

Comparison of Two Molecular Design Strategies for the Development of an Ammonium Ionophore More Highly Selective than Nonactin

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A series of ionophores for ammonium ion-selective electrodes was designed and synthesized, and their characteristics were examined. The design of the ionophores is based on two different strategies: (1) introduction of bulky blocking subunits (decalino groups) in 20- or 21-membered crown ethers (TD20C6 and TD21C6), the ring size of which is expected to be suitable for selective NH_4^+ recognition, as compared to the slightly smaller K^+ ; and (2) preorganized tripodal ionophores based on a 6-fold substituted benzene ring in order to complementarily recognize the tetrahedral NH_4^+ , in contrast to the spherical K^+ . Compared to nonactin, a natural product that is used as a representative NH_4^+ ionophore, the newly developed TD20C6 showed higher NH_4^+ selectivity over K^+ while retaining the selectivity over Na^+ ($\log K_{\text{NH}_4^+/\text{K}^+}^{\text{pot}} = -1.5$ and $\log K_{\text{NH}_4^+/\text{Na}^+}^{\text{pot}} = -2.5$). On the other hand, a tripodal ionophore with pyrazole nitrogen atoms as NH_4^+ binding sites showed high NH_4^+/K^+ selectivity but suffered from increased Ca^{2+} interference ($\log K_{\text{NH}_4^+/\text{K}^+}^{\text{pot}} = -2.1$ and $\log K_{\text{NH}_4^+/\text{Ca}^{2+}}^{\text{pot}} = -1.6$). As an overall conclusion, the cyclic ionophores TD19C6 and TD20C6 are the best ammonium-selective ionophores developed to date.

Because of their application to chemical sensors in the field of clinical or environmental analysis, the design and synthesis of ammonium ionophores has received much attention during the last two decades.^{1,2} Nonactin, a natural product shown in Figure 1, is the only available practically used ammonium ionophore at present. However, the NH_4^+ selectivity of nonactin over K^+ or Na^+ is not perfectly sufficient for practical use, and the development of a more highly selective ammonium ionophore as ion-sensing component for ammonium ion-selective electrodes has been desired. Recently, we developed a 19-membered crown ether derivative (TD19C6) shown in Figure 1 and realized an excellent

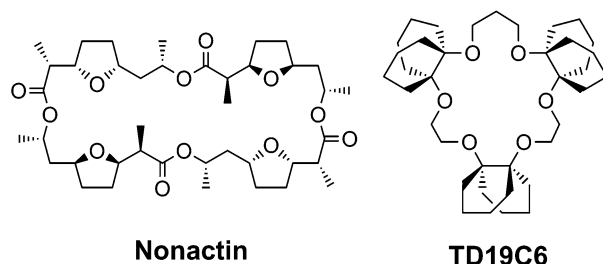


Figure 1. Chemical structures of nonactin (a natural product that is known as an ammonium ionophore) and TD19C6 (a synthetic ionophore that has a 19-membered crown ether with bulky subunits).

$\text{NH}_4^+/\text{Na}^+$ selectivity while retaining the NH_4^+/K^+ selectivity comparable to that of nonactin.² The design principle of TD19C6 is based on the combination of two factors, namely, the ring size of the crown ether suitable for the target cation (NH_4^+) and the introduction of the bulky blocking subunits to interfere with the complexation of other cations. A similar principle of molecular design based on a tetramethylethano subunit was successfully used in the development of Li^+ and Na^+ ionophores,^{3,4} but in the case of TD19C6, the NH_4^+/K^+ selectivity was not improved because of the similar ionic diameter of NH_4^+ and K^+ . On the other hand, Chin et al. focused on the different symmetry of NH_4^+ and K^+ for the design of an ionophore and were successful in high NH_4^+ selectivity over K^+ ($\log K_{\text{NH}_4^+/\text{K}^+}^{\text{pot}} = -2.6$). However, the developed ionophore still shows problems, such as low sensitivity or strong pH dependence.⁵ Thiazole-containing benzo-crown ethers⁶ or cage-type compounds⁷ have also been reported as ammonium ionophores, and their characteristics have been shown to be comparable or even superior to that of nonactin. In this work, we designed and synthesized eight ionophores on the basis of two different strategies for NH_4^+ recognition and

