CHEMISTRY LETTERS, pp. 1487-1490, 1979.

COMPLEX FORMATION ENTHALPIES OF TETRANACTIN WITH ALKALI IONS IN METHANOL

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The enthalpies of complex formation of tetranactin with alkali ions in methanol were measured by a micro-calorimeter. The enthalpies were mostly determined by conformational energies of complexes and solvation enthalpies of ions. The minimum enthalpy was observed for potassium ion complex. This tendency coincided with the ion selectivity of tetranactin.

Tetranactin, a macrotetrolide antibiotic produced by streptomyces, is known to have strong ion selectivity for metal ions$^{1-3)}$. Recently, Sakamaki et al$^{4,5)}$ calculated the conformational energy of tetranactin by summing up the non-bonded interaction energy (U_{NB}), torsional energy (U_{TOR}), and electrostatic energy (U_{EL}) of intra-ligand interaction as well as the energy of ion-dipole interaction (U_{ID}) according to Scheraga et al$^{6,7)}$. However, the tendency of calculated conformational energy ($U_{INT}+U_{ID}$ in Table I) for tetranactin-alkali ion complex did not agree with the ion-selectivity of tetranactin, *i.e.* maximum stability of complex with potassium ion, although the intra-ligand interaction energy ($U_{NB}+U_{TOR}+U_{EL}=U_{INT}$) showed a certain degree of cation selectivity. In this report, we show the good agreement between the enthalpies of complex formation of tetranactin with various alkali ions in methanol and the ion-selectivity of tetranactin and also show that they consist of the sum of the conformational energy and the desolvation energy of ions from methanol.

Tetranactin (Fig. 1) was isolated from crude macrotetrolide actin (gifted from Chugai Pharmaceutical Co. Ltd.) according to Ando et al$^{8)}$, and recrystallized twice from its acetone solution. Na-, K-, and

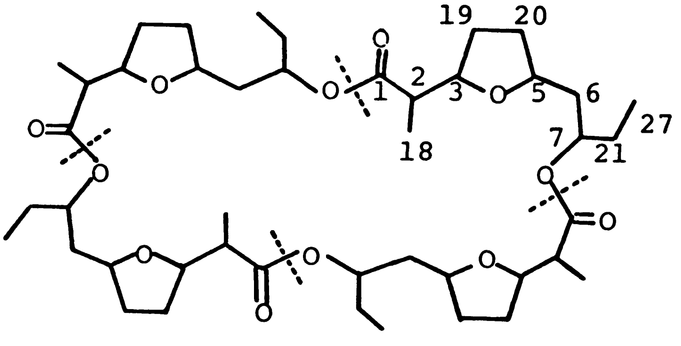

Fig. 1. Chemical Structure of Tetranactin

RbSCN (special grade, Nagoya Katayama Co. Ltd.) were used without further purification, and CsSCN (1st grade, Nagoya Katayama Co. Ltd.) was recrystallized from its acetone solution before use. Methanol (special grade, Nagoya Katayama Co. Ltd.) was distilled twice before use. The enthalpy of complex formation was directly measured by a twin-type microcalorimeter (Type RCM 1F, LESCA Co. Ltd.). The calorimeter has twin cells in a thermostated cabinet at 25°C. Each cell consists of two compartments separately by a partition wall. Tetranactin solution and metal ion solution are separately confined to the compartments in one cell. Solvent and the metal ion solution, whose concentration is equal to that of the ion solution in the former cell, are similarly confined in another cell (see Fig. 2). The liquids in each cell were mixed by rotating the cabinet. The produced heat gave the enthalpy of complex formation, since the heat of dilution of metal ion was cancelled with each other. The measurements for each metal ion were carried out at various concentrations of ion and tetranactin. Since the enthalpy per mole of tetranactin was independent of tetranactin concentrations, we took the value as the standard enthalpy of complex formation.

Table I. Conformational Energy (kcal/mol)

	U^*_{INT}	U^*_{ID}	$U_{INT}+U_{ID}$	ΔU_C
uncomplex	-41.35			
Na^+complex	-46.62	-79.42	-126.04	-84.69
K^+complex	-48.60	-63.85	-112.45	-71.10
Rb^+complex	-48.56	-53.09	-101.65	-60.30
Cs^+complex	-47.81	-45.80	-93.61	-52.26

$U_{INT}=U_{NB}+U_{TOR}+U_{EL}$

$\Delta U_C=U_{INT(complex)}+U_{ID}-U_{INT(uncomplex)}$

* Sakamaki *et al*, *Acta cryst.*, B32,768(1976);B33,52(1977)

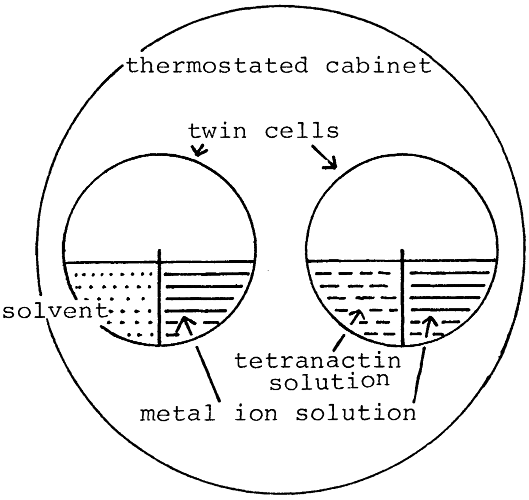

Fig. 2. Scheme of Cells

The enthalpy of complex formation ΔH^o from the calorimetric measurement is summarized in Table II together with the ionic radius⁹⁾ and the solvation enthalpy of ion from vacuum into methanol, ΔH^o_s,¹⁰⁾ and plotted against ionic radius in Fig. 3. It was found that the measured enthalpy of complex formation takes a minimum for potassium ion. This tendency coincided with the ion selectivity of tetranactin. It suggests that the complex formation enthalpy plays an important role in ion selectivity although it is necessary to evaluate the entropy to explain ion selectivity quantitatively. The entropy could not be estimated, for the present lack of precise complex formation equilibrium measurement at various temperatures.

