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NEW LIGAND SYSTEMS FOR IONS AND MOLECULES - AND ELECTRONIC EFFECTS UPON COMPLEXATION

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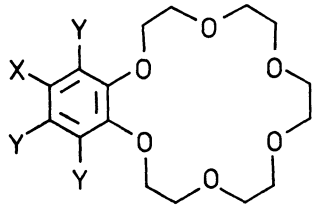
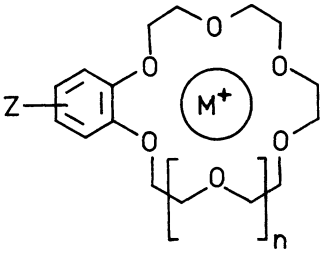
Abstract. Chromophore-ionophores are described, which upon complexation give ion-selective colour changes. Thus, dyestuffs can be influenced either in a hypsochromic or in a bathochromic way.
Bond formation and bond cleavage reactions as well as organic catalysts are likewise electronically influenced by ion-selective complexation, so that an accurate steering of reactivities by ions is possible.
Neutral guest molecules form definite complexes with crown ethers and their analogues. Crystalline phenyl hydrazine complexes can serve as stable reagents for the derivatisation of carbonyl compounds to the corresponding hydrazones in lipophilic solvents.
Volatile toxic substances, which are used as reagents for alkylation and acylation reactions, can be converted into crystalline stoichiometric neutral complexes.
It seems possible to develop receptor cavities for urea and other molecules of physiological interest.

It has been shown that the complex stability towards particular metal cations can be influenced by suitable substituents X in the benzene nucleus of benzo crown compounds [1]. For example, the complexation constant for alkali metal ions of benzo[18]crown-6 compounds[2], bearing electron-withdrawing substituents X,Y [cf. (2)] is lower than that of the unsubstituted benzo[18]crown-6 (1), owing to the electron-withdrawing effect which causes a reduction in the electron density and thereby in the donating power of the catechol oxygen atoms [3].



(1): X=Y= H

(2): X= Br, NO_2;
Y= H, Cl



(3)

We are interested in the reverse aspect, namely, whether and how strong the electronic properties of functional groups Z in the benzene nucleus [comp. (3)] can be influenced by the selective complexation of cations ($M^{\oplus}$) in the ionophore part of the molecule. The monocyclic ionophore structure in (3) may be

replaced by a cryptand system or any open chain neutral ligand (podand) [4].

I. Electronic Influence on Parts of Molecules by Crown Complexation

a) Dyestuff-Ionophores (Chromoionophores)

Chromophores can serve as structural elements that can be electronically influenced by the cation insertion into a neutral ligand cavity. Of interest in intramolecular combinations of dyestuffs with crown compounds [comp. (4)] are the type and strength of the absorptional changes which can be observed during the selective cation complexation. The chromophore seryes as a probe for the quantitative proof.

As shown e.g. by a stilbene dye, the dimethyl amino group of which is replaced by an aza[15]crown-5 substituent [comp. (4a), (4b)], one in fact obtains ionselective colour changes (Fig. 1,2) [5].

