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# Molecular Rearrangement of an Aza-Scorpiand Macrocycle Induced by pH. A Computational Study

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**Abstract:** Rearrangements and their control are a hot topic in supramolecular chemistry due to the possibilities that these phenomena open in the design of synthetic receptors and molecular machines. Macrocycle aza-scorpiands constitute an interesting system that can reorganize their spatial structure depending on pH variations or the presence of metal cations. In our case, the conformations change varies between the so called ‘open’ and ‘closed’, the last being found at lower pH. In this study, the relative stabilities of these conformations were predicted computationally by the Density Functional Theory approximation and the reorganization from closed to open was simulated by using the Monte Carlo Multiple Minimum method.

**Keywords:** pH controlled; supramolecular chemistry; synthetic receptors; aza-scorpiands; Density Functional Theory; Monte Carlo Multiple Minimum

## 1. Introduction

The possibility of controlling the conformation of chemical structures is interesting because opens the possibility of creating molecular machines and synthetic receptors that react to the desired stimuli.1 Among the molecular structures showing such property stand out the aza-macrocycles that show a coordinating tail, known as scorpiands. These systems merit attention due to their potential biological and pharmacological applications, since their ability to recognize hydrophilic and hydrophobic amino acids has been demonstrated.2 Receptors for amino acid sensing3 or drug delivery4 are two fields for their potential applications.

Changes in the protonation state are able to induce conformational reorganizations in scorpiand-like ligands.5,[6] It has been observed that the presence of metal centers produce similar effects. Also, the metal coordination is influenced by the protonation state because of electrostatic repulsion.7

In this study, pH variation that make the structure change from the so called 'closed' to 'open' conformations have been simulated.

## 2. Methods

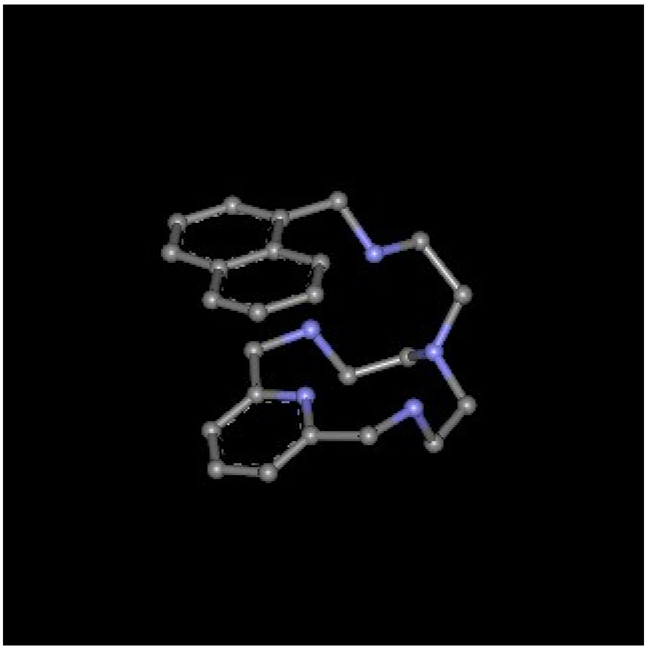
**MM Conformational search.** The simplified structures presented in Figure 1 were taken from X-ray geometries. Experimental values of the energy required to change the conformations from closed (**A**) to open (**B**) and vice versa, depending of the protonation state, are lacking. To have an understanding of the conformational stabilities involved in this process, the following simulation was undertaken. Conformation **A** is preferred for the mono- and diprotonated species. Preserving this conformation the molecule was triprotonated. Then, a conformational search was performed by Monte Carlo Multiple Minimum (MCMM) method8 with the MM+ force field,[9] by allowing the free change of the dihedral angles comprised in the carbon bridge that joins the two rings (tail). This method allows finding the lowest energy conformations of a molecule by randomly varying specified dihedral angles to generate new starting conformations and then energy minimizing each of those. Low-energy unique conformations are stored while high-energy or duplicate structures are discarded. Rotation is used for acyclic bond dihedral angles. The energy cut-off for discarding repeated structures was set to 6 Kcal/mol. Conversely, conformation **B** was di- or monoprotonated and treated with the same procedure, to see if it was able to reach the conformation **A**. These calculations were performed with the program Hyperchem version 7.5.[10]

The relative stabilities of these conformations were predicted by Density Functional Theory and the rearrangement was simulated by a Molecular Mechanics method.

