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Supramolecular Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713649759>

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Online publication date: 13 May 2010

To cite this Article Costero, Ana M. , Villarroya, J. Pablo , Gil, Salvador , Gaviña[†], Pablo and de Arellano, M. Carmen Ramírez(2003) 'Synthesis of a New pH-Dependent Ligand: Conformational and Complexation Studies', *Supramolecular Chemistry*, 15: 6, 403 – 408

To link to this Article: DOI: 10.1080/1061027031000116001

URL: <http://dx.doi.org/10.1080/1061027031000116001>

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Synthesis of a New pH-Dependent Ligand: Conformational and Complexation Studies

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Received (in Southampton, UK) 6 February 2003; Accepted 21 March 2003

A new macrocyclic ligand, **3**, which exhibits pH-induced conformational changes, has been prepared. This ligand consists of a crown ether derived from a *trans-anti-trans* 1,2,4,5-tetrasubstituted cyclohexane. Due to the stereochemistry of the substituents on the carbocyclic ring, two different low-energy conformations of the crown ether are possible. Ligand **3** has been studied in solution by ¹H NMR spectroscopy at different values of pH and temperature, showing that the conformation of the crown ether, and thus its complexing ability, is strongly pH-dependent. The solid-state structure of the ligand has been determined by X-ray diffraction.

Keywords: pH-switch; Complexation; Conformational transmitter; Crown-ether; Cyclohexane

INTRODUCTION

For several years there has been considerable interest in the use of proton-ionizable crown compounds for complexation and transport of metal cations from two aqueous solutions through an organic membrane [1]. Thus, compounds with pendent arms containing carboxylic or phenolic groups and compounds with a proton-ionizable group which extends into the macrocyclic cavity have been synthesised and used as carriers in transport experiments [2–4]. Lately, carboxylic or phenolic groups have been replaced by hydroxamic acids, carbamoyl functions or phosphonic acid mono-methyl esters giving new ligands which can be used in a similar way [5,6]. The pH-regulated ligands described to date exert their control by electrostatic

effects or by virtue of the fact that transfer of an aqueous phase anion into the organic medium is avoided in some cases. However, to the best of our knowledge, regulation produced by pH-induced conformational changes has received less attention. For this reason, we decided to study the complexation behavior of pH-regulated ligands derived from cyclohexane. The rigidity shown by the crown ether directly bound to a cyclohexyl moiety has been previously used by our research group in controlling the ability of the ligand to complex and transport cations [7,8]. Thus, the allosteric cooperativity observed in compounds **1** and **2** (Fig. 1) greatly increased the transport of cations across organic membranes. The allosteric behaviour observed in these ligands was due to the stereochemistry of the cyclohexane derivative in which only one site at a time has a favourable conformation for binding. Recently, related systems have been described by Koert *et al.* who have used perhydroanthracenes as conformational transmitters [9]. These authors were interested in the use of the prepared ligands as fluorescent sensors for transition metal cations.

The rigidity of the cyclohexyl system provides a relationship between the crown ether conformation and the equatorial or axial orientations of the substituents on the cyclohexane ring. Thus, it has been reported that in *trans*-cyclohexyl crown ethers with a bulky substituent at the 3-position, conformations with the equatorial substituent are more stable than those with an axial disposition [10]. Making use of the same principle, we decided to prepare compound **3**, which is a *trans*-cyclohexano-

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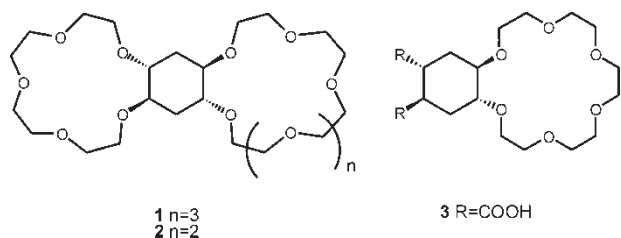


FIGURE 1 Regulated systems derived from cyclohexane.

