Macrocyclic effect and conformational analysis of the mixed-donor macrocycle 12-ane N_2O_2 by means of quantum chemical methods

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Abstract

Minimal GLO basis set *ab initio* and CNDO/2 calculations have been performed for four possible conformations of 1,7-dioxa-4,10-diazacyclododecane (12-ane N_2O_2) and their Li(I) complexes, using experimental bond lengths and angles. The special complex stability enhancement of cyclic ligands, known as the macrocyclic effect, has also been investigated by comparison with open chain analogues. The results indicate a good agreement between CNDO/2 and *ab initio* methods in the prediction of the lowest energy conformation of the free ligand, which is the alternate from with torsional angles of 68° and 66°, respectively. For the Li(I) complex, the CNDO/2 method predicts as expected a wrong conformation. The 12-ane N_2O_2/Li(I) complex is more flexible than either tetraaza or tetraoxa analogues. In addition, the lesser flexibility of the ring of the free 12-ane N_2O_2 ligand compared with that of macrocycles with only one sort of donor atom, reflects a higher energy requirement in arranging the donor atoms in a way suitable for complexation, leading to a lower net macrocyclic effect of the 'mixed-donor' macrocyclic ligand.

Introduction

We have already reported results for complex formation and conformational changes during complexation processes with alkali and alkaline earth metal ions of 12-membered macrocycles containing either oxygen or nitrogen atoms, 1,4,7,10-tetraazacyclododecane (12-ane N_4) and 1,4,7,10-tetraoxacyclododecane (12-ane O_4) [1, 2]. Comparative studies with their open chain analogues have been made, leading to some understanding of the special complex stability enhancement of cyclic ligands known as the macrocyclic effect. The ligand's solvation has also been investigated by statistical Monte Carlo simulations [3–5]. The role of the specific structure of water molecules above and below the ligand's plane, which helps to remove the metal ion's hydration water during complexation by offering alternative coordination sites, could be demonstrated by these investigations [4].

In order to understand steric effects, changes in the ligand's cavity and their energetic consequences during complexation, quantum chemical calculations have been performed for several trajectories for a lithium ion moving towards the ligand's cavity [6]. An explanation for the marked kinetic ligand inertness and the optimal pathway for entering the cavity have been reported.

The purpose of the present work was to investigate the most stable conformation of a 'mixed-donor' cyclic ligand, 1,7-dioxa-4,10-diazacyclododecane (12-ane N_2O_2) and its open chain analogues and their Li(I) complexes, based on quantum chemical investigations. Since *ab initio* calculations for systems of this size are still rather time-consuming, the possibility of a partial use of semiempirical methods in geometry optimization has also been explored. The results have been analyzed in comparison with those obtained for macrocycles with only oxygen or nitrogen coordination sites.

Methods of calculation

The semiempirical calculations reported here were of the CNDO/2 type, and the *ab initio* MO-SCF calculations were performed with a minimal GLO basis set, due to the size of the systems under investigation. The experimental values of comparable macrocyclic ligands from refs. 7 and 8 were used for the geometrical parameters (bond lengths and angles) of the cyclic and non-cyclic ligands, and kept constant throughout the calculations, except for torsion angles (see Fig. 1). In order to find the most stable conformation of the free ligand and its lithium complex, calculations were performed for four possible conformations: planar, chair, maxidentate and alternate. In the first one, all C, N and O atoms are located in the same plane (molecular plane). By moving the two opposite dimethylene bridges,

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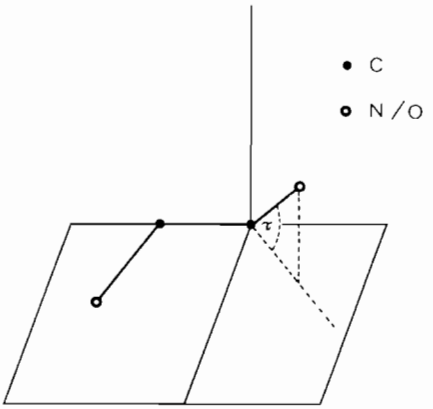

Fig. 1. Definition of torsion angle (τ).

of the planar form, above and below the molecular plane, the chair conformation is obtained. If all four dimethylene bridges are moved to the same side of the N_2O_2 plane, the maxidentate form is achieved. From this, the alternate form is generated by rotating the opposite N or O atoms to the opposite side of the plane formed by the C atoms. There exists an infinite number of conformations for the last two types, obtained from the set of geometrical parameters, depending on their torsion angles, while only one possibility exists for the others. Therefore, the maxidentate and alternate conformations had to be energy optimized with respect to torsion angles. More details of this optimization process are given in ref. 2.

