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SIMPLE EVALUATION OF ENANTIOMER-SELECTIVITY OF CROWN ETHER USING MEMBRANE ELECTRODE

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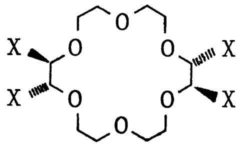
Enantiomer-selectivity of the crown ethers I through IV was evaluated by a membrane electrode method. Only chiral crown ether II showed some enantiomer-selectivity for both hydrochloride salts of phenylalanine methylester and phenylethylamine. This method was considered to be a convenient one for screening the enantiomer-selectivity of chiral crown ethers.

Chiral crown ethers have a great prospect as the chromatographic stationary phases for optical resolution of amino acids and their derivatives. Although many kinds of chiral crown ethers have been so far synthesized, very few show marked enantiomer-selectivity, one of which is Cram's binaphthocrown ether.1,2)

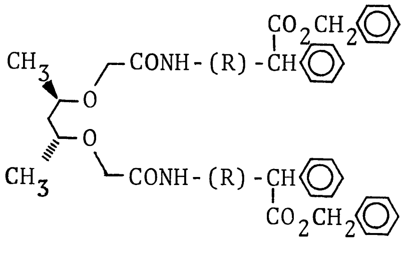
We have concentrated on the chiral crown ethers I and II, of which chiral units, tartaric acid and amino acid are commercially available, and which can be easily immobilized on packing supports for liquid chromatography. It is, however, necessary to see in advance if the chiral crown ether shows distinct enantiomer-selectivity on complexing amino acids and their homologs. On the other hand, crown ethers have been employed as the neutral carriers of ion-selective membrane electrode, and the selectivity coefficients are known to depend mainly on the stability of the crown ether-cation complexes.3) These observations motivated us to evaluate the enantiomer-selectivity of the chiral crown ethers by a membrane electrode method, using PVC(Polyvinyl chloride) membrane.

Chiral crown ether I was prepared according to the procedure of Lehn *et al.*4) Chiral crown ether II containing (S)-phenylalanine residue was synthesized by reaction of (S)-phenylalanine methyl ester with the tetra acid chloride of I in

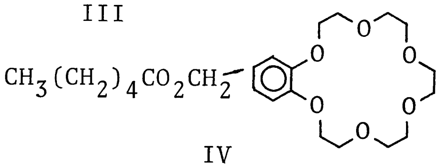


I: $X=CON(CH_3)_2$

II: $X=CONH-(S)-CH(CO_2CH_3)CH_2C_6H_5$



III



IV

the presence of triethylamine in chloroform. II: mp 195-196°C; $[\alpha]_{577}^{20} = +7.4$ (c 1.0, $CHCl_3$). Found: C, 61.67; H, 6.30; N, 5.28. Calcd for $C_{56}H_{68}N_4O_{18}$: C, 61.98; H, 6.27; N, 5.16. Noncyclic chiral carrier III was obtained in a similar way to the literature,5) from (R, R)-2,4-pentanediol, which was kindly given by Prof. Yoshiharu Izumi.6) III: $[\alpha]_{577}^{20} = -85.0$ (c 11.5, EtOH). Found: C, 70.03; H, 6.50; N, 4.31; M^+, 666. Calcd for $C_{39}H_{42}N_2O_8$: C, 70.25; H,6.35; N, 4.20; M^+, 666. The synthesis of achiral crown ether IV has been reported elsewhere.7)

PVC(50mg), carrier(2mg), and dipentylphthalate(120mg) were dissolved in tetrahydrofuran(2ml). The mixed solution was poured into a flat Petri dish of 24mm diameter, and then the solvent was evaporated slowly at room temperature. A disk of 3mm diameter was cut out from the PVC membrane, and incorporated into an electrode body of Orion Model 92. The electrochemical cell is as follows; Ag, AgCl/ 0.001M NH_4Cl/ PVC membrane/ measured solution/ 0.1M NH_4NO_3(salt bridge)/ KCl(sat)/ Hg_2Cl_2(s), Hg. All the measurements of e.m.f. were made at 25±0.1°C using a Corning pH meter 130. Selectivity coefficients, k_{RS}^{Pot}(preference to R isomer over S isomer), were determined by separate solution method, calculating from the equation, $\log k_{RS}^{Pot} = (E_R - E_S)/A$, where A denotes a slope of calibration curves, and E_R and E_S are the electrode potentials at the same concentration, respectively.

