

Hydrogen-Hydrogen Bonding: A Stabilizing Interaction in Strained Chelating Rings of Metal Complexes in Aqueous Phase

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ABSTRACT

Two H...H close contacts, classically associated with steric hindrance, were found to be H–H closed-shell bonding interactions which stabilize a zinc(II) complex with nitrilotri-3-propanoic acid, $[\text{Zn}(\text{NTPA})(\text{H}_2\text{O})_2]^-$, by *ca.* 11 kcal/mol in aqueous phase. The strain energy of three 6-member rings (*ca.* 40 kcal/mol) is significantly offset by these interactions the presence of which is indicated by the presence of a bond path, an elevated delocalization index, and a lowering of the atomic energy of each hydrogen atom involved in an H...H interaction by ~ 4 -5 kcal/mol. The difference between relevant bond path angles and geometrical bond angles in the 6-member coordination rings correlates well with strain energy and formation constants. Unexpectedly, the bite angle N–Zn–O is found to be the least strained.

INTRODUCTION

The hydrogen–hydrogen (H–H) bonding interaction has recently been characterized on the basis of the topology of the electron density [1-4] in conjunction with the quantum theory of atoms in molecules (QTAIM) [5] as distinct from the

dihydrogen bonding interaction [4,6-15]. H–H bonding is a ubiquitous interaction that is observed intra- and inter-molecularly in both calculated and experimental electron density distributions.

It is well-known that a bonding interaction results in lowering of atomic energies of atoms involved. Hence the same is expected when the nuclei of two closed-shell hydrogen atoms are linked by a bond path [16], a line of locally maximal electron density. The energy lowering of the two H–H bonded atoms, when compared with other hydrogen atoms in a similar electronic environment, is typically in the range of 1–10 kcal mol⁻¹, but a local stabilization may or may not be accompanied by a global stabilization [3]. The stabilizing nature of this interaction has been challenged in the literature [17,18] but is now generally accepted as more evidence has accumulated in the literature from both experiment [19-23] and theory [3,24-26]. (For a review, see Ref. [2] and references therein).

Our focus in this work is on intramolecular close contacts between H-atoms in metal complexes in order to establish if these constitute so called H-clashes or a stabilizing intramolecular interaction. This letter investigates the contribution of the H–H bonding interactions in five conformers of a zinc(II) complex with nitrilotri-3-propanoic acid, [Zn(NTPA)(H₂O)₂]⁻, which will be referred to as ZnNTPA for simplicity in this *Letter*, on the basis of density functional theory (DFT) B3LYP/6-311++G(*d,p*) calculations performed in aqueous phase where the solvent is modeled by the continuum model known as self-consistent reaction field (SCRF) [27]. These H–H interactions (they were also suggested in [Ni(NTPA)(H₂O)₂]⁻ [28]) together with a strain energy in the coordination rings are extensively characterized for the first time in solution phase. The

strain energy in the 6-member coordination rings of ZnNTPA is compared with that in the 5-member coordination rings in the complex of Zn(II) with nitrilotriacetic acid, ZnNTA, in solution phase.

RESULTS AND DISCUSSION

The energy of an atom in a molecule is well-defined within QTAIM through the application of the atomic statement of the virial theorem [5]. The physical meaning of atomic energies within DFT has recently been investigated and shown to follow the same trends as those obtained from MP2 wavefunctions [29]. In this letter, atomic energies include the perturbation to the internal energy of the system by the solvent since the wavefunctions are obtained from a fully interacting polarized solute and polarized solvent system ($\langle \Psi(f) | \hat{H} + \hat{V}(f) / 2 | \Psi(f) \rangle$).

