

(reaction 2). We are continuing our investigations of the chemistry of complexes 2 and 3 and are extending our studies to include the potentially more reactive Nb(III) analogs.

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Intramolecular Cation Exchange in [3]Cryptates of Alkaline Earth Cations¹

Sir:

Among the variety of properties displayed by natural and synthetic ligands of alkali and alkaline earth cations,²⁻⁵ a specially fascinating one resides in their ability to promote cation transport through natural or artificial membranes, either as carriers⁶ or by forming trans-membrane channels.⁷ Very little is known about such cation propagation along a chain of binding sites at the molecular level. We present here a study of cation jumping rates between binding sites inside the cavity of a synthetic molecule.

The macrotricyclic ligand, L, forms 1/1 inclusion complexes of the [3]cryptate type with various monovalent and bivalent cations.⁸ The stability constants of the alkaline earth cation complexes have now been determined by pH-metric titration; $\log K_s = 6.53, 6.97,$ and 8.0 for $\text{Ca}^{2+}, \text{Sr}^{2+},$ and Ba^{2+} cations, respectively (aqueous solutions of L + metal chloride salts). These bivalent [3]cryptates $[\text{M}^{2+} \subset \text{L}]^9$ display an intramolecular cation exchange process which may be studied by ¹³C nmr spectroscopy.¹⁰

The ¹³C Fourier transform nmr spectrum of L in D₂O displays four singlets with relative areas 1:2:1:2 corresponding respectively to the C_B-O, C_R-O, C_B-N, and C_R-N carbon atoms.¹¹

On addition of *alkali cation* salts the four ¹³C signals shift smoothly and level off at high cation/L molar ratios, indicating the progressive formation of weak $[\text{M}^+ \subset \text{L}]$ complexes⁸ with fast cation exchange.

When increasing amounts of salts of *alkaline earth*

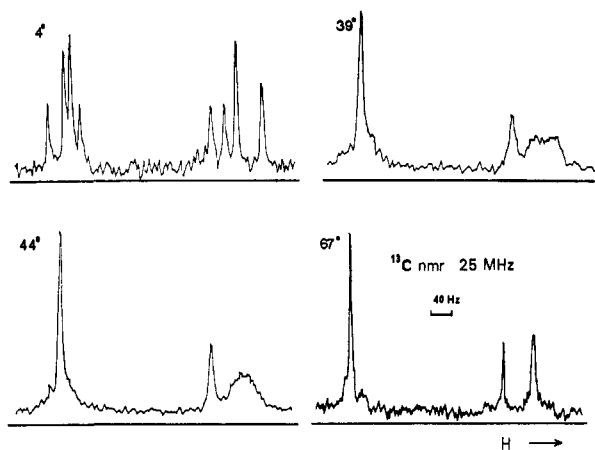


Figure 1. ¹³C FT nmr spectra of the $[\text{Ca}^{2+} \subset \text{L}]2\text{Cl}^-$ complex at different temperatures (D_2O solution of L + excess CaCl_2). At 4°, the chemical shifts are: 23.3, 25.2 (C_R-N); 26.1, 27.2 (C_B-N); 37.2, 39.6 (C_B-O); 37.9, 38.5 (C_R-O) ppm (downfield from CH₃ of internal *tert*-butyl alcohol).

cations ($\text{CaCl}_2, \text{SrCl}_2, \text{BaCl}_2$) are added to a D₂O solution of L, new ¹³C lines appear, which grow while the signals of the free ligand decrease to zero as one reaches a 1/1 stoichiometry. No further changes occur on addition of more salt. The new spectra are those of the bivalent [3]cryptates $[\text{M}^{2+} \subset \text{L}]$ and are temperature dependent (see Table I).

