

Mechanistic insights into a Zn-assisted ring-chain tautomerism process involving a 1,2,3,4-tetrahydroquinazoline and a Schiff base

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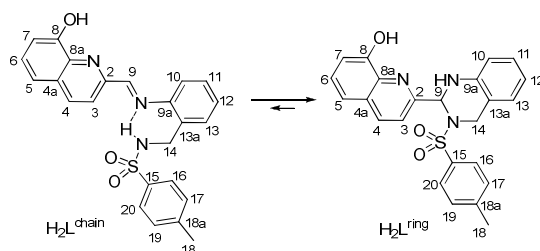
Abstract

Density functional theory calculations and spectroscopic monitoring of the reactions of the chain tautomer *N*-{2-[(8-hydroxyquinolin-2-yl)methyleneamino]benzyl}-4-methylbenzene-sulfonamide (H_2L^{chain}) and the ring tautomer 2-(3-tosyl-1,2,3,4-tetrahydroquinazolin-2-yl)quinolin-8-ol (H_2L^{ring}) against $Zn(OAc)_2 \cdot 2H_2O$ have been performed in order to clarify the role of the metal ion in the ring-opening/closing reaction under investigation. The results obtained show that, among the processes leading to zinc complexes that could occur, the path leading to $Zn(HL^{\text{ring}})_2$ is the energetically more favorable one. Thus, this path would be preferred in the presence of sufficient free ligand in solution, regardless of its tautomeric form. The latter is due to the formation of energetically similar key intermediate complexes $Zn(OAc)(HL^{\text{chain}})$ and $Zn(OAc)(HL^{\text{ring}})$. The process to afford $Zn_2(L^{\text{chain}})_2$ by dimerization of the intermediate complex $Zn(OAc)(HL^{\text{chain}})$ is energetically unfavourable and is only obtained in good yield by decreasing the stoichiometry of the ligand and at high reaction temperature.

Keywords: ring opening/closing, DFT calculations, zinc, NMR monitoring

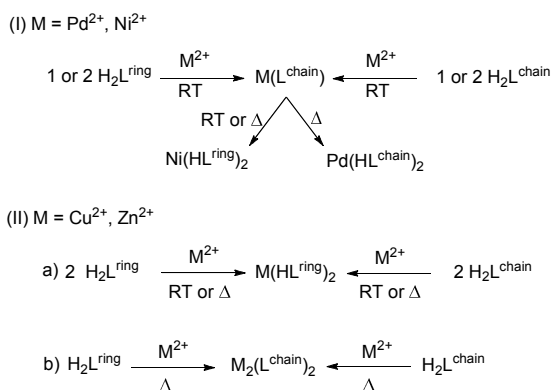
Introduction

Recently,¹ we have shown (Sch. 1) that in the absence of metal ions the chain tautomer *N*-{2-[(8-hydroxyquinolin-2-yl)methyleneamino]benzyl}-4-methylbenzene-sulfonamide (H_2L^{chain}) easily undergoes an intramolecular cyclization reaction to give the final more thermodynamically stable product, the ring tautomer 2-(3-tosyl-1,2,3,4-tetrahydroquinazolin-2-yl)quinolin-8-ol (H_2L^{ring}). In the presence of Pd^{2+} the tetrahydroquinazoline-imine tautomeric equilibrium is shifted towards the chain form, yielding $Pd(HL^{\text{chain}})_2$, while Ni^{2+} shifts the equilibrium towards the ring form to afford $Ni(HL^{\text{ring}})_2$ (Sch. 2, I). Besides, we have also demonstrated² that when the metal ions are Cu^{2+} and Zn^{2+} the metal-assisted ring-closing/opening process is tuned through varying ligand stoichiometry rather than the starting ligand tautomer (Sch. 2, II).



Sch. 1. Chain and ring tautomers of the ligand with the numbering scheme for NMR.

Thus, we have shown that $\text{Zn}(\text{HL}^{\text{ring}})_2$ is the main product obtained in the presence of sufficient free ligand in solution, while by decreasing the stoichiometry of the ligand, the course of this reaction can be fundamentally altered to produce $\text{Zn}_2(\text{L}^{\text{chain}})_2$ regardless of the starting ligand form. In this work, in order to shed light on the thermodynamics of the closing/opening of the tetrahydroquinazoline ring, molecular modeling studies of the various zinc complexes that could be involved were carried out. The theoretical studies and the spectroscopic monitoring of the reactions studied in this work (at room temperature and under reflux) led us to propose a pathway for the process and to clarify the role of the zinc(II) ion.



