

Stable Three-Center Hydrogen Bonding in a Partially Rigidified Structure

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Abstract: The three-center hydrogen bond in diaryl amide **1** was examined by IR and ¹H NMR spectroscopy, X-ray crystallography, and ab initio calculations. By comparing **1** with its structural isomers **2**, **3** and **4**, and with its conformational isomers **1a–c**, it was found that the two two-center components of the three-center interaction reinforce each other, that is, the enhanced stability of the three-center hydrogen bond is a

result of positive cooperativity between the two components. Substituents not involved in hydrogen bonding have little effect on the strength of the two- and three-center hydrogen bonds. To our knowledge, this is the first three-center

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hydrogen-bonding system that has been shown to exhibit positive cooperativity. Ab initio calculations of the geometries, vibrational modes, and ¹H NMR chemical shifts also support the experimental findings. These results have provided a new insight into the three-center intramolecular hydrogen bonding in a partially rigidified structure and have provided a reliable motif for designing stably folded structures.

Introduction

Hydrogen bonding plays an important role in the interaction, recognition, and conformations of both small and large molecules.^[1] Two-center hydrogen bonds (H-bonds), that involve one H-bond donor and one acceptor are the most familiar and have been extensively studied. Three-center H-bonds, with one donor and two acceptors (XHY type), or one acceptor and two donors (HXH type), also occur frequently in the solid-state structures of both small^[1c–d, 2] and biomacromolecules.^[1a, 3] 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. In contrast 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. Zimmerman and Murray have investigated intermolecular three-center hydrogen bonding in base pairing models and found that two-center H-bonds were more favorable than three-center ones.^[4] Gellman et al. recently reported intramolecular systems that experimentally probed the relative energetic merits of two-center versus three-center H-bonds.^[5] By designing depsipeptides that contain either excess H-bond donors or acceptors, it was found that there were negative cooperativities between the two-center components of the three-center hydrogen-bonding interactions. Bureiko et al. have carried out spectroscopic studies of three-center H-bonds in solution.^[6] The system investigated includes one intramolecular two-center component and another intermolecular two-center component with added H-bond acceptors. NMR and IR data showed the formation of the three-center bonds, which were found to lead to the weakening of the original intramolecular two-center H-bonds. Rozas et al. have performed ab initio calculations on intramolecular systems that may form three-center H-bonds.^[7a] Based on electron density critical point calculations, they concluded that three-center H-bonds are energetically weaker than regular two-center H-bonds. These previous theoretical and experimental results seem to suggest that three-center hydrogen bonding is an unfavorable process. This is, however, in sharp contrast to the numerous cases of three-center hydrogen-bonding systems observed, particularly in the solid state. For example, Martínez-Martínez et al. reported experimental observations on oxamide derivatives whose predominant conformations were found to be stabilized by three-center hydrogen-bonding interaction in both solution

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and in the solid state.^[8] Although the reported data strongly imply energetic advantages of the three-center H-bonds over their two-center components, no comparison that may provide further insights was made. It is possible that in the solid state, the existence of three-center H-bonds is enforced simply by the imbalance of donors and acceptors because of the interaction energy of other parts of the molecular system. Another possibility is that three-center hydrogen bonding itself is energetically favorable. Given appropriate alignment or confinement, such three-center interactions can readily form. In many of the model systems probed so far, a three-center interaction may have become energetically unfavorable due to the flexibility of the designed structures.