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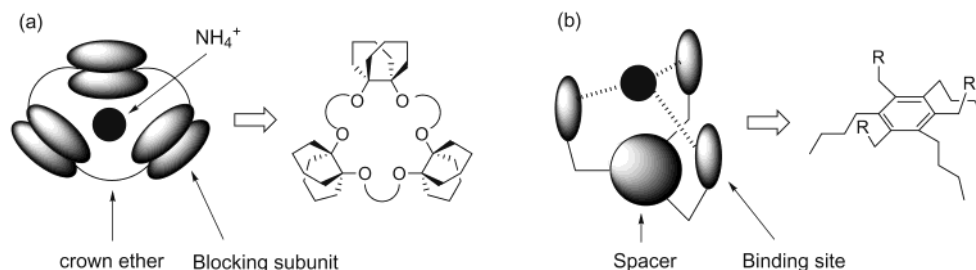


Figure 2. Schematic representation of the two approaches to the development of ammonium ionophores: (a) rigid crown ethers having a suitable diameter for NH_4^+ with bulky blocking subunits and (b) preorganized tripodal ionophores complementarily recognizing tetrahedral NH_4^+ with three binding sites.

examined their characteristics as ammonium ionophores for ion-selective electrodes.

EXPERIMENTAL SECTION

Reagents. The highest grade commercially available reagents were used for the preparation of the aqueous test electrolytes. The distilled and deionized water used had a resistivity of greater than $1.5 \times 10^7 \Omega \text{ cm}$ at 25°C . The electrode membrane solvent bis(1-butylpentyl) adipate (BBPA) was purchased from Fluka AG, Buchs, Switzerland. Poly(vinyl chloride) (PVC, high-molecular-weight type) used as the electrode membrane material was obtained from Sigma, Chemical Co. (St. Louis, MO). Synthetic procedures for ionophores are described in the Supporting Information.

The lipophilicity ($\log P_{\text{O/W}}$, the octanol–water partition coefficient) of the ionophores was measured according to a previously reported procedure.⁸

Electrode Preparation and emf Measurements. The PVC matrix-based membranes were prepared from a mixture composed of 3 wt % ionophore, 67 wt % BBPA, 30 wt % PVC, and 10 mol % (relative to the ionophore) anionic additive (KTCPB) for crown ethers and 25 mol % NaTFPB for tripodal ionophores KTA-1–KTA-5. The cocktail components dissolved in THF were poured into a vial and put on a hot plate. Slow evaporation of THF at 40°C gave ion-selective membranes of $\sim 100\text{-}\mu\text{m}$ thickness. A 6-mm-diameter circle was cut from a prepared membrane and placed on the tip of a PVC ion-selective electrode body assembly (Liquid Electrode Membrane Kit, DKK Co., Ltd., Tokyo, Japan). The prepared electrodes were immersed in 0.1 M aqueous NH_4Cl solution for more than 24 h for preconditioning before use. The external reference electrode was a double-junction-type Ag–AgCl electrode (HS-305DS, Toa Electronics, Ltd., Tokyo, Japan). The electrode potential (emf) measurements were performed at $25 \pm 0.5^\circ\text{C}$ using the electrochemical cell system, Ag | AgCl | saturated KCl | 0.3 M NH_4NO_3 || sample solution | ISE membrane | 0.1 M NH_4Cl | AgCl | Ag.

All sample solutions were prepared from the chloride salts of each cation without any pH-adjusting buffer reagent, except in the case of the electrode based on KTA-1, in which 0.1 M Tris–HCl buffer adjusted to pH 7.2 was used. The selectivity coefficients $K_{\text{I,J}}^{\text{pot}}$, where I stands for the primary ion (NH_4^+) and J for the interfering ion, were calculated from the response potentials in an alkali metal or alkaline earth metal chloride solution using the

separate-solution method (SSM; $[\text{I}] = [\text{J}] = 0.1 \text{ M}$) according to the recommendations of IUPAC and JIS.^{9–11}

RESULTS AND DISCUSSION

To recognize NH_4^+ selectively, two kinds of ionophore molecules were designed and synthesized as illustrated in Figure 2. The first concept of the molecular design uses cyclic crown ethers combined with three Decalino groups. This bulky subunit is known to act not only as a “block wall” in order to hinder the formation of sandwich-type complexes with larger cations but also as the origin of rigidity of the crown ether ring to prevent the formation of wrapping-type complexes with smaller cations. Furthermore, Decalino groups are desirable to increase the lipophilicity of the ionophore molecules, which is an important factor in view of the practical application.² Because the 19-membered crown ether (TD19C6) based on this approach showed almost the same NH_4^+/K^+ selectivity as that of nonactin, 20- and 21-membered crown ethers were selected to reduce the interference of the smaller K^+ ion.

