Natural Carboxylic Polyether Derivatives as Lithium Ionophores

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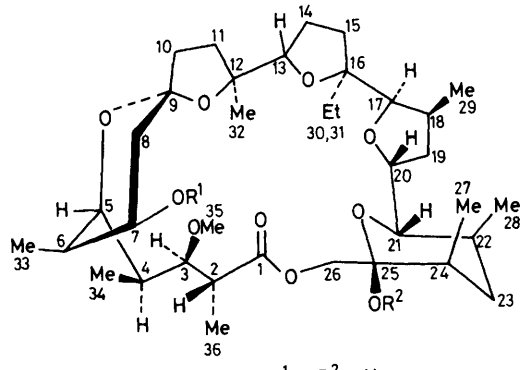
Two kinds of highly Li^+-selective ionophores, macrocyclic monensin monoacetate and ionomycin methyl ester, have been synthesized from natural carboxylic polyether antibiotics.

A number of ionophores for Li^+, including crown ethers and non-cyclic polyethers, have been synthesized to date.[1,2] However, Li^+-selective ionophores have not been obtained from natural or chemically-modified products. We have, therefore, attempted to obtain Li^+-selective ionophores from derivatives of natural products.

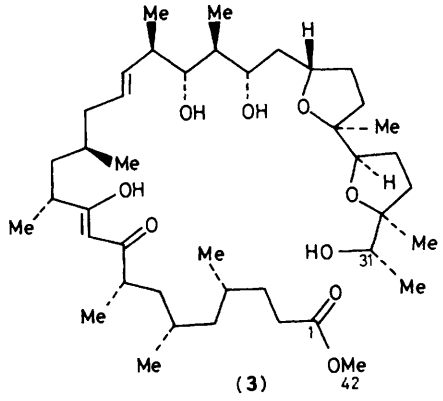
In order to create such ionophores by chemical modification of natural products, monensin and ionomycin were chosen as the basic materials for the modification. These molecules are known to form stable complexes with Na^+ and Ca^{2+},[1,3–5] where the ionic radii of these ions are close to that of Li^+. In this case, we expected to obtain Li^+-selective ionophores from the two carboxylic polyethers, namely, by lactonization of monensin to reduce the space for ion co-ordination, and esterification of the carboxy group of ionomycin, so that the binding power for divalent cations, such as Ca^{2+}, is reduced. As a result, two kinds of highly Li^+-selective ionophores, macrocyclic monensin monoacetate (**2**) and ionomycin methyl ester (**3**) have been obtained.

We describe here one example of obtaining Li^+-selective ionophores from natural products. Many ionophores other than that for Li^+ could be obtained by chemical modification of natural products similar to the modification described hereunder



(**1**) $R^1 = R^2 = H$

(**2**) $R^1 = COMe$, $R^2 = H$



(**3**)

The macrocyclic monensin was synthesized from hydroxycarboxylic acid, monensin (Sigma Chem. Co., St. Louis, Mo), according to Corey's lactonization,[6] to give compound (**1**) (90%, colourless oil) after silica gel column chromatography ($CHCl_3$–EtOAc 5:1).† Acetylation of (**1**) with acetic anhydride in pyridine for 4 days at 50 °C gave, after silica gel column chromatography (PhH–EtOAc 5:1), monoacetyl derivative (**2**) (30%, m.p. 177—180 °C).†‡

On the other hand, the methyl ester (**3**) of ionomycin was synthesized (75%, colourless oil) by treating ionomycin (CALBIOCHEM, American Hoechst Corp., La Jolla, Ca.) with methyl iodide and (1,8-diazabicyclo[5.4.0]undec-7-ene) (DBU) in benzene for 4 days at room temperature, followed by silica gel column chromatography ($CHCl_3$–EtOAc 1:2).†

The ion selectivity as ionophore was determined by electromotive force (e.m.f.) measurements. Electrode cells for e.m.f. measurements were implemented as shown in Scheme 1. The membrane containing the ionophore in this cell system was a matrix membrane of poly(vinyl chloride) (PVC), with which dibenzyl ether (DBE) was used as membrane solvent. Tetrakis(*p*-chlorophenyl)borate (TpClPB$^-$ K^+), which is frequently used for preventing the penetration of anions into membranes,[7] was added. The membrane preparation and the e.m.f. measurements have been performed according to the procedure of Moody and Thomas.[8] The ion selectivity factors (selectivity coefficients, $K^{pot.}_{i,j}$; i: primary ion; j: interfering ion) were measured at 25 °C by the fixed interference method (F.I.M.)[9] with 1×10^{-6}—1 M Li^+ (chlorides) as a primary ion and 1×10^{-1} M alkali and alkaline earth metal cation chlorides as interferents.

