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Intramolecular N–H···O and N–H···N hydrogen bonding patterns in *N*-benzyl and *N*-(pyridin-2-ylmethyl) benzamides

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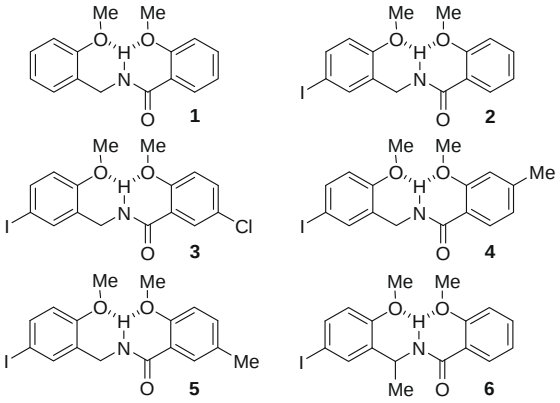
ABSTRACT

This Letter reports the evidences for intramolecular six-membered N–H···O hydrogen bonding in *N*-benzyl benzamides and five-membered N–H···N hydrogen bonding in *N*-(pyridin-2-ylmethyl) benzamide. Intramolecular six-membered N–H···X (X = O or F) hydrogen bonding in 2-methoxyl- or 2-fluorobenzamides is used to lock the amide proton from forming strong intermolecular N–H···O=C hydrogen bonding. As a result, for the first time the new intramolecular hydrogen bonding patterns are observed in the crystal structures of nine amides, whereas the whole molecules give rise to a new class of three-center hydrogen bonding motif. ^{1}H NMR study in chloroform-*d* also supports that this weak intramolecular hydrogen bonding pattern exists in solution.

In the past decade, assessment of new hydrogen bonding patterns had received great attention due to their potential applications in biological, materials and supramolecular sciences, and crystal engineering.[1] It has been found that, for peptides of natural and artificial amino acids, intra-molecular 10- or more-membered N–H···O=C hydrogen bonding patterns are most common,[2] which are also the major driving forces for the formation of various secondary structures.[3] In contrast, in aromatic amide, urea, and hydrazide derivatives, five- and six-membered N–H···O and N–H···N hydrogen bonds are most stable,[4] and have found extensive applications in preorganizing rationally designed monomers for efficient molecular recognition and self-assembly.[5] More recently, these motifs have been used to induce linear aromatic oligoamides to form various artificial secondary structures or foldamers.[6,7] It is expected that a combination of intramolecularly hydrogen bonded aliphatic and aromatic segments may lead to molecules that possess new interesting compact conformations and functions.[8] To realize this, building blocks with predictable conformations have to be developed. As an extension of our long-standing interest in intramolecular hydrogen bonding-driven supramolecular self-assembly of aromatic amide-derived architectures,[9] we herein report the X-ray and ^{1}H NMR evidences for the existence of new intramolecular hydrogen bonding patterns in such kinds of 'hybridized' amides, that is, the six-membered N–H···O hydrogen bonding in *N*-benzyl benzamides and the five-membered N–H···N hydrogen bonding in a *N*-(pyridin-2-ylmethyl) benzamide.

It has been reported that benzyl- and pyridine-2-ylmethylamine-derived benzamides tend to form intermolecular N–H···O=C or N–H···N(Py) hydrogen bonding.[10] Therefore, it appeared



that, for detecting any new weak intramolecular hydrogen bonding in such family of amides, this strong intermolecular interaction must be inhibited. We chose to introduce a strong six-membered N–H···OMe hydrogen bond to realize this purpose[4] and thus first prepared a number of relevant compounds, including **1**–**6**. Single crystals suitable for the X-ray analysis were grown for **1**–**6** by slow evaporation of their solution in suitable solvents.[11]