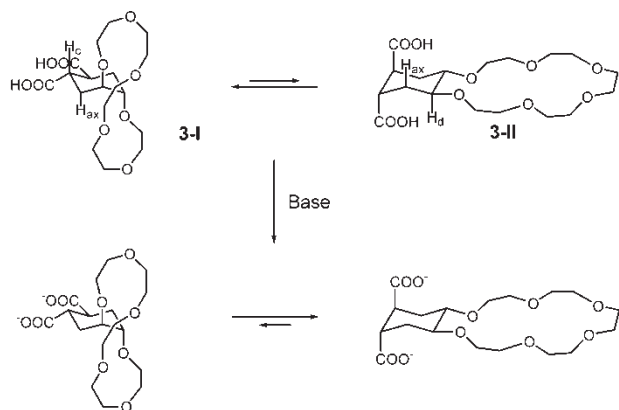
18-crown-6 derivative bearing two substituents at the 4- and 5-positions of the carbocyclic ring (Fig. 1). Due to the *trans* stereochemistry of these substituents, two different low-energy conformations of the cyclohexane ring, and thus of the crown ether moiety, are possible for each ligand (see Scheme 1). By choosing appropriate substituents with an acid/base character, we should be able to shift the conformational equilibrium to one side or the other depending on the pH of the medium [11]. Thus, we can expect that under basic conditions, the crown ether moiety of compound **3** will adopt a *trans*-diequatorial conformation, due to electrostatic repulsion of the charged substituents on the cyclohexane ring.

In addition, this controlled equilibrium should give us the possibility of regulating the complexing properties of this ligand, as it would be able to complex cations only if the crown ether moiety presents a *trans*-diequatorial conformation (lone pair on the oxygen atoms directed toward the center of the cavity).

RESULTS AND DISCUSSION

Synthesis

Ligand **3** was easily prepared from compound **4** by hydrolysis with NaOH in aqueous ethanol (84%)

SCHEME 1 Low-energy conformations of **3-I** and **3-II** deprotonated.

(Fig. 2). The synthesis of the starting diester **4** has been previously reported by our group [12].

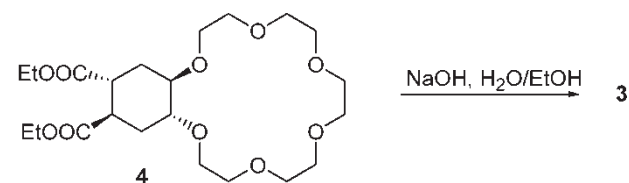
X-ray Diffraction

The definite stereochemistry of compound **3** was verified by X-ray diffraction. Single crystals were obtained by slow diffusion of hexane into a $CHCl_3$ solution. The asymmetric units were found to contain two molecules of chloroform and one water molecule per formula unit. The molecular structure shows the cyclohexyl ring adopting a chair conformation with both carboxylate groups in equatorial positions (Fig. 3). The carbonyl groups of each carboxylate are oriented in opposite directions: torsion angle $O(1)-C(8)\cdots C(7)-O(3)$ 129.8° . The $O(4)-C(7)-C(4)$ and $O(2)-C(8)-C(5)$ angles are far from ideal [$114.0(5)^\circ$ and $112.7(5)^\circ$, respectively].

A network of hydrogen bonds leading to a ladder type superstructure has been observed in the crystal (Fig. 4 and Table I). The water molecule, by the ether cavity, seems to be acting as hydrogen bond donor to the two oxygen atoms of the crown ether [$O(11)-H(11C)\cdots O(6)$ and $O(11)-H(11D)\cdots O(8)$] with $O\cdots O$ distances of 2.970(6) and 2.947(6) Å. One of the carboxylic acid groups is a hydrogen bond donor to the water oxygen of a neighbouring molecule, producing a linear chain of strong $O-H\cdots O$ interactions [$O(4)-H(4)\cdots O(11)\#2$], and a hydrogen bond acceptor of a chloroform molecule [$C(99)-H(99)\cdots O(3)$]. The water molecule is eventually acting as a hydrogen acceptor of the remaining chloroform molecule [$C(98)-H(98)\cdots O(11)$] with the water molecule oxygen atom being in a tetrahedral environment. A supramolecular synthon is observed for the dimers formed through the interactions of the remaining carboxylic acid group [$O(2)-H(2)\cdots O(1)\#1$] connecting two chains within the molecular ladder.

