Energetics and cooperativity in three-center hydrogen bonding interactions. I. Diacetamide-X dimers. X=HCN, CH$_3$OH.

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Energetics and cooperativity in three-center hydrogen bonding interactions. I. Diacetamide-X dimers (X=HCN, CH₃OH)

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High level ab initio calculations are carried out on diacetamide–X (DA–X) dimers, X=HCN, CH₃OH. The dimers are used as model systems to investigate the energetics and cooperative phenomena in intermolecular three-center hydrogen-bond (H-bond) interactions relative to two-center H-bond interactions. The trans–trans conformer of diacetamide is chosen as a suitable model for intermolecular three-center H bonding where one H atom is interacting with two acceptor atoms. The proton–acceptor atoms are rigidly held in the same molecule. For both model systems, it is found that the calculated interaction energy per H bond is appreciably smaller in the three-center than in the two-center H-bond dimers, suggesting possibly a general characteristic of intermolecular three-center H bonds, namely, a negative cooperativity. More importantly, it is found that frequency shifts, intensity factors, bond lengths, and ¹H nuclear magnetic resonance chemical shifts all support the energetic calculations in that the intermolecular three-center H-bond dimers exhibit marked negative cooperative effects. Despite the negative cooperativity, the three-center DA–HCN dimer is actually energetically favorable over the two-center counterpart, whereas the three-center DA–CH₃OH dimer is energetically unfavorable over the two-center counterpart. © 2001 American Institute of Physics. [DOI: 10.1063/1.1400141]

I. INTRODUCTION

Three-center or bifurcated hydrogen bonds are often found in the solid state of many compounds, and in the crystal structures of a number of biologically relevant systems. The existence of three-center H-bond interactions in solution has also been experimentally demonstrated. Two types of three-center H-bond interaction can be distinguished: (a) one that involves an H atom and two acceptor atoms (denoted A₁AH₂), and (b) one that involves an acceptor atom and two H atoms (denoted H₂AH₂). These two possibilities are depicted in Fig. 1. Although a vast number of examples are known in the solid state, three-center H bonds have been used mainly to account for the observed experimental facts. Compared to the tremendous amount of data available on two-center H bonds, relatively few model systems that provide insights on the strength of three-center H bonds have appeared. Gellman et al. recently reported intramolecular H-bond systems that experimentally probed the relative energetic merits of two-center versus three-center H bonds. By designing depsipeptides containing either excess H-bond donors or acceptors, it was found that there were negative cooperativity effects between the two-center components of the three-center H-bonding interactions. Rozas et al. applied the theory of atoms in molecules (AIM) to show that three-center interactions do exist and that they are energetically weaker than two-center hydrogen bonds. The systematic studies by Jorgensen et al., Gellman et al., and Zimmerman et al. have lead to the finding that A₁HA₂ three-center interactions would become favorable if both acceptors occurred in the same molecule and were rigidly held in the proper arrangement. Additional model studies are needed to further substantiate these findings.

The purpose of this paper is to study the energetics and cooperativity of three-center H-bond interactions in diacetamide–X dimer model systems (X=HCN, CH₃OH). The cooperative effects will be highlighted using several indications. The energy per hydrogen bond, defined as the interaction energy divided by the number of H bonds present in the dimer, will provide insight into the stabilizing or destabilizing effects of having a three center as opposed to a two center H bond, namely, to assess the relative stability of a three-center over a two-center H-bond configuration. We will examine the generality of the prediction that A₁HA₂ three-center interactions would become favorable if both acceptors occurred in the same molecule and were rigidly held in the proper arrangement. Besides energetics, attention is also given to other indicators of cooperativity such as the stretching and bending frequencies of the X–H group, the X–H...
between the two imide carbonyl groups; nevertheless, it is frequently observed in the solid state.\textsuperscript{10b,10c}

We have chosen the diacetamide (DA) molecule in the trans–trans conformation as a model system to investigate both the energetics and the cooperativity effects in three-center H-bond interactions of the type \( A_1HA_2 \). Because the acceptor atoms are part of the same molecule, this sort of interactions is often called three-center chelated hydrogen bonding.\textsuperscript{4a} For single proton donors we have chosen hydrogen cyanide (HCN), and methanol (\( CH_3OH \)). Unlike most C–H bonds, the triple \( N=\text{C} \) bond makes HCN a very effective proton donor molecule.\textsuperscript{11} The proton donor ability of methanol is also well recognized.\textsuperscript{12}