Table I. Spectral Parameters, Coalescence Temperatures, Exchange Rates, and Free Energies of Activation for Intramolecular Cation Exchange in $[\text{M}^{2+} \subset \text{L}]2\text{Cl}^-$ Cryptates^{10, 11, a}

Compound	¹³ C signal	$\Delta\nu, \pm 2$ Hz (temp, °C)	$T_c,$ ±4 °C	$k_c,$ sec ⁻¹	$\Delta G_a^\ddagger,$ ±0.3 kcal/mol
$[\text{Ca}^{2+} \subset \text{L}]2\text{Cl}^-$	C _R -N	48 (4)	40	107	15.4
	C _B -N	26 (4)	30	58	15.3
	C _R -N ^b	21 (32)	~105	~47	~19.5
$[\text{Sr}^{2+} \subset \text{L}]2\text{Cl}^-$	C _R -N	77 (5)	27	171	14.5
	C _B -N	26 (5)	15	58	14.5
$[\text{Ba}^{2+} \subset \text{L}]2\text{Cl}^-$	C _R -N	70°	<3	>155	<13.3
$[\text{La}^{3+} \subset \text{L}]3\text{NO}_3^-$	C _R -N	26 (32)	>93	<58	>18.6

^a $\Delta\nu$, separation of the ¹³C signals at temperature indicated; T_c , coalescence temperature; k_c , exchange rate at coalescence; ΔG_a^\ddagger , free energy of activation at coalescence calculated from T_c and k_c using the Eyring rate equation. The ¹³C-O data lead to the same results. The solutions were ca. 150–200 mM L in D₂O. ^b Parameters for the intermolecular exchange process. In the case of Sr²⁺, Ba²⁺, and La³⁺ all coalescences lie well above 100° since all signals are still sharp at this temperature; thus for these cations $\Delta G_a^\ddagger(\text{inter}) > 19$ kcal/mol. ^c Assumed value by analogy with the Sr²⁺ complex.

At +4° two sets of four ¹³C resonances are observed for the $[\text{Ca}^{2+} \subset \text{L}]$ complex (C-O set at low field, C-N set at high field, Figure 1). Within each set two signals (C_R-O, C_R-N carbons) have twice the intensity of the other two (C_B-O, C_B-N carbons). When the temperature is raised, the signals of same intensity within each set coalesce and a four-line spectrum (in fact only three lines since the C_R-O and C_B-O lines overlap) is obtained at higher temperatures. Similar results are obtained for the Sr²⁺ complex but the coalescences take place at lower temperatures than with Ca²⁺. In the case of Ba²⁺ only marked broadening of the upfield ¹³C_R-N signal is observed before freezing out the

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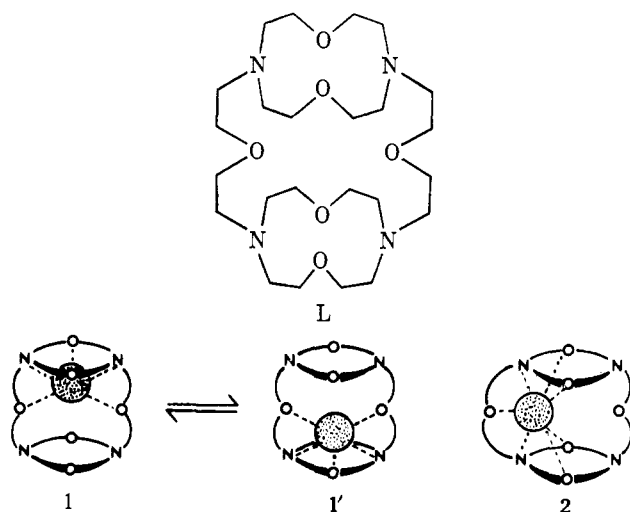
(10) The spectra have been measured on a Varian XL-100/15 spectrometer in the Fourier transform mode at 25.14 MHz with noise decoupling of the protons.

(11) The R and B subscripts designate respectively carbon atoms in the 12-membered rings and in the two bridges linking the two rings.

sample. Excess MCl_2 salt does not affect the results described. Finally the trivalent $[La^{3+} \subset L]$ cryptate obtained by addition of $La(NO_3)_3$ gives an eight-line ^{13}C pattern, similar to those observed at $+4^\circ$ with Ca^{2+} (Figure 1) and Sr^{2+} , which remains unchanged at 93° .