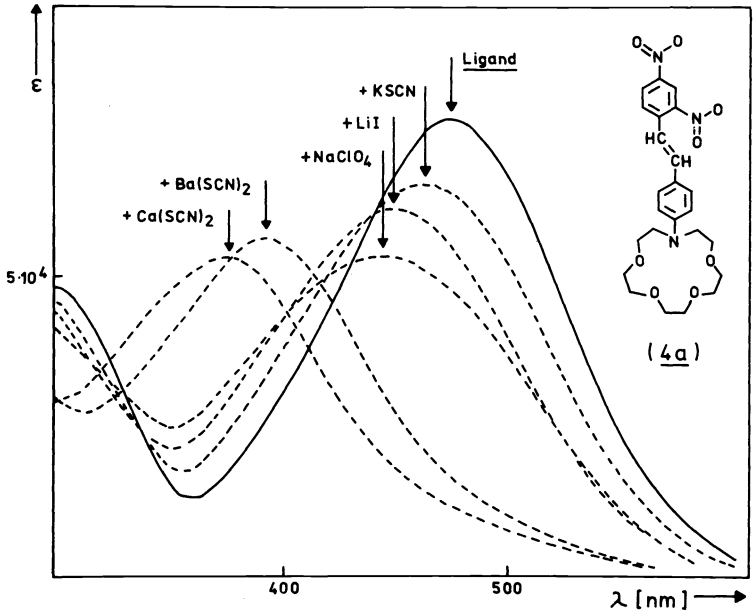


Fig.1. Hypsochromic UV/Vis absorptional changes in the complexation of the stilbene dye (4a) with various metal cations (in CH_3CN, tenfold excess of salt)

When the ionophore part is bound to the electron donating end of the chromophore, the cation insertion causes a hypsochromic shift and an intensity decrease. Figure 2 shows an aza[18]crown-6, thus containing one more oxygen atom, bound to the same chromophore. From a comparison of the spectral changes it can be gathered that the cation (assuming the charge of the cation remains the same), which bests fits into the ionophore, causes the greatest hypsochromic absorptional change. Doubly charged cations such as calcium and barium, even if they fit less suitably into the crown ether cavity, lead to stronger

absorptional shifts than monovalent ones on account of their higher charge density.

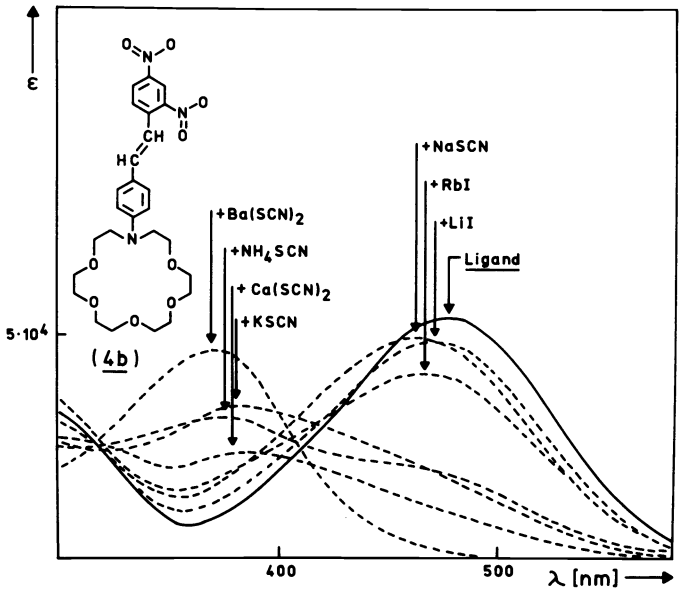


Fig.2. Hypsochromic UV/Vis absorptional changes of ligand (4b) by selective cation complexation (in CH_3CN, tenfold excess of salt)

When contrary to (4) the ionophore part is bound to the dye molecule such that the inserted cation supports the transfer of negative charge from the electron donating substituent to the remaining chromophore (in the transition from the ground state to the photoexcited state), one obtains, as shown with ligand (5) in Figure 3, strong bathochromic absorptional shifts and a simul-

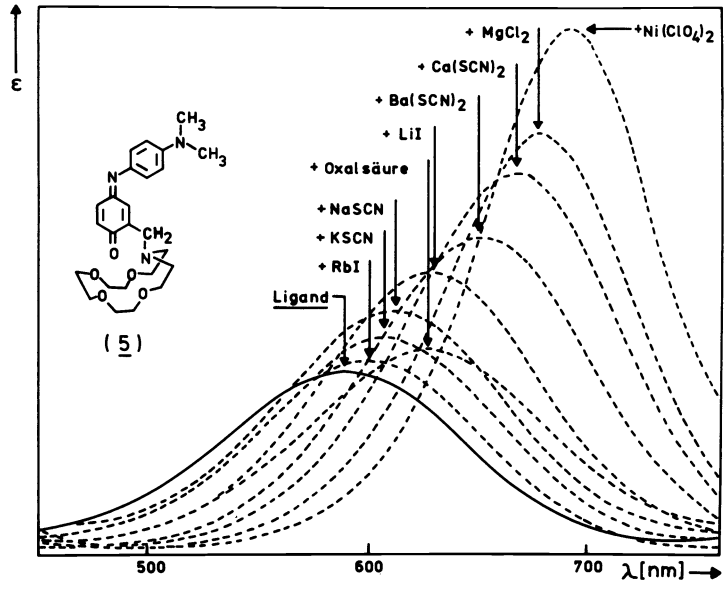


Fig.3. Bathochromic absorptional shift of the ionophore dye (5) on addition of salt (in CH_3CN)