Conformational Studies

Conformational studies of compound **3** in solution, at different values of pH, were carried out by 1H NMR techniques (1D, COSY, NOE and NOESY experiments). In general, NOE experiments were not conclusive because the molecule in both conformations (**3-I**/**3-II**) possesses a C_2 symmetry axis which makes both sides of the cyclohexane ring

FIGURE 2 Synthesis of compound **3**.

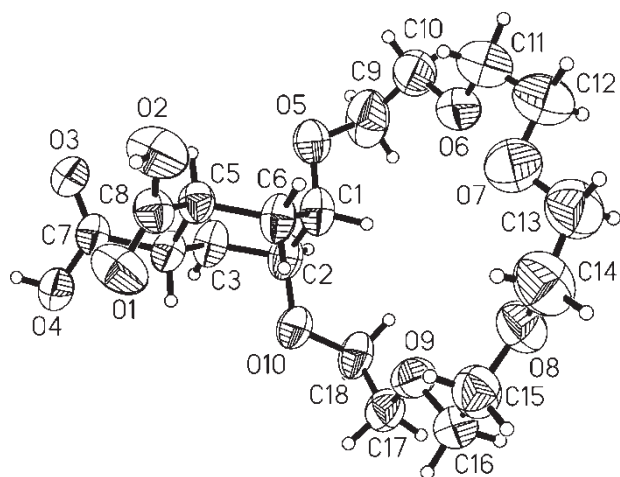


FIGURE 3 View of the molecular structure of **3** with crystallographic numbering scheme.

equivalent. ^1H - ^1H coupling constants would give more information about the spacial disposition, but unfortunately slow exchange on the NMR time scale led in all cases to broad signals (even over a range of temperatures). Thus, the area of the cross peaks in the COSY experiments, which is directly related to the coupling constant, turned out to be the most reliable proof of the preferred conformational arrangements [13]. The assignment of equatorial

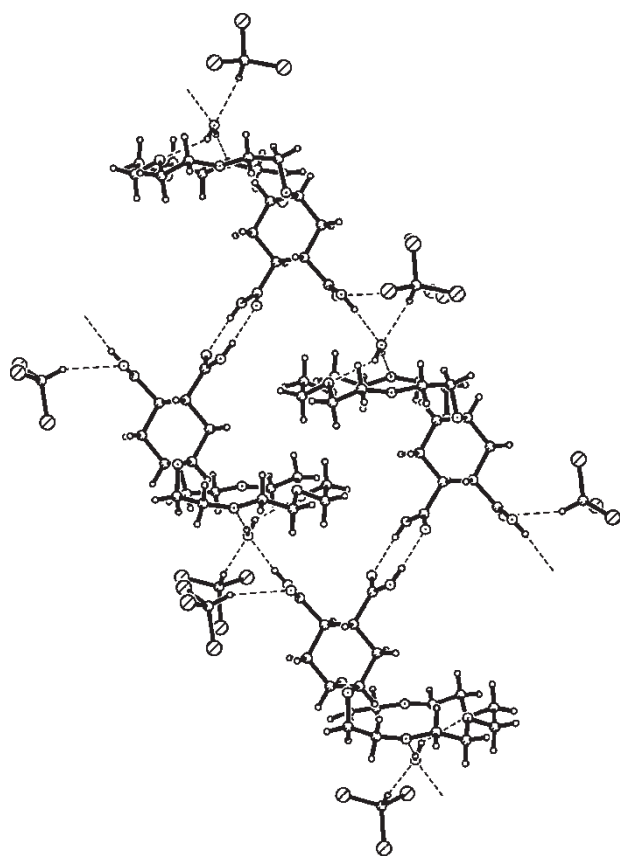


FIGURE 4 Superstructure observed in the crystal of compound **3**.

and axial protons was based on the fact that the equatorial protons in cyclohexane rings come to resonance about 0.5 ppm higher than axial protons.