Attempts were made to evaluate the enantiomer-selectivity of the chiral crown ethers I, II, and noncyclic chiral carrier III by a membrane electrode method. Achiral crown ether IV was also employed for comparison. Phenylalanine methylester hydrochloride(PAM) and phenylethylamine hydrochloride(PEA) were chosen here as ammonium salts. Calibration plots of PVC membrane electrodes based on I, II, and III for (R)- and (S)-PAM are depicted in Fig. 1.

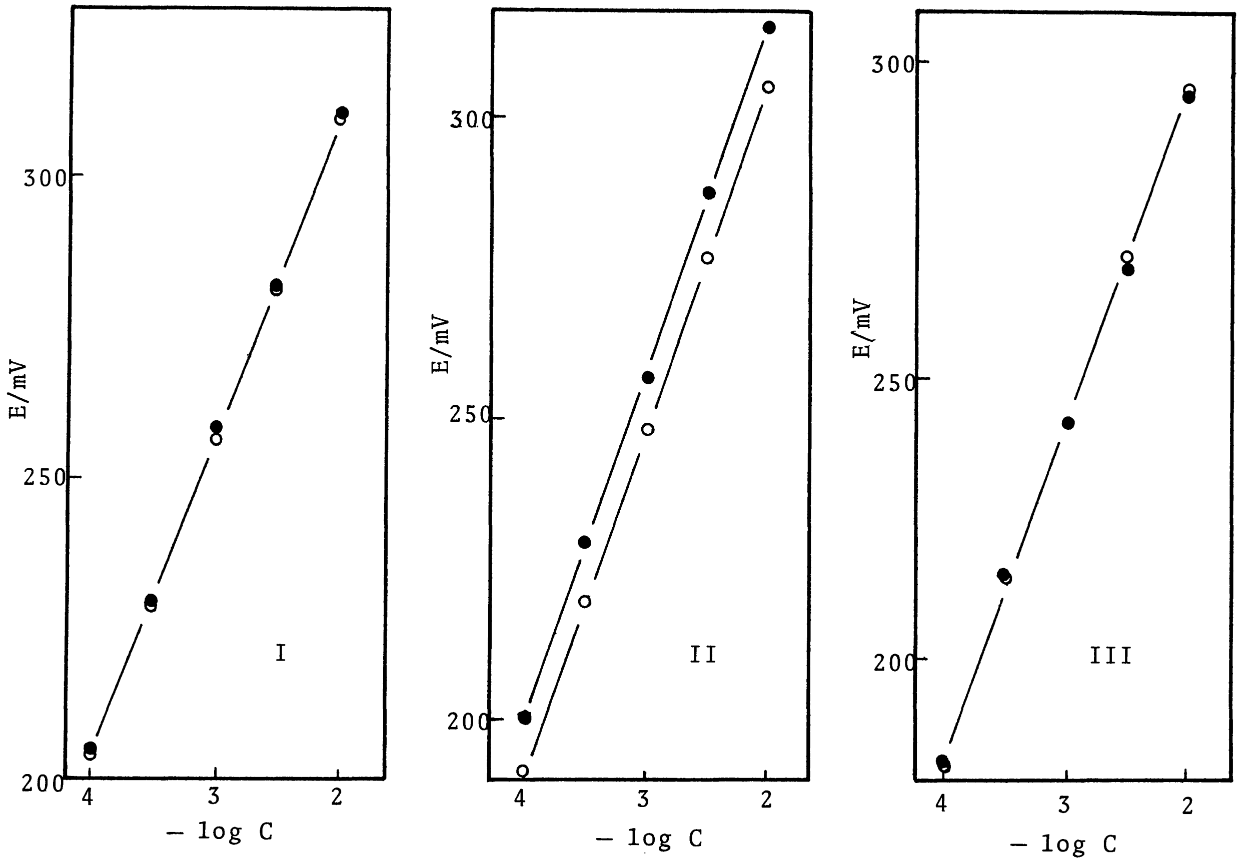


Fig. 1 Calibration plots of PVC membrane electrodes based on I, II, and III
●: (R)-PAM, ○: (S)-PAM, C(mol/l): Concentration of salts.