Sch. 2. Summary of the results obtained by reaction of Pd^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} with the chain and ring tautomers of the ligand in a 1:1 and 1:2 molar ratio.

Experimental

Spectroscopic monitoring

The reaction of $\text{H}_2\text{L}^{\text{ring}}/\text{H}_2\text{L}^{\text{chain}}$ and $\text{Zn}(\text{OAc})_2$ in a 1:1 and 2:1 molar ratios were performed as previously reported.² The ^1H NMR spectroscopic monitoring of the reactions was performed taking aliquots of the reaction mixtures at different times and temperatures and recording their ^1H NMR spectra.

Theoretical studies

All calculations were performed using the Gaussian 09W³ program package DFT level by means of the hybrid M06 functional.⁴⁻⁵ The standard 6-31G(d) basis set was used for C, H, O, S and N and the LANL2DZ relativistic pseudopotential was used for Zn. The starting point of these calculations was the crystal structure of $\text{Zn}(\text{HL}^{\text{ring}})_2$.² Firstly, the solved crystal structure obtained was minimized at a DFT level. The resulting energy value was taken as a reference for all subsequent calculations. On the optimized geometries a DFT minimization in CH_3OH solution by means of the polarizable continuum solvation model⁶ was performed. Harmonic frequencies were calculated at the same level of theory to characterize the stationary points and to determine the zero-point energies (ZPE). All the calculations were first performed in vacuum, and then in methanol to compare the solvent effect.

To explore the conformational preference of the zinc complexes, the dihedral angles C3–C2–C9–N3 in $\text{H}_2\text{L}^{\text{ring}}$ and C9–N2–C9a–C10 and C13a–C14–N3–S in $\text{H}_2\text{L}^{\text{chain}}$ were progressively incremented from 0° to 360° , and the resultant geometries were minimized using PM6. The most stable conformers were further minimized by DFT. It was considered that the conformation around the metal might not change significantly. Therefore, a tetrahedral coordination was used for zinc complexes. For the four most stable conformers of each complex the harmonic frequencies were calculated in vacuum and methanol solution. As a result, three possible stereoisomers of $\text{Zn}(\text{HL}^{\text{ring}})_2$, one conformer for theoretical $\text{Zn}(\text{HL}^{\text{chain}})_2$ and one for $\text{Zn}(\text{HL}^{\text{ring}})(\text{HL}^{\text{chain}})$ were obtained.

Results and discussion

The monitoring of the reaction between $\text{H}_2\text{L}^{\text{chain}}$ or $\text{H}_2\text{L}^{\text{ring}}$ and $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ was performed, in order to try to gain an insight into the ring opening/closing process. Accordingly, the spectrum of a mixture of $\text{H}_2\text{L}^{\text{chain}}$ or $\text{H}_2\text{L}^{\text{ring}}$ and $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ in 1:1 molar ratio showed that, at 65 °C, the reaction leads to $\text{Zn}_2(\text{L}^{\text{chain}})_2$ in both cases and that it is completed in 5 min. (Fig. 1).

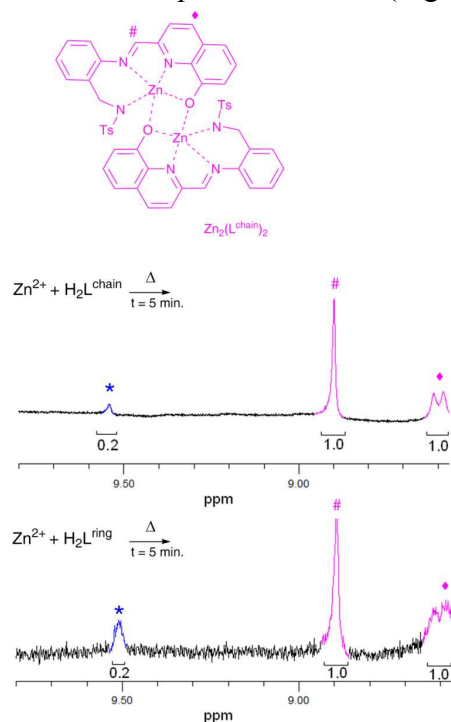


Fig. 1. Sections of the ^1H NMR spectra in $\text{dms}\text{-}d_6$ (8.5–9.8 ppm) corresponding to the monitoring of the reaction between $\text{H}_2\text{L}^{\text{ring}}$ or $\text{H}_2\text{L}^{\text{chain}}$ and $\text{Zn}(\text{OAc})_2$ in 1:1 molar ratio at 65 °C. Most representative proton signals of each species are marked by the symbols # and ♦. Integration values are under the corresponding signals. The signal marked with * corresponds to a minor product that could not be unequivocally identified.

