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Energetics and cooperativity in three-center hydrogen bonding interactions. II. Intramolecular hydrogen bonding systems

Ruben D. Parra  
*University of Nebraska - Lincoln*

Bing Gong  
*State University of New York, Buffalo, New York*

Xiao Cheng Zeng  
*University of Nebraska-Lincoln, xzeng1@unl.edu*

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Energetics and cooperativity in three-center hydrogen bonding interactions. II. Intramolecular hydrogen bonding systems

Rubén D. Parra
Department of Chemistry, University of Nebraska-Lincoln, Lincoln, Nebraska 68588

Bing Gong
Department of Chemistry, Natural Sciences Complex, State University of New York, Buffalo, New York 14260

X. C. Zeng
Department of Chemistry, University of Nebraska–Lincoln, Lincoln, Nebraska 68588

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High level ab initio calculations have been carried out on a number of intramolecular two- and three-center H-bonding structures containing the amide motif, $\text{NH}_2\text{C}=\text{O}$. These structures serve as model systems for probing the stability of intramolecular three-center H bonds of the type $\text{A}_1\text{HA}_2$. Particular attention is given to cooperative effects in the three-center H-bonding structures. A systematic assessment of cooperativity for intramolecular H-bonding systems is presented.

I. INTRODUCTION

In paper I of this work, we studied intermolecular three-center H-bonding interactions in diacetamide–X dimers (X=HCN, $\text{CH}_2\text{OH}$). Our previous results show that, in the model systems considered, the formation of an intermolecular three-center H bond is a process that gives rise to negative cooperative effects as clearly demonstrated by the energetics, geometry, vibrational frequencies, and proton chemical shifts. However, the issue of cooperativity in intramolecular three-center H bonding is still open to research. In this paper, we turn our attention to a number of systems containing intramolecular three-center H bonding of the type $\text{A}_1\text{HA}_2$. We investigate the effects of having the proton donor as well as the proton acceptor atoms rigidly held within the same molecule.

In this study, we mainly focus on the intramolecular H-bond interactions in a series of $R$–CONH–$R'$ molecules. The model structures are depicted in Fig. 1, where three-center H-bonded structures (1–4) are chosen to investigate cooperativity. Because the definition and evaluation of intramolecular H-bond interaction energies is by far not obvious, we have chosen to investigate the effects of cooperativity using properties other than energetics. The ability to define and describe cooperativity with parameters other than energetics is particularly important for intramolecular H-bonded systems. Several groups have shown that a quantitative treatment of cooperativity effects in intermolecular and intramolecular H bonds can be achieved in terms of the relative vibrational frequency shifts undergone by the A–H group involved in hydrogen bonding. Cooperative phenomena have been successfully studied by means of geometries, dipole moments, vibrational spectra, vibrational mode intensities, and quadrupole coupling constants. The cooperative effects manifested in these properties have been shown to parallel those seen in the energetics.

The parameters chosen to investigate cooperative effects should be sensitive to H bonding, and less (or not) sensitive to other interactions. In this study, the cooperative effects are described in terms of the N–H bond lengths, the N–H stretching and bending frequencies, and the N–H $^1\text{H}$–NMR chemical shifts. In paper I of this work we showed that the cooperativity effects manifested in these parameters correlate closely with those seen in the energetics. Thus these parameters should provide reliable information as far as cooperativity is concerned. A series of isodesmic reactions are also devised to gain insight into the enthalpy change associated with the formation of a three-center H-bonded structure from a pair of two-center H-bonded structures.

II. COMPUTATIONAL DETAILS

All the computations were carried out using the Gaussian 98 program. The geometries of the different systems were optimized at B3LYP/6-311+G(d,p) level. The same level of theory was used to compute harmonic vibrational frequencies that in turn were used to verify that each structure corresponded to a minimum on the potential energy surface. Vibrational frequencies were used to obtain the zero-point energy (ZPE) correction to the electronic energy. Geometry optimizations were also conducted at the MP2/6-31G(d) level to ensure that the results are robust, given the improvement in the correlation method. The optimized geometries were used to compute single point energies at the MP2/6-311+G(2d,2p) level, and $^1\text{H}$–NMR chemical shielding constants at the B3LYP/6-311+G(2d,p) level. In this study cooperative effects are highlighted using several indicators such as the frequency shifts undergone by the N–H stretching and out-of-plane bending modes, the in-
crease in the intensity of the N–H stretching mode, the
lengthening of the donor N–H bond, and $^1$H–NMR chemical
shifts.

