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N_{aryl}-substituted anthranilamides with intramolecular hydrogen bonds

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ABSTRACT

Hydrogen bonding interaction as one type of non-covalent force has proven itself to be highly efficient for constructing structurally unique artificial secondary structures. Here, the structure of N_{aryl}-substituted anthranilamide in solution is demonstrated by various NMR technique, the intramolecular hydrogen bonds between amide attached to arylamine of the same ring is proposed, which is supported by its crystal structure in the solid phase. The substituent on the nitrogen atom of arylamine plays an important role in forming the presence of intramolecular hydrogen bonds. The chemical shift of the N_{aryl}-H downfield changes obviously, due to the formation of intramolecular hydrogen bonds and the deshielding effect of oxygen, and the neighboring C–H is activated and shows downfield protonic signal too. The presence of intramolecular hydrogen bonds probably provides the explanation for the transformation from N_{aryl}-substituted anthranilamide to imine, which could be converted into 2-aryl quinazolinone finally.

1. Introduction

Due to its directionality and strength, hydrogen bonding interaction as one type of non-covalent force has proven itself to be highly efficient for constructing structurally unique artificial secondary structures.[1] Particularly, a number of hydrogen-bonding-mediated aromatic amide foldamers of well-defined conformations have been assembled,[2] some of which represent a new generation of non-ring receptors for saccharides,[3] alkylammoniums,[4] or encapsulation of water.[5] To achieve high binding stability and selectivity, the design of hydrogen-bonding-mediated molecular building blocks requires preorganization and rigidity of the backbones and binding sites of monomers, which is usually realized by making use of intramolecular hydrogen bonds.[6] Foldamers based on oligoanthranilamides that are induced by intramolecular hydrogen bonds to adopt well-established secondary structures exhibit special features.[7]

The amide units are commonly used as hydrogen-bond donors to form intramolecular hydrogen bonds with other *O*-groups or *N*-groups as hydrogen-bond acceptors[8] and they also work as hydrogen-bond donors and acceptors simultaneously to form intramolecular hydrogen bonds between adjacent amide–amide groups, to construct linear sheets and helical conformations.[9] In our research, the amide serves as hydrogen bond acceptor, the oxygen of which is attached to arylamine N–H of the same aromatic ring, in order to form intramolecular hydrogen bonds. The N_{aryl}-substituted oligoanthranilamides investigated here are very simple. However, the presence of intramolecular hydrogen bonds of these structures can be helpful to demonstrate the detailed structures and provide a probable explanation for the mechanism starting from N_{aryl}-substituted oligoanthranilamides, which can be converted into 2-aryl quinazolinones finally.

NMR spectroscopy is a research technique that exploits the magnetic properties of certain nuclei, and has been a powerful and inevitable tool for structure determination.[10] The intramolecular magnetic field around an atom in a molecule changes the resonance frequency, thus giving access to details of the electronic structure of a molecule. Herein, we demonstrated the structures of N_{aryl}-substituted anthranilamides by various NMR techniques, and verified the presence of intramolecular hydrogen bonds in solution, which was supported by crystal structures in the solid phase. Comparing

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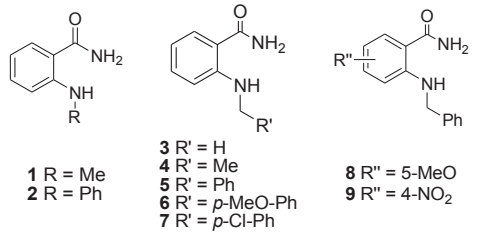
to the anthranilamides with the absence of intramolecular hydrogen bonds, the proton signals of amides, and arylamines showed different assignments.

2. Results and discussion

The chemical shift of N–H in amide is always assigned at lower magnetic fields, due to the deshielding effect of carbonyl group, comparing to the alkylamine or arylamine. However, anthranilamides **1**–**9** (Scheme 1) in DMSO-d_6 solution show the δ values of H-10s (–ArNH–) 8.00–10.05 ppm, which are assigned at the minimum magnetic fields; and while the δ values of H-1s and H-2s of the amide groups are found at 7.79–8.05 ppm and 7.12–7.46 ppm, respectively, due to the hindered rotation of C–N bond. The partial picture of ^{1}H NMR spectra of the anthranilamides **1**–**9** is shown in Fig. 1b. We propose that there is the presence of intramolecular hydrogen bonds in anthranilamides **1**–**9**, shown as in Fig. 1a. Therefore, the chemical shifts of the H-10s downfield changes obviously because of the deshielding effect of oxygen. Coupling with the adjacent proton, the H-10 shows a multiplet signal in the structures of **3**–**9**.



