

Ion–Dipole Interactions of Macrocyclic Ethers Using ^{13}C Dipole–Dipole Relaxation Time Measurements. Part XI: The Complexation of 1,4,7,10,13,16-hexaoxa-2,6-dioxocyclooctadecane with Ca^{2+} in CD_3OH^*

ÇAKIL ERK

Technical University of Istanbul, Chemistry Department, Faculty of Sciences, Maslak, TR–80626, Istanbul, Turkey.

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Abstract. The association constants, K_a , of Ca^{2+} complexes with the nonequivalent binding site macrocycle, 1,4,7,10,13,16-hexaoxa-2,6-dioxocyclooctadecane, were determined in CD_3OH solution using ^{13}C dipole–dipole relaxation time, T_1^{DD} , studies. The measurements of T_1^{DD} of the macrocyclic backbone for different stoichiometries ($n:m$) of complex formation were conducted under extreme narrowing experimental NMR conditions. The general equilibria given with $1/K_a[L_0]^{n+m-1} = (1-nP')^n(1-mP')^m/P'$ was used for identical cation and macrocyclic ether–ester concentrations in CD_3OH and the association constants found were comparatively small depending on the cyclic ether–ester segments. The $\log K_a$ values varied from 1.09 to 0.231 for 1:1 and from 2.43 to 3.61 for 1:2 and from 2.29 to 4.24 for 2:1 ligand to cation complex stoichiometries.

Key words: Macrocyclic oligo ether–esters, ion–dipole complexation, Ca^{2+} , ^{13}C NMR, dipole–dipole relaxation.

1. Introduction

Different methods have been used to investigate the interaction of cations with ether dipoles of macrocyclic ethers possessing good alkaline and alkaline earth cation binding properties. In particular, the current interest in the synthesis and characterization of such molecules encouraged studies on the complex formation mechanisms for molecular recognition [2]. DNMR methods and intramolecular relaxation time measurements have been used to investigate the molecular interchanges of the supramolecules in free and salt containing media [3–7].

Molecular dynamics and conformational aspects of the supramolecules play a prime role in molecular recognition. The molecular motion of the binding sites of a host molecule are affected due to electrostatic interactions of the host–guest

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system. Therefore, the changes in the molecular motion due to complex formation or inclusion could be a measure of the extent of the host–guest interaction [5, 6].

The dipole–dipole relaxation time, T_1^{DD} , is a function of the correlation time of a motion, τ_{CH} , which can be rather easily determined under extreme narrowing NMR conditions, although, it has to be specifically identified due to the overall motion depending on the molecule. The observed dipole–dipole relaxation time of ^{13}C – ^1H interaction under extreme narrowing conditions, in which $(\omega_{\text{C}} + \omega_{\text{H}})^2 \tau^2 \ll 1$, where ω is the frequency and τ_{CH} is the effective correlation time of spins, and η_{CH} is the nuclear Overhauser enhancement, is given as follows (Equations (1) and (2)):

$$1/T_1^{\text{DD}} = 9/2h^2\gamma_{\text{H}}^2\gamma_{\text{C}}^2r^{-6}\tau_{\text{CH}} \quad (1)$$

$$T_1^{\text{DD}} = 1.99T_1^{\text{observed}}/\eta_{\text{CH}} \quad (2)$$

Hertz [3] concluded that the observed relaxation rate of a spin in an equilibrium is the sum of the inverse of the relaxation times of spins of thermodynamically distinct complexing species proportional to their mole fractions, P_i in solutions, Equation (3).

$$1/T^{\text{DD}} = P_{\text{free}}/T_{\text{free}} + \Sigma P_{i\text{comp}}/T_{i\text{comp}} \quad (3)$$

This is certainly valid in the case of a fast cation-macrocyclic ether exchange rate, which is usually observed in polar solutions where the relaxation times of free and complexed sites are supposed to be much larger than the lifetimes of free and complexed molecules.

On the other hand, the association constant of a complex of any stoichiometry, can be calculated precisely by using the following formalism, Equations (4)–(7), when identical cation–macrocyclic ether concentrations, $[A_0^+] = [E_0]$, are used experimentally.



$$K_a = [A_n^+ E_m]/[A^+]^n [E]^m \quad (5)$$

$$K_a = P'[E_0]/([E_0] - nP'[E_0])([E_0] - mP'[E_0]) \quad (6)$$

$$1/K_a[E_0]^{n+m-1} = (1 - nP')^n (1 - mP')^m / P' \quad (7)$$

The different stoichiometries (m, n) of the equilibrium constants have been determined in this way considering that many interaction stoichiometries, ($n = 1, 2, 3, \dots, m = 1, 2, 3, \dots$) exist in solution.