The complexation energy balance for both types of ligands has been evaluated separately for the following two consecutive steps.

$$L(\text{conf.1}) \longrightarrow L(\text{conf.2})\ \Delta E(\text{conf}) \quad (1)$$

$$M^+ + L(\text{conf.2}) \longrightarrow ML^+(\text{conf.2})\ \Delta E(\text{bind}) \quad (2)$$

In the first step, ΔE(conf) is the energy difference due to conformation changes of the free ligand from its most stable conformation, L(conf.1), to that suitable for complexation, L(conf.2). The energy gain in the binding step, ΔE(bind), is represented by eqn. (2). Summation of both contributions results in the total stabilization energy (M^+ and ML^+ denote metal ion and metal–ligand complex, respectively).

For the open chain ligand 2,8-diaza-5,11-diazacyclododecane, L(conf.1) still represents its lowest-energy conformation, which is an expanded zig-zag form. L(conf.2) is the 'contracted' form analogous to that of the macrocyclic ligand in its ion complex.

Results and discussion

The most stable conformation of the free ligand

From the resulting total energies for the free cyclic ligand given in Table 1, a good agreement between *ab initio* and CNDO/2 methods is seen with respect to the prediction of the optimal conformation of the free 12-ane N_2O_2 ligand, and also the relative order of stability of the calculated conformations. The alternate form with a torsional angle of about 67° (66° from CNDO/2 and 68° from the *ab initio* method), is the preferred one, ahead of maxidentate, planar and chair forms, respectively. No experimental data have been published on the structure of this ligand so far, but comparison of other theoretical and experimental investigations of similar compounds shows the reliability of even minimal-basis-set calculations in geometry prediction [9–15].

TABLE 1. Optimized total energies (Hartree) and torsional angles (°) of the four possible conformations of the macrocyclic ligand 1,7-dioxa-4,10-diazacyclododecane, calculated by CNDO/2 and minimal-basis-set *ab initio* methods

Conformation	CNDO/2		*Ab initio*	
	Torsion angle	Total energy	Torsion angle	Total energy
Planar	0	−131.1943	0	−485.7105
Chair	0	−131.1594	0	−485.6805
Maxidentate	30	−131.2294	30	−485.7207
Alternate	68	−131.2405	66	−485.7809

The time consumption of the CNDO/2 calculations is about ten times less than that of the *ab initio* method, while the obtained structural result is almost identical. Therefore, the CNDO/2 method seems to be an acceptable computational tool for a rapid prediction of a macrocyclic ligand's conformation [16].

The most stable conformation of the 12-ane N_2O_2/Li(I) complex

In order to evaluate the conformational changes during the complexation process and the most stable conformation of the 12-ane N_2O_2/Li(I) complex, Li(I) was first positioned at the center of the ligand's cavity, and then the distance between the ion and the center of the ring (out-of-plane distance) for the planar and the maxidentate conformations, was optimized with respect to total energies. The final results are summarized in Table 2, and the energy contributions according to eqns. (1) and (2), together with the corresponding values for 12-ane N_4 and 12-ane O_4, are given in Table 3.

Results obtained by the CNDO/2 method have not been included in Tables 2 and 3, although some test calculations have been performed. In agreement with the previous findings [17, 18] this method is definitely unsuitable for the prediction of complex structures. In

TABLE 2. Optimization total energies (Hartree), stabilization energies (kcal mol^{-1}) and torsional angles (°) of 1,7-dioxa-4,10-diazacyclododecane/Li(I) complex in its four possible conformations, from *ab initio* calculations

Conformation	Torsion angle	Total energy	Stabilization energy
Planar	0	−492.2063	−9.66
Chair	0	−492.2246	−21.15
Maxidentate	30	−492.3407[a]	−94.00
Alternate	62	−492.3421[b]	−94.00

[a]Li(I) locates 0.7 Å above center of the cavity. [b]Li(I) is at the center of the cavity.