Scheme 1. Structures of N_{aryl}-substituted anthranilamides **1**–**9** investigated.

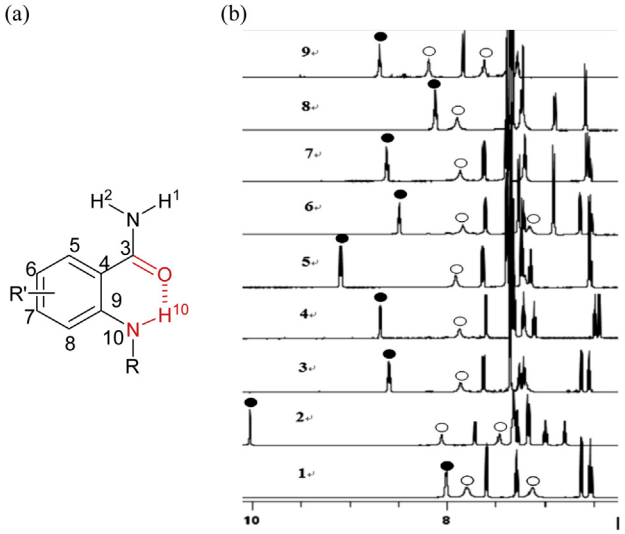


Fig. 1. (a) Structures with intramolecular hydrogen bonds. (b) Partial picture of ^{1}H NMR spectra of compounds **1**–**9** in DMSO-d_6 solution at 298 K, H-10: solid circle, H-1 and H-2: hollow circle.

Anthranilamides **1**–**9** dissolved in non-polar deuterated $CHCl_3$ solution also give the similar results: the δ values of H-10s (–ArNH–) are assigned at the minimum magnetic fields shown as in Fig. S1, showing the chemical shifts 8.33–8.65 ppm; and the protons of the amide groups give a broad and single peak near to 5.72 ppm. The ^{1}H NMR spectra in DMSO-d_6 and $CHCl_3$-d solution both indicate that the presence of intramolecular hydrogen bonds in anthranilamides **1**–**9**, which is verified further by dilution experiments of **3**. The chemical shifts of all protons are consistent for **3**, varying from 20 mM to 0.5 mM (Fig. 2).

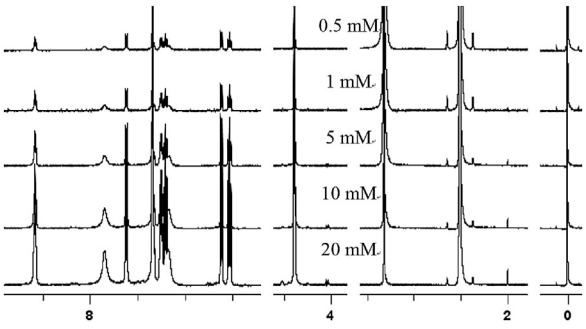


Fig. 2. ^{1}H NMR spectra of the dilution study of **3** in DMSO-d_6 from 20 mM to 0.5 mM at 293 K.

N-(α-methyl)-benzyl-anthranilamide **4** was picked out as a model to demonstrate the detailed structure in DMSO-d_6 solution. As listed in Table 1, a broad singlet signal at δ=7.85 ppm corresponds to H-1 of the amide group, and the δ value of H-2 is covered in the signal of H-16. A doublet signal at δ=8.67 ppm is identified for H-10 and has an obvious correlation with H-11 by the J=6.5 Hz. The signal assignments of active hydrogen atoms H-1, H-2, and H-10 are further confirmed by ^{1}H–^{15}N HSQC spectrum (Fig. 3), where the δ of *N*-amide is 105.1 ppm and the δ of *N*-arylamine is 85.2 ppm. The position of H-12 of methyl-is easy to be identified, showing a doublet signal at δ=1.43 ppm and J=7.0 Hz coupling with H-11. A multiplet signal at δ=4.62–4.56 ppm is designated to be H-11, linking to C-12, and coupled with the H-10 and H-12 in the neighborhood. A double doublets signal at δ=7.58 ppm and J=8.0, 1.5 Hz is identified as H-5, based on the results of COSY spectrum (see Supplementary data) where the H-5 has a correlation with H-6 and H-7, and HMBC spectrum (see Supplementary data) where it has a correlation with C-3 (–CO– group). By analogy to H-5, other remaining protons are assigned.