Accordingly, several studies have been recently reported from our laboratory for the estimation of the degree of binding of different macrocyclic structures by ^{13}C dipole–dipole relaxation time, T_1^{DD} , measurements with the understanding of

theory and practice to investigate the cation–dipole interactions for diamagnetic cations.

In the present work, the association constants, K_a , of Ca^{2+} with the nonequivalent multibinding macrocycle of 1,4,7,10,13,16-hexaoxa-2,6-dioxocyclooctadecane were determined in CD_3OH using ^{13}C dipole–dipole relaxation times. T_1^{DD} measurements of ^{13}C segments of the macrocyclic backbone for the different stoichiometries of complexes were estimated under extreme narrowing experimental NMR conditions, Equations (1)–(3) [6, 7].

2. Experimental

The experimental part of this work was carried out as described in our earlier reports [7]. The oligocyclic ether–ester molecule was synthesized according to our procedure reported recently [6c]. Cation–macrocyclic ether complex solutions were prepared with the identical appropriate concentrations, $[A_n^+] = [E_0]$ in CD_3OH and used for T_1 and NOE estimations.

The complexed cyclic ether mole fraction is obtained from $P = [A_n^+ E_m] / ([E_0] - (1 - m)[A_n^+ E_m])$ which could be simplified as $P' = P / (1 + (m - 1)P)$. The general formula obtained in this way, Equation (7), was used for the estimation of the association constants of various (n, m) stoichiometries. Values of $\ln K_a$ were estimated at ± 0.1 precision by linear least squares analysis. The samples of free and cation complexed macrocycle prepared in CD_3OH solutions in 10 mm NMR tubes were degassed and sealed. ^{13}C dipole–dipole relaxation time measurements were conducted at 15.0 MHz on a JEOL Model FX-60Q spectrometer, with the inversion recovery method with $2\pi - t_1 - \pi$ pulse sequences at 25 ± 0.5 °C [7]. NOE factor measurements were done at similar conditions to those used for inversion recovery studies with longest pulse repetition time, t_1 [4]. Representative results are displayed in Figures 1 and 2.

3. Results and Discussion

The structural recognition of multiple nonequivalent binding sites requires some structural organization of ground state complexes since the binding energies of any site of a cyclic host molecule are small compared to those of covalent bonds. However, the method presented in this work is not only capable of proving the well known ion–macrocyclic ether interactions but of giving information concerning the preferential ion–dipole interactions. However, K^+ and Na^+ complexing of some similar ether–esters have been also studied by a calorimetric method by Izatt *et al.* [2b].

Recent work has clearly shown that changes to internal motions of a cyclic ether backbone influence the relaxation times [6a]. The macrocycle has two carbonyls with an uniform cavity of an *anti, gauche, anti* unit conformation of the OCH_2CH_2 linkage, in both the free and complexed form [7]. This has an energy barrier for

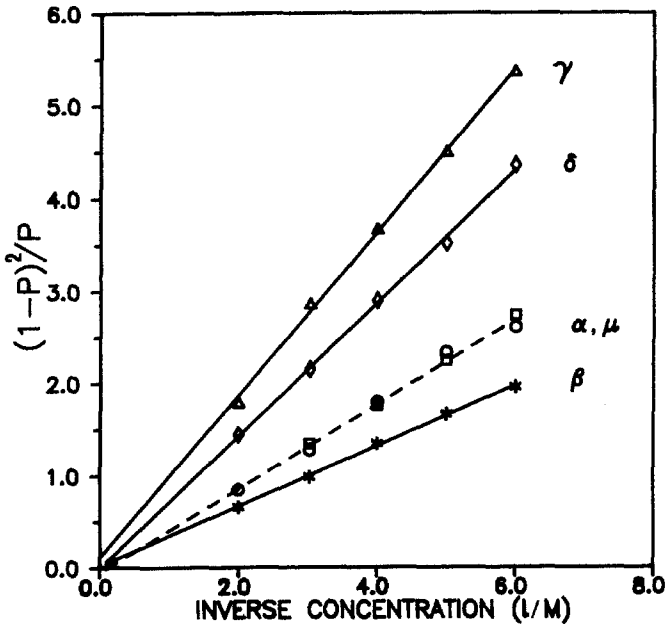


Figure 1. The dependence of $1/[E_0]$ versus $(1 - P')^2/P'$ of different ^{13}C segments for 1:1 stoichiometry of complex of $\text{Ca}^{2+}/2,6\text{-dioxo-18-crown-6}$ in CD_3OH .

