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Design features of ionophores for ion selective electrodes

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Abstract - Ionophores as components for analytically relevant ion selective electrodes have to exhibit a specified lipophilicity and a free energy of activation of < 45-65 kJ mol^{-1} for the ligand exchange reaction. The selectivity of membranes may be tuned by membrane-technological interventions (dielectric constant of membrane phase, ionophore concentration, concentration of ionic sites confined to membrane phase). Molecular modelling techniques can guide the design of ionophores of a given inherent selectivity and reduce the number of ionophore candidates to be synthesized. The selectivity enhancement expected for a covalent link of ionophore subunits is analyzed. Significant effects are predicted only if suitable ligand preorganization is realized.

INTRODUCTION

Ion carriers as a class of ionophores are lipophilic complexing agents having the capability of binding ions reversibly and to transport them across organic membranes by carrier translocation (refs. 1, 2). Ideally, selective ion carriers render a membrane permeable for one given sort of ion I only. For an analytically relevant application of ionophores in solvent polymeric membranes for ion selective electrodes (ISE) (ref. 4) or ion selective field effect transistors (ISFET) (ref. 5) at least the following four requirements 1) to 4) have to be met simultaneously (see also refs. 2, 3).

DESIGN FEATURES FOR IONOPHORES

1. Lipophilicity of ionophores

The lifetime of a chemical sensor based on a carrier doped solvent polymeric membrane is limited by substantial and irreversible changes in the membrane composition. To assure a reproducible sensor behaviour, all the membrane components have to be confined to the membrane phase over an analytically relevant time period. Depending on the geometry of the sensor, the type of sample and the technique of sensor use, widely different lipophilicities P (partition coefficient between water and octane-1-ol) of the ionophores are required (see Table 1). A reliable estimate for P may be obtained by thin-layer chromatography (ref. 2). Such estimated values log P_{TLC} are given in fig. 1 of ref. 3 for a series of neutral ionophores. Obviously, most of the ionophores discussed there have been designed to exhibit a sufficient lipophilicity for typical flow-through analysers even in continuous use in whole blood over a period of one month. There are however no relevant ionophores known that meet the requirements for an in-vivo use of ISFET's over time periods of 10 days or more (ref. 3). Here a further effort in ionophore design is necessary.

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TABLE 1. Required lipophilicity (log P) of neutral ionophores for analytically relevant applications in ion sensors

analytical application (continuous use in streaming fluid)	required lipophilicity (log P)	
	whole blood or serum sample	aqueous sample (e.g. urine)
typical ISFET (use over 10 days)	15.4 (ref. 6)	5.2 (ref. 6)
typical flow-through (use over 30 days)	8.4 (ref. 7)	2.3 (ref. 7)

2. Ionophore exchange kinetics

The ionophores should form relatively stable complexes with the primary ion I (ion I to be sensed with high selectivity) but, on the other hand, the exchange reaction of the selected ions at the membrane/solution interface must be sufficiently reversible. Therefore, the free energy of activation of the ligand exchange reaction,

$$IS + S' \rightleftharpoons IS' + S$$

where S and S´are ionophores, has to be relatively low. The limit for the free energy of activation of the ligand exchange reaction is probably around 45-65 kJ mol^{-1} (refs. 2, 3).

Theoretically related is the requirement that a sufficiently high and constant concentration of ionophore should be present in the membrane phase in the unloaded form. If a cation ionophore is predominantly present within the membrane phase in the loaded form, anion-permselectivity is induced. These findings are in agreement with the experimental evidence that the transport rate of ionophores passes a maximum when increasing the stability constant of the ionophore/ion interaction (ref. 8).

In order to keep the free energy of activation of the ligand exchange reaction sufficiently small, we have been focussing our design of ionophores on non-macrocyclic structures (see fig. 1 in ref. 3).