^1H NMR studies carried out with compound **3** in CDCl_3 , $(\text{CD}_3)_2\text{CO}$ and CD_3CN showed that the main conformation present in a neutral solution was **3-I**, in which the carboxylic groups were in the equatorial positions as observed in the solid state. COSY experiments showed strong correlation between H_b - H_{ax} , respectively (see Fig. 5). In that sense, low-level theoretical calculations using PM3 indicated that conformation **3-I** was around 3 kcal mol^{-1} more stable than **3-II**.

On the other hand, compound **3** is a dicarboxylic acid with acidity constants which have been potentiometrically determined as being $\log K_1 = 5.10$ (5) for the first dissociation and $\log K_2 = 8.04$ (9) for the second dissociation. Even though, these values have been determined in dioxane:water 70:30, it is possible to suppose that in pure water one of the carboxylic groups could be deprotonated. Very likely, the formation of an intramolecular hydrogen bond makes conformation **3-I** even more stable under these conditions. In fact, ^1H NMR experiments carried out in D_2O showed that the main conformation present in the equilibrium also was **3-I**.

As we mentioned previously, we would expect that in a basic medium, the electrostatic repulsion of the charged substituents would favour a *trans*-axial disposition of the carboxylate groups. In order to study the behaviour of ligand **3** in basic solution, several experiments were designed. These studies were carried out in D_2O , using Me_4NOH as base. The selection of this base was related to the large size of the tetramethylammonium cation that precludes its complexation in the crown cavity and only gives rise to the acid-base reaction. ^1H NMR techniques were used to study the influence of pH on the conformation of the ligand and experiments were carried out at different temperatures (20, 25 and 80°C) and also at different times (from 2 min to 2 h after the addition of the base) but in all cases the results were comparable. Experiments were carried out at different values of pH (4, 6 and 9) and it was observed that conformational changes were only representative at pH values higher than 9. The conformational change is induced by Coulombic repulsion when the carboxylates are formed and could be clearly observed in the ^1H NMR spectrum.

Thus, COSY experiments in basic solution showed strong correlations between H_a - H_{ax} and H_b - H_{eq} (Fig. 5). Moreover, protons H_a and H_{ax} were highfield shifted due to the shielding effect of the carboxylate groups confirming that a conformational change, induced by Coulombic repulsion between both carboxylates, had been produced.

TABLE I Hydrogen bonds for 3.2 CH₃Cl-H₂O (Å and deg)

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...O(1)#1*	0.82	1.87	2.689(5)	175.1
O(4)-H(4)...O(11)#2*	0.82	1.82	2.628(6)	167.7
O(11)-H(11C)...O(6)	0.81(2)	2.17(2)	2.970(6)	168(6)
O(11)-H(11D)...O(8)	0.80(2)	2.27(4)	2.947(6)	143(6)
C(98)-H(98)...O(11)	0.98	2.55	3.502(8)	164.5
C(99)-H(99)...O(3)	0.98	2.47	3.385(8)	155.9

*Symmetry transformations used to generate equivalent atoms: #1 - $x + 2, -y + 1, -z + 1$; #2 $x, y + 1, z$.

NOE experiments were not conclusive because of the C₂ symmetry axis. Thus, both H_{ax} and H_{eq} show a similar NOE effect when irradiating H_a and H_b. Only in NOESY experiments could the cross peaks of higher intensity between H_{ax} and H_a be observed, showing that both protons are close to one another as should be if H_a is axial (**3-II** conformation). Finally, the ammonium salt could be prepared, isolated and studied by ¹H NMR in several organic solvents being the main conformation in the equilibrium **3-II** in all the used solvents.

