Inorganica Chimica Acta, 166 (1989) 27–29

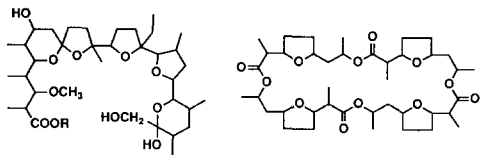
Specific Ag^+ Ion-transport Properties of Functionalized Biological Monensin Ionophore

HIROSHI TSUKUBE* and HAJIME SOHMIYA**

Department of Chemistry, College of Liberal Arts and Science, Okayama University, Okayama 700 (Japan)

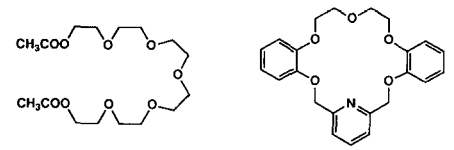
(Received August 10, 1989)

Monensin (**1**) is a typical naturally occurring ionophore having an acyclic polyether sequence and a terminal carboxylic acid moiety. It effectively accommodates a Na^+ ion into a characteristic pseudo-cavity and specifically transports it across a bio-membrane [1, 2]. Since it forms stable complexes with K^+, Rb^+ and Ag^+ ions as well as the natural guest Na^+ ion [3], it is expected to be chemically modified so that new cation-binding and transport functionalities could be attained†.



1: R = Na
2: R = CH_3

3



4

5

Fig. 1. Monensin derivatives and related ionophores.

Here we report the specific Ag^+ ion-transport properties of the monensin ester **2** which is characterized by a pseudo-cyclic polyether skeleton and a neutral terminal ester group. Its unique molecular structure remarkably offers a new and specific transport functionality which is not observed in naturally occurring monensin (**1**) and nonactin (**3**) ionophores and synthetic polyether compounds **4** and **5** (Fig. 1). Therefore, the present study clearly reveals that structural modification of the naturally occurring ionophore provides a new and promising methodology for use in designing a specific host molecule‡.

Experimental

Materials

The ionophores employed were obtained as follows: monensin (**1**) and monensin methyl ester (**2**) (Calbiochem); nonactin (**3**) (Fluka): crown ether **5** (Merck). The polyether **4** was prepared from acetyl chloride and hexaethylene glycol, and was fully characterized spectroscopically and had correct elemental compositions as determined by high resolution mass spectroscopy.

Transport Experiment

Transport experiments were performed at room temperature (*c.* 16 °C) in a U-tube glass cell (2.0 cm, i.d.) [6]. The ionophore, dissolved in CH_2Cl_2 (12 ml), was placed in the base of the U-tube, and two aqueous phases (Aq. 1 = $MClO_4$, 0.500 mmol/H_2O, 5 ml; Aq. 2 = H_2O, 5 ml) were placed in the arms of the U-tube, floating on the CH_2Cl_2 membrane phase. The membrane phase was constantly stirred with a magnetic stirrer. The transport rates were calculated from the initial rates of appearance of the guest cations into the Aq. 2 phase, which were determined by means of an atomic absorption method. The corresponding amount of ClO_4^- anion was also determined in each case by using an ion-selective electrode technique. Reproducibilities were confirmed as 15% or better. Typical results are summarized in Table 1.

^{13}C NMR Spectra

^{13}C NMR studies were carried out at a frequency of 25.12 MHz with a JEOL 90A spectrometer (see Table 2). The ionophore was normally in a concentration of 0.05 mol/l. A mixture of methanol and methanol-d_4 (4:1) was employed as a solvent. The assignment was made based on the published results [7].

Results and Discussion

Monensin methyl ester (**2**) specifically transported the Ag^+ ion together with the ClO_4^- anion in the same direction, as frequently observed in neutral carrier-mediated symport systems [6]. Although natural monensin (**1**) has been reported to bind Ag^+ ions more strongly than Na^+ and other

*Author to whom correspondence should be addressed.

**Holder of a Fellowship of the Japan Society for the Promotion of Science for Japanese Junior Scientists.

†Chemical modification of naturally occurring monensin ionophore has been achieved; see ref. 4.

‡New transport properties of the natural monensin ionophore **1** have been developed; see ref. 5.

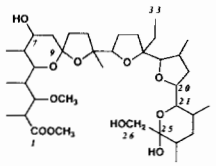
0020-1693/89/$3.50

TABLE 1. Cation transport properties of monensin derivatives and related ionophores

Ionophore	Transport rate ($\times 10^6$) (mol/h)									
	Li^+	Na^+	K^+	Ag^+	Cs^+	NH_4^+	Mg^{2+}	Ca^{2+}	Ba^{2+}	Pb^{2+}
1	*	*	*	2.1	*	0.4	*	*	1.1	1.6
2	*	0.7	*	4.8	*	*	*	*	*	*
3	0.4	2.1	1.9	4.4	5.0	1.7	*	*	*	*
4	*	*	*	*	*	*	*	*	*	*
5	*	0.4	4.4	7.2	2.0	0.9	*	*	*	*

(Transport conditions) Aq. 1: guest perchlorate, 0.50 mmol/H_2O, 5 ml. Membrane: carrier, 0.0372 mmol/CH_2Cl_2, 12 ml. Aq. 2: H_2O, 5 ml. Asterisk indicates below limit of detection ($<0.3 \times 10^{-6}$ mol/h).