Compounds **1**–**6** possess the identical backbone. However, crystal structures of **1**, **5**, and **6** have a triclinic space group, whereas those of **2**–**4** possess a monoclinic space group. For all the six compounds, the (N)H···O(Me) distance (r = 2.26–2.63 Å) in the benzyl amine moiety is longer than that in the benzamide moiety (r = 1.87–2.17 Å), but notably less than the sum of the van der Waals radii (2.72 Å) (Fig. 1).[12] These results indicate that the six-membered intra-molecular hydrogen bonding does form from

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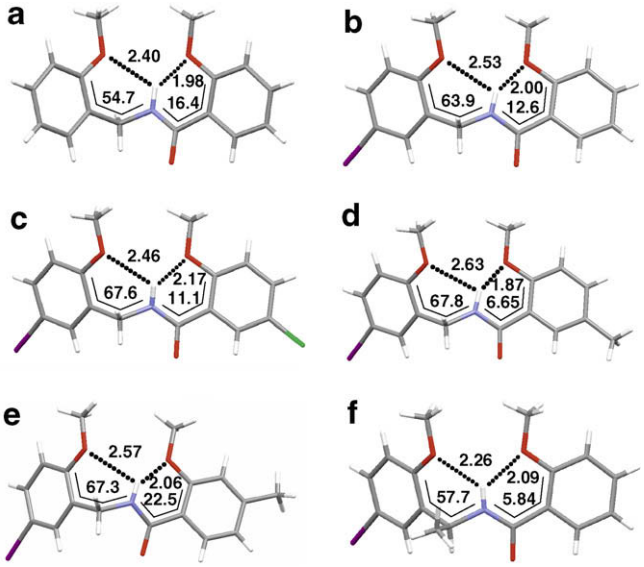


Figure 1. The crystal structures of (a) **1**, (b) **2**, (c) **3**, (d) **4**, (e) **5**, and (f) **6** and the related data of their two six-membered hydrogen bonds.

the benzylamine side, albeit weaker than that formed from the benzamide side. In all the structures, the torsion angles (54.7–67.8°) defined by the N–CH_2 bond and the connected benzene ring are significantly larger than that (5.84–16.4°) defined by the amide C–N bond and its neighboring benzene ring. This again reflects the lower stability of the former hydrogen bonding. The large torsions also caused all the molecules to adopt a saddle-shaped conformation (not shown). The fact that isomers **4** and **5** display different space groups may be ascribed to the effect of the methyl group on the benzamide ring on the packing pattern, even though neither of them forms any intermolecular interaction.

The halogen and/or methyl group on the benzene rings of compounds **2**–**6** also affect their respective packing behavior in the solid state. The packing structure of **1** is mainly stabilized by intermolecular π stacking and weak C=O H (Me, Ph) interactions (Fig. 2). For **2**–**6**, in addition to similar interactions, a pair of intermolecular C=O···I interactions are also generated, leading to the formation of unique dimeric structures (Fig. 3). Intermolecular C=O···I halogen bonds have been observed in crystal structures of several aromatic amides, which, however, usually lead to infinite linear packing patterns.[13] Therefore, the dimeric structures exhibited by **2**–**6** are obviously driven by the cooperative interaction of the two C=O···I halogen bonds, even though the latter should also be further stabilized by the two intramolecular hydrogen bonds as

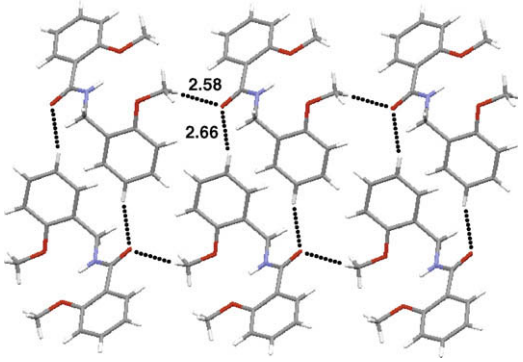


Figure 2. Packing pattern of compound **1**.