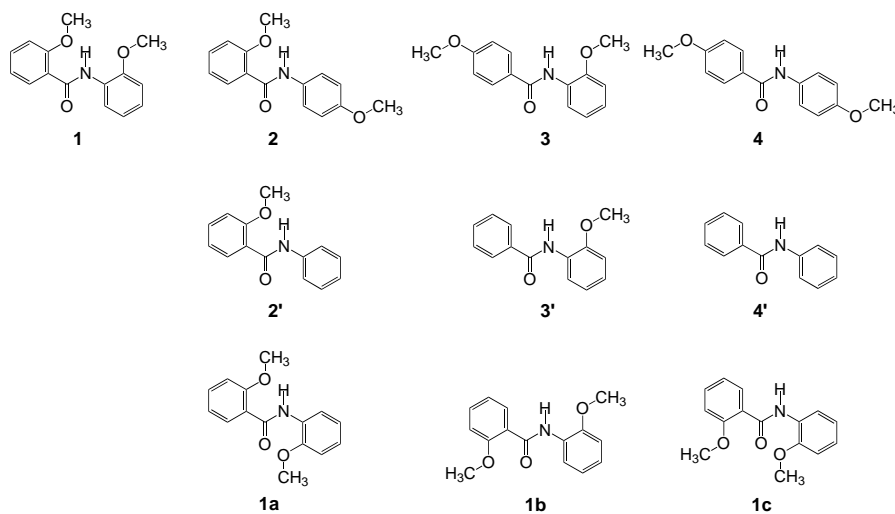
Indeed, cooperativity is a prominent, but not very well defined characteristic of multi-center or an array of interlinked two-center hydrogen bonding; this is considered as the enhancement of first hydrogen bond between a donor and an acceptor when a second hydrogen bond is formed between one of these two species and a third partner, leading to an overall stabilized system. Different definitions for cooperativity have been used in the literature.^[9] The sum of the non-additive, many-body energies has been considered as the energetic contribution of the cooperativity to the stability.^[10] This *energy-based definition* of cooperativity has been traditionally used in the discussion of cooperative phenomena in intermolecular hydrogen-bonded systems.^[11] Accordingly, cooperativity exists when the energy of an array of n interlinked H-bonds is larger than the sum of n isolated H-bonds. This non-additive property arises because the ability of donor and acceptor groups to form H-bonds is further increased by an increase in polarity when the H-bonds form part of a collective ensemble. There are two different mechanisms that can produce this effect:^[9c] 1) functional groups acting simultaneously as H-bond donors and acceptors form extended chains or rings in which the individual H-bonds enhance each other's strengths by mutual polarization, or 2) charge flow in suitably polarizable π -bond systems increases donor and acceptor strengths. This is sometimes referred to as resonance-assisted hydrogen bonding.^[12] Multi-center or interlinked H-bonds are not always cooperative in a positive sense. For example, it is usually energetically unfavorable for an electronegative atom to act as a double H-bond acceptor.^[13] This sort of general weakening is usually referred to as *negative cooperativity*.

The effects of cooperativity can also be manifested in properties other than energetics. For instance, several groups have shown that a quantitative treatment of cooperativity effects in inter- and intramolecular H-bonds could be done in terms of the relative vibrational frequency shifts undergone

by the A-H group involved in hydrogen bonding.^[14] Cooperative phenomena have been successfully studied by means of geometries, dipole moments, vibrational spectra, vibrational mode intensities, and quadrupole coupling constants.^[13] The cooperative effects manifested in these properties have been shown to parallel those seen in energetics. The ability to *define* and *describe cooperativity* with parameters other than energetics is particularly important for intramolecular hydrogen-bonded systems, since the definition and evaluation of intramolecular interaction energies is by far not evident owing to the nonexistence of reference systems.^[13b] Moreover, weak intramolecular H-bond interactions are energetically comparable to conformational and other intramolecular interactions. Some authors have already shown that the stability of a conformation containing an intramolecular H-bond is not necessarily related to the stability of the H-bond itself.^[15] Consequently, no discussion will be made regarding the energetic contribution to the stability.

It is desirable that the parameters chosen to investigate cooperative effects be particularly sensitive to hydrogen bonding, and less (or not) sensitive to other interactions. In this study, which includes both experimental and theoretical aspects, the cooperative effects are described in terms of the N–H bond lengths, the N–H stretching and bending frequencies, and the N–H ¹H NMR chemical shifts.