**IV. RESULTS AND DISCUSSION**

**Cooperative effects.** An array of interlinked hydrogen bonds can exhibit positive cooperativity, defined as the enhancement of the first H bond between a donor and an acceptor when a second H bond is formed between one of these two species and a third partner. The sum of the nonadditive, many-body energies has been considered as the energetic contribution of the cooperativity to the stability.\textsuperscript{13} This energy-based definition of cooperativity has been traditionally used in the discussion of cooperative phenomena in intermolecular H-bonded systems.\textsuperscript{14} Other definitions for the cooperativity have been used in the literature\textsuperscript{15} because the effects of cooperativity can be manifested in properties other than the energetics. For instance, 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 X–H group involved in the hydrogen bonding.\textsuperscript{10} Evidence of positive-cooperativity behavior has been seen also in measurements of geometries, dipole moments, vibrational spectra, vibrational mode intensities, and quadrupole coupling constants,\textsuperscript{17} suggesting a close correlation between these properties with the energetics as far as the cooperative effects are concerned.

**A. Diacetamide–HCN dimers**

(a) Energetics. The mean H-bond interaction energies, defined as the interaction energy per hydrogen bond, for the DA–HCN dimers are shown in Table I. The two-center H-bond interaction (\( -3.78 \) kcal/mol) appears energetically superior to the mean three-center H-bond interaction (\( -3.04 \) kcal/mol). This result is consistent with the fact that multiple H bonds do not always reinforce each other. This sort of weakening of an existing H bond by adding another acceptor/donor to the interaction is sometimes referred to as negative cooperativity.\textsuperscript{17a}

To quantify the cooperativity effects in multicenter H-bond systems we proposed to use a coefficient analog to the \( C_1 \) coefficient proposed by Koehler \textit{et al.}\textsuperscript{18}

\[
C_1 = \frac{(\Delta E_{\text{av}} - \Delta E)}{\Delta E}
\]

where \( \Delta E_{\text{av}} \) is the average difference in interaction energy for the two-center and the three-center systems and \( \Delta E \) is the difference in interaction energy for the three-center system compared to the two-center system.
Here, $\Delta E_{av}$ is the mean hydrogen-bond energy in the multi-center system and $\Delta E$ is the hydrogen-bond energy in the two-center system. A positive value of $C_1$, which defines the positive cooperativity, means that the H-bond energy of an array of $n$-center hydrogen bonds is greater than the sum of $n$ isolated hydrogen bonds. Naturally, a negative value of $C_1$ will define the negative cooperativity. For the DA–HCN dimers, $C_1 = -0.20$, namely, a 20% reduction of the strength of the two-center H bond upon formation of the three-center H bond.

It should be noted that even in the case of negative cooperativity, formation of a second H bond is overall energetically favorable when compared to the case without the presence of a second H bond. In other words, two H bonds together are usually more favored than one. As shown in Table I, the interaction energy of the three-center H-bond dimer is $-6.09$ kcal/mol, that is, 2.31 kcal/mol lower than that of the two-center H-bond dimer. Including zero-point energy corrections, the three-center H-bond dimer is still 2.50 kcal/mol more stable. This result confirms the prediction that $A_1H_2A_3$ three-center interactions become favorable if both acceptors occurred in the same molecule and were rigidly held in the proper arrangement.$^7$

(b) Geometries. Geometry of a three-center hydrogen bond can be described by the distances $r$, $d_1$, $d_2$, and the angles $\phi_1$, $\phi_2$, $\phi_3$ [see Fig. 3(a)]. A more stringent description should include the distances between the heavy atoms, $R_1$, $R_2$. The deviation of the H atom from the plane formed by the three heavy atoms, as measured by the sum $\phi_1 + \phi_2 + \phi_3$, is commonly used to characterize the three-center H bond. The geometric parameters used to describe the conventional two-center hydrogen bond are shown in Fig. 3(b).