3. Ion selectivity of membranes

The selectivity coefficients K_{ij}^{Pot} of ion selective electrodes are generally defined on the basis of the Nicolsky equation (1) (refs. 9-11) which describes the EMF-response of the membrane electrode cell to samples containing primary ions I^{z_i} and interfering ions J^{z_j}:

$$E = E_i^{\circ} + s \cdot \log\left(a_i + \sum_j K_{ij}^{Pot} (a_j)^{z_i/z_j}\right) \qquad (1)$$

E is the measured cell potential (EMF), E_i° is a standard potential of the cell, s is the slope of the response function (ideally 59.16 mV / z_i at 25°C), and a_i and a_j are the sample activities of the subscripted ions. Accordingly, the coefficients K_{ij}^{Pot} characterize the selectivity of a potentiometric sensor for interferents relative to the species of interest. From theoretical considerations (refs. 4,11,12) the following relationship was derived for the selectivity of liquid membrane electrodes based on neutral ionophores S that form complexes of the type $MS_n^{z_m}$ with cations M^{z_m} (I^{z_i} resp. J^{z_j}):

$$K_{ij}^{Pot} = \frac{(z_j K_j / c_r)^{z_i/z_j}}{z_i K_i / c_r} \qquad (2)$$

$$K_m = \sum_n \beta_{ms,n} k_m c_s^n + k_m \qquad (3)$$

Evidently, the cation selectivity of such sensor systems depends on various factors:

a) *The intrinsic selectivity behaviour of the ionophores,* which is characterized by the complex stability constants $\beta_{ms,n}$ referring to the liquid membrane phase. Some recent aspects of selective ligand design will be discussed below.

b) *The extraction properties of the membrane solvent* (plasticizer of PVC membranes), which are decisive for the magnitude of the ionic distribution coefficients k_m. The use of sufficiently polar solvents (high dielectric constant), such as nitroaromatic compounds, generally increases the selectivity for divalent relative to monovalent cations.

c) *The total amount of ionophores incorporated into the membrane,* which directly influences the concentration c_s of uncomplexed ligands. Assuming all other parameters in equations (2) and (3) to be constant, the following relationship can be found:

$$\frac{\partial \log K_{ij}^{Pot}}{\partial \log c_s} = \frac{z_i}{z_j} \bar{n}_j - \bar{n}_i \qquad (4)$$

where $\bar{n}_i$ and $\bar{n}_j$ are the mean degrees of complexation of the respective ions in the membrane phase. It appears that a relatively low ligand concentration favours the response to divalent cations and to cations forming complexes with a low stoichiometry number n.

d) *The amount of anionic or ionogenic sites trapped in the membrane phase,* which directly determines the total concentration c_r of anions R^- in the bulk membrane. These negative charges, necessary for inducing cation permselectivity, originate mainly from impurities of the polymeric material (refs. 13-15) or from specific additives such as tetraphenylborates (refs. 4,11,12). If all parameters except c_r are kept constant, the following relation is obtained from equation (2):

$$\frac{\partial \log K_{ij}^{Pot}}{\partial \log c_r} = 1 - \frac{z_i}{z_j} \qquad (5)$$

Obviously, a relatively high site concentration in the membrane favours the preference of divalent over monovalent cations.

As reported earlier (refs. 4,12), however, the anion concentration c_r cannot be varied independently without influencing another selectivity-determining parameter, namely the free ligand concentration c_s. The reason is that an increase of c_r leads to the simultaneous increase of the concentration of cationic complexes and thus to a decrease of c_s. If the equivalent of negative sites in the membrane exceeds the total equivalent of ligands available for cation binding, this results in a sharp decrease of the overall distribution parameters K_m (see eq. (3) with $c_s \rightarrow 0$), i.e.

$$K_m \sim k_m \text{ for } c_r > \frac{z_m}{n_m} c_s^{tot} \qquad (6)$$

where c_s^{tot} is the total ligand concentration, and n_m is the stoichiometry number of the preferential complex formation. From equations (2) and (6) it may be inferred that drastical selectivity changes can be induced by the addition of anionic sites especially when primary and interfering ions differ in charge or in complex stoichiometry. More details can be found elsewhere (ref. 12).

4. Intrinsic selectivity of ionophores

From 3) it becomes obvious that the selectivity of a membrane is characterized by the ionophore/ion stability constants only to a limited extent (see 3a)). Ideally, the free energy of transfer of the ions of interest from the sample to the membrane phase should be consulted for an adequate ionophore design. This would imply the calculation of the enthalpy and entropy of all participants involved in the transfer process. Possibilities exist to estimate reliable interaction energies (and thus enthalpies (see e.g. ref. 16)) but there is no methodology available for an adequate estimate of all relevant entropy terms involved. Nevertheless some useful predictions of the complexation by ionophores can be made on the basis of interaction energies alone. Corresponding molecular modelling tools may help to drastically reduce the number of possible candidates for ionophores for a given ion that meet the requirements mentioned above (1) to 3)). These tools will therefore ultimately help reducing the number of molecules to be synthesized.