The ^1H NMR spectroscopic monitoring of the reaction between $\text{H}_2\text{L}^{\text{chain}}$ or $\text{H}_2\text{L}^{\text{ring}}$ and $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ in 2:1 molar ratio at room temperature showed that $\text{Zn}(\text{HL}^{\text{ring}})_2$ is formed in both cases. The same results are obtained at 65 °C (Fig. 2). Regardless of the initial tautomer employed, $\text{H}_2\text{L}^{\text{ring}}$ remains as free ligand in solution in both cases. When starting from $\text{H}_2\text{L}^{\text{chain}}$, an unidentified species, also shown in Fig. 1, is formed as a minor product. However, this species is not detected when $\text{H}_2\text{L}^{\text{ring}}$ is used as a reactant at room temperature.

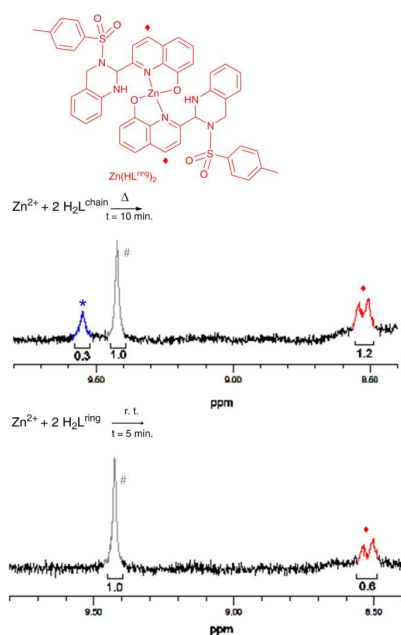
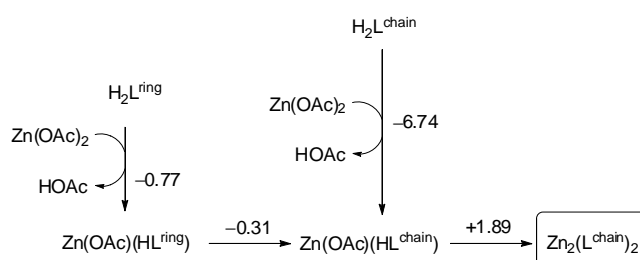
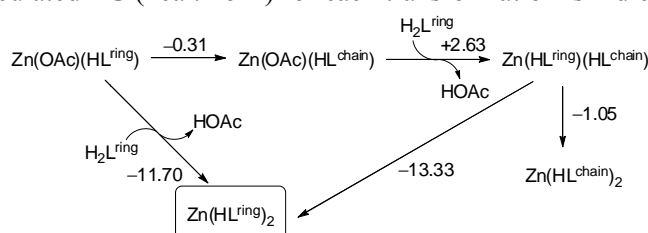


Fig. 2. Sections of the ^1H NMR spectra in $\text{dms}\text{-}d_6$ (8.4–9.8 ppm) corresponding to the monitoring the reaction between $\text{H}_2\text{L}^{\text{ring}}$ or $\text{H}_2\text{L}^{\text{chain}}$ and $\text{Zn}(\text{OAc})_2$ in 2:1 molar ratio at 65 °C. Most representative proton signal of the mononuclear complex are marked with ♦. The signals marked with # correspond to the phenol proton of unreacted $\text{H}_2\text{L}^{\text{ring}}$ and that with * to a minor product that could not be unequivocally identified. Integration values are under the corresponding signals.

Computational studies were undertaken in order to gain a further insight into why the two tautomers of the ligand, H_2L^{ring} and H_2L^{chain} , on reaction with Zn^{2+} in 1:1 molar ratio always give rise to the complex $Zn_2(L^{\text{chain}})_2$ while for a 2:1 molar ratio the complex $Zn(HL^{\text{ring}})_2$ is obtained. Besides, this study would also enable a more detailed identification of the relevant intermediates. Geometry optimizations and energy calculations were performed using the Gaussian 09W³ program package at the density functional theory (DFT) level by means of the hybrid M06 functional^{4,5} using the standard 6-31G(d) basis set. A polarizable continuum⁶ solvation model (methanol as solvent) was used for energy calculations to take into account the solvent effect. Taking into account that $Zn_2(L^{\text{chain}})_2$ is only obtained for a 1:1 molar ratio while complex $Zn(HL^{\text{ring}})_2$ is the final product for a 2:1 molar ratio, two processes were considered (Sch. 3 and 4).