taneous intensity increase. Here a participation of the carbonyl group in the coordination of the crowned cation is obvious. Figure 4 shows an example of an anthraquinone system (6) with both hypsochromic and bathochromic cation-induced shifts [6].

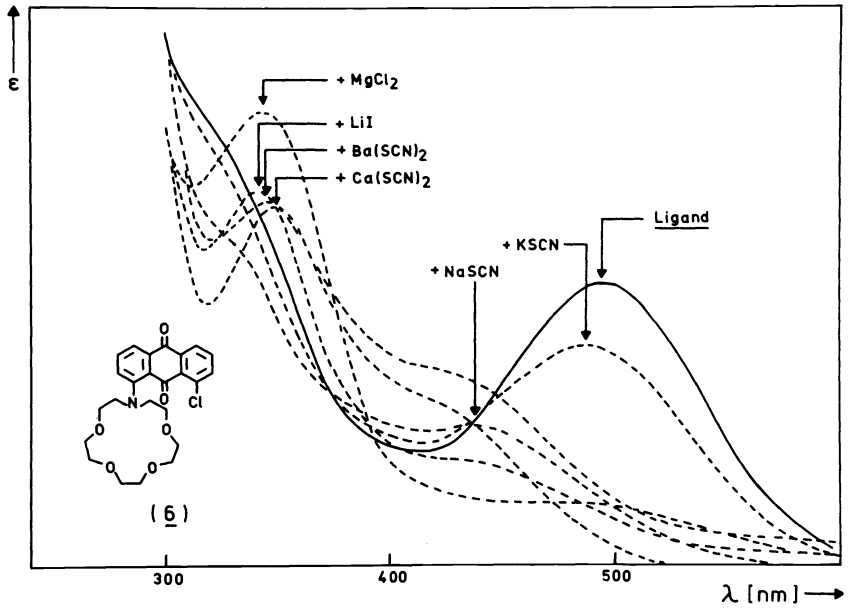


Fig.4. Cation-induced shifts of the aminoanthraquinone system (6) (in CH_3CN)

The absorptional changes of the dye crown compounds, which occur on addition of salt, may be strong enough to be followed visually in a test-tube.

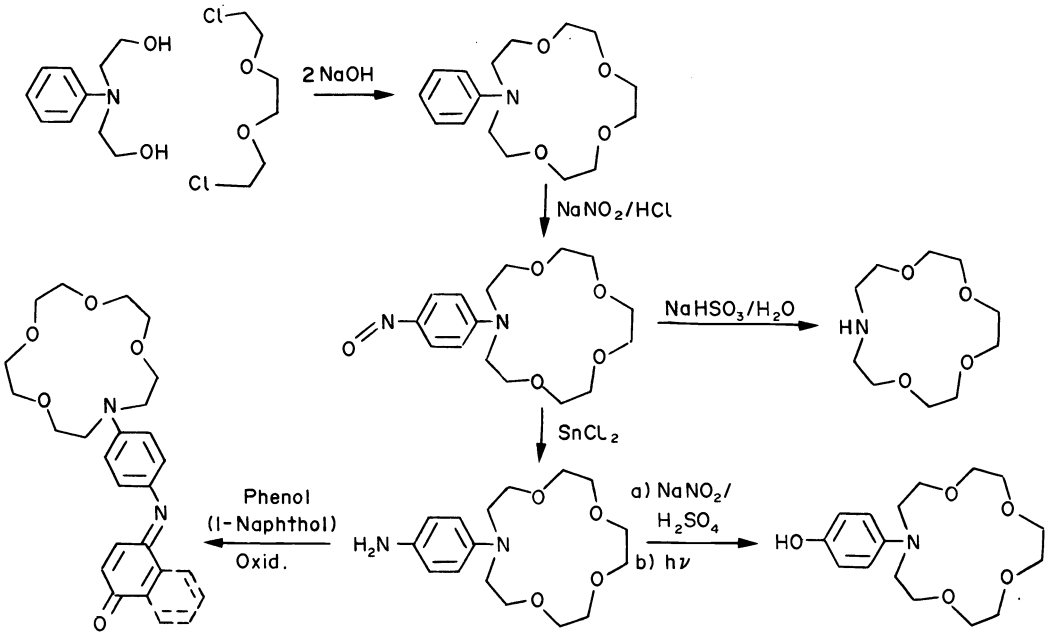
The synthesis of the phenylaza crown units as well as further ionophore dyes of the phenolblue-, naphtholblue-types can be achieved in the way shown in Scheme 1.