**Relative energies calculation.** In order to provide computationally derived relative stability estimates to have an understanding of the conformational energies, density functional theory (DFT) calculations were undertaken. The three protonation states - mono, di and tri - were combined with the two possible conformational states **A** and **B** giving six chemical structures. For each protonation, the conformation energies of optimized **A** and **B** were compared to see which one would be more stable into simulated water environment. It was considered the atomisation energy, this is, the stabilization of the molecule relative to the free constitutive atoms. Several combinations of exchange functionals and basis sets were tested. The method finally chosen was all-electron local density approximation (LDA)[11] with the Vosko Wilk Nusair (VWN) functional and the Slater basis valence quadruple zeta with four polarization functions (ZORA/QZ4P), under the restricted spin formalism. Water environment was simulated by the method COSMO.[12] Some results also presented in this paper were obtained with the "generalized gradient approximation Becke88 Perdew86"[13] (GGA-BP) gradient corrected exchange funtional and the TZ2P basis, with no solvent simulation. All these calculations were performed by means of the program Amsterdam Density Functional.[14]

**Table 1.** Torsion angles in the tail for different conformations obtained with MCMM, starting with the conformation **A**

| Conformation | Torsions allowed | a | b | c | d | e |
|---|---|---|---|---|---|---|
| **A** | - | -146.8 | 74.4 | -170.9 | 80.7 | 77.0 |
| 1 | 12-ring, d | -148.4 | 59.1 | 176.8 | 144.9 | 66.3 |
| 2 | 12-ring, b, d | 68.2 | 179.2 | -91.2 | 71.3 | 74.7 |
| 3 | a, b | -67.9 | -175.5 | 94.2 | -67.3 | 105.3 |
| 4 | d | -62.6 | -167.8 | -177.3 | -176.9 | -814 |
| 5 | 12-ring, a | -154.9 | 170.8 | 177.6 | 172.9 | -87.1 |
| **B** | - | 69.4 | -176.5 | -177.2 | -179.2 | 84.6 |



