structure determination were unsuccessful.

Recently, sulfonamide crowns of similar structure (compounds **66–70**) were synthesized.[50,51] These less lipophilic crowns, especially aliphatic compounds **69** and **70**, were tested as ionophores in ion-selective electrodes. The complexation of these proton ionizable crowns with Na, K, Ag, Hg, Pb and Cd ions in $CDCl_3$ were studied by NMR spectroscopy.

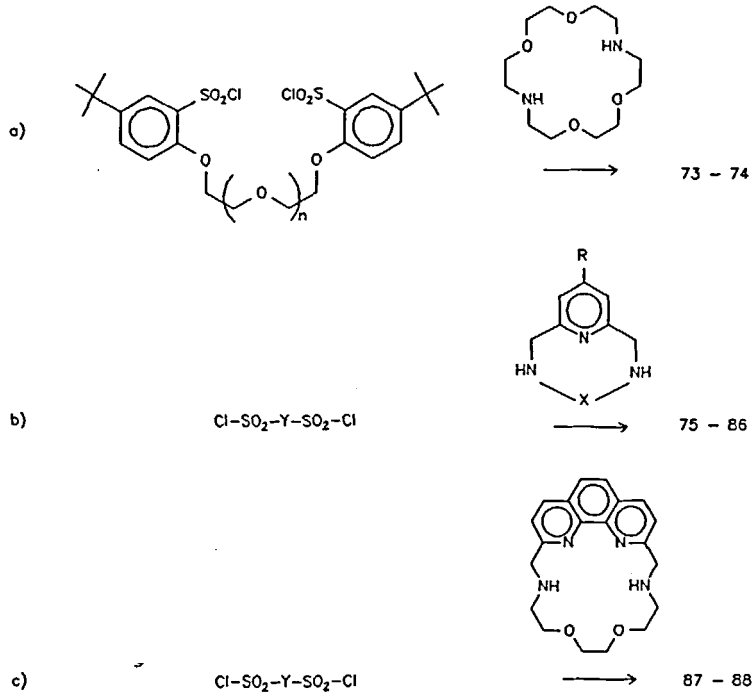
The properties and complexation applications of the compounds are presented in Table 2.

SUFONAMIDE CRYPTANDS

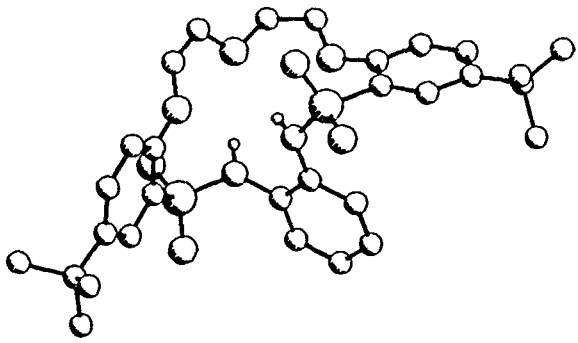
Crown compounds and cryptands have widely been used in analytical chemistry. Depending on the type, number and position of the donor atoms they can be selective for certain cations. Cryptands **73–88** contain secondary sulfonamido groups so their properties are expected to differ from that of proton ionizable crowns containing the NH group. The synthesis of a different type of cryptands was carried out according to the reactions shown in Scheme 2. Their properties have not been investigated yet.[52–54]

EXTRACTION AND TRANSPORT STUDIES OF SULFONAMIDES

Bis-sulfonamide crowns were tested as alkali metal ion carriers in single and competitive transport in an $H_2O—CH_2Cl_2—H_2O$ bulk membrane system.[55] The influence of different substituents, such as chloro and nitro groups, on the nitrogen phenyl ring of crown ethers were studied. For all studied ligands little or no transport of alkali metals occurred at pH values of the source phase below 13. In most cases the required pH of the source phase was 13.5 or 14 and the pH of the receiving phase was 7 or lower. This is an evidence that the transport is stimulated by a



Scheme 2



The crystal structure of compound 53.

proton-ionizable mechanism. The pK_a values for the sulfonamido group was found to be similar to that of phenols[56]: about 9–10. When the second group is introduced into the crown ring the pK_{a2} value would be about 3 pK_a units higher than pK_{a1}. Since no transport occurs below pH 13, both protons must be ionized for transport to occur.

In general, the transport mediated by bis-sulfonamides occurred at a much faster rate than by other proton-ionizable crowns previously reported. The high fluxes observed for alkali metal ions with the bis-sulfonamides might be a result of high extractability, formation of a 1:2 (ligand:metal) complexes and to some extent of the compact shape of ligand molecules containing small, highly lipophilic *t*-butyl groups.[25,55,57] There is some evidence that the crowns carry only one cation in the cavity (especially small crowns with the 17-membered ring) and the second cation outside the crown cavity, playing the role of co-cation.