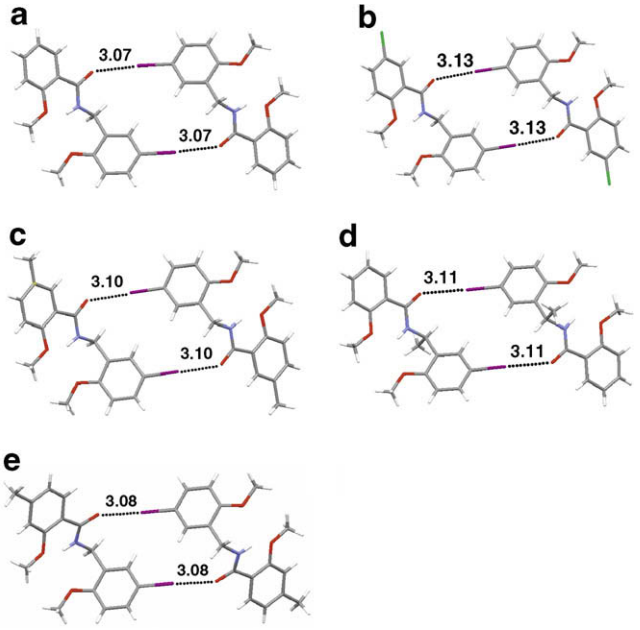
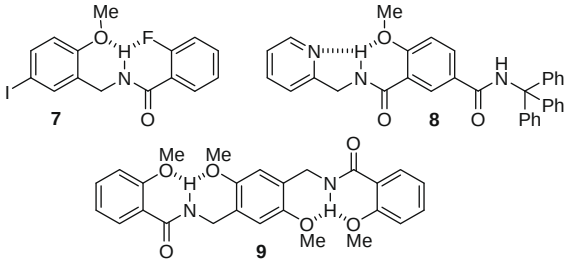


Figure 3. Dimeric structures of compounds **2**–**6** which are stabilized by two intermolecular C=O···I halogen bonds.

a result of conformational preorganization.[14] The chlorine atom in **3** does not form similar halogen bonding, which is consistent with the fact that it is weaker than iodine as a Lewis acid to accept electron.[15] It is also noteworthy that the methyl group at the benzyl methylene carbon of **6** does not greatly weaken the intramolecular hydrogen bonding, which raises the possibility of introducing a even larger group at this position while keeping the intramolecular hydrogen bonding.



Encouraged by the above results, we then prepared fluorine-substituted amides of the same backbone to test whether intramolecular six-membered N–H···F hydrogen bonding could lock the amide proton in similar way. Single crystal suitable for the X-ray analysis was obtained for one of them, that is, compound **7**. Its iodine-free analogue was found to be oily. Similar to **2**–**4**, this compound also possesses a monoclinic space group and the hydrogen bonding on its benzyl side is weaker than that on the benzamide side (Fig. 4). Moreover, two intermolecular C=O···I halogen bonds were also formed. It is reported that, in the crystal structures of aromatic amides in which fluorine acts as proton acceptor, the amide units also simultaneously form intermolecular N–H···O=C hydrogen bonding.[9e] Therefore, the intermolecular C=O···I halogen bonding of **7** should also play a role in locking the carbonyl oxygen from forming this intermolecular bonding.

Several amide derivatives of pyridin-2-ylmethylamine were also prepared for assessing the similar intramolecular five-membered N–H···N(py) hydrogen bonding pattern. For one of them, trityl-bearing **8**, single crystal was obtained successfully. The trityl

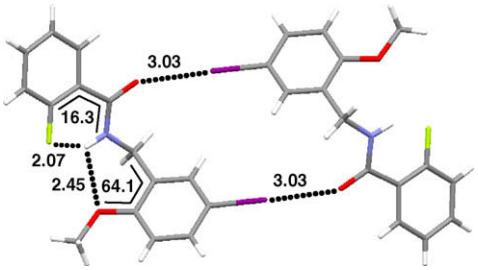


Figure 4. Dimeric structure and associated crystal data of compound **7**.