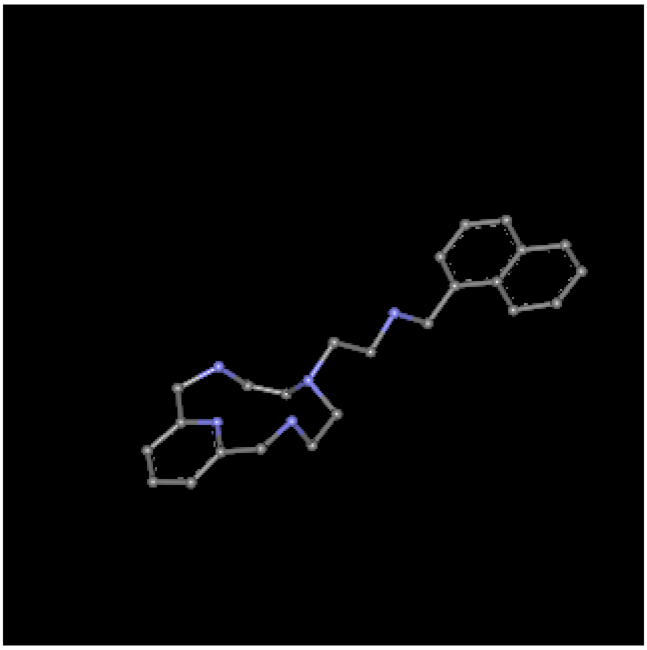


**Figure 1.** Conformations closed (**A**) and open (**B**) of the aza-scorpiand macrocycle studied

**Table 2.** Geometric parameters involved in the water box calculations for each conformation obtained from MCMM

| Conformation | Smallest Box Enclosing Solute / Å | | | Cubic Periodic Box Edge / Å | Maximum number of water molecules |
|---|---|---|---|---|---|
| | X | Y | Z | | |
| **A** | 6.90 | 6.19 | 7.73 | 18.10 | 216 |
| 1 | 7.65 | 5.87 | 7.80 | 18.10 | 216 |
| 2 | 8.08 | 6.91 | 9.07 | 18.10 | 216 |
| 3 | 7.76 | 5.71 | 10.75 | 21.51 | 329 |
| 4 | 7.49 | 5.42 | 15.48 | 30.96 | 980 |
| 5 | 7.30 | 5.17 | 19.91 | 31.81 | 1064 |
| **B** | 6.90 | 3.29 | 17.62 | 35.25 | 1447 |

**Table 3.** Calculated energies for each protonation state and conformation closed (**A**) and open (**B**)

| Starting conformation | Number of H+ | Method | Environment simulation method | Total Bond Energy/ kcal/mol |
|---|---|---|---|---|
| A | 1 | LDA/QZ4P | COSMO | -9171.05 |
| B | 1 | LDA/QZ4P | COSMO | -9162.84 |
| A | 2 | LDA/QZ4P | COSMO | -9178.82 |
| B | 2 | LDA/QZ4P | COSMO | -9152.72 |
| A | 3 | LDA/QZ4P | COSMO | -9133.36 |
| B | 3 | LDA/QZ4P | COSMO | -9134.40 |
| A | 3 | GGA-BP/TZ2P | vacuum | -8396.54 |
| B | 3 | GGA-BP/TZ2P | vacuum | -8408.01 |

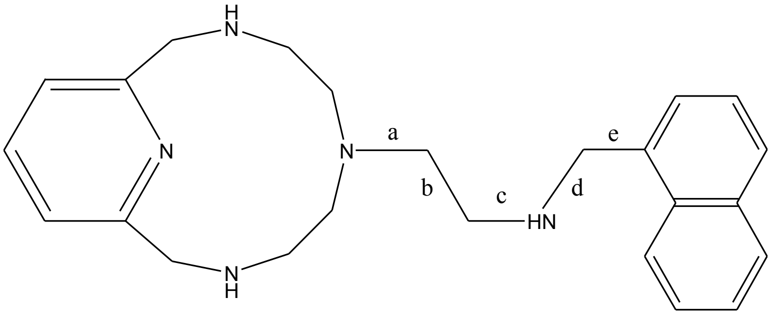


**Figure 2.** Labels for the dihedral angles

## 3. Results and Discussion

MM Conformational search. As the pH in the solvent decreases, the two macrocyclic secondary amines are first protonated, and then the bridge's secondary amine. Thus, H-bonds between the bridge and the macrocyclic amines and with the pyridine nitrogen in A are progressively weakening, and this makes conformation B more stable for the triprotonated species. To model these changes, MCMM was preferred to Molecular Dynamics (MD) trajectories because the conformational changes pursued were mainly torsions of the bridge atoms, and only MCMM give these straightforwardly. Furthermore, the groups attached to the extremes of the bridge were too large to switch efficiently under MD. Figure 2 shows the neutral chemical structure with the nomenclature used for the different dihedral angles that have been rotated in different runs. The labels point out the central bond that undergoes torsion for each dihedron. The conformational change between A and B can be done in several ways. It can imply complete torsion of the bond between the two carbon atoms in the bridge, b, and the consecutive bond that joins to the 12-ring amine a (eventually, e can be rotated to obtain the same enantiomer). Also, it can be done by inverting the 12-ring and rotating b and e. Thus, if we track the changes, we see that the sequence of torsion angles is not linear, but even corkscrewing in some cases. These are the changes that must overcome the main rotational barriers, since all the dihedral angles suffer minor changes to obtain B, due to the MM+ optimization.

Beginning with the closed conformation **A**, it was triprotonated and MCMM simulations were performed allowing different freedom degrees in different runs.