TABLE 2. Guest-induced ^{13}C NMR chemical shifts of the monensin methyl ester **2**[a]



Guest cation	Guest-induced ^{13}C NMR chemical shift (ppm)							
	C_1	C_7	C_9	C_{20}[b]	C_{21}[b]	C_{25}	C_{26}	C_{33}
Li^+	+0.2	−0.6	−0.1	+0.2	−0.6	+0.3	~0	+0.2
Na^+	+0.6	−1.1	~0	−1.6	−1.5	+0.3	+0.2	−0.1
Ag^+	+0.7	−0.7 (−0.1)[c]	+0.3 (+1.0)[c]	−0.6 (+0.1)[c]	+0.2	+2.4 (+3.8)[c]	−3.1	−0.1

[a]Monensin methyl ester **2**, 0.025 mmol; guest perchlorate, 0.025 mmol; CH_3OH–CD_3OD(4:1) 0.5 ml; (+) means low-field shift. [b]These signals could not be unequivocally assigned. [c]In these cases, two split signals were observed; the shifted values of minor components are in parentheses.

alkali metal cations [3], it exhibited moderate transport rates for Ag^+, Ba^{2+} and Pb^{2+} ions under the symport conditions employed. Esterification remarkably modified the ionophoric properties of biological monensin and significantly enhanced transport selectivity and efficiency for the Ag^+ ion.

Naturally occurring nonactin ionophore (**3**) was examined under the same symport conditions; it had polyether- and ester-linkages in a macrocyclic skeleton. It formed stable complexes with various metal cations [3] and effectively transported Na^+, K^+, Cs^+, Ag^+ and NH_4^+ cations. The macrocyclic synthetic polyether **5** also showed high transport rates for K^+, Ag^+ and Cs^+ ions. Since their transport selectivities were apparently lower than that of the acyclic monensin ester **2**, the macrocyclic structure did not always offer selective transport phenomenon. The acyclic polyether-ester **4** could not act as an effective ionophore of any guest cations examined. As frequently reported in synthetic acyclic carrier systems [6], it did not seem to form a pseudo-cyclic complex. However, the monensin methyl ester **2** had a suitable organization of polyether chain and terminal ester group for providing highly effective and selective cation-transport functionality.

The cation-binding behavior of the monensin methyl ester **2** was investigated by ^{13}C NMR spectroscopy. When an equimolar $AgClO_4$ salt was added to the monensin ester **2** solution, remarkable spectral changes were induced upon complexation (Table 2). The signals for carbons on the interior C–O–C sequences (C_9, C_{20}, C_{25} and C_{26}) of the pseudo-cavity as well as the terminal ester group (C_1) significantly shifted, and some of them were further split*.

*^{13}C NMR titration experiments indicated that the monensin methyl ester **2** formed several different types of kinetically static Ag^+ complexes, whereas dynamic and 1:1 complexation with the Na^+ ion was supported.

These spectral changes clearly indicated that the guest Ag^+ ion may be completely encased in the pseudo-cyclic monensin skeleton and effectively coordinated by the polyether chain and terminal ester moiety. A similar three-dimensional complex has been reported in the monensin **1**–Ag^+ complex system [8]. The $NaClO_4$ salt induced definite but somewhat different spectral changes from those obtained with $AgClO_4$, while only slight spectral changes were observed in the presence of Li^+ ion. Typically, Na^+ ion-induced shifts of C_9, C_{25} and C_{26} carbons were almost negligible. Although detailed complex structures are still unclear, the structural difference between Ag^+ and Na^+ complexes may reflect on the transport profile of the monensin ester **2**.

The present results clearly demonstrate that esterification of naturally occurring monensin ionophore remarkably offered specific cation-transport functions which could not be attained by natural monesin and nonactin ionophores and synthetic polyether ligands. Therefore, further modification of various natural ionophores may provide a useful synthetic strategy for developing a new type of host molecules.

Acknowledgements

The authors are grateful to Professor Kazuhiro Maruyama of Kyoto University for valuable discussions. This research was supported in part by a Grant-in-Aid from the Ministry of Education, Culture and Science of Japan.

References

1 G. R. Painter and B. C. Pressman, *Topics in Current Chemistry*, Vol. 101, Springer, Berlin, 1982, p. 1.
2 E. Choy, D. F. Evans and E. L. Cussler, *J. Am. Chem. Soc., 96* (1974) 7085.
3 B. G. Cox, N. Trung, J. Rzeszotarska and H. Schneider, *J. Am. Chem. Soc., 106* (1984) 5965.
4 E. J. Corey, K. C. Nicolau and L. S. Melvin, Jr., *J. Am. Chem. Soc., 97* (1975) 653; P. W. Smith and W. C. Still, *J. Am. Chem. Soc., 110* (1988) 7917; K. Maruyama, H. Sohmiya and H. Tsukube, *J. Chem. Soc., Chem. Commun.*, (1989) 864.
5 H. Tsukube, K. Tagaki, T. Higashiyama, T. Iwachido and N. Hayama, *J. Chem. Soc., Chem. Commun.*, (1986) 448.
6 H. Tsukube, *J. Coord. Chem., B-16* (1987) 101.
7 A. A. Ajaz, J. A. Robinson and D. L. Turner, *J. Chem. Soc., Perkin Trans. 1* (1987) 27.
8 A. Agtarap, J. W. Chamberlin, M. Pinkerton and L. K. Steinrauf, *J. Am. Chem. Soc., 89* (1967) 5737.