We recently reported crescent oligoamides whose backbones are rigidified by three-center H-bonds.^[16a] Amide **1**, the



simplest in this series of oligoamides, was found to adopt a well-defined conformation in both chloroform and the highly polar dimethyl sulfoxide. The stability of the three-center H-bond in **1** was confirmed by our preliminary experimental and theoretical studies. ¹H NMR spectroscopy indicated a significant downfield shift of the NH signal of **1** relative to those of its structural isomers **2** and **3**. Preliminary ab initio molecular orbital calculations on **1** and its conformational isomers **1a–c** showed that **1** was energetically favored over **1a–c**, with **1a–c** constrained to planarity.

We decided to carry out detailed theoretical and experimental investigations dealing with all aspects of the three-

center hydrogen bonding in **1** based on the following considerations:

- 1) Although our preliminary data suggested a highly stable three-center hydrogen-bonding system, the reasons for such a stability are still not clear.
- 2) Amide **1** can be compared to its conformational isomers **1a–c** and to its structural isomers **2–4** at the same time, which should provide insights into two-center and three-center hydrogen-bonding interactions.
- 3) The effect of substituents on the hydrogen-bonding strength can be probed by comparing **2** to **2'**, **3** to **3'**, and **4** to **4'**.
- 4) Amide **1** provides a relatively rigid system for studying three-center hydrogen bonding.

We believe this relatively rigid system represents a model with an hydrogen-bonding environment similar to those found in the solid-state structures and in the interiors of folded biomacromolecules, in which H-bond donors and acceptors are partially confined.

We choose to focus on the amide NH groups of **1** and those of its structural and conformational isomers, since changes in their bond length, stretching frequencies, and NMR chemical shifts directly reflect the corresponding changes in hydrogen bonding. By comparing the hydrogen-bonding stability of **1** with those of its structural and conformational isomers, the two components of the three-center hydrogen bonding are found to act cooperatively, leading to an energetically favored three-center hydrogen-bonding interaction.

Results and Discussion

Experimental studies: The most important experimental methods available today for detecting hydrogen bonding are NMR^[17] and IR^[18] spectroscopy. For an amide group, its NH signal usually shows a chemical shift to lower field when the group is hydrogen bonded. The IR frequencies of an amide N–H bond are always shifted toward lower frequencies when the group is hydrogen bonded. IR spectroscopy has an additional advantage over NMR spectroscopy: partial hydrogen bonding, involving some free and some hydrogen-bonded NH groups, exhibits two peaks in the IR spectrum. Both NMR and IR methods can distinguish between inter- and intramolecular hydrogen bonding, since the intermolecular peaks show concentration-dependent changes in their intensities or chemical shifts, while intramolecular peaks are unaffected.

¹H NMR and IR measurements were performed in chloroform on **1** and its structural isomers **2–4**, and on amides **2'–4'**. The X-ray crystallographic structures of **1–3** were determined; these further support the NMR and IR results. These results clearly indicate the presence of a highly favored three-center H-bond in **1** (vide infra).

¹H NMR measurements: At 1 mM, downfield shifts of the amide NH signals (independent of concentration) of **1–3** relative to that of **4** (1 mM) were observed. For **4**, no change in the amide H chemical shift was observed from 2 mM to lower concentrations, indicating the absence of intermolecular hydrogen bonding at low sample concentrations. The NH

chemical shifts of **1–3** are independent of the concentration in the range from 0.5 mM to 10 mM, consistent with formation of intramolecularly hydrogen-bonded rings in these molecules.

Comparison of the data (Table 1) for the differences of the NH chemical shifts of **1–3** and **4** in chloroform and in DMSO

Table 1. Measured chemical shifts and stretching frequencies of the NH groups of amides **1–4** and **2'–4'**.^[a]

