New Chiral Host Molecules Derived from naturally occurring Monensin Ionophore

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Chemically modified monensins bearing neutral terminal groups led to effective enantiomer-selective complex formation with several amine salts in a liquid membrane-type electrode system.

One of the most interesting subjects in host–guest chemistry is the design of new classes of chiral host molecules, because several chiral crown ethers have been used successfully in optical resolution and asymmetric reaction systems.[1] Here we present a new class of chiral host molecules derived from the naturally occurring monensin ionophore. The parent monensin is known to accommodate a Na^+ ion in a pseudo-cyclic cavity and to transport it selectively across a biomembrane. Since it is composed of several optically active segments, it may provide a chiral, ordered cavity to accommodate certain chiral guest species. We have prepared novel chiral host molecules derived from naturally occurring monensin and characterized their chiral recognition abilities for several guest amine salts. Ion-selective electrode studies revealed that some monensin derivatives exhibited comparable enantiomer-selectivities to chiral crown ethers. Although many kinds of naturally occurring ionophores have been investigated, this is probably the first example of a chiral host molecule derived from a naturally occurring ionophore exhibiting high chiral recognition abilities.[2]

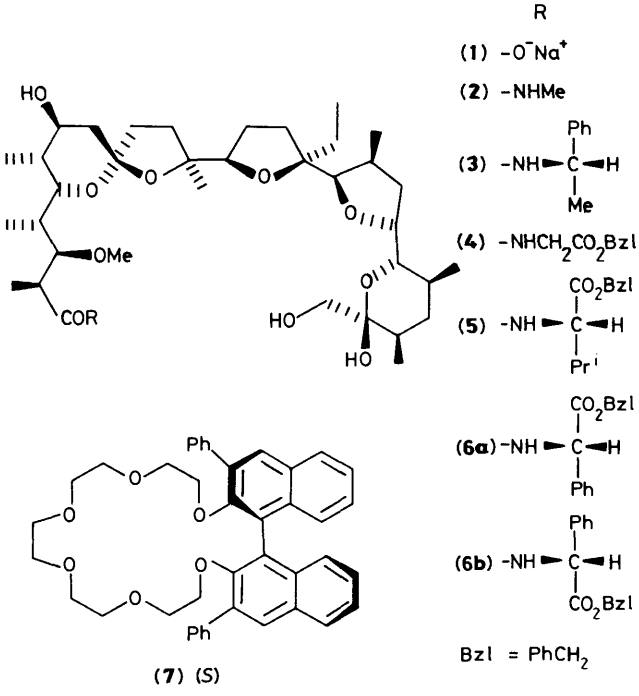
We introduced achiral and chiral neutral groups into the end of naturally occurring monensin by a modification of Corey's reaction.† The guest-binding properties of the monensin derivatives (**1**)—(**6**) obtained were characterized by the ion-selective electrode technique.[3] The monensin derivatives were incorporated into the electrode membrane, and the electrode potentials were measured as for normal ion-selective electrodes. The enantiomer-selectivity coefficient K_{SR}^{pot} was defined as $10^{(E_S - E_R)/0.058}$, where E_S and E_R represent the potentials for the (*S*)- and (*R*)-guest cation-containing solutions.[4] They could be correlated with the stability constants of the complexes between monensin derivatives and optically active cations in the membrane.[5] Typical results are summarized in Table 1.

The sensor electrodes incorporating natural monensin (**1**) and its modified derivatives (**2**)—(**6**) exhibited near-Nernstian responses to sample solutions of the amine salts examined in the range 1×10^{-1} to 1×10^{-4} mol dm^{-3}, indicating that they formed stable complexes with primary and secondary ammonium cations. Interestingly, the chemically modified monensins (**2**)—(**6**) showed excellent enantiomer-selectivities for several amine salts, whereas natural monensin (**1**) could not discriminate between their enantiomers. In particular, monensin derivatives having bulky and chiral terminal groups such as (**3**), (**5**), and (**6**) favoured the (*S*)-isomers of phenylalanine, leucine, and phenylglycine derivatives. Their potential differences, $E_S - E_R$, reached the high values of 30—51 mV, and enantiomer-selectivity coefficients K_{SR}^{pot} were calculated as 3.3—7.6. Since the monensin derivative (**6a**) showed somewhat higher enantiomer-selectivities than its diastereoisomer (**6b**), the enantiomer-selectivitiy was also dependent on the stereochemistry of the introduced terminal group as well as its chemical structure. A molecular