Complexation Studies

Several experiments were carried out to find out the influence of pH—and as a result of it of conformation—on complexation. Thus, complexation studies were carried out with sodium picrate in different solvents. First of all, it was necessary to know the crown ether conformation in the sodium

complex. The ¹H NMR spectra of the sodium complex in acetonitrile and in acetone demonstrated that the crown moiety presented a *trans*-diequatorial conformation with the carboxylic group in *trans*-diaxial positions. These data agree with the predicted behaviour that proposes the conformation **3-II** as the most suitable for complexing cations. Thus, conformation inversion is necessary to give rise to cation complexation. On the other hand, titration experiments with sodium picrate in acetonitrile demonstrated that the formed complex showed a 1:1 stoichiometry. The constant value determined in this experiment was around 1.7 M⁻¹ [14].

To know the influence of conformation on complexation, similar titration experiments were carried out using the tetramethylammonium salt of compound **3** as the ligand. These experiments showed the formation of a 1:1 complex, the constant value being in this case around 3300 M⁻¹. This result demonstrated that the influence of conformation on complexation is very important because when

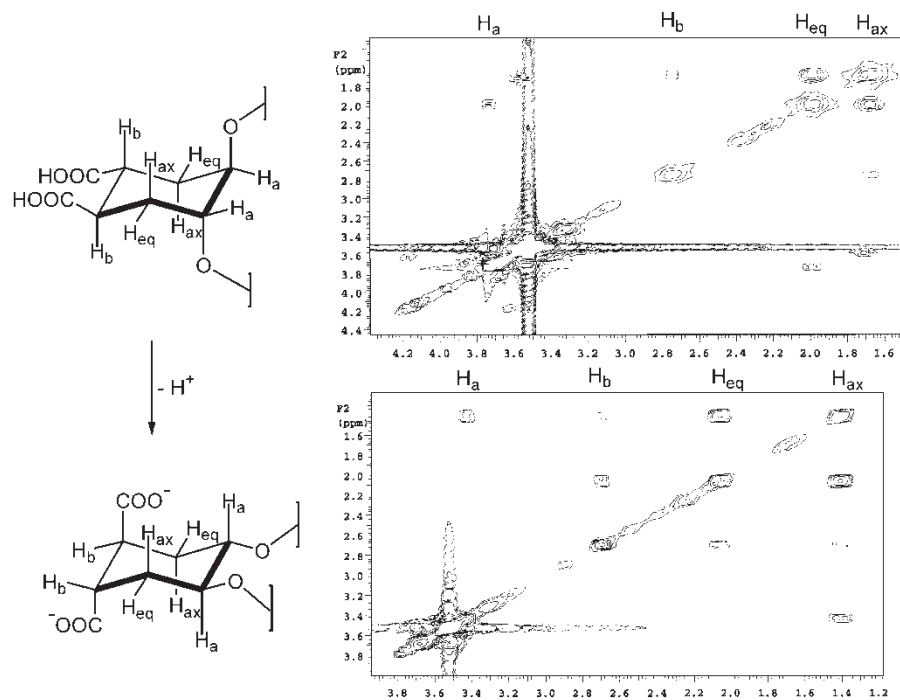


FIGURE 5 COSY experiments with compound **3**. Top: diacid; bottom: dianion.

conformation is fixed in **3-II** the complex is around 2×10^3 times more stable than when the conformation in solution is mainly **3-I**.

CONCLUSIONS

A new pH-regulated, crown ether based ligand has been prepared. NMR experiments clearly demonstrate that pH modifications induce conformational changes in these ligands. On the other hand, the rigidity of the cyclohexane moiety makes the control of complexation in the crown cavity possible by using basic media. The complexation constant of the tetramethylammonium salt of ligand **3** is 2×10^3 higher than the value evaluated for ligand **3** in a neutral medium.

EXPERIMENTAL

General

All commercially available reagents were used without further purification. The synthesis of precursor compound **4** has been reported previously [12]. Melting points are uncorrected. NMR spectra were recorded on either a Bruker AC250 or Varian Unity 300/400 spectrometer. Chemical shifts in ppm are referenced downfield from TMS. Mass spectra were determined on a VG-AUTOESPEC spectrometer.