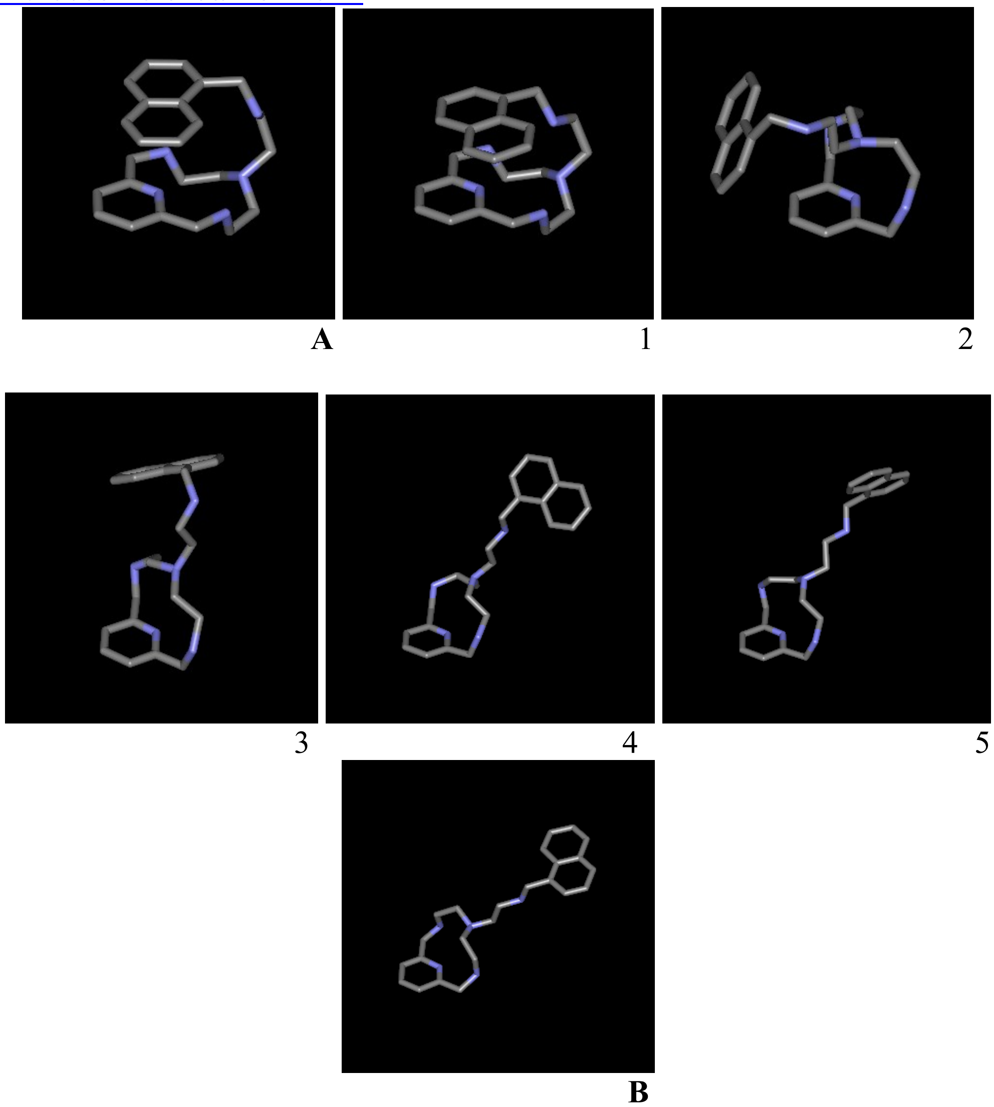


**Figure 3. A** and **B**, conformations from X-ray minimised in the periodic box. 1-5, conformations obtained from MCMM in vacuum and further minimisation in standard water density-constant TI3P box until their respective local minima, for different runs

These calculations were first attempted with the molecule in a water constant-density periodic box (standard water molecules TIP3P, equilibrated at 300 K and 1 atm., minimum distance between solvent and solute atoms: 2.3 Å), but the results did not converge and the program was unstable. For this reason, MCMM simulations were run in vacuum and the final conformations achieved were minimised in the referred periodic box boundary conditions.