group has been revealed to increase the crystallity.[9f,16] The compound has a $P\bar{1}$ space group with four molecules in one crystal cell. All the four molecules exhibited the expected N–H···N(py) hydrogen bonding. However, their (N)H···N(py) distances (r = 2.14–2.65 Å) and related torsion angles (θ = 2.2–13.5°) varied considerably to achieve the stacking structure of lowest energy. The crystal data of one of the four molecules and the packing pattern are shown in Figure 5. It can be found that the torsion angles of the two intramolecular hydrogen bonds are considerably smaller than those observed for the above benzyl-derived amides. Another four amide units, albeit bearing the large trityl group, still form intermolecular N–H···O=C hydrogen bonding. Moreover, the NH proton of one of them is hydrogen bonded to the CH_2-attached amide oxygen of another molecule. It is reasonable to propose that these forces, together with other possible interactions, contribute significantly to the stabilization of the parallel stacking of the *N*-(pyridin-2-ylmethyl)-benzamide backbone. Therefore, the above small torsion angles cannot be simply considered as evidence for that its five-membered N–H···N hydrogen bonding is more stable than the above six-membered N–H···O hydrogen bonding.

To test the scope of this weak intramolecular hydrogen bonding pattern, compound **9** was also prepared, which might be considered as a combination of two molecules of **1**. As expected, the intramolecular six-membered hydrogen bonding was exhibited from both sides (Fig. 6), which leads to the formation of an extended belt structure for the overall molecule.[17] The data of the bonding are very close to that of **1**, implying comparable stability.

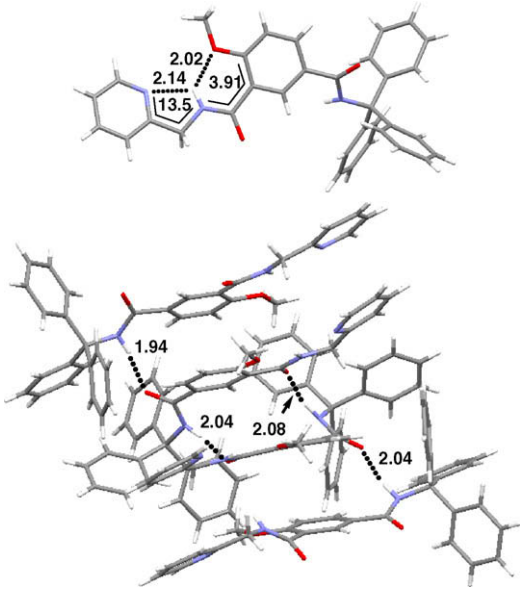


Figure 5. The crystal structure and packing pattern of compound **8**.

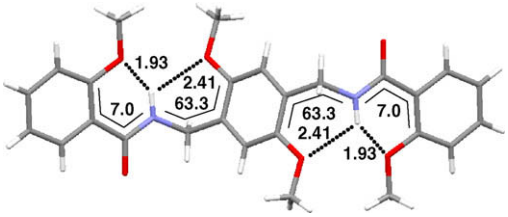
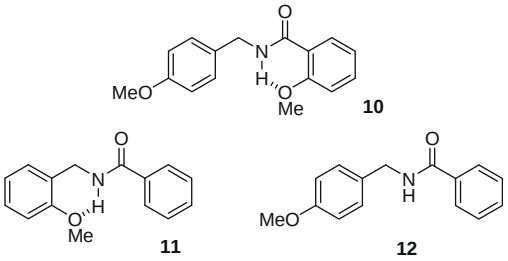


Figure 6. The crystal structure and associated crystal data of compound **9**.

These results suggest that the new weak bonding might be further utilized to generate even larger compact conformations.