Sch. 3. Proposed pathway for the formation of $Zn_2(L^{\text{chain}})_2$ either from H_2L^{ring} or H_2L^{chain} . Calculated ΔG ($\text{kcal}\cdot\text{mol}^{-1}$) for each transformation is indicated.



Sch. 4. Proposed pathway for the formation of $Zn(HL^{\text{ring}})_2$ either from H_2L^{ring} or H_2L^{chain} . Calculated ΔG ($\text{kcal}\cdot\text{mol}^{-1}$) for each transformation is indicated.

The first steps of each pathway would be common to both processes and these would involve the displacement of one of the acetate ligands in $Zn(OAc)_2\cdot 2H_2O$ by H_2L^{chain} or H_2L^{ring} to give $Zn(OAc)(HL^{\text{chain}})$ or $Zn(OAc)(HL^{\text{ring}})$, respectively (Fig.3). The similar energies found for both complexes might explain why both ligands provide the same final product. This displacement is energetically more favorable for the reaction between H_2L^{chain} and $Zn(OAc)_2\cdot 2H_2O$ (almost $6\text{ kcal}\cdot\text{mol}^{-1}$).

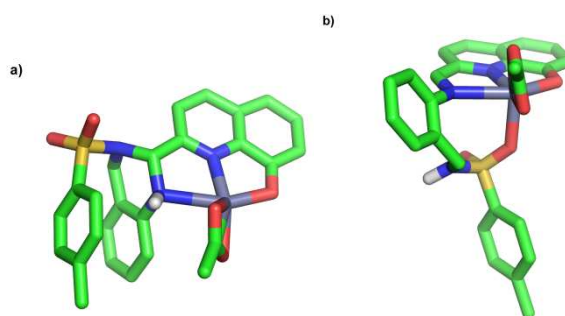
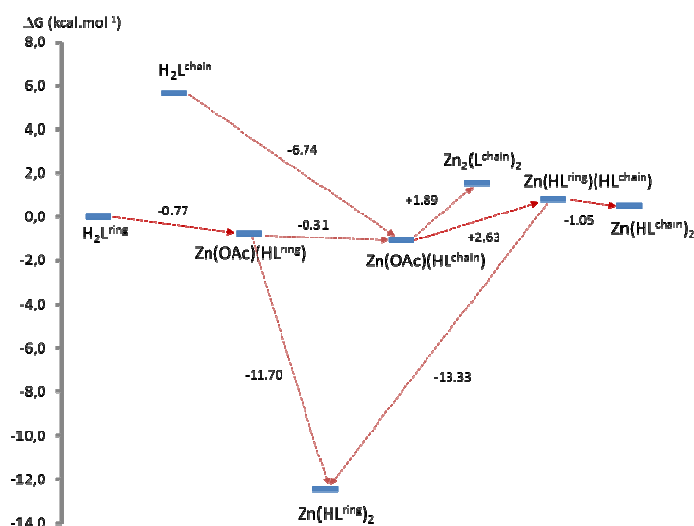


Fig. 3. Most stable conformers of a) $Zn(OAc)(HL^{\text{ring}})$ and b) $Zn(OAc)(HL^{\text{chain}})$.

For 1:1 molar ratio, i.e. in the absence of enough tetrahydroquinazoline ligand H_2L^{ring} in solution, the readily formed $Zn(OAc)(HL^{\text{chain}})$ or $Zn(OAc)(HL^{\text{ring}})$ via

$\text{Zn}(\text{OAc})(\text{HL}^{\text{chain}})$ would undergo a dimerization reaction to give $\text{Zn}_2(\text{L}^{\text{chain}})_2$ (Sch. 3). It must be noted that any $\text{H}_2\text{L}^{\text{chain}}$ free ligand in solution was observed. This conversion requires a calculated ΔG of $+1.9 \text{ kcal}\cdot\text{mol}^{-1}$ and this might explain the higher temperature required for the formation of $\text{Zn}_2(\text{L}^{\text{chain}})_2$ in comparison with the room temperature process that leads to the formation of $\text{Zn}(\text{HL}^{\text{ring}})_2$ in a 2:1 molar ratio (Sch. 4).