The Optimized DA–HCN dimers are shown in Fig. 4. Table II displays relevant geometric parameters for the dimers. The three-center DA–HCN dimer is symmetric with $d_1 = d_2 = 2.262$ Å, and $R_1 = R_2 = 3.175$ Å. The O⋯O distance ($R_3$) is calculated to be 2.802 Å. The H atom lies in the same plane of the three heavy atoms involved in the H bond ($\phi_1 + \phi_2 + \phi_3 = 360^\circ$). The HCN molecule is in the plane of the diacetamide molecule. The two-center H bond appears stronger than the three-center interaction as indicated by the geometric parameters. For instance, the donor C–H distance is shortened by 0.001 Å upon bifurcation. The weaker character of the three-center interaction is also reflected in longer H⋯O ($d_1$) and C⋯O ($R_1$ and $R_2$) distances. In other words, adding a second acceptor to the two-center H bond gives rise to negative cooperative effects.

![Figure 3](image1.png)

**FIG. 3.** (a) Geometrical parameters used to describe three-center H-bond interactions. (b) Geometrical parameters used to describe two-center H-bond interactions.

![Figure 4](image2.png)

**FIG. 4.** (a) Optimized three-center DA–HCN dimer. Distances given in Å. (b) Optimized two-center DA–HCN dimer. Distances given in Å.

<table>
<thead>
<tr>
<th>Two-center H-bond dimers</th>
<th>$\Delta E$</th>
<th>$\Delta E$/H-bond</th>
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<tr>
<td>DA–HCN</td>
<td>$-3.78$</td>
<td>$-3.78$</td>
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<tr>
<td>DA–CH$_3$OH</td>
<td>$-5.32$</td>
<td>$-5.32$</td>
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<tr>
<th>Three-center H-bond dimers</th>
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<th>$\Delta E$/H-bond</th>
<th>$E_{three} - E_{two}$</th>
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<tr>
<td>DA–HCN</td>
<td>$-6.09$</td>
<td>$-3.04$</td>
<td>$-2.50$</td>
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<tr>
<td>DA–CH$_3$OH</td>
<td>$-4.91$</td>
<td>$-2.45$</td>
<td>$0.18$</td>
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table I. MP2/6-311+ +G(2d,2p) interaction and relative energies (kcal/mol).
Two-center H-bond dimers

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<th></th>
<th>r</th>
<th>d</th>
<th>R</th>
<th>ϕ</th>
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<tr>
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<td>2.048</td>
<td>3.123</td>
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<td>1.921</td>
<td>2.860</td>
<td>161.6</td>
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Three-center H-bond dimers

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<th></th>
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<th>d$_2$</th>
<th>R$_1$</th>
<th>R$_2$</th>
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<th>ϕ$_3$</th>
<th>Σϕ$_1$</th>
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<td>2.262</td>
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<td>3.175</td>
<td>2.802</td>
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<td>360.0</td>
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<td>DA–CH$_2$OH</td>
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<td>129.6</td>
<td>153.6</td>
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Table II. Relevant structural parameters.*

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<th>b$_{out}$CH</th>
<th>b$_{in}$CH</th>
<th>1H–NMR</th>
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<td>1.00</td>
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<td>836</td>
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<th>b$_{out}$CH</th>
<th>b$_{in}$CH</th>
<th>1H–NMR</th>
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<tbody>
<tr>
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<td>1.00</td>
<td>1435</td>
<td>3.28</td>
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<tr>
<td>Three-center</td>
<td>3829</td>
<td>0.61</td>
<td>1408</td>
<td>2.55</td>
<td></td>
</tr>
</tbody>
</table>

*Bond lengths in Å; bond angles in degrees.

B. Diacetamide–CH$_2$OH dimers

(a) Energetics. Table I shows that the calculated H-bond interaction energy for the two-center dimer (−5.32 kcal/mol) is energetically superior to the average three-center H-bond interaction (−2.45 kcal/mol). The calculated C$_1$ coefficient (−0.54) demonstrates marked negative cooperative effects in the three-center H-bond dimer, that is, a 54% reduction in the strength of the two-center H-bond interaction. Moreover the two-center dimer is 0.18 kcal/mol more stable than the three-center dimer. Thus, energy data demonstrates that the preferred conformation for the DA–CH$_2$OH dimer is the one with a two-center H-bond rather than that with a three-center H bond. This result contrasts with the energetics of the DA–HCN dimers discussed previously.