Fig. 1 displays an example of a labeled ball-and-stick model of the energy-optimized geometry of ZnNTPA, conformer 5 (C5), as well as the corresponding molecular graph that exhibits curved H27–H28 and H31–H32 bond paths. Two H–H bond paths were found in each conformer of ZnNTPA (a full set of relevant computed data obtained for five conformers of ZnNTPA is included in Table S1, of the Supplementary Information). Representative data obtained for hydrogen atoms (they form a CH₂ fragment of the chelating arm of the ligand NTPA) in the conformer C1 is shown in Table 1. It is seen in Tables 1 and S1 that the atomic energy of H–atoms involved in the H–H interaction is usually, but not always, lower when compared with the energy of a geminal H–atom ($\Delta E(\text{H}) < 0$). However, the differences E_{stab} , (**H31** – H30) – (**H34** – H35) for the **CH31–H34C** interaction and (**H27** – H26) – (**H28** – H29) for the **CH27–H28C** interaction, found in the conformer C1 and shown in Table 1 as an

example, are always negative and can be interpreted as the locally stabilizing energy contribution by the H–H bonding interactions. There are two H–H bond paths in each conformer and on average the stabilizing contribution of the stronger positive interaction is about 7.5 kcal mol⁻¹. The total stabilizing contribution of about 10.8 ± 1.9 kcal mol⁻¹ is very significant as it is equivalent to about 8 log *K* units of a complex formation constant (1.36 kcal mol⁻¹ is equivalent to 1 log *K* unit).

The presence of H–H bonding interactions can be confirmed by analysis of the atomic energies of the same H-atoms when they are and are not involved in the intramolecular interaction – selected data are shown in Table 2. As an example, the energies of H31 in conformer C1 and H30 in conformer C3 are lowered by 4.82 and 5.14 kcal mol⁻¹, respectively, when they are involved in the H–H bonding. From a full data-set shown in Table S2 of the Supplementary Information it follows that on average, the decrease in the atomic energy of atoms involved in H–H bonding interaction is 4.5 kcal mol⁻¹. We have also established that the H–H interactions found in ZnNTPA show all typical characteristics of chemical bonding, such as a linear decrease in a bond length with an increase in the electron density at a bond critical point, or a decrease in the QTAIM-defined delocalization index [30], DI(H,H), with an increase in the bond length. The latter is shown in Fig. 2, where only αCH–HCβ interactions are included (see Fig. S1, Supplementary Information, for numbering of C-atoms).

It has been reported that a molecule is strained when the bond path angles (BPA) differ from the geometrical bond angles (GBA) [5]. The larger the difference DIF = BPA – GBA the larger is the strain energy, regardless of the sign. In the case of a ring structure, the inward and outward bending of BPA is associated with the negative and

positive value of DIF, respectively. It is seen in Table S3 (Supplementary Information) that all DIFs, except for the C-N-Zn angle in all three chelating arms, are negative.

We used DIF values to map the strain energy distribution within the 6-member rings of the ZnNTPA complex. The largest strain energy is associated with the bonds of the C-O-Zn 6-member ring fragment. Surprisingly, the smallest strain energy is related to the bonds of the bite angle O-Zn-N, which has been used in classical interpretations of metal complexes geometry to evaluate stability of a complex by comparing it with an ideal bite angle value [31]. The magnitudes of the DIF, $|\text{DIF}|$, are significantly larger than zero and this clearly indicates that the $-\text{CH}_2-\text{CH}_2-\text{COO}^-$ arms of the NTPA ligand are strained when they form 6-member rings on complexation with a metal ion.