III. RESULTS AND DISCUSSIONS

Geometries. The formation of an intramolecular H bond
is accompanied by structural changes that help the proton
donor and the proton acceptor units to attain a proper ar-
rangement for the interaction. Relevant structural parameters
are depicted in Fig. 3(a) of Paper I. An H bond in a six-
membered ring is described in terms of $r$, $d_1$, $R_1$, and $\phi_1$.
An H bond in a five-membered ring is described in terms of
$r$, $d_2$, $R_2$, and $\phi_2$. The N–H distance, $r$, will be discussed in
the context of cooperative effects. A three-center H bond is
characterized by the combination of the structural parameters
used to describe the independent two-center H bonds. Table I
lists the relevant geometric information.

Both B3LYP and MP2 optimized geometries show that
an H bond in a six-membered ring has a more favorable
geometry arrangement than that in a five-membered ring.
This is reflected in shorter $O$–$H$ distances ($d_1<d_2$) and
larger N–H–O angles ($\phi_1>\phi_2$). Table I shows that a phe-
nyl group strengthens the H bonds, as seen by shortening of
the O–$H$ distances and widening of the N–H–O angles.
The O–N distances, $R_1$ and $R_2$, are shortened only when
the phenyl group is directly involved in the H bonds.

The calculated dihedral HNC=$O$ angles are around
173.4 degrees and 180.0 degrees in the five- and six-
membered ring systems, respectively. The larger $sp^2$ hybrid-
ization at the nitrogen atom leads to a more acidic character
of the amide motif, which in turn enhances the H-bond in-
teraction in the six-membered ring structures.

Vibrational and $^1$H–NMR results. It is well known that
certain normal modes of vibration are significantly disturbed
by H-bond formation. The changes are so distinctive that
vibrational studies indeed provide the most commonly used
criteria for the presence of an H bond. Some major spectral
changes, relative to the reference systems, that are expected
to occur when an H bond forms are (1) the N–H bending
frequency increases, (2) the N–H stretching frequency de-
creases, and (3) the intensity of the N–H stretching fre-
quency increases. The intensity behavior is determined by
the charge distribution in the H bond and its movement dur-
ing vibration, and is therefore as characteristic of H-bond
formation as is the $\nu_{N-H}$ frequency shift.

Table II displays the N–H bond lengths and $^1$H–NMR
chemical shifts of the B3LYP geometries. It is worth men-
tioning that the corresponding values for the MP2 optimized
structures are within 4% of those calculated with the B3LYP method and therefore are not reported. Also shown in Table II are the B3LYP/6-311+G(d,p) vibrational frequencies. Table III shows the changes relative to the reference systems in a way that helps the discussion of cooperative phenomena. Intensification factors ($\Lambda$), defined as the intensity of the $\nu_{N-H}$ mode in a given H-bonded system divided by that in the corresponding reference structure, are also shown in Table III.

Table III shows that formation of a two-center H bond in a five-membered ring produces a small change in the N–H stretching frequencies ($\nu_{N-H}$), and a sizeable blueshift of the out-of-plane bending mode ($b_{N-H}$). The predicted frequency shifts for 2b and 4b are close to each other, indicating similar strength of the H-bond interaction in both structures; the same is true for 1b and 3b. The $\nu_{N-H}$ mode is slightly blue-shifted in 2b and 4b, and slightly redshifted in 1b and 3b. The predicted shifts to the blue of the $b_{N-H}$ mode in 1b and 3b are more than twice of those in 2b and 4b. The N–H bond elongations as well as the $^1$H–NMR chemical shifts found in 1b and 3b are larger than the corresponding changes found in 2b and 4b. The results clearly show that the weak H-bond interaction involved in the five-membered ring systems is greatly enhanced by the presence of a phenyl group in the ring.

Table III shows that an H bond in a six-membered ring produces a sizeable redshift in the $\nu_{N-H}$ mode, a large blue-shift in the $b_{N-H}$ mode, and a considerable shift to lower field of the $^1$H–NMR chemical shielding constants. As in the five-membered ring systems, the presence of a phenyl group enhances the strength of the H bond in the six-membered ring systems. As expected, the superior strength of the H-bond

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**TABLE I. Relevant H-bond structural parameters.**

<table>
<thead>
<tr>
<th></th>
<th>B3LYP/6-311+G(d,p) optimized geometries</th>
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<tr>
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<td>$R_1$</td>
<td>$\phi_1$</td>
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<td>$R_3$</td>
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**TABLE II. Calculated parameters for the N–H bonds.**