For a 2:1 molar ratio, $\text{Zn}(\text{OAc})(\text{HL}^{\text{ring}})$ or $\text{Zn}(\text{OAc})(\text{HL}^{\text{chain}})$ via $\text{Zn}(\text{OAc})(\text{HL}^{\text{ring}})$ would undergo an alternative, energetically more favorable process (Sch. 4, $\Delta G_{\text{calc}} = -11.7 \text{ kcal}\cdot\text{mol}^{-1}$), which is the displacement of the remaining acetate ligand by $\text{H}_2\text{L}^{\text{ring}}$ in solution, to provide the experimentally obtained $\text{Zn}(\text{HL}^{\text{ring}})_2$. This transformation is energetically more favorable than the dimerization of $\text{Zn}(\text{OAc})(\text{HL}^{\text{chain}})$ to give $\text{Zn}_2(\text{L}^{\text{chain}})_2$ (Sch. 3, $\Delta G_{\text{calc}} = +1.89 \text{ kcal}\cdot\text{mol}^{-1}$) or the formation of $\text{Zn}(\text{HL}^{\text{chain}})_2$ via $\text{Zn}(\text{HL}^{\text{ring}})(\text{HL}^{\text{chain}})$ (Sch. 4, $\Delta G_{\text{calc}} = +2.63 \text{ kcal}\cdot\text{mol}^{-1}$). Therefore, in the presence of sufficient free $\text{H}_2\text{L}^{\text{ring}}$ in solution, the formation of $\text{Zn}(\text{HL}^{\text{ring}})_2$ would be preferred. A complete Gibbs free energy profile for the formation of experimentally obtained complexes $\text{Zn}(\text{HL}^{\text{ring}})_2$ and $\text{Zn}_2(\text{L}^{\text{chain}})_2$ either from $\text{H}_2\text{L}^{\text{ring}}$ or $\text{H}_2\text{L}^{\text{chain}}$ is shown in Sch. 5.



Sch. 5. Complete Gibbs free energy profile for the formation of $\text{Zn}(\text{HL}^{\text{ring}})_2$, $\text{Zn}_2(\text{L}^{\text{chain}})_2$ and theoretical $\text{Zn}(\text{HL}^{\text{chain}})_2$ either from $\text{H}_2\text{L}^{\text{ring}}$ or $\text{H}_2\text{L}^{\text{chain}}$. Calculated ΔG ($\text{kcal}\cdot\text{mol}^{-1}$) for each transformation is indicated

Conclusions

The monitoring of the reaction between $\text{H}_2\text{L}^{\text{chain}}$ or $\text{H}_2\text{L}^{\text{ring}}$ and $\text{Zn}(\text{OAc})_2\cdot 2\text{H}_2\text{O}$ in 1:1 and 2:1 molar ratios show that the isolation of $\text{Zn}_2(\text{L}^{\text{chain}})_2$ or $\text{Zn}(\text{HL}^{\text{ring}})_2$ depends in the stoichiometry of the reaction but not in the initial ring or chain reactant. Besides, this study shows that in the presence of Zn^{II} the ring closing/opening is a fast process.

DFT studies show that, for a 1:1 molar ratio and starting with $\text{H}_2\text{L}^{\text{ring}}$, the readily formed species $\text{Zn}(\text{OAc})(\text{HL}^{\text{ring}})$ undergoes a ring-opening reaction to give $\text{Zn}(\text{OAc})(\text{HL}^{\text{chain}})$ and subsequently a dimerization that results in $\text{Zn}_2(\text{L}^{\text{chain}})_2$. However, in the presence of sufficient free ligand in solution, $\text{Zn}(\text{HL}^{\text{ring}})_2$ would be energetically preferred via $\text{Zn}(\text{OAc})(\text{HL}^{\text{ring}})$ or $\text{Zn}(\text{OAc})(\text{HL}^{\text{chain}})$. The similar energies found for the latter both intermediate complexes explain why both ligands provide the same final product, depending on the molar ratio employed.

References

- [1] A. M. García-Deibe, J. Sanmartín-Matalobos, C. González-Bello, E. Lence, C. Portela-García, L. Martínez, M. Fondo, *Inorg. Chem.*, **2012**, *51*, 1278.
- [2] J. Sanmartín-Matalobos, C. Portela-García, L. Martínez, C. González-Bello, E. Lence, A. M. García-Deibe, M. Fondo, *Dalton Trans.*, **2012**, *41*, 6998.
- [3] Gaussian 09, Revision A.2, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.
- [4] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.*, **2008**, *120*, 215.
- [5] Y. Zhao, D. G. Truhlar, *Acc. Chem. Res.*, **2008**, *41*, 157.
- [6] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.*, **2005**, *105*, 2999.