The isolated intermediate products para-phenylene diamine- and para-aminophenol-analogous azacoronands [2] are of interest because their redox properties ought to be altered by cations.

CORRIGENDUM

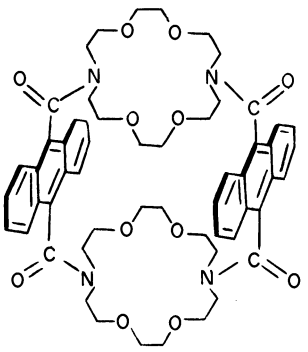
A page was inadvertently omitted in the manuscript of F. Vögtle published in *Pure & Appl. Chem.*, Vol.52, No.11 (November 1980), pp.2405-2416. The missing page is printed on this sheet which may please be inserted between pages 2408 and 2409.

Scheme 1. Steps in the synthesis of crown dyes



b) Fluorophore-Ionophores

Fluorescent dye-crown ethers offer another possibility of conveniently detecting the electronic influence of the crown complexation: Thus fluorophore-ionophores of type (7) [7a] show a change in the fluorescence after complexation. Further the above compound, which was originally conceived as a model for an ion tunnel molecule in membranes, proved to be an appropriate molecular probe for following structural changes therein in particular for determi-



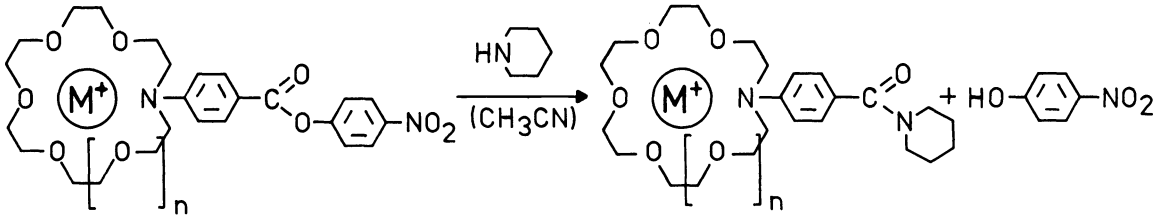
(7)

ning phase transition temperatures in lipid membranes [7b]. The molecule in its cation-complexed form is not embedded in the double layer under tunnel formation, as expected, but adheres to the surface of the membrane.

c) Ion-Selective Steering of the Reaction Rate by Crown Complexation

Following the knowledge that the electronic properties of chromophores could be strongly influenced by selective complexation, the question arose whether the reactivity of functional groups Z [in (3)] might be electronically and selectively altered by crown ether complexation. The biological relevance of this aspect is clear from the fact that biochemical reactions are more or less dependent on the concentrations of particular salts. The study of simple model systems for salt-dependent reactions and catalyses appears to constitute a basic step in this respect. In order to quantify the influence of cations on the reactivity of functional groups that are bound electronically to crown systems, we studied two different substrates.

In the first reaction, para-nitrophenyl esters (8) of the "crowned" para-aminobenzoic acid were solvolyzed by an excess of piperidine in the presence of various salts [8].