Monensin, which is a non-cyclic carboxylic polyether, is a Na^+-selective ionophore (column A, Figure 1; in Figure 1, $K^{pot.}_{Li,j}$ values are indicated as a function of radii of cations).[3] The monensin derivative (**1**) with the macrocyclic structure develops Li^+ selectivity (column B, Figure 1). This is

Ag; AgCl, KCl(satd.)|0.3 M NH_4NO_3|sample solution|membrane|0.01 M LiCl, AgCl; Ag

[membrane composition: 3 wt% ionophore, 1 wt% KTpClPB, 66 wt% DBE, and 30 wt% PVC]

Scheme 1

† Satisfactory elemental analyses and i.r. spectroscopic data were obtained for all new compounds. Selected spectroscopic data for compound (**1**): ^1H n.m.r. (400 MHz, $CDCl_3$), δ 4.68 [d, *J* 10.2 Hz, OH(2nd.)], 3.97 [dd, *J* 3.0, 11.0 Hz, 21-H], 3.85 [7-H], 3.36, 4.74 [dd, *J* 11.0 Hz, 26-H_{AB}], 3.04 [q, *J* 7.5 Hz, 2-H]. Compound (**2**): ^1H n.m.r. (400 MHz, $CDCl_3$), δ 4.26 [q, *J* 7.4 Hz, 7-H], 2.05 [s, 38-H]. Compound (**3**): ν_{CO} ($CHCl_3$) 1724s cm^{-1}; ^1H n.m.r. (400 MHz, $CDCl_3$), δ 3.67 [s, 42-H]. ^1H n.m.r. data of compounds (**1**) and (**2**) were assigned on the basis of those of monensin in ref. 10.

‡ The diacetyl derivative (30%, m.p. 227—230 °C; ref. 6: m.p. 225—228 °C) was also obtained; however, the Li^+ selectivity was poor (log $K^{pot.}_{Li,Na}$ = +0.1).

Table 1. Comparison of selectivity factors, $K^{pot.}_{Li\,j}$, of Li^+-selective ionophores.

Ionophore	log $K^{pot.}_{Li\,j}$ j = Na^+	K^+	Mg^{2+}	Ca^{2+}	Reference
Macrocyclic monensin monoacetate [DBE]	−1.5	−2.5	−4.7	−4.7	This work
Ionomycin methyl ester [DBE]	−1.3	−1.9	−2.9	−2.1	This work
Dodecylmethyl-14-crown-4 [NPPE]	−2.4	−2.3	−5.2	−4.3	2a
Non-cyclic polyether diamide[b] [NPOE]	-2.4_5	−2.6	−4.0	−2.9	2b
Non-cyclic polyether diamide[c] [TEHP]	−1.3	−1.6	−2.4	−3.5	2c
Non-cyclic polyether diamide[d] [DOPP]	−1.3	−2.2	−2.2	−1.7	2d

[a] Solvent used with the ionophore for the determination of $K^{pot.}_{Li\,j}$ in brackets; DBE: dibenzyl ether; NPPE: 2-nitrophenyl phenyl ether; NPOE: 2-nitrophenyl phenyl ether; TEHP: tris(2-ethylhexyl) phosphate. [b] *N,N*-Dicyclohexyl-*N',N'*-di-isobutyl-*cis*-cyclohexane-1,2-dicarboxamide (ETH1810). [c] *N,N,N',N'*-Tetraisobutyl-5,5-dimethyl-3,7-dioxanonane diamide [carrier (**13**) in ref. 2c]. [d] 1,2-Bis(octanoylamino-*N,N'*-diethoxy)-4-t-butyl benzene.