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<tr>
<td>$\nu_{N-H}^{a}$</td>
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<td>3612</td>
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<td>3571</td>
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<tr>
<td>$b_{N-H}^{a}$</td>
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<td>639</td>
<td>583</td>
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<td>633</td>
<td>640</td>
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<td>1.010</td>
<td>1.010</td>
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<td>3541</td>
<td>3622</td>
<td>3620</td>
<td>3625</td>
<td>3623</td>
<td></td>
</tr>
<tr>
<td>$b_{N-H}^{a}$</td>
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<td>701</td>
<td>688</td>
<td>751</td>
<td>556</td>
<td>564</td>
<td>554</td>
<td>563</td>
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<tr>
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<td>1.012</td>
<td>1.013</td>
<td>1.009</td>
<td>1.009</td>
<td>1.009</td>
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<tr>
<td>$\delta_{N-H}^{c}$</td>
<td>8.43</td>
<td>9.21</td>
<td>9.61</td>
<td>10.43</td>
<td>6.99</td>
<td>7.13</td>
<td>7.33</td>
<td>7.48</td>
<td></td>
</tr>
</tbody>
</table>

---

*a Frequencies in cm$^{-1}$.

*b Bond lengths in Å.

*c Values relative to the calculated chemical shift of TMS (=31.91 ppm).
interaction in a six-membered ring over that in a five-membered ring is manifested in the larger N–H bond elongations, frequency shifts, and proton chemical shifts observed in the former. The relative strength of the two-center H-bond systems follows the order 4b, 2b<3b, 1b<4a, 3a<2a, 1a.

Three-center H-bonds and cooperative effects. Table III shows that among the three-center H-bond structures (1–4) the largest frequency and chemical shifts occur in structure 1. This indicates that structure 1 presents the strongest three-center H-bond interaction followed by structure 3. Structure 4 has the weakest three-center H bond.

Structures containing three-center H-bond interactions are particularly suitable to investigate cooperative phenomena in multicenter H-bond interactions. To investigate whether the components of a three-center interaction reinforce each other, that is, whether positive cooperative effects are taking place in the three-center systems studied, we pay particular attention to structural and spectral changes. Here, the cooperative effects are described in terms of the N–H bond lengths, the N–H stretching and bending frequencies, the intensity factor, and the 1H NMR chemical shifts.

Table III shows that the N–H bond lengths in 1–3 are increased, relative to the reference geometries, more than in 1a–3a, and 1b–3b, respectively. The effect is more pronounced in 1. This enhanced lengthening of the N–H bond is commonly used as one index to quantify cooperative effects.\(^4\)\(^5\) The N–H bond in 4 presents no further elongation with respect to 4a.

Compared to the corresponding two-center H-bond structures, the N–H bending mode is further blueshifted in 1–4. The N–H stretching mode is further redshifted upon formation of the three-center structures 1 and 3. Relative to 2a and 4a, this mode is slightly blueshifted in 2 and 4.

Formation of a three-center H bond in 1 and 3 increases the intensification factor relative to 1a and 3a, respectively. Structure 4 shows a negligible increase in the intensification factor, and structure 2 shows a decrease.

In addition to vibrational studies, 1H NMR chemical shifts can also be used to reveal cooperative phenomena.\(^6\) As illustrated in Table III, a three-center H-bond interaction produces an enhanced shift to lower fields of the 1H NMR signal. The effect is more pronounced in structures 1 and 3.

In summary, the combination of \(\nu_{N-H}\) and \(b_{N-H}\) frequency shifts, intensification factors, \(^1\)H–NMR chemical shifts, and N–H bond lengths lead us to the conclusion that positive cooperative effects are clearly present upon formation of a three-center H bond in structures 1 and 3. However, the same indicators show that formation of a three-center H-bond interaction in 2 and 4 is not accompanied by the manifestation of positive cooperative effects. In fact, the \(\nu_{N-H}\) stretching modes and the intensity factors of 2 and 4 suggest a weakening of the H-bond interaction, relative to 2a and 4a, respectively.