Furthermore, in solutions containing about equal amounts of complex and of free ligand, (i) the spectra and coalescence temperatures given by the complexes are unaffected and (ii) the averaged four ^{13}C lines of the $[M^{2+} \subset L]$ complex and the four ^{13}C signals of free L remain sharp and separate even at 99° for $M = Sr$ and Ba ; for $M = Ca$ line broadening occurs and coalescence sets in at 99° .

The observations described above may be interpreted as follows. (1) The $[M^{2+} \subset L]$ complexes display an *intramolecular cation exchange* process interconverting two species in which the cation is located unsymmetrically in the molecular cavity. (2) The symmetry-breaking operation converts the D_{2h} symmetry of free L into C_{2v} . The schematic C_{2v} structures **1** and **2** in



which the cation is displaced toward one ring or toward one bridge both agree with the ^{13}C nmr data. However, form **2** looks less favorable on molecular models and the cation location does not correspond to that found in the crystal structure of the $[2Ag^+ \subset L]$ complex¹² which is similar to the location in **1**. Thus, although species **2** may not be rigorously excluded, we favor a structure of type **1** for the $[M^{2+} \subset L]$ cryptates. The cation may complete its coordination shell with one or two anions and/or water molecules. Thus, the spectral changes observed may be attributed to the intramolecular process $\mathbf{1} \rightleftharpoons \mathbf{1}'$. (3) The free energies of activation ΔG_o^\ddagger for process $\mathbf{1} \rightleftharpoons \mathbf{1}'$ (Table I) decrease with increasing size and decreasing hydration energy of the cations, $Ca^{2+} > Sr^{2+} > Ba^{2+}$. Indeed, the smaller the cation and the higher its surface charge density, the more ligand interaction energy it will lose in the transition state of the $\mathbf{1} \rightleftharpoons \mathbf{1}'$ jump. This is even more so for the La^{3+} complex in which the barrier to intramolecular exchange is higher than 18.5 kcal/mol (Table I). (4) An *intermolecular* cation exchange process is also present, but its rate is much slower and its free energy of activation much higher (>19 kcal/mol) than those of the intramolecular process (see Table I). Cation ex-

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change rates in [2]cryptates are slower the higher the stability of the complex.¹³ In the stable $[M^{2+} \subset L]$ cryptates intermolecular cation exchange is indeed slow¹⁴ and the rates follow the sequence $Ca^{2+} > Sr^{2+} > Ba^{2+}$, *i.e.*, a reverse order with respect to the intramolecular process. This points out the fundamental difference between the two processes: cation jump between binding sites or removal of the cation from its complex. (5) Both intra- and intermolecular cation exchange is fast for the weak complexes of L with alkali cations.

The results described here show that the alkaline earth [3]cryptates of ligand L are "fluxional" type complexes¹⁵ of cations other than transition metal ones. They also indicate that it may be possible to build synthetic molecules which may function as channels for the flow of metal cations.

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Demonstration of Enzymic Hydrogen Transfer from Substrate to a Flavine¹

Sir:

Flavoenzymes catalyze the oxidation of $RCH(X)CO_2^-$ ($X = OH, NH_3^+$) *via* the intermediate formation of reduced flavine. The α -hydrogen removed from substrate during flavine reduction may be either released directly to solvent, transferred to a basic group on the protein,² or transferred to flavine itself.³ We wish to report the first direct evidence for an *enzyme-catalyzed* transfer of substrate hydrogen to a flavine. The direct demonstration of this phenomenon in enzymic reactions, which has until the present not been feasible due to the rapid exchange rates of reduced flavines, has been accomplished by the use of the flavine analog, deazaFMN, in which the N-5 nitrogen is replaced by CH.⁴ Bruice and his colleagues have previously used deazaflavines in model reaction studies to demonstrate direct hydrogen transfer between substrate and flavine.⁵

More detailed evidence to be presented in a subsequent communication⁶ shows that the flavoprotein N-

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