It is possible ordering the resulting conformations obtained and figuring a movie in which **B** is obtained from **A** in successive steps, which are relative minima. Table 1 and Figure 3 display different conformations obtained as local minima, all of them from **A**, with their respective values for the torsion angles. As said, these conformations result from MCMM and minimisation within their corresponding water periodic boxes. For clarity, water molecules have been removed from Figure 3. Table 2 shows the parameters involved in the periodic box boundary step.

The conformations for the 12-ring obtained with MM+ are distorted with respect the X-ray diffraction model as well as the DFT simulations. Furthermore, it seems that ring torsion is not well achieved for macrocycles, with the algorithms currently implemented in MCMM for ring inversion. In spite of these drawbacks, conformation 5, near **B,** is obtained and the sequence can be illustrative of the conformation change.

Unfortunately, it was not possible obtaining a conformation near **A** from **B** with MCMM, due probably to the huge number of freedom degrees involved and the underestimation of H-bond interaction in MM+ that implied calculation times beyond our possibilities. The entropy of **B** must be the greatest.

.**Relative energies calculation.** DFT calculations to compare the relative stabilities of conformations for each protonation state were tried by using different exchange functionals and basis sets. Water environment was simulated by the COSMO method. Relativistic contributions were not considered significant because there were no heavy nuclei involved. The determinant importance of hydrogen bonds in the conformational equilibrium made necessary using several polarization functions. In fact, BP86/TZP and GGA-BP/TZ3P did not give good results, and all-electron QZ4P basis was necessary. All the calculations performed assigned the correct energy order for the triprotonated species: the extended conformation **B** was found more stable. But this result was also found with the monoprotonated stage when QZ4P was not used. LDA was useful to estimate properties in big molecules and it was the only method that allowed good results within reasonable calculation time (ca. eight hours with a Pentium 4 3.2GHz running on Windows XP, 1Gb RAM). Although the predicted values for atomization energies estimated are maybe not accurate, the method qualitatively predicted the experimental results. Table 3 shows the results obtained. The integration accuracy was four decimal places. Three decimal places were also tried to see the influence in the final result. It was seen that the dispersion of the result was lower than the differences between the values to be compared. The conclusions were, thus, unchanged.

In order to have a confirmation with a more complex functional of the trends obtained, GGA-BP/TZ2P was used for a simulation without solvent. Only two calculations were performed to compare atomization energies of the triprotonated species both, in its crystal conformation, **B**-open, and in the diprotonated one, **A**-closed. The integration accuracy was fixed in three decimal places. The calculation time for each process was eight days approximately with the same computer. These gave more reliable stability prediction at greater protonation state. The results are displayed in Table 3.

The optimized conformations obtained were compared with the crystal ones. Using the Carbó index measured through Coulomb integrals and the local Newton-Raphson as superposition algorithm, the similarity was quantified. Thus, monoprotonated **A** and its minimized conformation obtained by LDA/QZ4P showed Carbó index equal to 0.932, and triprotonated **B** and its respective optimization gave 0.964.

## 4. Conclusions

MCMM method was useful in the present study, but some drawbacks must be pointed out. Thus, ring torsions in macrocycles do not seem well simulated. The pH dependent opening of the scorpiand was easy to predict, but the reverse effect was not possible to be simulated.

DFT was a good method to give account of the experimental stability, although all-electron basis was necessary. The LDA approximation with the COSMO method was enough to obtain relative stabilities clearly according to the experiments at lower protonation. At more acidic pH, the more complex functional GGA-BP with a somewhat simple basis gave more reliable results.

The optimized conformations obtained were well-agree with the crystal ones, as verified by Quantum Molecular Similarity.

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## Conflicts of Interest

The authors declare no conflict of interest.