Energetics. The relative stability of a two-center H bond in a six-membered ring over that in a five-membered ring is displayed in Table IV. It is seen that the relative energies depend on the level of theory. At the HF level, 4a is clearly more stable than 4b. At the MP2 level, the stability of 4a over 4b is increased by 0.88 kcal/mol. Also at the HF level, 3a is much more stable than 3b, whereas 2a is less stable than 2b. At the MP2 level, however, the stability of 3a over 3b is significantly reduced by 1.90 kcal/mol, whereas 2a is now much more stable than 2b. The results show the need to use correlated methods to better account for the H bond interaction, and for the enhanced electron delocalization that is taking place through the aromatic rings. For large systems, however, energy calculations with higher correlated methods and larger basis sets become rapidly impractical. It is seen that zero-point energy corrections to the energies are small for 4a–4b, and 3a–3b, and negligible for 2a–2b, and 1a–1b.

One notable feature of the energy results is the reduction of the stability of the six-membered ring conformations, upon replacement of either carbon–carbon double bond in 4a and 4b by a phenyl group. The effect is very significant in 3b where the phenyl group is part of the five-membered ring. In fact, 3a is just 0.78 kcal/mol more stable than 3b. The presence of two phenyl groups (1b,1a) actually reverses the stability order at both the HF and MP2 levels.

The reduced stability of a six-membered ring may be attributed in part to the geometric changes brought about by the presence of a phenyl ring. Table II shows, for instance,
TABLE V. Mulliken charge distributions (e).\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>4b</th>
<th>3b</th>
<th>2b</th>
<th>1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>(q_N)</td>
<td>-0.28</td>
<td>-0.39</td>
<td>-0.25</td>
<td>-0.38</td>
</tr>
<tr>
<td>(q_O)</td>
<td>-0.39</td>
<td>-0.55</td>
<td>-0.39</td>
<td>-0.55</td>
</tr>
<tr>
<td>(q_H)</td>
<td>0.23</td>
<td>0.24</td>
<td>0.23</td>
<td>0.24</td>
</tr>
<tr>
<td>(q_{Sb})</td>
<td>4a</td>
<td>3a</td>
<td>2a</td>
<td>1a</td>
</tr>
<tr>
<td>(q_{Sb})</td>
<td>-0.34</td>
<td>-0.51</td>
<td>-0.35</td>
<td>-0.56</td>
</tr>
<tr>
<td>(q_O)</td>
<td>-0.46</td>
<td>-0.45</td>
<td>-0.58</td>
<td>-0.58</td>
</tr>
<tr>
<td>(q_H)</td>
<td>0.29</td>
<td>0.36</td>
<td>0.32</td>
<td>0.41</td>
</tr>
</tbody>
</table>

\(^a\)Mulliken charges computed at the B3LYP/6-311+G(2d,p).

\(^b\)Oxygen atom involved in the five-membered H-bond structures.

\(^c\)Oxygen atom involved in the six-membered H-bond structures.

that the H-bond geometry of structure 3 exhibits a significant improvement over that of structure 4b. The corresponding geometric changes observed in 3a relative to 4a are not as significant. It is also seen that the presence of a phenyl ring in structure 2a improves, relative to 4a, the H-bond geometry, whereas only minor changes are seen in going from 4b to 2b. Despite these geometric changes, we still see a reduction in stability of the six-membered ring in 2a–2b compared to 4a–4b. Thus factors other than changes in the H-bond geometries need to be considered to better understand the relative stabilities of the structures.

Trends in the electronic charge redistributions may provide some additional insight into the relative stabilities of the five- and six-membered H-bond structures. Table V displays the computed Mulliken charges of the atoms directly involved in the H-bond interactions, i.e., H, N, and O. It is seen that the major change in going from 4a to 3a is an increase of the negative charge on the nitrogen atom. More substantial changes are observed, though, in going from 4b to 3b, where the negative charge of the oxygen atom is increased along with that of the nitrogen atom. Thus the secondary electrostatic interaction between nitrogen and oxygen is expected to be more repulsive in 3b. In fact, 3a is 3.01 kcal/mol more stable than 3b at the HF level. Accordingly, the energetic enhancement of the H-bond interaction in 3b, expected from geometry considerations, can really be appreciated once the important dispersion energy component is included at the MP2 level.

A similar Mulliken charge analysis helps rationalize the relative stability of 2a and 2b. From Table V, it is seen that an increase in the negative charge of the methoxy oxygen occurs in going from 4a to 2a, while no important changes are seen in going from 4b to 2b. Thus a more repulsive nitrogen–oxygen interaction is expected in 2a than in 2b. In fact, 2a is actually 0.19 kcal/mol less stable than 2b at the HF level. Therefore, the energetic enhancement of the H-bond interaction in 2a, expected from geometry considerations, is partly offset by the secondary repulsive nitrogen–oxygen electrostatic interaction. The MP2 method is again particularly important to better describe the energetics of the H-bond interaction. The relative stability of 1a and 1b may also be traced partly to the combination of geometric and electrostatic effects.