	4	3	2	1	2'	3'	4'
$\delta(\text{CDCl}_3)$	7.63 (0.00)	8.49 (0.86)	9.61 (1.98)	10.61 (2.98)	9.83 (2.20)	8.56 (0.93)	7.78 (0.15)
$\delta([\text{D}_6]\text{DMSO})$	9.97 (0.00)	9.27 (-0.70)	9.98 (-0.01)	10.68 (0.71)	10.12 (0.15)	9.43 (-0.54)	10.25 (0.28)
$\Delta\delta^{[b]}$	2.34	0.78	0.37	0.07	0.29	0.87	2.47
ν	3442 (0)	3433 (-9)	3373 (-69)	3340 (-102)	3367 (-75)	3426 (-16)	3437 (-5)

[a] Values of chemical shifts (δ) are in ppm and are relative to that of TMS. Stretching frequencies (ν) are in cm^{-1} . Values in parentheses are relative to **4**; NMR and IR measurements were carried out at a sample concentration of 1 mM. The spectrum of pure CHCl_3 was subtracted in IR measurements. [b] $\Delta\delta = \delta([\text{D}_6]\text{DMSO}) - \delta(\text{CDCl}_3)$.

further revealed the presence of intramolecular H-bonds in **1–3**. When the solvent was changed from chloroform to DMSO, the NH signal of **1** showed the smallest change (0.07 ppm) and those of **2** and **3**, which are expected to be involved in two-center H-bonds, showed larger changes (0.37 ppm for **2** and 0.78 ppm for **3**) compared with **1**. However, the solvent-related changes in the NH chemical shifts of amides **2** and **3** become insignificant when compared to the 2.34 ppm shift of **4**, whose amide H atom is completely exposed to solvent molecules.

In chloroform, relative to **4** (Table 1), amide **1** has the largest downfield shift (2.98 ppm) of its NH signal; amide **2** exhibits the second largest downfield shift (1.98 ppm), and amide **3** has the smallest change (0.86 ppm). The NMR data reveal the relative strength of the H-bonds in **1–3** as: three-center of **1** > two-center of **2** > two-center of **3**. It needs to be pointed out that the downfield shift of **1** is larger than those of **2** and **3** combined; this implies a cooperative effect^[16b] in the three-center hydrogen bonding in **1**.

Amides **2'–4'**, which can be viewed as being derived from **2–4** by removing the methoxy groups that are not involved in intramolecular hydrogen bonding, showed NH chemical shifts that are very similar to those in **2–4** (Table 1). The solvent-dependent changes in the NH chemical shifts of **2'–4'** are also very similar to those of **2–4**. These results indicate that, relative to **1**, the chemical shift changes observed in the NH signals of **2–4** are mostly not due to the changes in the position of the methoxy substituents. Therefore, the NH chemical shift of each compound can be viewed as a direct reflection of its hydrogen-bonding type and strength.

IR measurements: The N–H stretching frequencies (ν) of amides **1–4** were measured in CHCl_3 solution (1 mM) by IR spectroscopy (Table 1). There is no intermolecular hydrogen bonding for **4'** at this concentration because no new band corresponding to the NH stretching frequency was observed from 2 mM to lower concentrations. Similar to the above NMR

results, the IR data indicate that **1–3** adopt exclusively the intramolecularly hydrogen-bonded conformations, since each compound displays only one N–H stretching maximum that is independent of concentration changes (from 1 mM to 10 mM). The N–H stretching frequencies of **1–3** are red shifted relative to **4'**. Amide **1** demonstrates the largest shift (-102 cm^{-1}), amide **2** exhibits the second largest shift (-69 cm^{-1}), and amide **3** shows the smallest shift (-9 cm^{-1}). The IR data have provided additional evidences for the relative strength of the H-bonds in **1–3**. The fact that the red shift of **1** is much larger than those of **2** and **3** combined, again supports a cooperative effect in the three-center hydrogen bonding in **1**. As shown in Table 1, the N–H stretching frequencies of **2'–4'** are very similar to those of **2–4**. The IR data parallel the above NMR data and clearly indicate that the changes seen in **2–4** relative to **1** are due to the hydrogen-bonding environment surrounding each NH group. Thus, the N–H stretching frequency of each compound can be used as a reliable indicator of its hydrogen-bonding type and strength.