(8a)-complex: n= 0

(8b)-complex: n= 1

It was found that the reaction rate is significantly higher in the presence of salts than in their absence (Figure 5). As expected, the reaction of (8a) is most strongly enhanced by sodium ions since the sodium cation fits best into the crown ether cavity of the [15]crown-5; the same applies to $K^{\oplus}$ ions and the [18]crown-6-skeleton (8b). Doubly charged cations, such as Ba^{2+}, cause a still stronger activation of the ester bond in (8a) and (8b); the reactivity is particularly enhanced in the (8b)-Ba^{2+}-complex, where the crown ring size matches the ionic radius of Ba^{2+}.

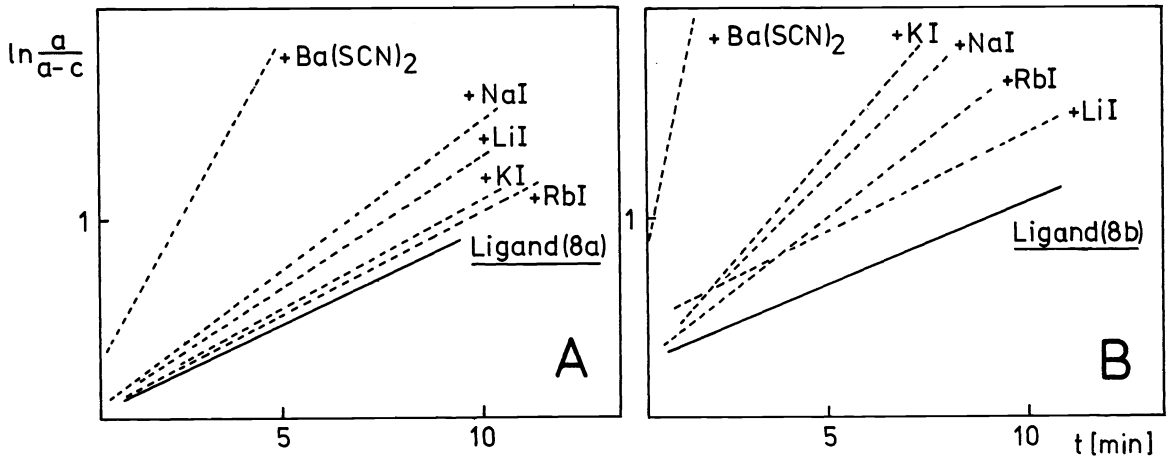


Fig.5. Influence of different, added salts in the aminolysis reaction of (8a) [A] and (8b) [B] in acetonitrile. *The slopes of the linear plots give the relative reaction rate constants.* a: overall phenol/phenolate concentration at the end of the reaction; c: phenol/phenolate concentration at time t, calculated by extinction measurement at λ = 422 nm

The reaction rate of (8a) increases with an increasing $Na^{\oplus}$ concentration, which may indicate a displacement of the equilibrium of complex formation in the direction of the crown-salt complex; the same applies to (8b) as a result of an increase in $K^{\oplus}$ salt concentration. Replacement of the iodide salts by the thiocyanates causes only minor changes. In contrast to the crown systems (8), p-nitrophenol benzoate itself shows almost no salt-dependent reactions under analogous conditions; in addition, the aminolysis of p-dimethylamino benzoate is only minimal and unspecifically influenced by salts.

Thus, on the whole, it may be concluded that the crown ether substitution in substrates like (8) allows a specific cation-dependent control of the solvolysis rate [8].

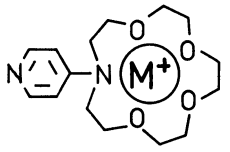
Substituent constants σ for the free aza crown groups of (8) ($\sigma \approx -0.9$) and for their $Na^{\oplus}$-, $K^{\oplus}$-cation complexes ($\sigma \approx -0.5$ to -0.7) can be estimated.