## References and Notes

1. Kinbara, K., & Aida, T. (2005). Toward intelligent molecular machines: directed motions of biological and artificial molecules and assemblies. *Chemical reviews*, *105*(4), 1377-1400.
2. Blasco, S., Verdejo, B., Bazzicalupi, C., Bianchi, A., Giorgi, C., Soriano, C., & García-España, E. (2015). A thermodynamic insight into the recognition of hydrophilic and hydrophobic amino acids in pure water by aza-scorpiand type receptors. *Organic & biomolecular chemistry*, *13*(3), 843-850.
3. Bernier, N., Esteves, C. V., & Delgado, R. (2012). Heteroditopic receptor based on crown ether and cyclen units for the recognition of zwitterionic amino acids. *Tetrahedron*, *68*(24), 4860-4868..
4. Aydın, I., Aral, T., Karakaplan, M., & Hoşgören, H. (2009). Chiral lariat ethers as membrane carriers for chiral amino acids and their sodium and potassium salts. *Tetrahedron: Asymmetry*, *20*(2), 179-183.
5. Verdejo, B., Acosta-Rueda, L., Clares, M. P., Aguinaco, A., Basallote, M. G., Soriano, C., ... & García-España, E. (2015). Equilibrium, Kinetic, and Computational Studies on the Formation of Cu2+ and Zn2+ Complexes with an Indazole-Containing Azamacrocyclic Scorpiand: Evidence for Metal-Induced Tautomerism. *Inorganic chemistry*, *54*(4), 1983-1991.
6. Verdejo, B., Ferrer, A., Blasco, S., Castillo, C. E., González, J., Latorre, J., ..& García-España, E. (2007). Hydrogen and copper ion-induced molecular reorganizations in scorpionand-like ligands. A potentiometric, mechanistic, and solid-state study. *Inorganic chemistry*, *46*(14), 5707-5719.
7. Pallavicini, P. S., Perotti, A., Poggi, A., Seghi, B., & Fabbrizzi, L. (1987). N-(aminoethyl) cyclam: a tetraaza macrocycle with a coordinating tail (scorpiand). Acidity controlled coordination of the side chain to nickel (II) and nickel (III) cations. *Journal of the American Chemical Society*, *109*(17), 5139-5144.
8. a) Chang, G., Guida, W. C., & Still, W. C. (1989). An internal-coordinate Monte Carlo method for searching conformational space. *Journal of the American Chemical Society*, *111*(12), 4379-4386; b) Saunders, M., Houk, K. N., Wu, Y. D., Still, W. C., Lipton, M., Chang, G., & Guida, W. C. (1990). Conformations of cycloheptadecane. A comparison of methods for conformational searching. *Journal of the American Chemical Society*, *112*(4), 1419-1427; c) Kolossváry, I., & Guida, W. C. (1993). Torsional flexing: Conformational searching of cyclic molecules in biased internal coordinate space. *Journal of computational chemistry*, *14*(6), 691-698.
9. Allinger, N. L. (1977). Conformational analysis. 130. MM2. A hydrocarbon force field utilizing V1 and V2 torsional terms. *Journal of the American Chemical Society*, *99*(25), 8127-8134.
10. Hypercube (2005). HYPERCHEM. Version 7.5. Hypercube Inc., 1115 NW 4th St., Gainsville, FL 32601-4256, USA.
11. Versluis, L., & Ziegler, T. (1988). The determination of molecular structures by density functional theory. The evaluation of analytical energy gradients by numerical integration. *The Journal of chemical physics*, *88*(1), 322-328.
12. a) Klamt, A., & Schüürmann, G. (1993). COSMO: a new approach to dielectric screening in solvents with explicit expressions for the screening energy and its gradient. *Journal of the Chemical Society, Perkin Transactions 2*, (5), 799-805; b) Pye, C. C., & Ziegler, T. (1999). An implementation of the conductor-like screening model of solvation within the Amsterdam density functional package. *Theoretical Chemistry Accounts*, *101*(6), 396-408.
13. Perdew, J. P., & Burke, K. (1996). Comparison shopping for a gradient-corrected density functional. *International journal of quantum chemistry*, *57*(3), 309-319.

14. ADF2006.01, SCM, Theoretical Chemistry, Vrije Universiteit, Amsterdam, The Netherlands, http://www.scm.com