Crystal structures: As shown in Figure 1, the crystal structure of **1** shows an intramolecular three-center interaction; the N–H bond is involved in both a five- and six-membered ring H-bond, leading to a perfectly planar molecule reminiscent of a typical three-center H-bond.^[19] The six-membered ring H-bond in **2** is preserved in its solid-state structure. Amide **2** adopts a nearly flat conformation due to the presence of this two-center intramolecular H-bond. The five-membered ring H-bond in **3**, which persists in solution as indicated by IR and NMR data, is disrupted in the solid state. Instead of forming an intramolecular H-bond, the NH group of **3** is involved in intermolecular hydrogen bonding; this indicates the marginal stability of the five-membered ring H-bond observed in solution. Positive cooperativity in the three-center hydrogen bonding in **1** is clearly indicated by these results: the presence of the six-membered ring component helps the formation of the five-membered ring component, which would otherwise be disrupted as shown by the solid-state structure of **3**.

Theoretical studies: Computational studies not only can verify the above experimental results but also provide additional insights into this novel three-center hydrogen-bonding system. Furthermore, structures that can not be probed experimentally, such as the conformational isomers of **1**, can be easily investigated by theoretical methods. We thus decided to carry out detailed ab initio calculations on amides **1–4** and the conformational isomers **1a–c**.

To investigate whether positive or negative cooperative phenomena play a role upon formation of the three-center H-bond structure **1**, we payed particular attention to struc-

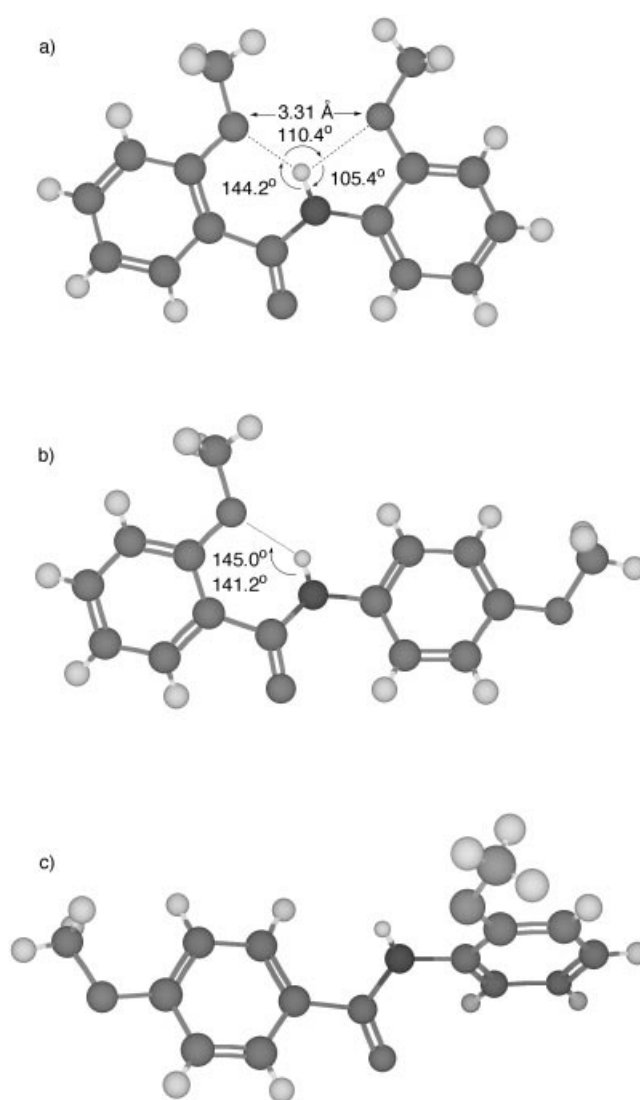


Figure 1. a) Crystal structure of **1**. The molecule adopts a flat conformation with a typical 3-centered H-bond. b) Crystal structure of **2**. This molecule is also planar. c) Crystal structure of **3**. The molecule is nonplanar. Dihedral angles are 29.7° (between the amide group and the benzoyl ring) and 34.8° (between the amide group and the aniline ring). The amide group is involved in intermolecular hydrogen bonding.

tural and spectral changes relative to the structural isomers **2–4**, and conformational isomers (**1a–c**) of **1**. Structures **2'–4'** are also included to explore substituent effects on the relative strength of the two-center H-bonds. It is important to note that in previous work the geometries of isomers **1a–c** were constrained to be planar;^[16a] in this study the planarity constraint has been removed. The computational results are summarized in Table 2.