In the case of I and III, the electrode response for the R isomer is very similar to that for the S isomer. Thus, it is suggested that I and III have no enantiomer-selectivity. On the other hand, a distinct difference of electrode response of II was observed between the two isomers, the selectivity coefficient

Table 1.
Electrode properties of PVC membranes based on crown ethers I through IV

Crown ether	Salt	Slope (mV/decade)	k_{RS}^{Pot}	Crown ether	Salt	Slope (mV/decade)	k_{RS}^{Pot}
I	(R)-PAM (S)-PAM	56 56	1.0	I	(R)-PEA (S)-PEA	56 56	1.0
II	(R)-PAM (S)-PAM	56 56	1.4	II	(R)-PEA (S)-PEA	55 55	1.5
III	(R)-PAM (S)-PAM	55 55	1.0	III	(R)-PEA (S)-PEA	55 55	1.0
IV	(R)-PAM (S)-PAM	59 59	1.0	IV	(R)-PEA (S)-PEA	59 59	1.0

of (R)-PAM for (S)-PAM, k_{RS}^{Pot}, being 1.4. This result suggests that II prefers the R isomer to the S isomer on complexing them. For PEA systems, II has a similar enantiomer-selectivity. All the results obtained here are summarized in Table 1.

Taking into account the fact that neither I nor III has any enantiomer-selectivity in spite of their chirality, a crown ether seems to require a macrocycle which binds ammonium salts strongly, and bulky chiral side chains, in order to show some enantiomer-selectivity. Since these selectivity coefficients do not at all depend upon the kind of plasticizer unlike those of usual metal cation-selective membrane electrodes,[8,9] the enantiomer-complexing selectivities of chiral crown ethers seem to be reflected directly in these coefficients.

Transport of the ammonium salts through liquid membrane containing chiral crown ether II was carried out in separate experiments,[10] and the selectivity coefficient of (R)-PAM over (S)-PAM in transport, k_{RS}^{Tr}, was 1.4, which is coincident with the value of k_{RS}^{Pot} of the systems.

It is also big advantage of this method that only small quantity of crown ether, less than several milligrams, is required to prepare a PVC membrane. Thus, this membrane electrode method seems to be a simple and convenient one for preliminary screening of enantiomer-selectivity of chiral crown ethers.

References

1) L. R. Sousa, G. D. Y. Sogah, D. H. Hoffman, and D. J. Cram, J. Am. Chem. Soc., 100, 4569 (1978).
2) G. D. Y. Sogah and D. J. Cram, J. Am. Chem. Soc., 101, 3035 (1979).
3) G. A. Rechnitz and Ehud Eyal, Anal. Chem., 44, 370 (1972).
4) J. M. Girodeau, J. M. Lehn, and J. P. Sauvage, Angew. Chem., 87, 813 (1975).
5) D. Ammann, R. Bissig, M. Güggi, E. Pretsch, W. Simon, I. J. Borowitz, and L. Weiss, Helv. Chim. Acta., 58, 1535 (1975).
6) K. Ito, T. Harada, A. Tai, and Y. Izumi, Chem. Lett., 1979, 1049.
7) K. Kimura, H. Tamura, and T. Shono, J. Electroanal. Chem. Interfacial Electrochem., 105, 335 (1979).
8) M. Mascini and F. Pallozzi, Anal. Chim. Acta., 73, 375 (1974).
9) H. Tamura, K. Kimura, and T. Shono, Bull. Chem. Soc. Jpn., 53, 547 (1980).
10) M. Newcomb, R. C. Helgeson, and D. J. Cram, J. Am. Chem. Soc., 96, 7367 (1974).

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