The values of U_{INT}, U_{ID}, $U_{INT}+U_{ID}$ and the conformational energy difference between uncomplexed form and complex, ΔU_C, *i.e.* $U_{INT(complex)}+U_{ID(complex)}-U_{INT(uncomplex)}$, are shown in Table I . ΔU_C can be regarded as internal energy difference of complex formation excluding ion solvation effect. By adding the solvation effect to ΔU_C, the internal energy difference of complex formation in solution can be given. The internal energy change in liquid state can be approximated by the corresponding enthalpy change, or $\Delta U_C=\Delta H^o_C$. Thus we can calculate the complex formation enthalpy as Eq. 1.

$$\Delta H^o=\Delta H^o_C-\Delta H^o_S \qquad (1)$$

where ΔH^o_S is the solvation enthalpy of ion in methanol. Both measured and calculated complex formation enthalpies are plotted against ionic radius in Fig. 3. The solid line shows the enthalpy measured by calorimetry, the broken line the calculated value, and the dot-and-dashed line the first term of Eq. 1, *i.e.* conformational energy difference of complex formation. The values represented by solid and broken lines agree well with each other. This agreement should be emphasized to be splendid when one noted our neglect of the solvation effect of tetranactin itself. This matter

Table II. Complex Formation Enthalpy ΔH^o(kcal/mol).

	ΔH^o	ionic radius(Å)	ΔH^o_s
Na^+complex	-9.9	0.95	-75.3
K^+complex	-15.4	1.33	-55.8
Rb^+complex	-12.4	1.48	-49.4
Cs^+complex	-11.5	1.69	-42.8

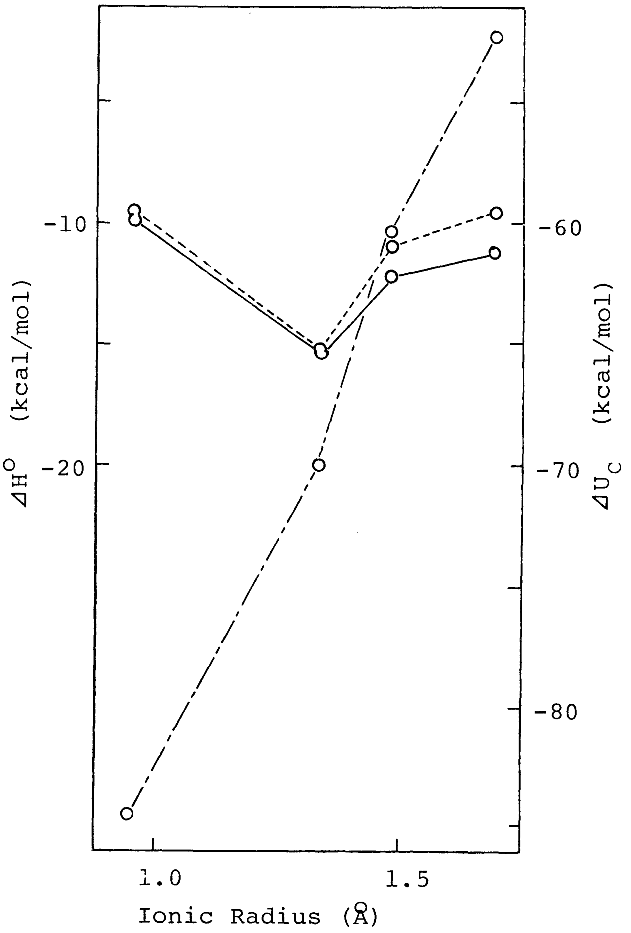

Fig. 3. Complex Formation Enthalpy *vs.* Ionic Radius.

——o—— : by calorimetric study
----o--- : by Eq. 1 (see context)
-·-o-·- : conformational energy

does not mean the smallness of the solvation enthalpy of tetranactin, but small difference in solvation enthalpy of tetranactin between its uncomplexed form and complex. The carbonyl groups of tetranactin, which turn out to be exposed to the solvent, are solvated by methanol molecules by hydrogen bonding in uncomplexed form. The methanol molecules desolvate as complex forms and the desolvation energy should be large enough. Nevertheless, the desolvation effect could be cancelled by the hydrogen bonding of the methanol molecules with another methanol in solvent. Also, the electrostatic effect on solvation by the central ion of tetranactin complex would be fairly small in enthalpy because of the large radius of macrolide sphere. Then the difference in solvation enthalpy of tetranactin itself between the uncomplexed form and complex could be neglected as a first approximation. Some deviation of calculated values from experimental values may be attributed to the above mentioned neglection. For the present, Eq. 1 seems to suffice to elucidate the experimental values of complex formation enthalpy, although the relationship of Eq. 1 is very simple.

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(Received September 7, 1979)