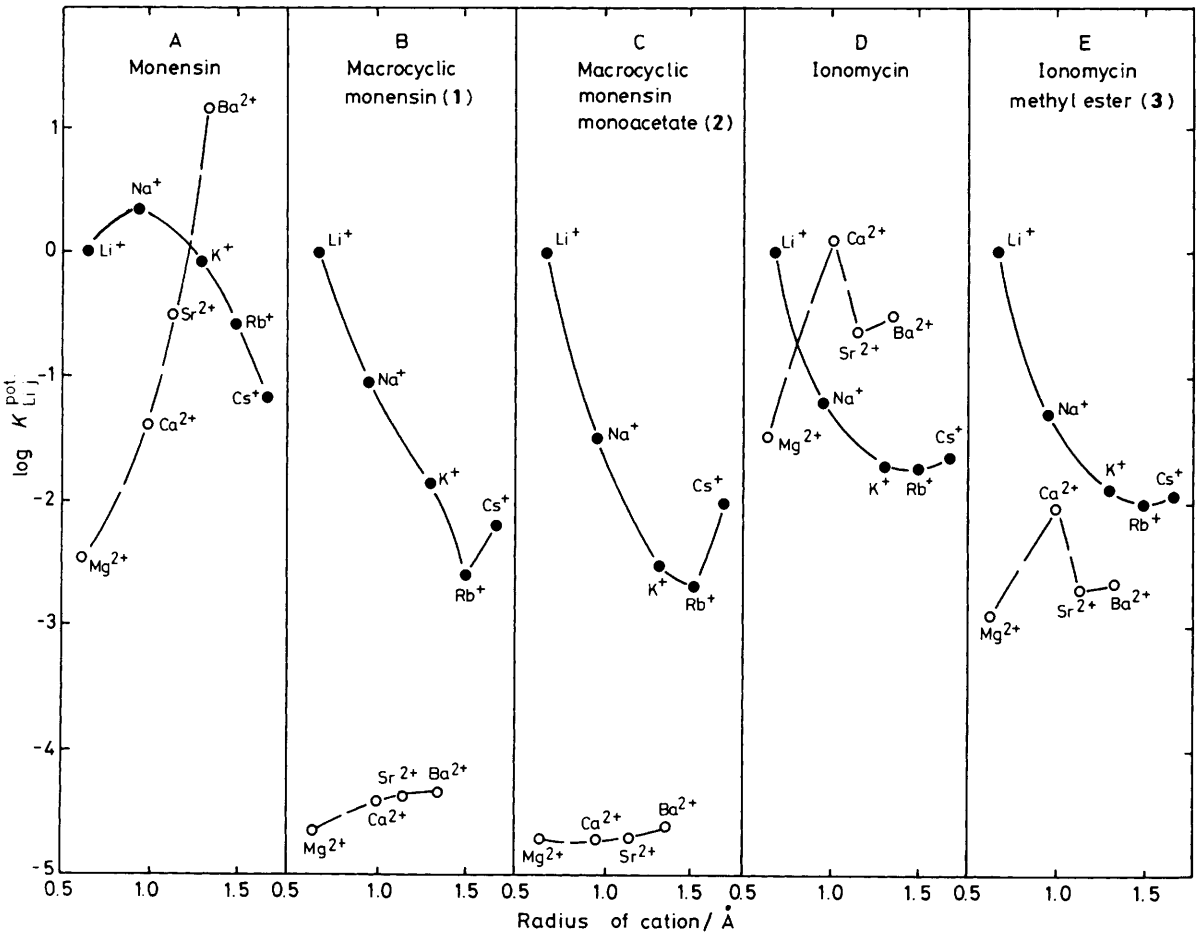


Figure 1. Selectivity factors (log $K^{pot.}_{Li\,j}$; j: interfering ion) for monensin, ionomycin, and their derivatives. The data in column A were measured by us earlier.

ascribable to the reduction of the radius of cavity at the position of ion coordination because of lactonization. Further, acetylation of the hydroxy group improves the Li^+ selectivity (column C, Figure 1). The reason could be a 'block' that is disadvantageous for Na^+ co-ordination as reported by Kimura *et al.*[2a] on lipophilic crown-4 derivatives.

On the other hand, ionomycin, which is a naturally occurring carboxylic polyether antibiotic, has a high selectivity to Ca^{2+} [4,5] (column D, Figure 1), but the contribution of the carboxy group in the co-ordination of the divalent cation, for which the selectivity of the divalent cation can be reduced by its esterification (column E, Figure 1), is important.

As shown in Figure 1, relatively small changes in natural products can result in quite large modification of the ion selectivity order.

The selectivity factors, $K^{pot.}_{Li\,j}$, of these two derivatives of

natural products are compared with those of other reported synthetic Li^+-selective ionophores[2] in Table 1. Further investigation on improving Li^+ selectivity by synthesizing several derivatives of natural products is in progress.

Now that the unique chemical modification of natural products for syntheses of various ionophores with high selectivity to particular ions has been demonstrated, evaluation of the derivatives of ionophore-related substances is the subject of current studies.

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