Table 1
The numbering scheme of molecular structure of compound **4** and the full assignment of the proton and carbon peaks

	Atom	^{1}H	^{13}C	HMBC
	1	7.85	—	—
	2	7.20	—	—
	3	—	172.2	—
	4	—	149.3	—
	5	7.58	129.5	C3, C4, C6
	6	7.09	132.7	C4, C7
	7	6.47	112.9	C8
	8	6.42	114.61	C7
	9	—	145.9	—
	10	8.66	—	C8, C11
	11	4.62–4.56	51.9	C13, C14
	12	1.43	25.4	C11, C13
	13	—	114.56	C12, C15
	14, 15	7.34–7.28	129.0, 127.1	C13, C16
	16	7.19	126.2	C14, C15

Carbon C-3 presents chemical shift at δ=172.2 ppm, which is assigned as –CO– of amide group. C-11 and C-12 are identified at 51.9 and 25.4 ppm, respectively, based on the correlations observed with atoms H-11 and H-12 in the HSQC spectrum (see Supplementary data). In the same way, carbons C-5 to C-8 and C-14 to C-18 are assigned. The quaternary carbon C-4 shows the chemical shift at δ=149.3 ppm, based on the correlations observed with C-5 and C-3 in the HMBC spectrum (see Supplementary data).

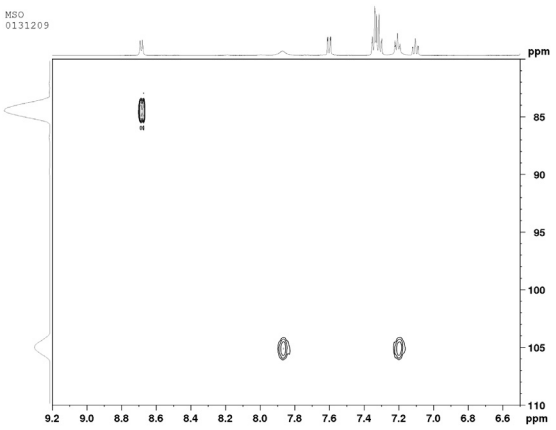


Fig. 3. $^{1}H-^{15}N$ correlation spectrum of compound **2** (HSQC) in DMSO-d_6 solution at 298 K. The horizontal axis shows 1D ^{1}H spectrum; the vertical axis shows ^{15}N projection.

Other remaining quaternary carbons C-9 and C-13 are assigned, according to the same procedure.

2-Methyl-2-phenyl-1,2,3,4-(*H*)-quinazolinone **10**, with amide and arylamine groups existed in the same ring, gives the δ values of H-1 and H-9 as two singlet signals at δ=8.77 and 7.51 ppm, respectively (Fig. 4b). With the absence of intramolecular hydrogen bonds, the proton signal of amide is assigned at higher magnetic fields than arylamine. The positions of H-1 and H-9 in DMSO-d_6 solution are verified further by the $^{1}H-^{15}N$ HSQC spectrum (Fig. 4c), where the δ value of *N*-amide is 128.3 ppm and the δ value of *N*-arylamine is 86.6 ppm.

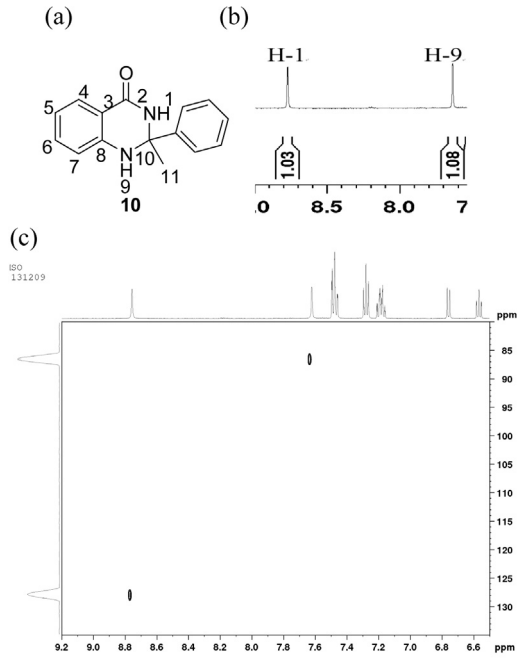


Fig. 4. Compound **10**: (a) Partial numbering. (b) Partial picture of ^{1}H NMR spectrum. (c) The $^{1}H-^{15}N$ HSQC spectrum in DMSO-d_6 solution at 298 K.