It is interesting to note that the hydrogen atom becomes progressively more positive as the H-bond structures go from a five- to a six-membered ring, and then to a three-center H-bond interaction. This is more evident in the sequences 3b→3a→3, and 1b→1a→1, respectively, which are also the ones where positive cooperative effects are clearly present.

Additional insight into the energetics can be gained from models 2, 2a–2c, and their structural isomers 3, 3a–3c. These models differ from each other in the relative position of the phenyl and vinyl groups. The structural isomers can be used to shed light into the influence of the position of the phenyl ring on the relative stability of the isomers. Table IV shows that the reference structure is more stable if the phenyl group is attached to the amide carbon (2c) rather than to the nitrogen atom (3c). However, this stability is decreased upon formation of a two-center H bond. The effect is more drastic for the 3b–2b pair. The picture that emerges is that the five-membered ring conformation is energetically stabilized by having a phenyl group attached to the nitrogen atom (3b), so much that 3b is just 0.13 kcal/mol less stable than 2b, after correlation and zero-point energy corrections. Interestingly, having a phenyl group attached to the amide carbon seems to have an adverse energetic effect on the six-membered ring conformation. If it were to provide additional stabilization, we would expect a larger relative stability of 3a over 2a (2.39 kcal/mol), compared to that of 3c over 2c (3.86 kcal/mol). It is seen that the formation of a three-center H bond actually reverses the stability of 3c over 2c. Table IV shows that structure 3 is 1.05 kcal/mol more stable than structure 2. This reverse in stability can be traced to the combined energetic effects of having a phenyl group attached to nitrogen in the five-membered ring (energetically favorable), and having a phenyl group attached to the amide carbon in the six-membered ring (energetically unfavorable).

Isodesmic reactions. We devised some relevant isodesmic reactions as an alternate tool for calculating the enthalpy change associated with the formation of an intramolecular three-center interaction. Because of the conservation of the total number and types of bonds, good results can be obtained for isodesmic reactions involving very similar systems due to the cancellation of errors on the two sides of the reaction.\(^{2,12}\) The B3LYP/6-311+G(d,p) optimized geometries were used to calculate MP2/6-311+G(2d,2p) energies. After zero-point energy corrections, the enthalpy values (at 0 K) are obtained for the following reactions:

<table>
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<tr>
<th>Reaction</th>
<th>(\Delta H_0) (kcal/mol)</th>
</tr>
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<tbody>
<tr>
<td>(A) (4a + 4b \rightarrow 4 + 4c)</td>
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</tr>
<tr>
<td>(B) (3a + 3b \rightarrow 3 + 3c)</td>
<td>0.52</td>
</tr>
<tr>
<td>(C) (2a + 2b \rightarrow 2 + 2c)</td>
<td>0.23</td>
</tr>
<tr>
<td>(D) (1a + 1b \rightarrow 1 + 1c)</td>
<td>0.51</td>
</tr>
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The isodesmic gas-phase reactions show that the formation of the three-center H-bond structures 1–4 from their
corresponding five- and six-membered ring conformations is marginally an endothermic process. This is not to be regarded necessarily as the manifestation of negative cooperativity, but rather as evidence that factors other than hydrogen bonding can be important in determining the energetics of conformations containing intramolecular H bonds.13

IV. SUMMARY

A comprehensive ab initio study has been conducted on a series of amide structures containing intramolecular two- and three-center H-bonding interactions. The superior strength of a two-center H bond in a six-membered ring as opposed to a five-membered ring is demonstrated by a consortia of H-bonding indicators: N–H frequency shifts, intensification factors, N–H bond lengths, and 1H NMR chemical shifts. The same indicators are used to reveal the existence of nonpairwise additive phenomena upon formation of the three-center H-bond systems.15 Unlike the three-center H bonding which was found to be weaker than two-center H bonding in flexible peptide systems,16 the three-center systems 1 and 3 are rather robust, which, when combined with proper structural scaffolds, should serve as a reliable basic folding unit for designing a variety of unnatural, folded structures.17

The ab initio results show that the relative stability of isomers containing a H bond does not necessarily parallel the strength of the H bond itself. In fact, the results are sometimes counterintuitive. The use of geometric and spectroscopic parameters proves useful in examining cooperative phenomena particularly in intramolecular multicenter H-bond systems.

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