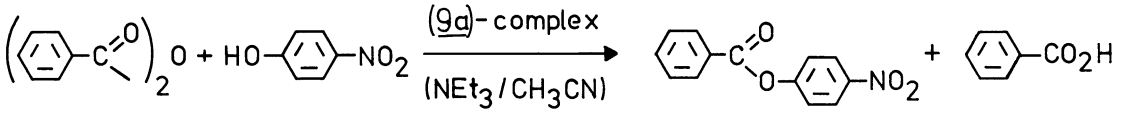
d) Ion-Selective Steering of the Catalyst Activity by Crown Complexation

From the study of the above reactions it follows that the reactivity of suitable substrates can in fact be influenced strongly and selectively by crown complexation. The question now is whether and to what extent the nucleophilicity or the basicity of appropriate substances e.g. pyridino compounds can be selectively varied by the crown ether complexation. Owing to the known

catalytic activity of the 4-dimethylamino pyridine (DMAP) [9], it was interesting to synthesize crowned derivatives.

As a model reaction we chose the following transacylation reaction [8]:



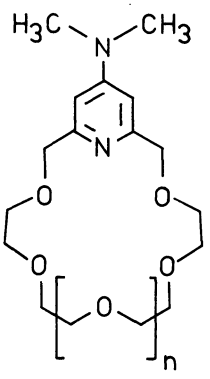


The results show that this reaction can be influenced specifically by salts when the DMAP-analogous pyridino crown (9a) is used as a catalyst. With pyridine, DMAP and the pyridino-substituted aza crown (9a), an increase of the reaction velocity is usually observed in the presence of inorganic salts. Under the pyridino crown (9a) catalysis, the enhancement is nevertheless least for the sodium salt within the series of iodides employed. With pyridino crown (9a), the reaction is hampered when the NaI concentration is raised. However with DMAP instead of (9a), an increase in the rate of reaction occurs in that case.

This suggests that the equilibrium of complex formation is more strongly shifted to the side of the crown complex of (9a), the nucleophilicity of which is less than that of the free ligand (9a).

The conclusion to be drawn from both types of reactions of (8) and (9) is that, because of the electron pull of the positive cation charge in the crown complex, complex formation by p-aminobenzoic acid crowns (8) and DMAP-analogous crowns (9) can significantly and ion-selectively alter the reactivity of the functional groups considered as well as the reactivity of the catalysts.

Other types of salt effects were to be expected with the DMAP-crown (10), where the ionophore part does not replace the dimethylamino group but encloses the pyridino nitrogen. Here added cations should competitively block the pyridino nitrogen against reacting with the acyl group. This seems to be the case at higher salt concentrations. At lower cation concentrations, however, the acylation rate is enhanced especially by cavity-filling cations pointing presumably to a stabilization of the acylpyridinium intermediate through additional intramolecular coordination of the crowned cation at the carboxyl oxygen [10].

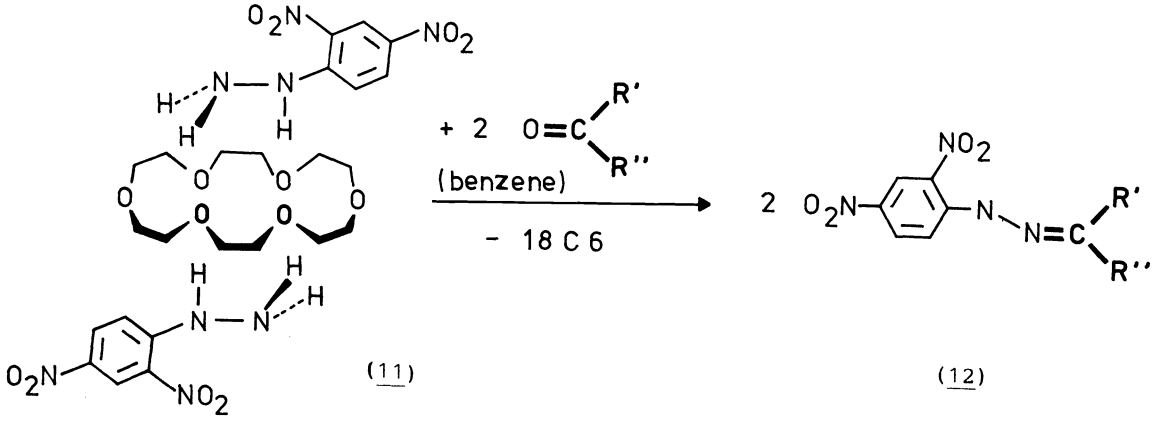


(10)