Table 2. Calculated parameters for the N–H bonds.

	4	3	2	1	1a	1b	1c	2'	3'	4'
$\nu_{\text{NH}}^{\text{[a]}}$	3480	3485	3437	3423	3455	3474	3467	3433	3483	3482
$b_{\text{NH}}^{\text{[a]}}$	566	599	640	681	508	634	440	648	623	563
$r_{\text{NH}}^{\text{[b]}}$	1.008	1.009	1.011	1.013	1.012	1.011	1.011	1.012	1.009	1.008
$\delta_{\text{NH}}^{\text{[c]}}$	7.27	8.46	9.80	10.43	9.12	7.92	6.56	9.92	8.56	7.48

[a] Frequencies in cm^{-1} ; stretching frequencies are scaled by 0.9613;^[27] b_{NH} stands for bending mode. [b] Bond lengths in Å. [c] δ_{NH} is the calculated chemical shift relative to that of TMS.

The data in Table 2 show that the N–H bond lengths are elongated, relative to the reference geometries, upon formation of a two-center H-bond. The formation of a three-center H-bond gives rise to a larger increase of the N–H bond lengths. This increase of the N–H bond lengths can be used as one index to quantify cooperative effects. The greater $\Delta r_{\text{N-H}}$ values for structure **1** clearly indicate the existence of sizeable non-pairwise effects.

The data in Table 2 also show that formation of an H-bond in **3**, **3'**, and **1b** produces a small blue shift of the N–H stretching frequencies. This result suggests that a rather weak H-bond interaction be involved; this weak H-bond interaction is expected to occur in a five-membered ring because the angular geometry is unfavorable.

On the other hand, formation of an H-bond in a six-membered ring (**1a**, **2**, **2'**) produces a sizeable red shift in the N–H stretching mode. The stronger interaction of an H-bond in a six-membered ring relative to that in a five-membered ring is manifested in the larger $\Delta \nu_{\text{N-H}}$ frequency shifts observed in the former. The N–H stretching mode is further red shifted in the bifurcated system, indicating that positive cooperative effects are taking place.

Another important mode of vibration that exhibits cooperative effects is the bending N–H mode (b_{NH}). A study of the in-plane N–H bending mode is complicated by its mixing with other vibrational movements. The N–H out-of-plane bending mode, however, presents a less complex situation with spectral changes that are comparable to those occurring in the N–H stretching mode. The data in Table 2 show that a three-center H-bond produces a much larger blue shift in this mode than those found in any of the two-center H-bond systems.

Cooperative effects are also evident in the ^1H NMR signal of the proton participating in hydrogen bonding. The data in Table 2 indicate a shift to lower field upon formation of an H-bond. The shift is larger when the two-center H-bond is in a six-membered ring as opposed to a five-membered ring. The ^1H NMR chemical shift downfield is larger upon formation of a three-center H-bond.

The above ab initio results, in combination with the experimental data, unequivocally demonstrate that positive cooperativity between the two-center components, rather than a response to unfavorable contacts in alternative conformations, is responsible for the observed stability of the three-center H-bond in **1**. While one may argue that the conformation of **1** is favored because of the unfavorable O to O repulsion that exists in each of its conformational isomers **1a–c**, similar stabilization in **1**, which is attributed to cooperativity, is also observed by comparing **1** with its structural isomers **2–4**, and with structures **2'–4'**, which do not contain any O to O repulsive interactions.