It is known that NTPA forms much weaker complexes than nitrilotriacetic acid (NTA) [32] with most metal ions. The atoms in NTPA are considerably more crowded than in NTA when these ligands are involved in a complex with the same metal ion. It is reasonable, thus, to assume that the ligand NTPA should be strained more than NTA in metal complexes. Following on that, we compared the average DIF values of relevant GBAs in Zn complexes with NTA (four conformers [33]) and NTPA (five conformers), Table 3. As anticipated, the 5-member rings in ZnNTA are strained significantly less than 6-member rings in ZnNTPA. We note that the signs of DIFs of the relevant GBAs are the same in both complexes and, importantly, the bite angle O-Zn-N in ZnNTA is also characterized by the smallest deviation from the geometrical bond path. Clearly, the bite angle cannot be regarded as the main source of strain energy in both complexes; the main contribution to strain energy must be linked with the interaction of a carboxylic group with a central metal ion. This is rather unexpected result (the bite angle is usually

considered when strength of a metal complex is concerned) and a large number of metal complexes with amino acids must be investigated to find out if this is a physical property of a general nature.

It was of interest and importance to find out if DIF values (a theoretical parameter) correlate with the computed strain energy of as-in-complex ligands and reported formation constants of the Zn(NTA) and Zn(NTPA) complexes. The average values of $\text{DIF}_{\text{ring}} = \sum |\text{BPA-GBA}|$, where DIF_{ring} refers to the sum of all angles in either three 5- or 6-member rings in the Zn(NTA) and Zn(NTPA) complexes, were found to be 46.2 and 72.9°, respectively. Interestingly, the ratio $\text{DIF}_{6\text{M-ring}} / \text{DIF}_{5\text{M-ring}} = 1.58$ correlates well with the ratio of strain energies [33] $E_s(\text{NTPA}) / E_s(\text{NTA}) = 1.89$, and the ratio of formation constants, [32] $\log K(\text{ZnNTA}) / \log K(\text{ZnNTPA}) = 1.97$. Even though the methodology adopted here can be seen as a simplification, it appears that the computed from the QTAIM analysis BPA and GBA values might be used as a predictive tool for trends in stability of metal complexes. This is a promising feature particularly for ligands which still have to be synthesized provided that one is able to energy-optimize a hypothetical metal complex as the above analysis of atomic and strain energies is applicable only for structures at the equilibrium.

CONCLUSIONS

It has been shown here that when the three arms of the ligand NTPA are attaining the structure observed in the metal complex, they are strained much more than the arms in the NTA ligand. Without a doubt this large strain energy is due to crowding of ligand's atoms in a complex. Generally, the resultant intramolecular H...H short contacts are

classically viewed as steric hindrance destabilizing the molecule [31,34] to explain the experimentally determined trend, such as $\log K(\text{ZnNTPA}) \ll \log K(\text{ZnNTA})$. We have theoretically demonstrated here that two H...H short contacts present in each ZnNTPA conformer are the H–H bonding, hence stabilizing, interactions. The computed in the as-in-ligand strain energy incorporates 10–11 kcal mol⁻¹ stabilizing contribution coming from the H–H bonding. In other words, the overall energy of the complex would be larger by about 11 kcal mol⁻¹ and this would decrease stability of a complex by *ca.* 8 log *K* units. Then it is reasonable to assume that, since $\log K(\text{ZnNTPA}) = 5.3$, this complex is formed due to decrease in the strain energy in the ligand made by the intramolecular H–H interactions, or bonding. It is also important to note that in the energy-optimized structure (which is at the equilibrium) there are no net repulsive or attractive forces present since they must cancel by definition. From this it follows that an argument of effective repulsion destabilizing forces due to steric hindrance cannot hold.

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ELECTRONIC SUPPLEMENTARY INFORMATION:

Structures and selected properties of five conformers of ZnNTPA; Properties of H-atoms in five conformers of ZnNTPA; Atomic energies $E(\text{H})$ of the same H-atoms which are or are not involved in H–H bonding; Average differences (DIF) between the AIM-computed bond path angles (BPA) and geometrical bond angles (GBA), $\text{DIF} = \text{BPA} - \text{GBA}$, in three 6-membered rings of five conformers of the Zn(NTPA) complex; a structure of ZnNTPA showing the numbering of C-atoms .