II. Complexation of Neutral Molecules

We have viewed up to now the complexation of cations exclusively. Recently, however, complexes of neutral uncharged guest molecules with crown ether-like host molecules have also been reported. These include the acetonitrile complex of [18]crown-6 as well as complexes with malonodinitrile, benzene sulfonamide, dimethyl acetylene dicarboxylate etc. [11].

We have been able lately to systematically synthesize complexes of crown compounds with phenyl hydrazine and its substitution products [12]. The complexes have a 1:2 stoichiometry and display the following hydrogen bonded structure (11) [13]:

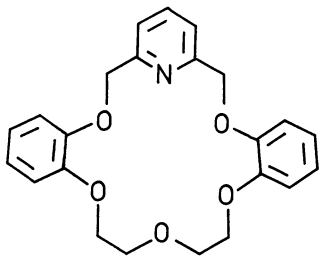


(11) (12)

With carbonyl compounds the hydrazones (12), too, can be synthesized in unpolar solvents [12].

In TABLE 1 are listed a few other new neutral molecule complexes of [18]-crown-6 and the particularly suitable dibenzopyridino crown (13) [2,11], which

we have been able to isolate [14].



(13)

TABLE 1. Crystalline, stoichiometric complexes of crown host compounds with uncharged neutral guest molecules [14]

Crown Host	Guest Molecule	Stoichiometry (Host:Guest)
[18]crown-6	dimethyl sulfate	1:1
"	methane sulfonyl chloride	1:2
"	methyl tosylate	1:2
"	acetamide	1:2
"	thioacetamide	1:2
benzo[15]crown-5	thioacetamide	1:2
dibenzopyridino[18]crown-6 (13)	N,N-dimethylnitrosamine	2:1
"	benzylchloride	2:1
"	acetic anhydride	2:1

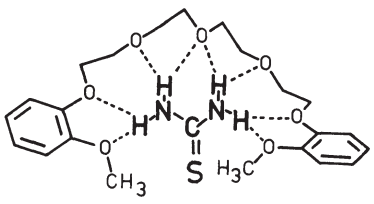
Besides dimethyl formamide, acetamide [11] etc. the guest molecules comprise volatile, highly toxic substances like dimethyl sulfate, methyl tosylate, mesyl chloride, acetic anhydride etc. which are often used as alkylation and acylation reagents. Since the complexes of these reagents are crystalline, stoichiometric, stable, easily dosable and can be well characterized, they may be used for derivatisations instead of the original reagents [12,14].

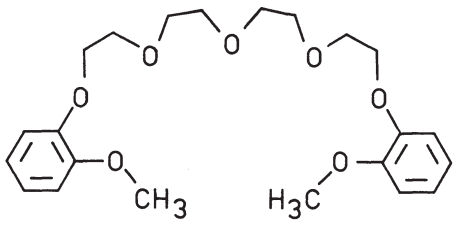
Figure 6 shows dimethyl sulfate beside a sample of the non-volatile [18]-crown-6-dimethyl sulfate complex. Still more basic crown compounds like (10), which we recently synthesized, should prove to be even better CH_3- and CH_2-receptor molecules.

Fig.6. Samples of dimethyl sulfate (right) and the [18]crown-6-dimethyl sulfate complex (left side) [14]

Medicinally interesting guest molecules for the encapsulation with ligands are urea and several other molecules which appear in the physiological domain. As we have been able to show, urea forms complexes both with acyclic and cyclic crown type ethers [15].

X-ray analyses of these first urea and thiourea complexes of open-chain podands synthesized by us reveal hydrogen bonds between the NH_2-groups of the guest molecule and the heteroatoms of the crown host [4,13]. An example is given in Figure 7.