MOLECULAR MODELLING OF IONOPHORES

For this purpose the overall ion-ligand interaction energy E_{Int} is estimated as a sum of three types of contributions:

$$E_{Int} = E_{Ion\text{-}Ligand} + E_{Conformation} + E_{Ligand\text{-}Ligand} \qquad (7)$$

Calculation of the individual contributions: The conformational energy, i.e. the energy needed for the ligand to adopt the conformation in the complex, and the ligand-ligand interaction energies are calculated by using standard molecular mechanics procedures (MM2 (ref. 17), in the present version with a steepest descent energy minimization).

The ion-ligand interaction energy is approximated by the following potential function:

$$E_{Ion\text{-}Ligand} = \sum(A_i/r_i^{12} + B_i/r_i^{6} + C_i/r_i^{2} + q_i q_{ion}/r_i) \qquad (8)$$

A_i, B_i and C_i are constants fitted on the basis of ab initio interaction energies of selected model complexes, r_i is the distance between the ligand atom i and the ion, q_i and q_{ion} designate atomic net charges obtained by ab initio calculations on the isolated species. Atoms of the same kind in similar chemical environments are grouped into the same classes and are forced to have the same constants.

It should be kept in mind that both the molecular mechanics and the pair potential techniques can be considered as extrapolation procedures. In both cases model parameters are developed on the basis of a limited number of experimental data or data from ab initio calculations. Unfortunately, no exact documentation of the data base used for the development of molecular mechanics parameters for MM2 is available. The user therefore performs calculations somewhat on his own risk. The only guarantee he has is the fact that the well reputed program was used world-wide successfully in different applications. In order to test the reliabilty of the molecular mechanics technique for a case relevant for an ionophore design, various calculations were performed on 18-crown-6 (see Table 2). The results obtained by different molecular mechanics techniques have been compared with some ab initio calculations (ref. 22). Although all relative conformation energies are in proximity, the sequence of stabilities of the different conformations is predicted to be different. The values in Table 2 indicate that the accuracy of the methods is not better than about ± 20 kJ/mol. The reliability of the MM2 technique is documented by the comparison of the results with corresponding ab initio calculations (last two lines in Table 2).

TABLE 2. Conformation energy of 18-crown-6 (in kJ/mol) in the C_1-conformation (Na^+-complex) and D_{3d}-conformation (K^+-complex) relative to the C_i-conformation (conformation of the free ligand) obtained by different methods

Method of computation	Structure of the fully relaxed system		X-ray structure (position of the H-atoms relaxed by MM2)	
	C_1	D_{3d}	C_1	D_{3d}
WBFF (ref.18)	18.4	32.8	-	-
MM1 (ref. 19)	25.5	16.4	-	-
AMBER (ref. 20)	39.3	4.6	-	-
AMBER/RIMINI (ref. 21)	12.1	-9.6	-	-
MM2	28.0	-10.5	23.9	-20.3
Ab initio	-	-	15.2	-24.4

In the derivation of the pair potential parameters from ab initio calculations the root-mean-square of the deviations between interaction energies calculated by ab initio and pair potential techniques is obtained as well. This is typically around 5-10 kJ/mol (refs. 23-26). The uncertainties increase with increasing dissimilarity between molecules used for the derivation of the potentials and the molecules for which they are applied.

As a test of interest, results of interaction energy calculations obtained with both the pair potential technique and the ab initio approach are presented for 18-crown-6 in Table 3. The results indicate that the deviations are in the range of 0-30 kJ/mol. Since several ethers were used for the derivation of pair potentials, including 1,2-dimethoxy ethane (ref. 26), this case is a relatively favourable one.

In the present study similar uncertainties result for the conformation energy and for the ion-ligand interaction energy estimates. Both uncertainties are around 20 kJ/mol. Thus the model is definitely unsuitable to predict reliable ion selectivities but should be capable of predicting the ability of a ligand to complex ions.