(b) Geometries. The optimized structural parameters of the three-center and two-center DA–CH$_2$OH dimers are displayed in Table II. The optimized dimers are shown in Fig. 5. Table II shows that the bifurcated dimer has two different hydrogen-bond distances, $d_1 = 2.404$ Å and $d_2 = 2.111$ Å. The atoms directly involved in the bifurcated H bond are all in the same plane ($ϕ_1 + ϕ_2 + ϕ_3 = 359.9°$).

Table II also shows that, relative to the three-center dimer, the O–H bond length is longer and the H-bond distance shorter in the two-center dimer. That is, adding a second acceptor to the two-center H-bond interaction gives rise to negative cooperative effects that are apparent in the structural parameters.

(c) Vibrational frequencies and $^1$H chemical shifts. Frequency calculations at the MP2/6-31+G(d,p) indicate that the two-center DA–CH$_2$OH is a local minimum; however, the corresponding three-center dimer is a first-order saddle point with a small negative frequency (−8.8 cm$^{-1}$). Table III shows that the harmonic O–H stretching mode in the two-center dimer is found at 3745 cm$^{-1}$. This mode is shifted upward 84 cm$^{-1}$ in the three-center H-bond dimer. The O–H bending mode in the three-center dimer is redshifted by 27 cm$^{-1}$, compared to the two-center dimer. The increase in the O–H stretching frequency along with the decrease in the O–H bending frequency is another manifestation of the negative cooperative effects that occur in the three-center dimer. The intensity factor calculated for the three-center DA–HCN dimer is stronger than the three-center dimer in agreement with the energetics, geometry, and frequency-shift data.
dimer is 0.61. This reduction in the O–H mode intensity further demonstrates the destabilizing effects of adding a second acceptor to the two-center interaction.

Table III also lists the $^1$H–NMR chemical shifts of the methanol molecule. The stronger H-bond interaction in the two-center DA–CH$_3$OH is clearly indicated by its relatively larger proton chemical downfield shift.

V. CONCLUSIONS

Intermolecular three-center H-bond interactions of the type A$_1$HA$_2$, where A$_1$ and A$_2$ belong to the same molecule, have been studied using $ab$ initio molecular orbital and density functional theory. The diacetamide–X dimers (X=HCN, CH$_3$OH) were used as model systems. The trans–trans conformer of diacetamide was chosen as a suitable model for a system having two proton acceptor atoms held in the proper arrangement to form a three-center H bond.

For both model systems, we found that the calculated interaction energy per H bond is appreciably lower in magnitude in the three-center than in the two-center H-bond dimers. This suggests possibly a general characteristic of intermolecular three-center H bonds, namely, a negative cooperativity. More importantly, we found that frequency shifts, intensity factors, bond lengths, and $^1$H–NMR chemical shifts all correlate well with the energetic calculations in that the intermolecular three-center H-bond dimers exhibit marked negative cooperative effects. Despite the negative cooperativity, interestingly, the three-center DA–HCN dimer is actually preferred energetically over the two-center counterpart, whereas the three-center DA–CH$_3$OH dimer is less preferred energetically than the two-center counterpart. Additional secondary electrostatic interactions may be responsible for the relative stability found in the DA–CH$_3$OH dimers. For instance, the secondary attractive interaction between the oxygen of methanol and one of the hydrogen atoms of diacetamide increases the energy of the three-center dimer compared with that of the two-center counterpart. Indeed, the orientation of the proton–donor molecule can be another important factor in predicting the energetic merits of three-center H-bond interaction.

This study and previous studies by other researchers$^{5,6}$ support the notion that intermolecular three-center H-bond formation is a process that gives rise to negative cooperative effects. However, the issue of cooperativity in intramolecular three-center H bonding is still open to further research. In paper II of this work, we will turn our attention to a number of systems containing intramolecular three-center H bonding of the type A$_1$HA$_2$.

ACKNOWLEDGMENTS

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4. (a) G. A. Jeffrey, An Introduction to Hydrogen Bonding (Oxford Univer-
Three-center hydrogen bonding. I