Fortunately, we obtained the crystal structures of compound **5** and **10**, respectively, by slow diffusion of CH_3OH and $CH_3COCH_2CH_3$ solution at room temperature for some days. In the solid phase of compound **5** (Fig. 5a), we observed the intramolecular hydrogen bonds intuitively between the oxygen of amide group and N–H of

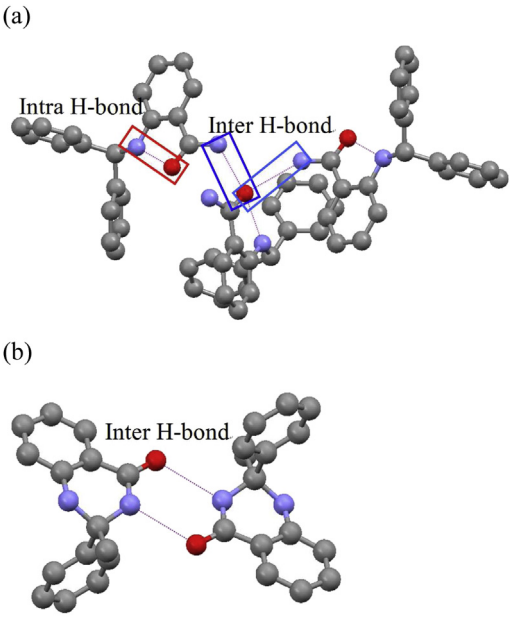


Fig. 5. Crystal structures: (a) Packing diagram of compound **5**, intramolecular hydrogen bonds: red rectangle, and intermolecular hydrogen bonds: blue rectangle. (b) Dimer structure of compound **10** by intermolecular hydrogen bonds.

arylamine group, with the distance of O–N was 2.687 Å. The intermolecular hydrogen bonds were also observed between oxygen and N–H of amide groups, with the distance of O–N was 2.859 Å and 2.900 Å separately. For compound **10**, the formation of quinazolinone-4(*H*) prevented the free rotation of amide group, there was no intramolecular hydrogen bonds observed. However, the amide units of compound **5** functioned as hydrogen bond donors and acceptors simultaneously to form a dimer complex by intermolecular hydrogen bonds (Fig. 5b).

A few of *N*-substituted anthranilamides with intramolecular hydrogen bonds have been reported previously, however, nobody has provided the detailed signal assignments and demonstrated the presence of intramolecular hydrogen bonds. For example, Buchwald et al. synthesized N_{aryl}-substituted anthranilamides, and the ^{1}H NMR signals of ArNH- were assigned 9.44–9.78 ppm (300 MHz, $CDCl_3$) at the minimum magnetic fields,[11] due to the intramolecular six-membered rings between amides and arylamines formed by hydrogen bonds. For the simplest substrate Anthranilamide (see Supplementary data), or other 2-amino benzamides,[13] there was the absence of intramolecular hydrogen bonds found, showing chemical shifts of N_{aryl}-Hs in the higher magnetic fields comparing to the amides of the same aromatic rings, probably because of the rapid exchange of the two protons of N_{aryl}-Hs. These results suggest that the substituent on the nitrogen atom of arylamine plays an important role in forming the presence of intramolecular hydrogen bonds, which can tolerant the N_{aryl}-substituted anthranilamides with varied electronic properties.

Due to the presence of the intramolecular hydrogen bonds, the proton signals of N_{aryl}-Hs downfield shifted obviously mentioned above and the neighboring C–Hs were involved in too, and presented downfield shifts 4.62–4.56 ppm of compound **4**, comparing to the precursor α-methylbenzylamine (4.00–3.96 ppm). (Fig. 6) Therefore, the N_{aryl}-substituted anthranilamides were oxidized easily to imines, which were converted to 2-aryl quinazolinones finally, as shown in Scheme 2.[12,13] In our pervious report, the *o*-(*N*-diphenylmethyl-amino) benzamide **5** was transferred into the imine, which was verified indirectly due to the isolation of diphenylmethanone as one by-product, under the established conditions.[12]