In summary, the three-center H-bond system considered in this work presents positive cooperative effects as consistently manifested by increased donor N–H bond lengths, enhanced red shifts of the N–H stretching frequencies, larger blue shifts of the out-of-plane bending frequencies, and larger downfield of the ^1H NMR chemical shifts. The relative H-bond strength follows the order three-center > two-center (six-membered ring) > two-center (five-membered ring); this is consistent with the conclusion based on experimental results.

A comprehensive ab initio study of cooperative phenomena in a number of intramolecular hydrogen-bonding systems that contain the amide motif is currently under way, and the results will be published elsewhere.

Conclusion

Our results from experimental measurements clearly indicate that the three-center H-bond is favorable relative to two-center H-bond interactions. The data presented strongly suggest that the two components of the three-center interaction act cooperatively. This is further confirmed by ab initio calculations. To the best of our knowledge, this is the first model system in which positive cooperativity is found in an intramolecular three-center H-bond. The N–H chemical shift and stretching frequency, which are little affected by substituents that are not involved in hydrogen bonding, are directly related to the type and strength of the H-bond that is involved. Therefore, IR and NMR spectroscopy should provide reliable means for assaying the folding of oligomers whose backbones are rigidified by the type of three-center H-bonds seen in **1**. Several factors may be responsible for the observed positive cooperativity: 1) the semi-rigid structure of **1**; 2) the reduced electronegativity of the ether O atoms compared with carbonyl O atoms, which may alleviate secondary electrostatic interaction that is associated with many hydrogen-bonded complexes;^[18b, 20] and 3) the weak C–H...O hydrogen bonding^[21] between the amide carbonyl O and its nearest aromatic H atoms. Such a system helps rationalize the frequent occurrence of three-center H-bonds in the crystal structures of small molecules and biomacromolecules. Unlike the three-center hydrogen bonding which was found to be weaker than two-center hydrogen bonding in flexible peptide systems,^[5] the three-center system described here is 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.

Experimental Section

Synthesis of amides 1–4, and 2'–4': All chemicals were purchased from Aldrich, Fluka, and Sigma and used as received. The amides were synthesized by treating a solution of the corresponding alkoxyanilines in chloroform in the presence of triethylamine with a solution of the corresponding benzoyl chloride in chloroform at 0 °C. The products gave satisfactory results on elemental, ^1H and ^{13}C NMR analysis.

X-ray crystallography: Several crystals of each compound were indexed on a Siemens SMART CCD diffractometer by using 40 frames with an exposure time of 20 seconds per frame. All of them exhibited monoclinic lattice. One crystal for each compound with good reflection quality was chosen for data collection, which was carried out at room temperature (273 K). The total number of reflections collected in the hemisphere of the reciprocal lattice of the monoclinic cells were 5659, 11546, and 5701 for compounds **1**, **2**, and **3**, respectively. The corresponding numbers of unique reflections (with associated $R(\text{int})$) were 1870 (0.0326), 3776 (0.0329), and 1828 (0.0321). An empirical absorption correction using the program SADABS^[22] was applied to all observed reflections. The structures were solved with the direct method by using the SHELXS and SIR97 programs;^[22, 23] both programs yielded the same structures. Full-matrix least-square refinement on F^2 was carried out by using the SHELXTL

program.^[22] The final agreement factors $R1$, $wR2$ [$I > 2\sigma(I)$] are 0.0371, 0.0828 for compound **1**, 0.0439, 0.1009 for **2**, and 0.0411, 0.0848 for **3**. The final structures were checked for additional symmetry with the MISSYM algorithm^[24] implemented in the PLATON program suite.^[25] No additional symmetry was found. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-160139, CCDC-160140, and CCDC 160141. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Ab initio calculations: The ab initio calculations were performed using the Gaussian98 program package.^[26] Geometry optimizations were performed at the B3LYP/6-311++G(d,p) level. The so optimized geometries were used to compute harmonic vibrational frequencies at the B3LYP/6-31G(d) level, and ¹H NMR magnetic shielding at the B3LYP/6-311+G(2d,p) level.

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