Potentiometric Titrations

These were carried out in dioxane–water (70:30 v/v) using a reaction vessel water-thermostatted at $25.0 \pm 0.1^\circ\text{C}$ under nitrogen (0.1 mol dm^{-3} tetrabutylammonium perchlorate). The titrant was added by a Crison microburette 2031. The potentiometric measurements were made using a Crison 2002 pH-meter and a combined glass electrode. The titration system was automatically controlled by a PC computer using a program that monitors the e.m.f. values and the volume of titrant added. The electrode was dipped in dioxane–water (70:30 v/v) for half an hour before use. It was calibrated with a hydrogen concentration proven by titration of well known amounts of HCl with CO_2 -free LiOH solution and determining the equivalent point by Gran's method that gives the standard potential $E^{0'}$ and the ionic product of water ($K'_w = [\text{H}^+][\text{OH}^-]$, $\text{p}K'_w = 15.9 \pm 0.1$) [15,16]. The computer program SUPERQUAD [17] was used to calculate the protonation constants.

X-ray Crystallography

Suitable single crystals of $3 \cdot 2\text{CHCl}_3 \cdot \text{H}_2\text{O}$ were grown by slow *n*-hexane–chloroform diffusion: colourless block of $0.53 \times 0.53 \times 0.40 \text{ mm}$ size, monoclinic, space group $P2_1/n$, $a = 15.366(2)$,

$b = 11.435(1)$, $c = 17.358(2) \text{ \AA}$, $\beta = 95.381(9)^\circ$, $V = 3036.7(6) \text{ \AA}^3$, $Z = 4$, $2\theta_{\text{max}} = 50^\circ$, diffractometer Nonius CAD4, Mo-K α ($\lambda = 0.71073 \text{ \AA}$), ω -scan, $T = 293(2) \text{ K}$, 10745 reflections collected of which 5338 ($R_{\text{int}} = 0.0785$) were independent, direct primary solution and refinement on F^2 using SHELX97 program [18], 342 refined parameters, water molecule hydrogen atoms located in a difference Fourier synthesis and refined with restrained O–H bond length, rigid OH hydrogen atoms, others riding, $R1[\sum \|F_o\| - |F_c|]/\sum \|F_o\|, I > 2\sigma(I)] = 0.0758$, $\max \Delta/\sigma = 0.001$, $\max \Delta\rho = 0.42e \text{ \AA}^{-3}$. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 173785. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax +44(0)-1223-336033 or e-mail deposit@ccdc.cam.ac.uk).

Compound 3. A solution of NaOH (416 mg, 1.4 mmol) in H_2O (2 ml) was added to a solution of the diester **4** (480 mg, 1.4 mmol) in ethanol (30 ml). The mixture was stirred for 7 h and then acidified with HCl. The solution was evaporated and the crude product dissolved in acetonitrile. The organic phase was dried with anhydrous Na_2SO_4 and the solvent evaporated to give the acid compound **3** (84%) as a white solid. ^1H NMR (250 MHz, CDCl_3) δ 6.95 (bs, 2H), 3.85 (m, 2H, H_d), 3.60 (m, 20H), 2.83 (m, 2H, H_c), 1.99 (m, 2H, H_{eq}), 1.76 (m, 2H, H_{ax}); ^{13}C NMR (62.5 MHz, CDCl_3) δ 180.4, 74.1, 71.2, 70.5, 67.9, 38.8, 27.4; HRMS (FAB^+) ($\text{M}^+ + \text{Na}$) Calcd for $\text{C}_{18}\text{H}_{30}\text{O}_{10}\text{Na}$ m/z 429.1725; Found: 429.1736. Combustion analysis Calcd for $\text{C}_{18}\text{H}_{30}\text{O}_{10} \cdot 2\text{H}_2\text{O}$; C, 48.86; H, 7.69. Found: C, 48.88; H, 7.72.

Acknowledgements

This work was supported by the EC (project FI4WCT960022) and DGICYT (PB98-1429). The authors are grateful to Dr Juan Soto, from Universidad Politecnica de Valencia, for his assistance in the potentiometric measurements. MCRA thanks the Generalitat Valenciana (project GVD0C-99-22).

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