Table 1. Enantiomer-selectivity coefficient (K_{SR}^{pot}) at 20 °C for chiral amine derivatives.[a]

	K_{SR}^{pot}				
Host	PheOMe·HCl	LeuOMe·HCl	Ph-GlyOMe·HCl	ProOMe·HCl	Phenethylamine·HCl
(**1**)	1.2	1.3	1.1	1.0	0.90
(**2**)	1.8	2.3	2.1	1.0	1.0
(**3**)	6.2	6.0	5.1	1.2	0.43
(**4**)	2.1	1.9	2.7	1.0	0.59
(**5**)	6.2	7.6	5.1	1.0	0.40
(**6a**)	5.7	5.3	4.9	1.1	0.42
(**6b**)	4.3	3.4	3.3	1.0	0.53
(**7**)	4.0	10.4	18.4	1.3	0.49

[a] Membrane composition: 1 wt% potassium tetrakis-(*p*-chlorophenyl)borate, 3 wt% ionophore, 30 wt% poly(vinyl chloride), 66 wt% dibenzyl ether. Cell assembly: Ag; AgCl/0.3 M NH_4NO_3/sample solution/membrane/0.01 M NaCl/AgCl; Ag. Reproducibility: ±0.3.



† A typical synthetic procedure is as follows. In the presence of di-2-pyridyl disulphide (30 mg) and triphenylphosphine (45 mg), monensin free acid (30 mg) was treated with L-ValOBzl (100 mg; Bzl = $PhCH_2$) in CH_2Cl_2 at room temperature for 1 day. After reflux for 1 day, the mixture was washed with dil. HCl and then with saturated aqueous $NaHCO_3$. Chromatography (silica gel, CH_2Cl_2/AcOEt) gave the monensin derivative (**5**) (24 mg); see E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., *J. Am. Chem. Soc.*, 1975, **97**, 653.

All the monensin derivatives (oily materials) were fully characterized spectroscopically and had correct elemental compositions determined by high resolution mass spectroscopy. *Selected spectroscopic data* for (**5**): ^1H n.m.r. (400 MHz, $CDCl_3$), δ 0.85—2.23 (52H, identical to parent monensin), 2.29 (1H, m), 2.57 (1H, m), 3.38 (3H, s), 3.50 (3H, m), 3.60 (1H, m), 3.75 (1H, br.s), 3.84 (1H, dd), 3.92 (1H, d), 4.13 (2H, m), 4.28 (1H, m), 4.56 (1H, q), 5.12 (1H, d), 5.20 (1H, d), 6.74 (1H, d), and 7.35 (5H, m); *m/z* 882.5318; calc. for $C_{48}H_{77}O_{12}NNa$: $(M + Na)^+$, 882.5347; ν_{max} ($CHCl_3$) 1720 and 1650 cm^{-1}.

combination of pseudo-cyclic monensin cavity, neutral terminal, and chiral, bulky residue significantly provides excellent chiral recognition. The enantiomer-selective complexations of these monensin derivatives were confirmed by means of 400 MHz ^{1}H n.m.r. spectroscopy. When 1 equiv. of (*S*)-phenylglycine benzyl ester toluene-*p*-sulphonate was added to a $CDCl_3$ solution of the monensin derivative (**5**), the 31-H resonance shifted to 70 Hz higher field, but the (*R*)-phenylglycine benzyl ester salt only induced a shift to 4 Hz higher field. The stoicheiometry of complexation was also determined as 1 : 1 by ^{1}H n.m.r. titration experiments. The chiral crown ether (**7**) was also examined under the same conditions; (**7**) is one of the best ionophores for chiral recognition of ammonium guest species.[1,4] Its enantiomer-selectivity coefficients were generally satisfactory, but our modified monensins (**3**), (**5**) and (**6a**) exhibited higher enantiomer selectivities for phenylalanine methyl ester and phenethylamine salts.

The present study clearly demonstrates the unique chiral-recognition properties of podand-type monensin derivatives. Since Suzuki *et al.* recently reported selective Li^+-cation binding of a cyclic monensin derivative,[6] the naturally occurring monensin ionophore is thought to have a suitable structure for molecular design. Further structural modification of various naturally occurring ionophores provides a new possibility in design of chiral and specific host molecules.

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