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Table 1 Properties of H-atoms and the stabilization energy, E_{stab} , of H–H bonding in Zn(NTPA). $q(\text{H})$ is the charge on an H-atom and $E(\text{H})$ is its atomic energy; BL is the bond length in the energy-optimized structure. Atoms printed in bold are involved in the H–H bonding interaction.

H–H bond	BL / Å	Atom	$q(\text{H})/\text{au}$	$E(\text{H})/\text{au}$	$\Delta E(\text{H})^{\text{a}}$	$E_{\text{stab.}}^{\text{a}}$
CH31–H34C	2.196	H31	0.021	-0.62015	−4.83	−7.66
		H30	0.029	-0.61245		
		H34	0.033	-0.61065	−2.83	
		H35	0.040	-0.60614		
CH27–H28C	2.003	H27	0.035	-0.60726	1.03	−3.15
		H26	0.036	-0.60890		
		H28	0.032	-0.62226	−4.19	
		H29	0.026	-0.61559		

(a) in kcal mol⁻¹.

Table 2 Atomic energies $E(\text{H})$ of H-atoms in conformers of ZnNTPA; atoms in bold are involved in the H–H interaction. $\Delta E = E_{\text{H}(\text{bonded})} - E_{\text{H}(\text{non-bonded})}$ in kcal mol^{−1}.

Zn(NTPA)	Atom	$E(\text{H})$ / au	ΔE / kcal mol ^{−1}
C1	H31	−0.62015	−4.82
C3	H31	−0.61246	
C3	H30	−0.62065	−5.14
C1	H30	−0.61245	
C4	H29	−0.62169	−3.50
C5	H29	−0.61611	
C5	H28	−0.62439	−5.53
C4	H28	−0.61557	

Table 3 Comparison of the average differences between QTAIM-computed bond path angles (BPA) and geometrical bond angles (GBA) of relevant fragments in 5-member and 6-member rings in the Zn(NTA) and Zn(NTPA) complexes, respectively. (All angles in degrees).

Zn(NTPA)			Zn(NTA)		
Bond angle	BPA-GBA		Bond angle	BPA-GBA	
	Avg.	St.Dev		Avg.	St.Dev
O-Zn-N	-2.06	0.11	O-Zn-N	0.96	0.14
C-N-Zn	2.95	1.34	C-N-Zn	3.22	0.36
C-O-Zn	-9.33	0.50	C-O-Zn	5.64	0.23