The second concept is based on the tridimensional shape of the ionophores. Preorganized noncyclic tripodal ionophores based on a 6-fold substituted benzene ring as a spacer unit were selected,¹² since several receptors/ionophores have recently been developed for cation or anion recognition using this kind of approach.^{5,13–18} To distinguish the tetrahedral NH_4^+ from spherical cations complementarily, a series of binding units was introduced into this tripodal unit. In addition to the conformational effect, a cation– π interaction is also expected in the case of NH_4^+ binding.^{7,19} Although ethyl groups seem to be sufficient to show

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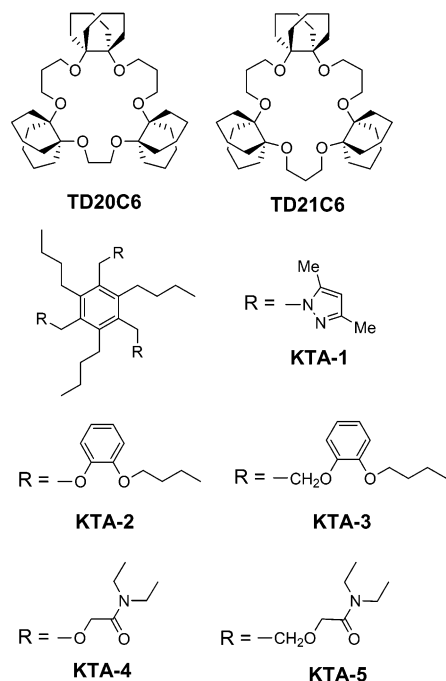


Figure 3. Chemical structures of the newly synthesized ammonium ionophores.

a preorganization effect, the longer butyl groups were chosen to increase the lipophilicity of the ionophores. As binding sites, nitrogen atoms of pyrazole rings, oxygen atoms of phenolic ethers, and oxygen atoms of amide carbonyl groups were selected for investigation. Thus, the two crown ethers TD20C6 and TD21C6, and the tripodal ionophores KTA-1 to KTA-5 shown in Figure 3 were newly designed and synthesized.

The lipophilicity parameters ($\log P_{O/W}$) of TD20C6 and TD21C6 are 14.6 and 15.2, respectively, which are higher than that of TD19C6 (13.5) as a result of the increase in the ratio of carbon to oxygen atoms, and these values are much superior to that of nonactin (5.8). The characteristics of the electrodes based on TD20C6 and TD21C6 were examined on the basis of the optimized condition for TD19C6 (see Experimental Section). As shown in Figure 4, these ionophores showed theoretical Nernstian response over a wide concentration range and a good detection limit lower than 1×10^{-5} M. The electrode response slopes were 59.3 and 59.1 mV/decade for TD20C6 and TD21C6, respectively. The selectivity coefficients of the NH_4^+ electrodes based on TD19C6, TD20C6, TD21C6, and nonactin are shown in Figure 5. Although every electrode shows good NH_4^+ selectivity, it should be pointed out that TD20C6 and TD21C6 have higher NH_4^+/K^+ selectivity ($\log K_{\text{NH}_4^+/\text{K}^+}^{\text{pot}} = -1.5$ and -1.6 , respectively), as compared to those of TD19C6 (-1.0) and nonactin (-1.0). Because the crown rings become more flexible as the ring size is increased, the interference of small cations, such as Li^+ , Na^+ , or Ca^{2+} , is increased in the order of TD19C6 < TD20C6 < TD21C6, probably as a result of the formation of wrapping-type complexes. However, the $\text{NH}_4^+/\text{Na}^+$ selectivity of TD20C6 is still comparable to that of nonactin. Therefore, it is concluded that the characteristics of TD20C6 as NH_4^+ ionophore are superior to those of nonactin in view of practical use.