(14)

Fig.7. Structure of the thiourea complex of the podand (14) [13]

It might be an interesting goal to obtain urea-ligand complexes which are stable in water and can be used as specific urea-receptors.

OUTLOOK

The concept of the intramolecular dye-ionophore combination might be a valuable source for the investigation of electronic and solvent effects. With $Ag^{\oplus}$ as the cation to be complexed, it should be possible to obtain sensitive photographic layers where a single Ag-particle could assume the role of the hitherto prevailing microcrystallites. Instead of silver less light-sensitive and easier available cations might be employed, owing to the direct energy coupling: hν ——> chromophore ——> ionophore ——> cation.

The results achieved with the fluorophore molecule, which reacts sensitively to structural changes of the membrane, will stimulate the synthesis of similarly structured, but more lipophilic tunnel molecules that can be embedded in the membrane and where polar groups bond to arms might allow a "gating" effect [7b].

The activation or desactivation of bonds by crown ether complexation could be exploited for the synthesis of new protecting groups which can be split off under salt catalysis.

A variety of new receptor cavities for the specific binding of neutral guest molecules with the structural elements XH_3 and XH_2, $HX-YH_2$ etc. (X,Y= C,N,O,S ...) can be tailor-shaped in future.

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REFERENCES

[1] Review: F.Vögtle and E.Weber, in S.Patai: *The Chemistry of the Ether Linkage*. Wiley, London, in press.

[2] For a new nomenclature proposal for crown compounds and related ligands see: E.Weber and F.Vögtle, *Inorg.Chim.Acta*, in press.

[3] R.Ungaro, B.El Haj and J.Smid, *J.Am.Chem.Soc. 98*, 5198-5202 (1976); K.H. Pannell, W.Yee, G.S.Lewandos and D.C.Hambrick, *J.Am.Chem.Soc. 99*, 1457-1461 (1979).

[4] F.Vögtle and E.Weber, *Angew.Chem. 91*, 813-837 (1979); *Angew.Chem., Int. Ed.Engl. 18*, 753-776 (1979).

[5] J.P.Dix and F.Vögtle, *Angew.Chem. 90*, 893-894 (1978); *Angew.Chem., Int. Ed.Engl. 17*, 857-858 (1978); *Chem.Ber. 113*, 457-470 (1980).

[6] J.P.Dix and F.Vögtle, unpublished.

[7] [a] P.Koo Tze Mew and F.Vögtle, unpublished; [b] I thank Prof.Dr.G.Maaß, Dr.B.Tümmler and Dipl.-Chem.U.Herrmann (Medizinische Hochschule Hannover) for communicating these results and for cooperation.

[8] J.P.Dix, A.Wittenbrink-Dix and F.Vögtle, *Naturwissenschaften 67*, 91-93 (1980).

[9] G.Höfle, W.Steglich and H.Vorbrüggen, *Angew.Chem. 90*, 602-615 (1978); *Angew.Chem., Int.Ed.Engl. 17*, 569-582 (1978).

[10] F.Vögtle, I.Panagiotidis and J.P.Dix, unpublished work.

[11] Short overview: F.Vögtle, W.M.Müller and E.Weber, *Chem.Ber. 113*, 1130-1137 (1980); cf. [1].

[12] F.Vögtle and W.M.Müller, *Chem.Ber.*, in press.

[13] I thank Prof. Dr. W. Saenger and Dipl.-Chem. R.Hilgenfeld (Max-Planck-Institut für Experimentelle Medizin, Göttingen) for cooperation and communicating this result.

[14] F.Vögtle and W.M.Müller, *Naturwissenschaften 67*, 255-256 (1980).

[15] [a] Overview: ref. [4]; F.Vögtle, G.Oepen and W.Raßhofer, *Justus Liebigs Ann.Chem. 1979*, 1577-1584; F.Vögtle, G.Oepen and W.Raßhofer, *Chem.Ber. 112*, 3034-3036 (1979); [b] in contrast to Pedersen [16] we were able to isolate urea complexes of cyclic crown compounds.

[16] C.J.Pedersen, *J.Org.Chem. 36*, 1690-1693 (1971).