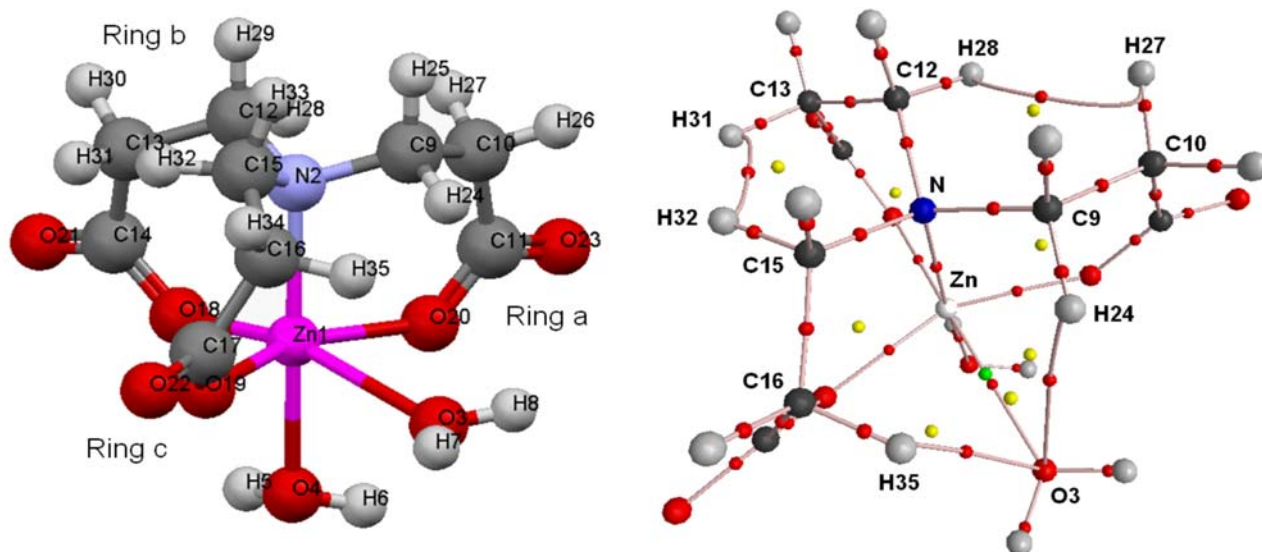


Fig. 1 Ball and stick model of the optimized geometry of ZnNTPA complex (conformer C5) in the solvated state with the atom and ring labeling scheme (left) and the corresponding molecular graph showing the H–H bond paths between H27 and H28 and between H31 and H32 atoms.

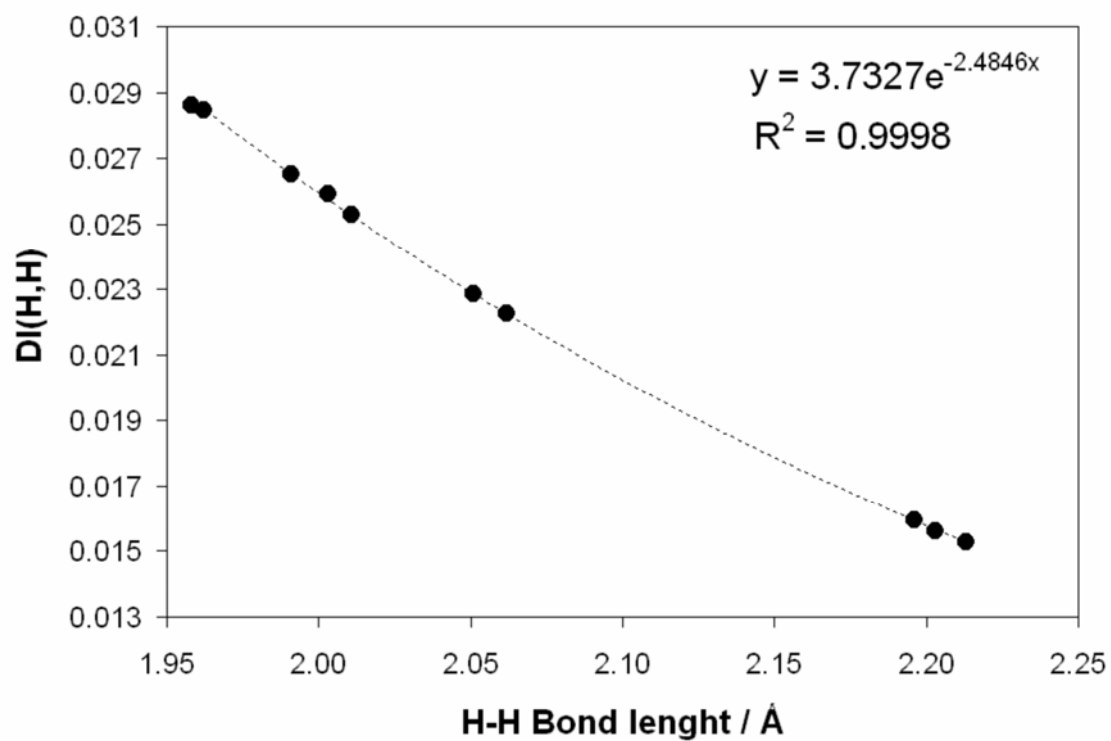


Fig. 2 Correlation between QTAIM delocalization index (DI(H,H)) and the internuclear separation of hydrogen atoms linked by a bond path.