On the other hand, the selectivity coefficients of the electrodes based on tripodal ionophores KTA-1–KTA-5 are shown in Figure

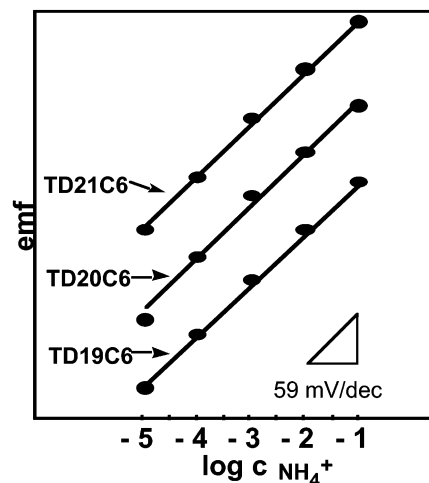


Figure 4. EMF response curves of the electrodes based on TD19C6, TD20C6, and TD21C6, which have 19-, 20-, and 21-membered crown ethers with three blocking subunits, respectively.

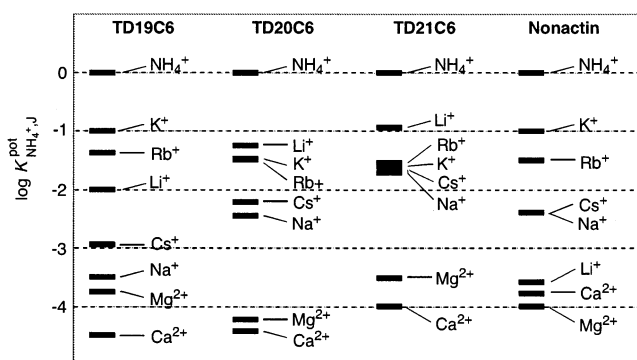


Figure 5. Potentiometric selectivity coefficients of the ISEs based on TD19C6, TD20C6, TD21C6, and nonactin.

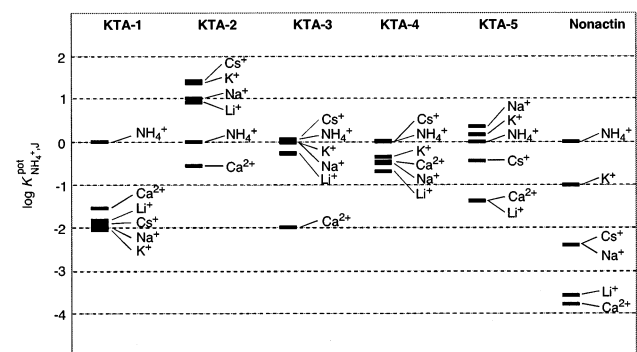


Figure 6. Potentiometric selectivity coefficients of the tripodal ionophores KTA-1, KTA-2, KTA-3, KTA-4, KTA-5, and nonactin.

6. Among the five ionophores examined, only KTA-1 showed high NH_4^+ selectivity, especially over K^+ ($\log K_{\text{NH}_4^+/\text{K}^+}^{\text{pot}}$ selectivity, -2.1), although the sensitivity is not as good as reported for a similar ionophore in the literature (detection limit, 1×10^{-3} M)⁵, and it was found that the interference of Ca^{2+} is serious. The selectivity of the ether-type ionophores KTA-2 and KTA-3 is quite different, which is caused by the length of the methylene unit connecting the binding sites and the spacer benzene ring. KTA-2 shows no selectivity for NH_4^+ ,²⁰ and extremely poor selectivity was observed for NH_4^+ over alkali cations in the case of KTA-3. The amide-type ionophore KTA-4 showed a limited NH_4^+ selectivity, but it is far from that of nonactin. Moreover, an increase

in the Ca^{2+} interference is observed in the case of KTA-4 and KTA-5.

In conclusion, the strategy based on the rationally designed crown ether showed better results in the development of novel ammonium ionophores. Among the newly synthesized ionophores, TD20C6 possessing a 20-membered crown ring and three Decalino groups is the best ammonium ionophore developed to date. In addition, 19-membered TD19C6 is also an excellent ammonium ionophore as a result of its high $\text{NH}_4^+/\text{Na}^+$ selectivity.

(20) 1,3,5-Triethyl-2,4,6-tris(2-methoxyphenyloxymethyl)benzene, which has a structure similar to KTA-2, is reported to have NH_4^+ selectivity over K^+ and Na^+ . However, even under the reported membrane and measurement conditions (ref 7, Supporting Information), the selectivity pattern for KTA-2 was not improved significantly. Therefore, the observed lower selectivity might be attributed to a sterical effect of the butoxy groups in KTA-2.

SUPPORTING INFORMATION AVAILABLE

Supporting Information Available: Detailed synthetic procedures for ionophores. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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