The ratios of the distances of the above hydrogen and halogen bonds and the sum of the van der Waals radii of the corresponding bonded atoms are summarized in Table 1. This ratio parameter has been used to evaluate the relative stability of different hydrogen bonds.[18] For all the molecules, the value of the hydrogen bond formed on the CH_2 side is notably larger than that formed on the C=O side, reflecting their relatively lower stability. For **2**–**4** that possess the same $P21/c$ space group, the values of the hydrogen bonds on the CH_2 side are only slightly higher than that of their intermolecular I···O=C halogen bonds. Considering that the ratio values might be affected by many discrete factors, including the steric effect, π stacking, and the position of substituents, we may consider that these two forces are comparable in strength, both arranged among the weak non-covalent interactions.[1a]



In order to test whether the above intramolecular O···H–N hydrogen bonding occurs in solution, we also prepared compounds **10**–**12**. Their ^{1}H NMR spectra were recorded in $CDCl_3$ (2.0 mM). Compared to that of **1** (8.37 ppm), the NH signal of **10** appeared at 8.12 ppm ($\Delta\delta$ = −0.25 ppm), while the signals of the NH protons of **11** and **12** appeared at 6.64 and 6.29 ppm ($\Delta\delta$ = −0.35 ppm), respectively. These large differences clearly indicate that the methoxyl oxygens on the benzyl ring of **1** and **11** were engaged in

Table 1
The ratios of the distances of the hydrogen or halogen bonds of compounds **1**–**9** and the sums of the van der Waals radii of the bonded atoms[a]

Compound	Hydrogen bond (I)[b]	Hydrogen bond (II)[c]	Halogen bond
1	0.88	0.73	–
2	0.93	0.74	0.88
3	0.90	0.80	0.89
4	0.97	0.68	0.89
5	0.94	0.75	0.89
6	0.83	0.77	0.89
7	0.90	0.78	0.87
8	0.78	0.74	–
9	0.89	0.71	–

[a] The van der Waals radii of H, O, N, F, and I is 1.20, 1.52, 1.55, 1.47, and 1.98 Å, respectively.[12]
[b] The hydrogen bonding in the CH_2-incorporated ring.
[c] The hydrogen bonding in the amide C–N bond-incorporated ring.

intramolecular hydrogen bonding. Further evidence came from the NOESY spectrum of **1**, which displayed NOE connections between the amide hydrogen and the hydrogen atoms of both methyl groups but not the 6-hydrogen of the benzyl benzene. These observations can be rationalized by considering that, in relatively dilute chloroform solution, intermolecular N–H···O=C hydrogen bonding of these molecules was weak such that they existed mainly in the single molecular state. In contrast, in the solid state, these intermolecular interactions became strong due to favorable stacking and absence of the solvent molecules. It is also noteworthy that the downfield shifting of **11** relative to **12** was slightly larger than that of **1** relative to **10**. This difference can be explained by considering the fact that the benzamide-based intramolecular hydrogen bonding in **1** weakened the hydrogen bonding formed on the side of benzyl unit. The ^{1}H NMR signals of the amide protons of **1**, **10**, **11**, and **12** in DMSO-d_6 (2.0 mM) appeared at 8.59, 8.61, 8.86, and 8.97 ppm, respectively. These results should reflect the weakness of the benzyl-based intramolecular hydrogen bonding in **1** and **11**. In highly competent solvent like DMSO, this weak interaction cannot survive and consequently, the methoxyl unit at the benzyl ring might mainly serve as a steric hindrance group to weaken the hydrogen bonding between the amide proton and the solvent molecules.

In conclusion, we report the first systematic study that supports the formation of weak intramolecular six-membered N–H···O and five-membered N–H···N hydrogen bonding in *N*-benzyl or *N*-(pyridin-2-ylmethyl) benzamides in both the solid state and solution. In order to observe the weak interactions, we have developed an efficient approach—introducing a strong intramolecular hydrogen bond to lock the NH protons of the amides from forming intermolecular N–H···O=C hydrogen bonding. The new approach may find further applications in studying intramolecular weak hydrogen bonding motifs. We also demonstrate that the iodine atom is useful in increasing the crystallinity of aromatic molecules, even although its capacity of forming intermolecular halogen bond should also be considered when designing new structures. The work represents the first step for exploring intramolecular hydrogen bonding patterns in amides with 'hybridized' aliphatic/aromatic segments. We are currently investigating their possible application in constructing new longer secondary structures by designing oligomers that consist of these hydrogen bonded molecular synthons.

Acknowledgments

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