TABLE 3. Energies (kcal mol^{-1}) obtained from *ab initio* calculations, for the complex formation process of Li(I) with macrocyclic ligands and their open chain analogues (processes 1 and 2 correspond to eqns. (1) and (2) in text)

Process	Total energy		
	12-ane N_2O_2	12-ane N_4	12-ane O_4
Cyclic ligand			
1	+0.31	+0.91	+5.30
2	−95.19	−123.60	−57.60
(1+2)	−94.88	−122.70	−52.30
Open chain ligand			
1	+13.93	+17.70	+44.80
2	−87.85	−107.60	−61.31
(1+2)	−73.92	−89.90	−16.50

our case, a torsion of over 140° is predicted by the CNDO/2 method, which is definitely incompatible with the size and usual binding distances for the lithium ion (ionic radius = 0.60 Å). In the following sections, we therefore report only the results from the *ab initio* calculations as far as metal ion complexes are concerned.

According to Table 2, no significant difference between stabilization energies of the maxidentate form with a torsion angle of 30° and the alternate form with a torsion angle of 62° are found, indicating a highly flexibility of the 12-ane N_2O_2/Li(I) complex. In the first isomer, Li(I) is placed at the centre of the cavity. In the second one, N and O are situated in the same plane and Li(I) is 0.7 Å above the molecular centre of this plane. The results for complex calculations have been summarized in Table 4 in comparison with the optimized conformations of 12-ane N_4 and 12-ane O_4 and their Li(I) complexes. Within this series, the 12-ane N_2O_2/Li(I) complex is the only case where conformational changes can take place easily. This is in agreement with some experimental observations [19, 20]. The ring cavity has been contracted by the small Li(I) in all cases. The presence of hydrogen atoms bound to nitrogen donors, as in the 12-ane N_2O_2 and 12-ane N_4 ligands, restricts also the possibilities of ring

TABLE 4. The most stable conformations of macrocyclic compounds, calculated by the *ab initio* method (torsional angles given in parentheses)

System	12-ane N_2O_2	12-ane N_4	12-ane O_4
Free ligand	alternate(66)[a]	alternate(70)	maxidentate(65)
Li(I) complex	alternate(62)[b] maxidentate(30)	alternate(64)	maxidentate(56)

[a]68° by CNDO/2 method. [b]Higher than 140° by CNDO/2 method.

deformation due to ion–hydrogen repulsion, which does not occur in 12-ane O_4.

Comparison of the energy consumption by the change of the ligand's structure either within the same conformation (torsion) or switching between conformations, allows one to conclude that the order of conformational flexibility of free ligands is 12-ane N_2O_2 < 12-ane N_4 < 12-ane O_4. For example, changing from the most stable conformation of the free ligands to the energetically nearest one, which is the maxidentate form with torsion angles of 30° for 12-ane N_2O_2, 60° for 12-ane N_4 and 65° for 12-ane O_4, requires an energy input of 0.8, 4.0 and 4.6 kcal mol^{-1}, respectively.

Macrocyclic effect

In order to analyze the 'macrocyclic effect', prestrain energy consumption and energy gain during complexation for both cyclic and non-cyclic ligands have to be evaluated. In all cases of Table 3, the energy requirement to prepare the ligands for complexation (prestrain energy, cf. eqn. (1)) for cyclic ligands is considerably less than for their open-chain analogues. As expected, the amount of energy consumption during this process follows the previously shown order of the free ligands' flexibility, i.e. 12-ane N_2O_2 < 12-ane N_4 < 12-ane O_4.

Considering the energy set free in the binding step (eqn. (2)), the 12-ane N_4/Li(I) complex gains more energy than 12-ane N_2O_2 and than 12-ane O_4 complexes, respectively. This order also remains valid for non-cyclic ligands. The relative higher energy contribution of this process compared to prestrain requirements determines also the final order of complex stabilities (overall stabilization energies as shown in Table 3); Li(I)/12-ane N_4 > Li(I)/12-ane N_2O_2 > Li(I)/12-ane O_4. The energy difference between both processes leads to the order of the macrocyclic effects as 12-ane O_4 > 12-ane N_4 > 12-ane N_2O_2 (Table 3). Enhanced stability of the macrocyclic complex with mixed donor atoms compared to its open-chain analogue is still present and follows mainly from the ligand's prestrained conformation. The magnitude of this effect, however, is considerably smaller than in the case of the corresponding ligands with either only N or O atoms as coordination places.

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