Unexpectedly, but similarly to macrocyclic compounds, the bis-sulfonamide podands require ionization of both protons in order to form extractive complexes.[26–55] At pH = 13 of the aqueous phase extraction was negligible. Only ligands with strong electron withdrawing nitro groups in para positions of the N-phenyl units (compounds **38–40**) are acidic enough to be good extractants at pH values down to 12.[26] The complexing behaviour of the open chain and macrocyclic bis-sulfonamides towards Na and K ions was compared. The extraction experiments were carried out in the presence or absence of tetramethylammonium (TMA) cations. The pH was adjusted to the required level by TMA hydroxide or by addition of the appropriate metal hydroxide. It was found that the big ammonium ion is also extracted into the organic phase and the extracted complexes consist of the ligand in the dianion form, a metal cation and the TMA cation in 1:1:1 ratio.[26] It was assumed that formation of the complex with one metal ion in which the ligand is wrapped around the cation is followed by association of the big TMA cation as co-cation outside the pseudocavity. Without TMA being present and when the pH was adjusted by a higher concentration of hydroxide, the complex stoichiometry was found to be 1:2 (ligand:metal).[26] The conclusion was that the observed extractability of Na and K ions by bis-sulfonamide podands is high (up to 80%), that the ligands extracted two cations: one inside and the second outside the pseudocavity as co-cation. The size of the pseudocavity and the nature of the co-cation influenced the selectivity.

The difference between the data obtained from extraction experiments, in which the thermodynamic equlibrium is reached, and the data from transport mediated by sulfonamides indicates that there is a significant influence of kinetic factors on cation transport. Unusual properties of alkali cation transport mediated by macrocyclic bis-sulfonamides were attributed to the formation of 1:2 (ligand:cation) complexes in which both cations possess different properties and partially to kinetic factors controlling transport.[55]

SULFONAMIDES AS IONOPHORES IN ION-SELECTIVE ELECTRODES (ISE)

Open chain ligands, podands, crown ethers and their derivatives and rarely cryptands have been investigated as sensors in ISE. In spite of the importance of the selectivity factor in potentiometric sensors the kinetics of complexation and its reversibility play the most important role in choosing components for electrode membranes. This is the reason why some nonmacrocyclic compounds, such as lipophilic diamides of dicarboxylic acids are known as good and selective ionophores in membrane electrodes.[58] In contrast, highly selective, strong binders such as some cryptands cannot be used in ISE sensors. The sulfonamido group was introduced as the active site in a novel class of ionophores. Simple noncyclic compounds, podands and crown ethers are among many tested sulfonamides. Disulfonamides, compounds **26–29**, and mixed sulfocarboxydiamides, **18–25** and **30–34**, were investigated.[18] Most of them show preference towards large monovalent cations, but the selectivity was generally low. Sulfonamide podands, compounds **35–46**, were studied as ion carriers in ISE and a similar pattern of selectivity, a preference for large monovalent cation K^+, Rb^+, Cs^+, was found.[27] Also, all compounds tested showed good ionophoric behaviour for guanidinium ion. The podands with the longest polyether chains (4 ether oxygen atoms) and those with nitro groups on the amide phenyl ring showed a greater selectivity for guanidinium over potassium ions.[59] These electrodes possess the highest known selectivity for guanidinium$^+$/K^+.[60,61]

The bis-sulfonamide crowns were applied as ionophores in IS PVC-membrane electrodes and tested towards alkali and alkaline earth metal cations.[62] Ten compounds tested, with 17, 18, 20, 21 and 23 atoms in the macrocyclic ring, showed preference for the large monovalent ions, such as K^+, Rb^+, Cs^+. However, the obtained selectivities were not as good as that of the standard valinomycin electrode. There is no significant influence of the ring size on the selectivity, also the effect of the electron withdrawing chlorine atom on the phenyl ring of the sulfonamido group is not the same in all cases. It was shown that the conformation of the ligand molecule and mutual interaction of both sulfonamido groups plays an important role and is responsible for cation inclusion. Most of the investigated crowns have a rather rigid conformation which was confirmed by X-ray structures of compounds **53**, **59** and **60**.[23,24] It is interesting that the more selective in ISE was the crown with larger (23-atoms) and therefore the less rigid ring. The lower pH of the inner electrode solution did not affect the selectivity coefficients, which was rather surprising. Bis-sulfonamide crowns were also tested as ionophores for Zn^{+2} and Cd^{+2}. In the activity range between 10^{-5}–10^{-2} the slope for Cd was over Nernstian, but the selectivity for Cd^{+2} over K^+ was rather poor.[29]

PRECLINICAL ANTITUMOR DRUG DISCOVERY SCREEN

The American National Cancer Institute (NCI) has recently selected some bis-sulfonamide crowns and podands for screening tests against cancer and Aids.[62,63] However the biological activity was not high enough for clinical applications.

ACKNOWLEDGEMENTS

Financial support of this work from the C.P.B.P. 01.15 and 03.08 problems is kindly acknowledged. The authors wish to thank Dr. Andrzej Cygan for computer drawings of the compounds.

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