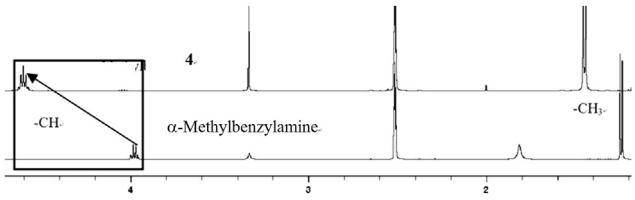
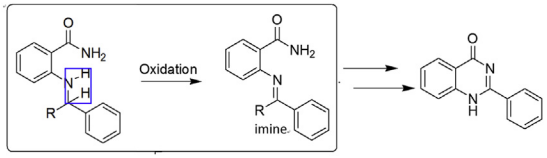


Fig. 6. Partial picture of ^{1}H NMR spectra of compound **4** and α-methylbenzylamine in DMSO-d_6 solution at 298 K.



Scheme 2. The transformation from N_{aryl}-substituted anthranilamides to 2-aryl quinazolinones.

3. Conclusion

In conclusion, we demonstrated the detailed structures of N_{aryl}-substituted anthranilamides in solution by various NMR technique for the first time. The intramolecular hydrogen bonds between $-CONH_2-$ and aryl–NH– was observed, which was verified by crystal structures in the solid phase. The neighboring C–Hs were involved in, and presented downfield chemical shifts. Therefore, it probably provided the explanation for the mechanism from N_{aryl}-substituted anthranilamides to imines by oxidation, which were further converted into medically important 2-aryl quinazolinones. Besides, we believe that this research will be helpful for the accurate designation of protonic signals of anthranilamide derivatives.

4. Experimental section

4.1. Compounds

N_{aryl}-substituted-anthranilamides **2**–**9** were prepared from the Ullmann coupling reactions between 2-iodobenzamide and aniline or α-substituted benzylamines, under the reaction conditions with the presence of the base K_2CO_3 (2 equiv), under argon atmosphere (1 atm, with extrusion of air), at 110 °C for 4 h in DMSO. N_{aryl}-methyl-anthranilamide **1** was prepared according to the reported method.[14]

2-Methyl-2-phenyl-1,2,3,4-(*H*)-quinazolinone **10** was prepared according to the reported method,[15] starting from 2-aminobenzamide and phenylacetylene in the presence of $Ph_3PAuNTf_2$, under argon atmosphere (1 atm, with extrusion of air), at 100 °C for 24 h in toluene.

Anthranilamide, α-methylbenzylamine, and other organic reagents were purchased from Beijing J&K Chemical Scientific Company.

4.2. Spectra

4.2.1. NMR spectra. All spectra were recorded on a Bruker Advance III 500 spectrometer equipped with a 5-mm BBFO probe, in DMSO-d_6 solution at 298 K. Data processing was carried out with TopSpin 3.2 version (Bruker, German). The ^{1}H and ^{13}C NMR spectra were operated at 500 and 125 MHz, respectively. Pulse programs for all spectra were as follows: ^{1}H NMR spectra, zg30; ^{13}C NMR spectra, zgpg30; Cosy spectra, cosygpppqf45; ^{1}H–^{13}C and ^{1}H–^{15}N HSQC spectra, hsqcetgp; ^{1}H–^{13}C HMBC spectra, hmbcgplpndqf.

Chemical shifts were given on the δ scale (ppm) and were referenced to the residual solvent signals (δ_H=2.50 ppm, δ_C=38.5 ppm); Coupling constants *J* were reported in hertz (Hz). The abbreviations s, d, and m were used for singlet, doublet, and multiplet, respectively.

4.2.2. X-ray crystallographic spectra. Single crystals of **5** and **10** were prepared by slow diffusion of CH_3OH and $CH_3COOCH_2CH_3$ solution at room temperature.

Datas for compounds **5** and **10** were collected at 173 K with Mo *K*α radiation (λ=0.73073 Å) on a Rigaku Saturn 724 + CCD diffractometer with frames of oscillation range 0.5°. All structures were solved by direct methods, and non-hydrogen atoms were located from difference Fourier maps. All non-hydrogen atoms were subjected to anisotropic refinement by full-matrix least-squares on F^2 by using the SHELXTL program.

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Supplementary data

Supplementary data include copies of NMR spectra of all compounds mentioned above, and crystal data for compound **5** and **10**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.09.057.

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