TABLE 3. Comparison of the interaction energies (in kJ/mol) obtained by the pair potential model on complexes of 18-crown-6 with those obtained by ab initio computations

Cation	Structure	Experimental ion positions		Optimized ion positions by the pair potential approach
		ab initio	pair pot.	
Li^+	Li^+-complex	-317	-317	-317
Na^+	Na^+-complex	-343	-349	-355
	K^+-complex	-288	-303	-303
K^+	K^+-complex	-263	-294	-294

Combination of the pair potential approach with molecular mechanics computations: The pair potentials for ion-ligand interaction energy calculations have been introduced into the MM2 program package. The optimization routine has been modified and is now working with a steepest descent algorithm as an additional minimization procedure. The capability of this program to optimize the structure of complexes is demonstrated in a study on the K^+-complexation of

18-crown-6. The X-ray structure of the uncomplexed 18-crown-6 molecule has C_i-symmetry. In this conformation no stable complex formation is possible (ref. 27). In several complexes, including the K^+-complex, a D_{3d} conformation of the ligand has been observed where the six oxygen atoms form a cavity around the cation (ref. 28). If a K^+-ion is introduced into the center of the free ligand (C_i-conformation), the present program automatically finds an optimal structure which is very close to the one observed experimentally. The formal reaction pathway starts with a symmetrical structure (C_i), passes over a chiral intermediate and finally reaches a structure very close to the expected D_{3d} conformation.

SO-CALLED CHELATE EFFECT/LIGAND PREORGANIZATION

In the past years, many efforts were concentrated on the synthesis of so-called bis(crown) compounds and on their application as cation selective ionophores in membrane electrodes (refs. 29-33). In these well praised ligands two crown ether units are linked by hydrocarbon or other bridges. Apparently, the aim is to increase the probability (i.e. the stability) of complex formation with specific cations that yield 1:2 complexes with the nonbridged ligand subunits. This would correspond to a chelate effect in a general sense and may be expected to have some influence on the ion selectivity behaviour of the resulting membrane electrodes. A more detailed analysis of the expected magnitude of such selectivity-modifying effects is given elsewhere (ref. 33). It was shown earlier (ref. 34-36) that a considerable part of the classical chelate effect represents only an apparent extra-stability which disappears with the appropriate choice of standard states. This point was stressed by Fraústo da Silva (ref. 36) who suggested a redefinition of a true chelate effect. The recommended quantity C.E. describes to which extent complexes of the type MS′ would be formed relative to competing products MS_n if polydentate ligands S′ and unidentate ligands S were offered simultaneously to the metal ions M in solution:

$$\text{C.E.} = \log \frac{c_{ms'}}{c_{ms,n}} = \log \frac{\beta_{ms'} c_{s'}}{\beta_{ms,n} c_s^n} \tag{9}$$

The remaining difference in complexation enthalpy (term C_{rep} in equation (10)) between unidentate and polydentate ligands is due to the fact that, in the latter molecules, electrostatic and steric repulsion between the coordinating groups (including conformational energy) may already be built in to some extent (ligand preorganization, see also refs. 37,38) and may therefore increase the enthalpy of the free ligands. This results in a favoured complex formation of polydentate relative to unidentate ligands. If both ligands are added in excess and with the same total molarities of donor atoms, one obtains for the ideal case with $c_S = n\, c_{S'}$ resp. $x_S = n\, x_{S'}$ (x: mole fractions)(ref. 33):

$$\text{C.E.} \cong C_{rep} - (n-1) \log x_{s'} \tag{10}$$

For the present discussion, the comparison between membrane systems with nonbridged and bridged ionophores (n=2) is of special interest. According to equations (2), (3), and (9), the selectivity increase for the primary ions relative to interferents of the same charge, resulting from covalently linking two ligand subunits, may be described by:

$$\log K_{ij}^{Pot}(S) - \log K_{ij}^{Pot}(S') \cong \text{C.E.}(i) - \text{C.E.}(j) \tag{11}$$

Obviously, the bridged ligands offer no significant gain in ion selectivity as long as primary and interfering ions form complexes of exactly the same stoichiometries in the respective membranes. A contrasting behaviour is expected only when the interfering species are predominantly uncomplexed (i.e. purely solvated) or when they predominantly form 1:1 complexes with the nearly identical ligand units in both membrane systems:

$$\log K_{ij}^{Pot}(S) - \log K_{ij}^{Pot}(S') \cong C.E.(i) \quad (\text{for } C.E.(j) \cong 0) \tag{12}$$

Since the ionophore concentration in typical membrane compositions for ion selective electrodes corresponds to a mole fraction of around 10^{-2}, a selectivity improvement for the primary ions by about two orders of magnitude is predicted for this case. In practice, however, such ideal discrimination of interferents by the bridged ligands, although often claimed, is usually not observed. The realized effects are considerably smaller than predicted or even insignificant (see also ref. 33).

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