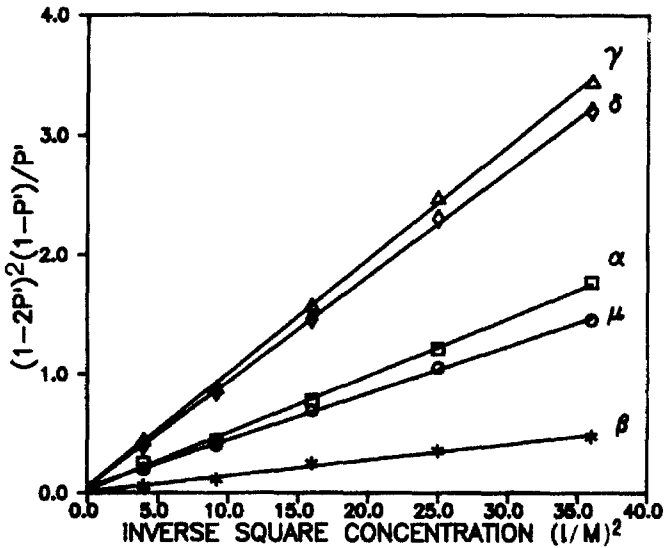
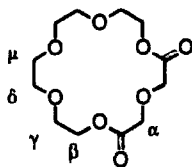


Figure 2. The dependence of $1/[E_0]^2$ versus $(1 - P')(1 - 2P')^2/P'$ of different ^{13}C segments for 2:1 stoichiometry of complex of $\text{Ca}^{2+}/2,6\text{-dioxo[18]crown-6}$ in CD_3OH .

Table I. The $\log K_a$ of Ca^{2+} complexing with 1,4,7,10,13,15-hexaoxa-2,6-dioxocyclooctadecane in various ligand/cation ($m : n$) stoichiometries measured at 15 MHz, in CD_3OH at $25 \pm 0.5^\circ\text{C}$.



^{13}C line freq. (ppm)	$\log K_a$ (1 : 1)	$-\Delta G$ (1 : 1) kJ M^{-1}	$\log K_a$ (1 : 2)	$-\Delta G$ (1 : 2) kJ M^{-1}	$\log K_a$ (2 : 1)	$-\Delta G$ (2 : 1) kJ M^{-1}
44.4 β	1.10	1.37	3.60	4.49	4.24	5.28
47.8 α	0.79	0.99	3.53	4.41	3.02	3.77
48.3 γ	0.23	0.28	2.43	3.04	2.29	2.86
49.8 δ	0.35	0.43	2.34	2.92	2.42	3.01
49.9 μ	0.78	0.97	3.44	4.29	3.20	3.99

an internal motion of around 10.5 kJ M^{-1} as reported with T_1^{DD} work from our laboratory [7a,b].

The residence time of a cation in the macrocyclic ring governs the segmental motions of the "nonequivalent" ligand sites of the ether-ester molecule. Preferential cation binding behavior was detected using ^{13}C dipolar relaxation time measurements. The methylene carbons attached to oxygen dipoles were found to be the most affected part upon complexation.

The association constants of complexes of 1 : 1, 2 : 1 and 1 : 2 ratio of this molecule with Ca^{2+} ion were determined by Equations (3)–(7) (Figures 1 and 2). The mole fraction, P^i , of each complex stoichiometry was first obtained, then Equation (3) was used to estimate the stability. Therefore, it could be considered that not only a single 1 : 1 ratio but also different complex stoichiometries (n, m) should be involved in solutions due to strong macrocyclic ligand/cation interactions (Table I).

This is also reported in an X-ray study of the same macrocyclic molecule [8] and some complexes of unusual stoichiometries [5]. However, the degree of ether-ion aggregation (or encapsulation) is not only a function of the ligand ring size. The following evidence is also in agreement with the considerations given above. Increased ion-ether concentrations caused a lower relaxation time because of the poly(ion-ether) nature of the complex which restricts the cation-ligand exchange rate and overall motions, as well as the internal rotations of the bound macrocyclic backbone. This has also been observed in our previous studies of relaxation time measurements of crown ether complexes [6, 7].

The results of Ca^{2+} ion complexation with the above molecule are similar to those obtained with guests like Na^{2+} , where the main factor determining complexing power is the cation-ligand exchange rate, as well as the ring flexibility [7a, 9]. These conclusions have been recently supported by computer studies [10].

The charge densities of alkali or alkaline earth cations are particularly involved in selective complexation. As different types of stoichiometries exist in solution, different methods may give different complex formation parameters. The relatively rigid and more polar segment of a molecule interacts rather strongly giving a higher equilibrium constant. The 1 : 1 association constant of the Ca^{2+} complex of 2,6-dioxo[18]crown-6 in methanol- d_3 obtained in this work is rather small. This is not surprising due to the double charge of the cation. However, KSCN and NaSCN complexes of this compound in the calorimetric study of Izatt *et al.* using calorimetry exhibited higher values [2b].

Work to determine the thermodynamics of host-guest interactions using the relaxation time of ^{13}C dipole-dipole interactions is in progress for novel macrocycles.

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